Patent Foramen Ovale: Echocardiographic Evaluation and Clinical Implications*

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Patent foramen ovale embryology and anatomy

The interatrial septum is the product of two embryonic layers – the septum primum and the septum secundum to its right. The septum secundum has a central defect, which is covered by the septum primum. The covered defect area is called the fossa ovalis.

Patent foramen ovale is an essential component of fetal circulation. During intrauterine life, the placental blood enters the umbilical veins and reaches the fetal right atrium through the inferior vena cava. The eustacian valve, located at the entrance of the inferior vena cava into the right atrium, diverts the blood flow jet towards the fossa ovalis in the center of the interatrial septum. Since at that stage of fetal life the right atrial pressure is higher than the left, the septum primum, which acts like a flap, is displaced toward the left atrium and creates a gap between the septum secundum and the septum primum known as the patent foramen ovale. In late fetal life, blood is shunted from right to left across the PFO. After birth, the left atrial pressure increases and exceeds that of the right atrium. As a result, the septum primum flap moves to a position that closes the patent foramen ovale and this stops the right-to-left shunt. During the first year of life, growth of fibrous tissue seals the communication completely in approximately 75% of individuals. In the remaining 25% or so, the sealing process is incomplete and therefore there is a residual potential interatrial communication – the PFO. In most of these individuals the combination of higher pressure in the left atrium and the overlap of the septum primum over the septum secundum maintains the foramen in a nearly completely closed position. Still, in many of these individuals there may be a small trickle of left-to-right interatrial shunt. However, maneuvers or conditions that increase right atrial pressure or decrease left atrial pressure may result in shifting of the flap toward the left atrium, with wider communication and right-to-left interatrial shunting across the PFO.

* This review deals with a specific medical problem observed in the individual whose medical condition is the main theme of this special issue of *IMAJ*. Another review in this publication focuses on echocardiography as a tool in the evaluation of findings with a high likelihood of cardiogenic embolism [1].

Clinical significance of PFO

PFO is almost always a benign condition. Many hundreds of millions of people have PFO, and the chances of a PFO-related complication are extremely slim. PFO is therefore not considered a condition that requires routine screening, follow-up or treatment. There are, however, two well-known complications associated with PFO: namely, hypoxia and paradoxical embolization.

PFO is a common finding, with a prevalence of 25–30% in the general population

Hypoxia and PFO

Significant right-to-left shunting may result in arterial desaturation. Patients with elevated right atrial pressure who also happen to have PFO may become desaturated. The degree of right-to-left shunting is determined by right and left atrial hemodynamics. Patients with an elevated right atrial pressure due to pulmonary hypertension, right ventricular infarction, or severe tricuspid insufficiency or stenosis may develop hypoxia if there is an associated PFO. The degree of arterial desaturation is directly related to the PFO cross-sectional area and to the pressure gradient between the right and the left atrium.

In rare instances patients with PFO may suffer from a condition where the supine position could lead to arterial desaturation and dyspnea. Resuming the upright position relieves the hypoxia as well as the symptom. While the exact mechanism of this syndrome (known as platypnea orthodeoxia) is not fully understood, it has been clearly shown that in the supine position these patients have an increased right-to-left shunt across the PFO. In the absence of other morbidities the platypnea orthodeoxia syndrome can be completely cured by PFO closure [2].

PFO = patent foramen ovale

Paradoxical embolism

Paradoxical embolism was first described by Cohnheim in 1877 [3]. Blood clots formed in the venous system or in the right atrium may cross a PFO and embolize via the arterial system to vital organs, including the central nervous system, the heart, the abdominal organs and the limbs. In a few instances clots have been imaged by echocardiography as they crossed the atrial septum from right to left through a PFO. However, in an individual patient with an embolic event, when the source of the embolism is not clearly documented, the contribution of a coexisting PFO is debatable.

It has been shown that the incidence of PFO is higher (40%) in young patients who suffered a stroke [3]. However, a higher prevalence of PFO was not observed in elderly patients (who have a much higher incidence of stroke and other embolic events) [4].

Higher risk for paradoxical embolism [5,6]

Higher risks for paradoxical embolism may be related to hemodynamic or anatomic factors. Anatomic factors include large PFOs, large eustacian valves that divert the inferior vena caval blood flow in the direction of the atrial septum and the PFO, and atrial septal aneurysm.

