



Patent Foramen Ovale in Pulmonary Medicine

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Patent foramen ovale (PFO) is a common embryologic remnant that is usually clinically occult. Yet, a PFO may manifest clinically in two important ways, including serving as a conduit for emboli (bland, septic, or gas) and as a pathway for venous admixture or right-to-left shunt (as following pulmonary embolization or due to streaming of blood). The diagnosis of PFO is made by contrast-enhanced transesophageal echocardiography, usually using agitated saline injectate. Treatment involves closure of the PFO, which is indicated when clinical sequelae (e.g., paradoxical embolization and/or refractory hypoxemia due to right-to-left shunt) prompt correction. Options include surgical closure and deployment of a device from a catheter (e.g., a clam shell-like device that straddles the PFO).

Clin Pulm Med 2003;10(2):111-119

Key words: Patent foramen ovale, Right-to-left shunt, Paradoxical embolism, Pulmonary diseases, Acute respiratory distress syndrome, Chronic obstructive pulmonary disease, Sleep apnea, Pulmonary embolism, Pneumonectomy, Diaphragmatic paralysis.

Patent foramen ovale (PFO) is a common embryologic remnant that is usually clinically occult but that can predispose to significant clinical events, including hypoxemia due to right-to-left shunt or paradoxical embolization due to gas, bland, or septic emboli. The current paper reviews the impact of PFO in clinical pulmonary medicine. After discussing the developmental anatomy of PFO, we review the epidemiology, general mechanisms encouraging shunt and paradoxical embolization, and then specific clinical events predisposing to PFO-related morbidity. We then discuss diagnostic methods for detecting PFO and treatment options, including

deployment of closure devices from catheters and surgical closure.

DEVELOPMENTAL ANATOMY

The embryogenesis of a PFO relates to the development of the atrial septum, which involves a series of events (Figure 1). Septation of the atria begins at approximately 30 days, with the growth of the septum primum downward toward the endocardial cushions. The orifice that remains is called the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A second opening called the ostium secundum appears in the

posterior portion of the septum primum. The septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ostium secundum forms the foramen ovale, through which fetal blood passes from the inferior vena cava to the left atrium. At birth, the increased volume of pulmonary blood flow returning to the left atrium increases left atrial volume and pressure sufficiently to close the foramen ovale functionally (1).

EPIDEMIOLOGY OF PFO

PFO is found commonly in the general population. For example, a post-mortem examination study of 965 human hearts revealed PFO in 27.3% (2). With increasing age, the size of the PFO was found to increase while the frequency decreased from 34.3% in individuals <30 years old to 20.2% in individuals >80 years old. Other echocardiographic series using both saline contrast and color doppler have found PFO in 9.2% of 1000 patients and with no gender predilection (3).

SEQUELAE OF PFO

A PFO most commonly appears as a tunnel-like defect of varying length (2.4

1068-0640/03/1002-111 \$3.00

Clinical Pulmonary Medicine

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to 19.5 mm) between a thicker, less compliant septum secundum and a thinner, more compliant septum primum (4). Normally, left atrial pressure is slightly higher than right atrial pressure. However, transient elevations of right-sided pressures (such as during cough or Valsalva maneuver) can cause a right-to-left pressure gradient and shunting through a PFO as detected by contrast microbubbles traversing from the right to the left atrium (5). This right-to-left shunting predisposes to hypoxia or paradoxical embolism.

CLINICAL CONSEQUENCES OF PFO: PARADOXIC EMBOLISM AND RIGHT-TO-LEFT SHUNT

PFO becomes clinically evident when emboli cross or when right-to-left shunt develops. Types of emboli

that can cross the PFO include gas, bland emboli, and septic emboli. Paradoxical gas embolism causing an ischemic brain injury has been recently described in sport divers. In a retrospective cohort review, the risk of decompression illness was 4.5-fold greater and there was a higher frequency of ischemic brain lesions among divers with PFO than in divers without PFO (6). Iatrogenic paradoxical air embolism has also been described in patients with pulmonary hypertension. Two reported instances occurred during saline-enhanced echocardiography, while two occurred when unused ports of a multilumen catheter were being flushed (7).

