Patent foramen ovale in children: Unique pediatric challenges and lessons learned from adult literature

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ABSTRACT

A patent foramen ovale (PFO) is a frequent incidental finding during echocardiography in otherwise healthy children. In most healthy children with a diagnosis of isolated incidental PFO, no further follow-up or intervention is necessary. In some children, PFO is associated with certain clinical syndromes such as cryptogenic stroke, decompression sickness, migraine, and platypnea-orthodeoxia syndrome. This review discusses PFO anatomy, diagnostic imaging, PFO-associated clinical situations, management options, and the role of PFO in certain congenital heart disease. This review also highlights the current deficiency of pediatric data guiding management of these uncommon but important PFO-associated conditions. Future multicenter randomized controlled studies are necessary to guide the management of these unique and challenging PFO-associated conditions.

Keywords: Children, decompression sickness, management, migraine, patent foramen ovale, platypnea-orthodeoxia syndrome, stroke

INTRODUCTION

A patent foramen ovale (PFO) is the most frequent incidental diagnosis of a communication between the two atria during echocardiography in otherwise healthy children. In most healthy children with an isolated PFO, no further follow-up or intervention is necessary.

The foramen ovale is a natural and essential part of fetal cardiac development [Figure 1]. Embryologic development of the atrial septum and PFO has been described earlier and is beyond the scope of this article. In fetal life, the PFO facilitates unrestricted and preferential streaming of oxygen- and nutrient-rich
placental blood from the inferior vena cava (IVC) into the left side.\(^3\),\(^4\) Restricted right-to-left atrial (LA) flow in a fetus results in underdevelopment of the left-sided cardiac chambers.\(^5\) A left-to-right shunt across the PFO in a fetus is always abnormal and indicates critical cardiac lesions such as mitral atresia or stenosis, and hypoplastic left heart syndrome. Constriction of the PFO in such fetuses predisposes to pulmonary venous hypertension and is an independent predictor of poor outcomes.\(^6\)

At birth, with the first breath, the lungs expand and pulmonary blood flow increases which increases the LA pressure. Simultaneously, the rapid reduction in return from IVC due to removal of the placenta leads to a rightward shift of the primary septum which then opposes the secondary septum, thus functionally “closing” the PFO. The anatomic closure, however, is gradual and may remain incomplete, with persistent patency in up to 20%–30% of adults.\(^7\),\(^8\) The morphology of the PFO varies depending on the characteristics of the upper margin of the primary septum, the thickness of the secondary septum, and the characteristics of the remaining atrial septum.\(^9\) The flap valve mechanism of the isolated fossa ovalis remains a potential site for interatrial shunting later in life.

PFO is also commonly associated with other congenital heart diseases (CHDs). In some children with certain critical CHD such as tricuspid atresia, mitral atresia, and total anomalous pulmonary venous connection, a PFO serves as an essential component for survival. In these children, the shunting at the level of PFO could be either left to right or right to left based on the specific CHD [Figures 2-4].

This review focuses mainly on children with an isolated PFO and associated clinical syndromes such as cryptogenic stroke, decompression sickness, migraine, and other rare conditions. In children with PFO-associated clinical syndromes, currently, there is a deficiency of data guiding clinical management. Even though there is evidence regarding the management of PFO in adult patients with cryptogenic stroke, similar pediatric data are lacking and simply extrapolating adult data to pediatric patients are not acceptable.