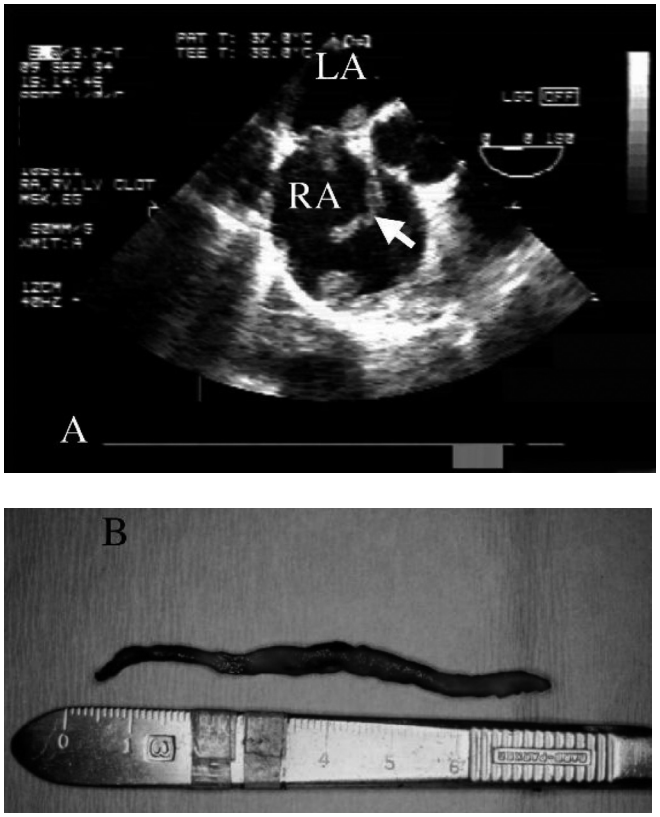

Figure 1. TEE in a 42 year old women with pulmonary embolism and stroke, showing **[A]** a large, elongated clot (arrow) crossing the atrial septum via a PFO. Part of the clot is therefore in the right atrium and the rest in the left atrium (LA). **[B]** The clot, a cast of a lower extremity vein, was surgically removed.

Atrial septal aneurysm [Figure 1]

Atrial septal aneurysm is defined as a bulge of at least 1 cm in the atrial septum toward one of the atria [7]. This entity was first described in 1934 [8]. In a pathology report from 1978, ASA was found in 16 of 1578 autopsies (1%) [9]. Those authors also noted that there were often tiny fibrin thrombus tags on the surface of the aneurysm, and an actual thrombus was noted at the base of one aneurysm. The anatomic appearance of an ASA led the authors to postulate that this finding might prove to be obvious on echocardiography (none of these patients had an echocardiogram).

In vivo, ASA is best seen with transesophageal echocardiography. In ASA the septum is usually quite mobile. ASA was observed in 2.2% of individuals in the community and in 7.9% of patients with embolic events. The incidence of patent foramen ovale in ASA patients is nearly 60% [10], more than twice that found in the general population. There have also been rare case reports of blood stagnation and clot formation within an ASA on TEE [11]. In one prospective study, only the combination of ASA and PFO was associated with a higher risk for embolic stroke [12].

Venous thrombosis and a hypercoagulable state

Deep vein thrombosis increases the risk for paradoxical emboli in patients with PFO. Clots may be dislodged and embolize to the lungs, leading to pulmonary hypertension that frequently results in elevated right atrial pressure. The high right atrial pressure may favor the movement of clots from the right atrium to the left atrium if there is a PFO present. Figure 2 shows such a sequence, where the 'smoking gun' responsible for paradoxical embolization was documented by TEE [13]. Similarly, hypercoagulable prothrombotic states increase the likelihood of intravenous and right heart blood clots, and these may embolize paradoxically via a PFO [14].

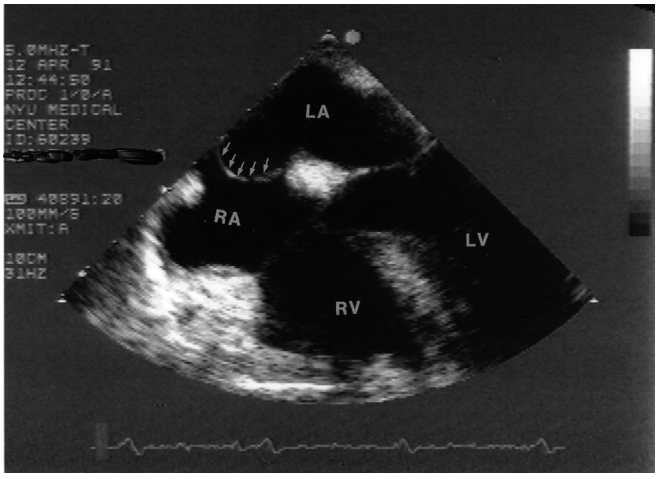

Figure 2. TEE shows an ASA (small arrows). Note a bulge of more than 1 cm toward the right atrium (RA), diagnostic of ASA.