Regarding bland embolization, the presence of PFO predisposes to ischemic stroke with an odds ratio of 3.10, an association which increases in the presence of atrial septal aneurysm (odd

ratio of 15.59 (8)). The cooccurrence of both cardiac abnormalities has been shown to be a significant predictor of recurrent stroke (9). Also, the diameter of a PFO has been found to be an independent risk factor for ischemic events (10).

Under physiologic conditions, right-to-left shunt through a PFO occurs when right-sided pressures increase during Valsalva-like maneuvers, such as coughing and straining (11). Pathologically, high right atrial pressures promote right-to-left shunt and can occur in several conditions, as outlined in Table 1. Also, right-to-left shunt has been observed with normal right-sided pressures, due to streaming effects, especially with anatomic changes in the chest (Table 1).

The sections that follow examine the impact of PFO in specific clinical circumstances.

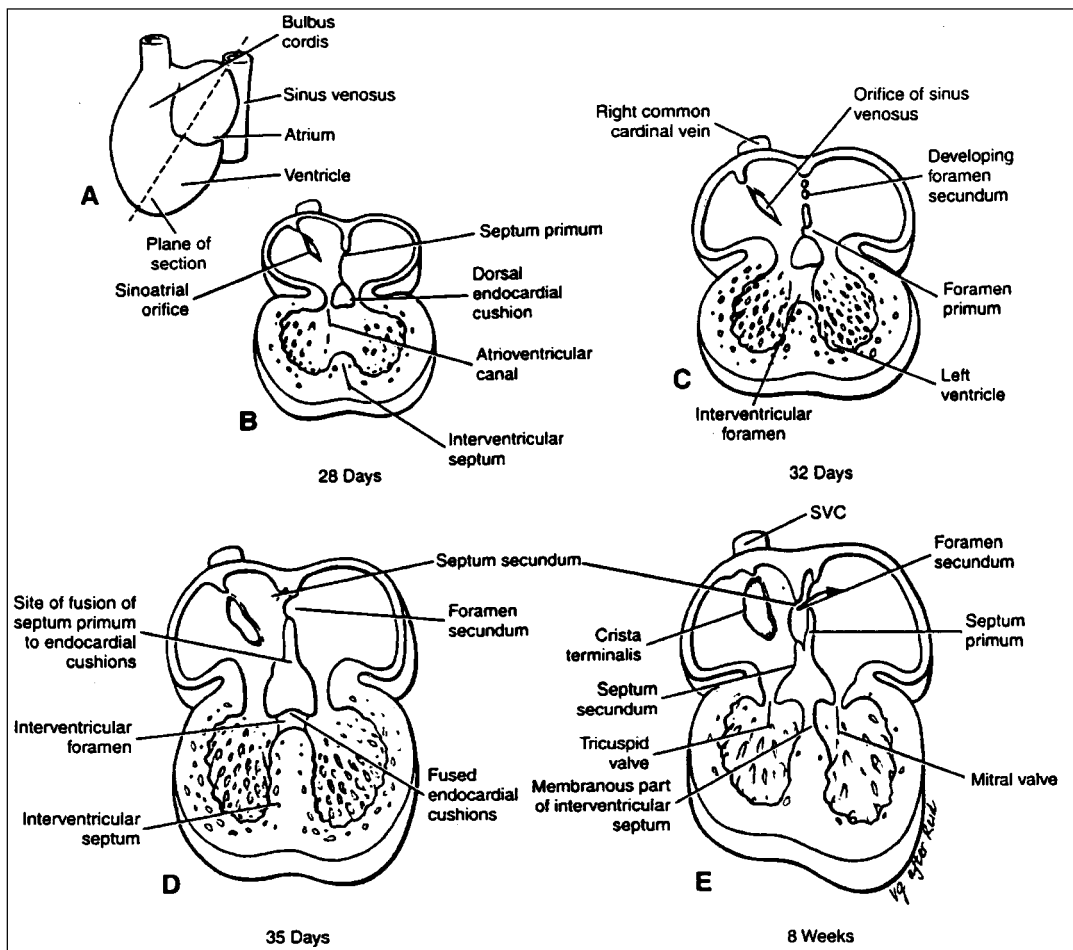


FIGURE 1. Atrial septal development. A, The plane of the coronal sections. B, Early appearance (during the fourth week, about 28 days) of the septum primum, interventricular septum, and dorsal endocardial cushion. C, Section of the heart (about 32 days) showing perforation in the dorsal part of the septum. D, Section of the heart (about 35 days) showing the foramen secundum. E, The heart after it is partitioned into four chambers (about 8 weeks). Used with permission from Color Atlas of Clinical Embryology, Ch. 11, 202.