**IMAGING**

A PFO can be visualized by transthoracic echocardiography (TTE) from multiple views, but it is best visualized with the atrial septum relatively perpendicular to the transducer, such as in the subcostal coronal and sagittal views. On two-dimensional imaging, it is most commonly seen as a small slit-like defect in the mid atrial septum with the rightward margin extending more inferiorly than the leftward margin.
aneurysmal or fenestrated). An atrial septal aneurysm is defined in adults as a patulous (10–15 mm) excursion of the floppy septum during the cardiorespiratory cycle, but there is no clear definition available for pediatric patients. Trans-septal left-to-right flow by color Doppler helps confirm the presence of a PFO. A transthoracic para-coronal view with 30° rotation and cranial angulation can help define the margin of the limbus, the oval fossa, and the PFO. In patients with suboptimal subcostal acoustic windows, the left parasternal short-axis view may provide a clue to the presence of a PFO. Turning the patient to a right lateral decubitus position for a high right parasternal view can help delineate the interatrial septum. Apical views are prone to false dropout at the atrial septum due to the atrial septum being parallel to the ultrasound beam and color flow in this view is not diagnostic. Agitated saline contrast improves the diagnostic yield of echocardiography, especially in situations with inconclusive color Doppler imaging and particularly for right-to-left shunting [Video 1]. Microbubbles generated by agitating normal saline enhance the backscatter of the ultrasound beam, thus highlighting blood flow. Provocative maneuvers such as the Valsalva maneuver followed by release (forced expiratory effort against a closed glottis followed by strain release), cough, and compression of the IVC transiently increase right atrial (RA) pressure above LA pressure and further enhance the sensitivity of contrast study for the detection of right to LA shunting.[11–15] In patients on mechanical ventilation, a Valsalva equivalent is achieved by the end-inspiratory pressure hold maneuver. The saline contrast study is performed by placing a large-bore intravenous cannula in the most proximal location, agitation of a combination of saline (80%), with addition of air (10%) and patient’s blood (10%), followed by rapid intravenous administration and simultaneous capture of a long digital loop (either 4–6 s or 6–10 cardiac cycles).[16,17] A lower extremity saline contrast injection is more likely to uncover a PFO than an upper extremity injection.[18] The saline microbubbles are too large to cross the pulmonary capillary bed, and in the absence of a right-to-left shunt, the microbubbles remain confined to the right side of the circulation. Visualization of contrast in the left-heart chambers indicates either intracardiac (within three beats of RA opacification) or intrapulmonary shunting (at least five beats after RA opacification). The number of microbubbles in the left heart is utilized to quantify right-to-left shunt (small; 3–9 microbubbles, moderate; 10–30 microbubbles, large; more than 30 microbubbles).

Even though transesophageal echocardiography TEE is considered the “gold standard” for detection of a PFO in adults, in most children, TTE is adequate for a typical left-to-right shunt.[19–21] In children, TEE is only considered if TTE imaging is inadequate, in clinical scenarios where the diagnosis is critical, and for procedural assistance during cardiac surgery or catheterization.[14] Typically, four-chamber and bicaval views in the mid-esophageal position and atrial septal views in the deep transgastric view are utilized to evaluate a PFO. The sensitivity for PFO detection by TEE has been reported to be as high as 95% in the presence of both the leftward bulging of the interatrial septum and dense contrast filling of the right atrium following a single injection.[22] In children, there is no or minimal role for advanced imaging (three-dimensional echocardiography, computerized tomography, and cardiac magnetic resonance imaging) for the diagnosis of PFO. Even though transcranial Doppler echocardiography has been utilized for the noninvasive diagnosis of a right-to-left shunt by detecting microbubble signals in the middle cerebral artery, the test does not distinguish intracardiac and extracardiac shunts.[23–26] Intracardiac echocardiography (ICE) is primarily utilized for procedural assistance during cardiac catheterization.[27]

**PATENT FORAMEN OVALE-ASSOCIATED CLINICAL SCENARIOS**

In healthy children with incidental findings of isolated PFO, a small left-to-right shunt from the left atrium to the right atrium is not hemodynamically significant. In a very small subset of these children, PFO could be involved in paradoxical right-to-left shunt and associated clinical syndromes. Children with PFO and underlying CHD are a unique population and should be managed on a case by case basis.

**Isolated asymptomatic patent foramen ovale**

In healthy children with incidental finding of isolated PFO, no further treatment or follow-up is recommended. There is no current evidence guiding practitioners on how to discuss the rare possibility of future complications associated with isolated PFO in some children. For
example, in an Internet-based survey of cardiologists of the British Congenital Cardiac Association about the follow-up of isolated PFO, a majority (81%) of practitioners agreed on no follow-up and a predischarge discussion on implications such as scuba diving was suggested.\(^{28}\) Much variations in practice currently exist in the management and counseling of such patients and need both further study and standardization. Therefore, physicians must individualize care and provide the necessary information without causing undue anxiety to the child and parents.