ASA = atrial septal aneurysm
TEE = transesophageal echocardiography

Diagnosis of PFO [Figures 3 and 4]

Transthoracic echocardiography and transesophageal echocardiography

Until the introduction of echocardiography, PFO could be diagnosed at autopsy or during right heart catheterization, when a catheter crossed the interatrial septum ('probe-patent PFO'). The differential diagnosis was PFO versus atrial septal defect. Today echocardiography is the modality of choice for the diagnosis of PFO. While transthoracic echocardiography can occasionally reveal a PFO, TEE demonstrates the interatrial septum in great detail. Its various anatomic components (septum primum, septum secundum, fossa ovalis) can easily be distinguished, and the actual size of the PFO can be defined. ASA can be clearly visualized.

Color Doppler occasionally demonstrates the interatrial blood flow jet through a PFO. Since left atrial pressure is usually higher than that in the right, the shunt direction is frequently from left to right. However, because the interatrial pressure gradients are frequently small, the demonstration of right-to-left shunting with color Doppler is usually difficult or even impossible. Therefore, contrast echocardiography is considered to be superior to color flow Doppler in demonstrating interatrial communication across a PFO [15].

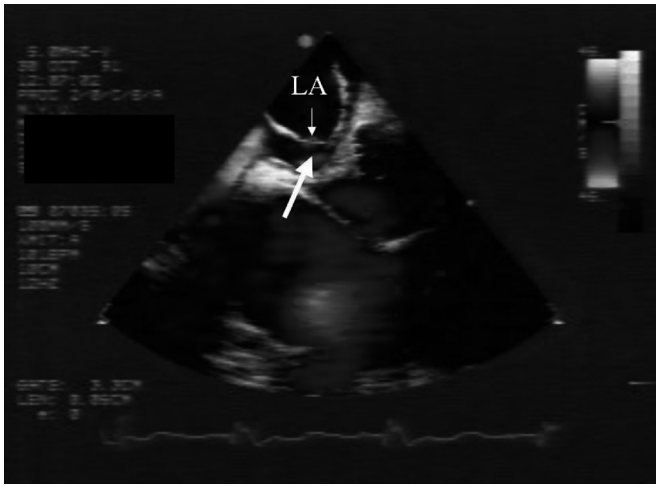

Figure 3. TEE in a 62 year old man with hypoxia. Color Doppler flow imaging during release of the Valsalva maneuver shows higher right atrial pressure, the septum primum (thin arrow) is shifted toward the left atrium (LA) creating a larger PFO diameter (thick arrow). A right-to-left color flow jet is noted.

Complications due to PFO are rare. These include paradoxical embolism and hypoxia

Contrast echocardiography with intravenous saline injection

Contrast echocardiography is a useful and practical method for the evaluation of intracardiac shunts. The intravenous injection of 5–10 ml agitated saline (or any other sterile solution, including blood) creates a cloud of microcavitations that normally travel with the blood through the right-sided chambers into the pulmonary artery. The microcavitations are trapped in the pulmonary capillaries, and therefore no microcavitations appear in the left heart. With the presence of a right-to-left shunt, the microcavitations bypass the pulmonary circulation and appear in the left heart immediately (within one heart beat) after they appear in the right heart [16]. The appearance of three microcavitations in the left atrium after intravenous injection is considered diagnostic of a PFO. The amount of right-to-left shunting (expressed by the number of microcavitations that appear in the left atrium) can be increased significantly by maneuvers that augment venous return to the right atrium and increase pressure or decrease left atrial pressure. Such maneuvers include as the release stage of the Valsalva maneuver, the Muller maneuver, cough, elevation of the lower limbs, or liver compression. Using this technique, PFO was diagnosed in 28% of 606 patients who underwent TEE at the Mayo Clinic. This prevalence of PFO was not significantly different from autopsy findings at that institution [17].

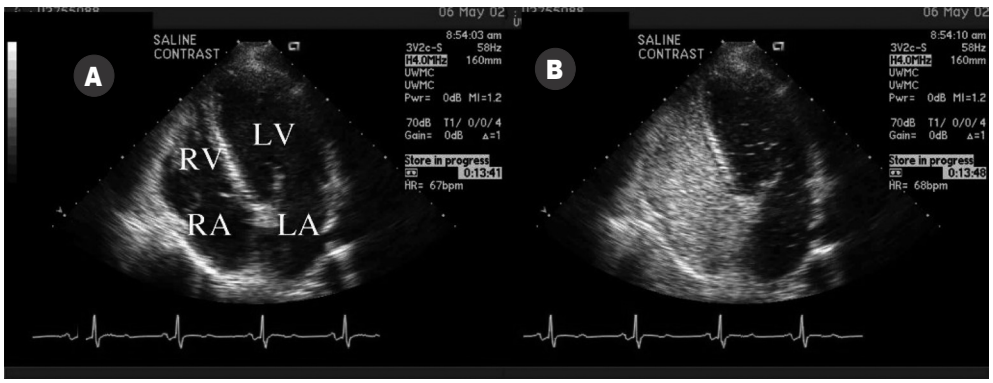

Figure 4. TTE in a 29 year old woman with sudden diplopia. Apical four chamber view before **[A]** and after **[B]** intravenous agitated saline injection. Note opacification of the right heart chambers and the presence of microcavitations in the left heart chambers, which indicates right-to-left shunting at the atrial level.