VENOUS THROMBOEMBOLISM

In patients with venous thromboembolism, PFO offers a conduit for paradoxical embolization following occlusion of pulmonary arteries. Indeed, the prevalence of PFO in patients with venous thrombophlebitis is higher than in the general population (17.5%–35%), raising the possibility that PFO protects against hemodynamic collapse in pulmonary embolism (PE) by decompressing acutely elevated right heart pressures (12,13). A recent case report in which right-to-left shunt was found to resolve 1 month after massive PE supports this possibility (14). On the other hand, PFO can also be associated with adverse outcomes in patients with PE. For example, in one series, the presence of PFO conferred a 10-fold increased mortality risk and a 5-fold increased risk of major adverse events during the hospital course. The risk of peripheral arterial embolism is also increased in these patients (13).

POSTPNEUMONECTOMY

Anatomic changes following pneumonectomy can predispose to shunt through a PFO; for example, shunt increases with upright posture. Indeed, a distinct syndrome of dyspnea with hypoxemia associated with sitting or standing from recumbency, referred to

as the “platypnea-orthodeoxia syndrome,” was first described by Burchell and coworkers in 1949 (15). Later, this syndrome was reported after pneumonectomy by Schnable and coworkers (16). The syndrome occurs after predominantly right-sided pneumonectomy and usually appears 1 to 12 months following surgery (17), although the onset may be as soon as 1 day postoperatively (18–20).

Earlier reports attributed this phenomenon to several features: development of an interatrial pressure gradient induced by increased pulmonary vascular resistance, the weight of the resulting right-sided hydrothorax on the right atrium, and decreased right ventricular compliance (16,21,22). More recent reports indicate that the postpneumonectomy rotation of the heart shifts the right atrium while the inferior vena cava remains fixed. The right atrial orifice straddles the limbus of the inferior vena cava, leading to directional streaming of blood from the inferior vena cava into the left atrium through the PFO. Also, the weight of the heart in the shifted position pulls downward to newly open or widen the PFO (23). This mechanism has been confirmed angiographically (24) as well as by magnetic resonance imaging (MRI) (23). Hypovolemia further exacerbates the platypnea in these patients by decreasing the cardiac output. Blood

transfusion in one such patient ameliorated the desaturation (25).

PULMONARY HYPERTENSION

Approximately 26% to 29% of patients with pulmonary hypertension have been found to have a PFO (26,27). The presence of a PFO in these patients does not lead to any detectable influence on resting hemodynamics or exercise intolerance. Additionally, based on a mathematical model of survival for patients with primary pulmonary hypertension, the presence of a PFO is not associated with an adverse effect on survival (26). Following lung transplantation for severe pulmonary hypertension, leaving the PFO with a small shunt uncorrected does not lead to unfavorable outcomes (27). However, long-term follow-up in this set of patients is not available.

DIAPHRAGMATIC PARALYSIS

Though very uncommon, unilateral diaphragmatic paralysis can predispose to right-to-left shunt through a PFO. Indeed, a recent report presented the third available case of idiopathic right hemidiaphragmatic paralysis leading to right-to-left shunting through a PFO (28–30). This patient's oxygenation dramatically improved after closure of the PFO with a CardioSEAL atrial septal umbrella device deployed during cardiac catheterization. Similar to patients with a pneumonectomy, the mechanism of shunting in this setting is thought to be directional streaming of inferior vena caval blood promoted by shift of the interatrial septum. This mechanism has been visualized during corrective surgery by Murray and coworkers (29). In addition to resolution of shunt by closing the PFO, improvement of the diaphragm paralysis can lead to shunt resolution. For example, in a report by Cordero and coworkers, the shunt resolved once the hemidiaphragm spontaneously improved after 6 weeks (30).