**Cerebrovascular accident and transient ischemic attack**

Paradoxical right-to-left shunt via a PFO could lead to stroke, especially in patients with hypercoagulable disorders (primary or acquired, including prolonged immobilization, malignancy, pregnancy, etc.), sickle cell anemia, indwelling central venous catheters, and transvenous cardiac pacing lead.\(^{29-31}\) Right-to-left shunt via PFO is further augmented in patients on a left ventricular assist device secondary to a reduction in LA pressure potentially leading to hypoxemia and rarely, paradoxical emboli.\(^{32,33}\) Rarely, a PFO can also be involved in extension of a vegetation in endocarditis or RA myxoma with possible paradoxical embolism.\(^{34}\) The etiology of pediatric stroke varies widely and an extensive multidisciplinary workup is necessary to evaluate for cardioembolic, thrombophilia, arteriopathy, inflammatory, genetic, and metabolic disorders.\(^{31,35}\) Cryptogenic stroke is a diagnosis of exclusion and the role of PFO in the causation and the risk of recurrence, especially in children, is unclear. Recent randomized controlled trials in adult patients have demonstrated PFO closure to be superior to medical therapy in patients with cryptogenic stroke (long-term follow-up of RESPECT trial, GORE REDUCE trial, and CLOSE and DEFENSE PFO TRIALS).\(^{36}\) Even though some comparisons could be possibly drawn from adult literature, there are unique challenges in the younger age group that need to be considered.\(^{37-39}\)

Currently, PFO closure for primary stroke prevention in children is not recommended.\(^{40}\) In adult patients between 18 and 60 years of age with a PFO, embolic-appearing cerebral infarction, and no other possible stroke etiology, clinicians may recommend closure following a discussion of potential benefits and risks (level C).\(^{35}\) Thus, there may be a place for PFO closure in select children, especially those older than 16 years based on the extrapolated adult data, but it needs further evaluation in pediatric multicenter randomized controlled trials. Anatomic characteristics such as aneurysmal atrial septum, hypermobile atrial septum, large right to left shunt, prominent Eustachian valve, and Chiari network are considered high risk in the adult patient with cryptogenic stroke, but similar pediatric data are lacking.\(^{41}\)

In children with either cryptogenic stroke or stroke in the setting of sickle cell disease, antiplatelet therapy is indicated for secondary prevention. Medication compliance, however, can be challenging in children on chronic antiplatelet or anticoagulant regimens and should be taken into consideration during the decision-making regarding PFO closure. Even though PFO closure is more effective for secondary stroke prevention in relatively younger adult patients (under 45 years of age) as compared to older adults, this is still unproven in the pediatric population.\(^{42,43}\) Similarly, PFO closure for secondary stroke prevention for clinically suspected TIA in children is not currently supported and needs further study.

Suggested workup for evaluation of children with a cerebrovascular event and PFO includes electrocardiography, monitoring of cardiac rhythm based on symptoms, thrombophilia workup, along with consideration of neurology, hematology- oncology, and infectious disease consultation based on the clinical context.

**Decompression sickness**

Rapid ascent could lead to decompression sickness in the deep-sea divers due to the formation of nitrogen bubbles within the tissues which eventually enter the arterial circulation leading to vascular occlusion. Intermittent right-to-left shunt across the PFO could lead to further increase in stroke risk. Divers with a PFO and history of severe or recurrent decompression illness could be considered for transcatheter PFO closure, especially if the patient wants to continue unrestricted diving. PFO closure is usually successful in most of these patients with relatively low risk. However, a small subgroup of patients with a residual shunt could still develop decompression illness. Therefore, patients must be counseled regarding the possibility of a residual shunt during preprocedure evaluation.\(^{44,45}\) Currently, there are no available pediatric data guiding the management of PFO in young scuba divers.