Transcranial Doppler

Transcranial Doppler can be used to detect microcavitation in the cerebral circulation after the intravenous injection of agitated saline. With the Doppler transducer placed on the skull, characteristic signals that can be visualized on the spectral Doppler tracing of arterial blood flow are diagnostic of microcavitations in transit. While this simple and inexpensive technique provides a useful link between right-to-left shunting and cerebral arterial

blood flow, it cannot distinguish between PFO and other forms of right-to-left shunt (such as ventricular or atrial septal defects, or pulmonary arteriovenous fistulae) [18].

The role of echocardiography in the treatment of PFO

Patients with embolic stroke, transient ischemic attacks and other embolic events are frequently referred for echocardiography to evaluate the heart and the aorta for possible sources of embolism. In many of these patients, when TTE does not offer a conclusive diagnosis, TEE is performed. The echocardiographic study includes contrast injection for the demonstration of PFO, which is expected to be found in 25–30% of all patients. Only after the demonstration of PFO by echocardiography, and only after a comprehensive clinical and echocardiographic search for other source of emboli have failed to offer an alternative explanation, can specific treatment of PFO be considered.

In patients with PFO, primary prevention of stroke is not indicated. While several secondary prevention options are available for patients with PFO and stroke (e.g., anticoagulation and closure), their efficacy has not yet been proven

Treatment modalities

As noted before, given the large number of individuals with PFO and the relatively small incidence of paradoxical emboli, the primary prevention of future embolic events is not indicated in most asymptomatic patients with echo-confirmed PFO. In patients with embolic events and an echo-confirmed PFO and no other source of embolism, secondary prevention options include medical treatment, interventional procedures (percutaneous, transcatheter PFO closure) and surgical closure.

Medical therapy

Most practitioners agree that secondary prevention after embolic stroke (or peripheral embolic event) without obvious etiology ("cryptogenic" stroke or embolus) requires long-term therapy with anticoagulation or antiplatelet agents. This therapy should be considered whether PFO is present or not. To date, there has been no information to suggest that one of these is superior to the other. In multicenter studies the risk of recurrent stroke in patients with echo-confirmed PFO was not significantly different in patients who were randomized to long-term warfarin or aspirin therapy [19]. In the most recent practice guidelines from the American Academy of Neurology it was stated: "In patients with cryptogenic stroke and atrial septal abnormalities the evidence is insufficient to determine if either warfarin or aspirin is superior in preventing stroke or death, but minor bleeding was more frequent with the use of warfarin" [20].

PFO closure

Recent technological advances have produced a plethora of endovascular devices that can be delivered by a catheter and placed to seal a PFO. A trained operator can install this device with high success and a low complication rate. This procedure is almost always performed under echocardiographic guidance and monitoring, using TEE or intracardiac echocardiography. Endovascular PFO closure has almost completely replaced surgical closure of PFO, which requires thoracotomy and cardiopulmonary bypass.

To date, there has not been convincing evidence that device (or surgical) closure of PFO is superior to medical therapy in the secondary prevention of stroke. PFO closure does not guarantee freedom from embolization. In fact, 2–4% of the patients who underwent PFO device closure suffered from recurrent stroke or transient ischemic attacks [6,21]. The most recent practice guidelines from the American Academy of Neurology state: "There is insufficient evidence to evaluate the efficiency of surgical or endovascular closure of FPO" [19].

At present there are several ongoing multicenter prospective randomized studies that may eventually guide the clinician to select the best option for secondary prevention of stroke in PFO patients [6].

Special considerations

In special clinical scenarios it appears that PFO closure may be more effective in the secondary prevention of stroke and other embolic events. These include patients at high risk for paradoxical embolization due to anatomic, hemodynamic and co-morbidity issues mentioned earlier in this review. PFO should also be closed in patients with the platypnea orthodeoxia syndrome. Patients with PFO who undergo open heart surgery that requires opening one of the atria (e.g., mitral valve surgery) should have the PFO closed. The possibility of PFO should therefore be aggressively explored in such patients.

Conclusions

PFO is a common finding, with a prevalence of 25–30% in the general population. Complications are rare. These include paradoxical embolism and hypoxia. Echocardiography is the best modality for making the diagnosis, since it can evaluate PFO anatomy, identify complicating factors, and guide repair procedures. In most patients, detection of PFO and primary prevention of embolism is not indicated. While several secondary prevention options are available for patients with PFO and stroke, their efficacy has not yet been proven.

TTE = transthoracic echocardiography

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