OBSTRUCTIVE AIRWAYS DISEASE

Chronic obstructive pulmonary disease (COPD) can also predispose to shunting through a PFO. For example, Begin and coworkers (31) reported a PFO with a right-to-left shunt following an episode of right heart failure in

TABLE 1. Conditions predisposing to right-to-left shunt across a patent foramen ovale.

With increased right-sided pressures
Associated with pulmonary hypertension
Pulmonary embolism
Primary pulmonary hypertension
Chronic obstructive pulmonary disease
Asthma
Mechanical ventilation and PEEP
High altitude pulmonary edema
Associated with decreased right ventricular compliance
Right ventricular infarction
Associated with increased right atrial pressure
Right atrial myxoma
Carcinoid heart disease
Tricuspid stenosis
Cardiac tamponade
Without increased right-sided pressures
Post-pneumonectomy
Hemidiaphragmatic paralysis
Ascending aortic elongation/enlargement
Some cases of platypnea-orthodeoxia

TABLE 2. Summary of selected studies reporting right-to-left shunt through a patent foramen ovale complicating other clinical events. (5,44–64)

Associated Abnormalities	Reference	Year	Number of Cases
Right atrial myxoma	Dear et al. (44)	1958	1
Right ventricular infarction	Rietveld et al. (45)	1983	1
Cardiac tamponade	Fraker et al. (46)	1984	1
Metastatic cardiac disease	Gallerstein et al. (47)	1984	1
Right atrial myxoma	Rosso et al. (48)	1985	1
Presumed right ventricular dysfunction	Strunk et al. (49)	1987	4
Pulmonary hypertension due to RA and Sjogren's syndrome	Inoue et al. (50)	1990	1
Right ventricular infarction	Gudipati et al. (51)	1991	1
Aneurysmal dilatation of septum primum	Langholz et al. (5)	1991	2
Left ventricular assist device	Baldwin et al. (52)	1991	2
Pericardial effusion	Adolph et al. (53)	1992	1
Cardiac tamponade	Thompson et al. (54)	1992	1
Ascending aortic aneurysm	Laybourn et al. (55)	1997	2
Aortic elongation	Popp et al. (56)	1997	1
Heart transplantation	Ouseph et al. (57)	1997	1
Carcinoid heart disease	Boglioli et al. (58)	1997	1
Kyphoscoliosis and atelectasis	Allen et al. (59)	1997	1
Right atrial myxoma	Saito et al. (60)	1998	1
Surgical removal of hydatid cyst	Patakas et al. (61)	1999	1
Aortic aneurysm, eventration and idiopathic	Godart et al. (62)	2000	9
Aortic aneurysm with atrial septal aneurysm	Faller et al. (63)	2000	1
Left ventricular assist device	Kilger et al. (64)	2000	1

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a patient with COPD. In a prospective study of 20 patients with severe COPD (forced expiratory volume in the first second less than 50%) and 20 control subjects (forced expiratory volume in the first second/forced vital capacity ratio >70%), PFO was detected in 70% of patients with COPD using transesophageal echocardiography (TEE). Patients with PFO had higher pulmonary artery systolic pressures (38.3 mm Hg \pm 7.3) and had greater desaturation by pulse oximetry (2.6% \pm 1.4%) after Valsalva maneuver. The degree of oxygen desaturation correlated with the severity of the pulmonary hypertension. Furthermore, repeated hypoxic episodes may exacerbate the pulmonary hypertension (32).

Regarding PFO and asthma, one death in a patient with acute severe asthma has been attributed to severe right-to-left shunt through a PFO resulting from pulmonary hypertension (33).

ACUTE RESPIRATORY FAILURE

In one study of 46 patients, PFO was detected in 15% of patients with acute

respiratory failure requiring mechanical ventilation. In these individuals, addition of positive end-expiratory pressure (PEEP) increased the shunt fraction in 86% (34). This mechanism may account for the failure of oxygenation to improve with PEEP in some patients on mechanical ventilation.