**Migraine**

PFO is more prevalent in children and adolescents suffering from migraine with aura.\(^{46,47}\) However, no evidence currently exists to support PFO closure in children with migraines. Despite lack of evidence, symptomatic improvement after PFO device closure has been reported in a survey-based observational study of children with migraine with aura.\(^{38}\) There could be a role for PFO closure in a select subset of patients with refractory and disabling symptoms who fail to improve despite medical therapy. This area needs further study, ideally with randomized controlled trials before recommending such therapy.
Pregnancy

Pregnancy is a condition of altered coagulation, hormonal, and cardiovascular parameters. PFO-related stroke, although rare, could happen secondary to hypercoagulation and paradoxical emboli. In patients with a prior history of PFO-related stroke, future stroke recurrence risk is high, especially during subsequent pregnancy and immediate postpartum period. Future prospective studies are needed to evaluate the true prevalence of PFO and paradoxical emboli during pregnancy, especially in young adults.\[49\]

Platypnea–Orthodeoxia syndrome

The platypnea–orthodeoxia syndrome is a very rare pathology characterized by a combination of shortness of breath and systemic hypoxia in the upright position. Some patients with PFO could have associated platypnea–orthodeoxia syndrome.\[50\] These patients would likely benefit from device closure of PFO, but evidence in the pediatric population is lacking.

Congenital heart disease

The incidental diagnosis of PFO by TEE during a cardiac surgery must be conveyed to the surgical team to plan the cardiopulmonary bypass and/or circulatory arrest strategy and possible primary closure of the PFO at the end of the case based on the underlying heart disease and planned surgery. In patients undergoing transvenous pacemaker lead implantation, the operator should be aware of the possibility of pacemaker lead malposition due to the presence of PFO. Therefore, lead position should be confirmed in multiple imaging planes to avoid inadvertent lead placement into the left heart.

MANAGEMENT OF PATENT FORAMEN OVALE

In patients with PFO-associated conditions requiring closure, PFO is predominantly closed via a percutaneous device. Transcatheter closure of PFO can be accomplished safely and effectively in the pediatric age group.\[51\]

There are multiple devices available for transcatheter device closures including Amplatzer™ PFO Occluder (Abbott Inc., Abbott Park, IL) and the Gore Cardioform™ Septal Occluder (W. L. Gore and Associates, Flagstaff, AZ). The FDA currently approves both the devices for transcatheter closure of PFO in the USA. The Amplatzer™ Septal Occluder (Abbott) has been used sometimes in smaller children for PFO closure due to size constraints of the standard Amplatzer PFO occluder device which is available only in 18, 25, and 35 mm diameter sizes. There are also other devices, such as Occlutech PFO Occluder (Occlutech), currently approved for use in Europe and other countries. The procedure in young children is usually performed under general anesthesia.

Various imaging modalities including TTE, TEE, and ICE have been used to assist with device delivery.\[52,53\]

The venous delivery sheath size depends on the size and type of device (usual range: 6–10 French). Right heart catheterization and hemodynamic measurements are usually not required in patients with cryptogenic stroke and an otherwise structurally normal heart. ICE provides better visualization of the septal rims and may obviate the need for general anesthesia in some patients.\[54\] Limitations of ICE include the cost of the probe, the need for a second venous access for ICE catheter (8 French), the need for an experienced operator, and rare complications including vascular injury, cardiac perforation, and atrial arrhythmias. Certain anatomical features of PFO, especially a tunnel-like PFO, could make the procedure more challenging, leading to either device malposition or incomplete deployment of the RA disc. Various techniques such as balloon angioplasty, septostomy or even creating an iatrogenic ASD and delivering the device through the iatrogenic ASD to close the newly created ASD as well as PFO with the same device have been utilized for successful PFO closure.\[55\]

Some newer techniques have been attempted for nondevice transcatheter PFO closure. These include the RFx closure system (Cierra Inc, Redwood City, CA) which uses radiofrequency energy to oppose the primum and secundum septum. In one follow-up study, 45% of the study patients had a significant residual shunt at 6-month follow-up.\[56\] Another recent technique is the NobleStitch device (By HeartStitch, Fountain Valley, CA) which delivers two transcatheter sutures across the atrial septum.\[57\] The main limitation is the size of the delivery system (14 French), especially for younger children. Major complications from transcatheter PFO closure are low (0.2%–1.5%). The device embolization rate is very low and device thrombosis is rare. Patients are usually placed on aspirin and/or clopidogrel for 6 months following the device closure. The inability to take antiplatelet agents could be a relative contraindication for PFO device closure.

Surgery to close a PFO is rarely needed, and mainly done in two situations. First, surgical PFO closure may be needed in a patient with an isolated PFO who is either unsuitable for or has had a complication (such as device embolization, erosion, perforation, or a residual shunt) from the percutaneous device closure attempt. Some of the less common reasons for surgical referral include child too small for device closure, documented allergy to nickel, and inability to tolerate antiplatelet therapy.\[37,43\] Surgical closure is accomplished by either primary suture or patch closure via either a traditional median sternotomy or a minimally invasive technique through a “mini-sternotomy” or video-assisted thoracoscopic surgery.\[58\] The second more common category includes the management of PFO in patients with underlying CHD. Unlike the former
category, the management of PFO in these patients calls for judgment based on associated lesions and the expected postoperative course. Table 1 summarizes common CHDs with a beneficial effect of maintaining a PFO during postoperative recovery. A description of all the situations related to associated CHD is beyond the scope of this article. In general, it is beneficial to leave behind a small atrial level communication to either decompress the right side of the heart or maintain adequate cardiac output when diastolic dysfunction of the right ventricle is expected following an incision on the right ventricle in repairs such as tetralogy of Fallot and neonatal truncus arteriosus, or when the functional right ventricular volume is diminished as in Ebstein's anomaly or pulmonary atresia with an intact ventricular septum. Techniques of subtotal closure of PFO such as one-way flap have been described to maintain a unidirectional flow of blood. In patients being considered for placement of a left ventricular assist device, it may be necessary to close the PFO to reduce subsequent hypoxemia.

CONCLUSIONS

An isolated incidental PFO is a common benign finding with very rare associated complications. Therefore, in children with isolated PFO, routine cardiology follow-up, physical activity restriction, and additional cardiac testing are not recommended. Counseling of the family of a child with incidental PFO diagnosis needs to be done with care. Even though there are adult guidelines with a strong level of evidence supporting the decision-making regarding diagnosis and management of PFO-associated special situations, similar guidelines and supporting evidence are lacking for pediatric population. In children with PFO-associated special situations, a personalized approach along with interdisciplinary discussions is necessary prior to any medical or interventional treatment, especially in the background of lack of robust pediatric data [Table 2].

Future direction

Diagnostic criteria for atrial septal aneurysm in the pediatric population need to be established by consensus. Future randomized controlled studies with multicenter collaboration are necessary to provide the best possible evidence and guide future management in children. The key areas to focus on would be how to counsel the family of a child with incidental PFO diagnosis, standardization of diagnosis and follow-up of incidental isolated PFO diagnosis, management of PFO-associated special conditions such as stroke, complex migraine, pregnancy, decompression sickness, and management of PFO in patients with underlying CHDs.

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Table 1: Examples of congenital cardiac defects with beneficial effect of maintaining a patent foramen ovale during postoperative recovery

| CHD | Evidence |
|-----|----------|
| Tetralogy of fallot | None |
| Pulmonary atresia with intact ventricular septum | Weak |
| Truncus arteriosus | Weak |
| Ebstein's anomaly | Nil. |

CHD: Congenital heart disease

Table 2: Summary of current evidence in relation to the management of patent foramen ovale in children

| Evidence |
|----------|
| Incidental PFO diagnosis | None |
| Counseling and follow up guidelines | Weak |
| Diagnostic modality of choice | Weak |
| TEE versus TTE versus TCD | Weak |
| PFO closure indication | None |
| PFO and cryptogenic stroke | Weak |
| PFO and deep diving | Weak |
| PFO and migraine | Weak |
| PFO and pregnancy | None |
| Risk stratification | Weak-none |
| PFO and associated special situations | Weak-none |

PFO: Patent foramen ovale, TCD: Transcranial Doppler, TTE: Transthoracic echocardiography

Conflicts of interest

Seshadi Balaji serves as a consultant for yoR labs and Milestone Pharmaceuticals.

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