PFO may affect the mechanism by which prone posture enhances oxygenation in patients with ARDS. Under usual circumstances, prone positioning produces an improvement in oxygenation in 70% of the patients with ARDS with a mean increase of partial pressure of arterial oxygen/fraction of inspired oxygen (PaO₂/Fio₂) ratio by 63 (35). The mechanism of improved oxygenation lacking a PFO has been suggested to be modification of ventilation distribution and improvement of the ventilation/perfusion relationship (36). In contrast, prone positioning in ARDS patients with a PFO may improve oxygenation due to decreased right-to-left shunting. Legras and coworkers have described a patient with PFO who developed ARDS and refractory hypoxemia. Prone position on the same ventilator settings was associated with

an immediate and dramatic improvement in oxygenation, i.e., the PaO₂/Fio₂ ratio increased from 59 to 278. A contrast-enhanced transcranial doppler (TCD) detected a significant decrease in the right-to-left shunt in the prone position (37). This case report highlights use of prone positioning as a possible mechanism of decreasing the right-to-left shunt. Another patient with refractory hypoxemia in the late phase of ARDS was found to have a right-to-left shunt on a contrast-enhanced echocardiogram and underwent surgical correction of the PFO to improve oxygenation (38).

HIGH-ALTITUDE PULMONARY EDEMA

The presence of a PFO may predispose to the development of pulmonary edema at high altitude. For example, in one study of 12 climbers, 5 were detected to have PFO by contrast doppler echocardiography, two of whom (40%) developed high-altitude pulmonary edema. The right-to-left shunting induced by high-altitude pulmonary hypertension may exacerbate the hypox-

emia, setting up a vicious cycle of worsening hypoxemia, worsening pulmonary hypertension, and worsening right-to-left shunt (39).

OBSTRUCTIVE SLEEP APNEA

PFO may have special implications in patients with obstructive sleep apnea (OSA). In a prospective study of OSA patients who lacked any other pulmonary disease, contrast-enhanced TEE detected PFO in 69%. The mean pulmonary artery systolic pressure in these patients was 32 ± 10.3 mm Hg, which was significantly higher than in control subjects. The mean pulmonary systolic pressure did not correlate with the respiratory disturbance index (RDI) or with the extent of desaturation after a Valsalva maneuver. One third of these patients with OSA and PFO experienced significant desaturation after a Valsalva maneuver. However, there was no correlation between the RDI and the degree of oxygen desaturation (40).

Contributing to the pulmonary hypertension and right-to-left shunt in OSA patients are acute elevations of catecholamine levels (41–43) that follow episodes of apnea and that may further increase the right-to-left shunting in the presence of PFO.

In addition to the aforementioned conditions with which PFO has been associated with clinical sequelae, scattered reports regarding other conditions are available (Table 2).

DIAGNOSIS OF PFO

As noted, arterial embolization and/or hypoxemia may prompt diagnostic suspicion of PFO. Specific diagnostic clues may be orthodeoxia, paradoxical worsening of hypoxemia with application of PEEP in

ARDS, desaturation during Valsalva maneuver, and stroke complicating PE. Diagnostic modalities to detect PFO include echocardiographic techniques, oximetry during maneuvers, dye dilution techniques, lung scanning, MRI, and cardiac catheterization.

The diagnostic performance of each of these techniques for detecting PFO is summarized in Table 3 and each is discussed below.

Contrast-Enhanced TEE

Contrast-enhanced TEE is widely considered the diagnostic procedure of choice for detecting PFO (70,71) (Figure 2). The diagnosis of right-to-left shunt is confirmed by the appearance of contrast in the left-sided chambers of the heart, with the timing of the appearance indicating whether the shunt is intracardiac or intrapulmonary. In intracardiac shunt, the contrast appears in the left-sided chambers within three cardiac cycles of injection, whereas in intrapulmonary right-to-left shunt, the bubbles appear later (i.e., 4 to 6 cycles after injection) because of a need to traverse the pulmonary circulation (64). Several technical considerations are important. First, the maximum number of microbubbles required for diagnosis has been reported to be 1 to 5 (65,72,73). Notably, the correlation between the size of the PFO and the degree of left atrial opacification is low (64). Second, to visualize the PFO, a high echocardiographic cut through the right and left atria is recommended. Third, because of its superior resolution, TEE is preferred to transthoracic echocardiography. With postmortem findings as the gold standard, TEE has been shown to have the following diagnostic performance for de-

tecting PFO: 89% sensitivity, 100% specificity, 100% positive predictive value, and 96% negative predictive value.

Color doppler TEE is complementary to contrast-enhanced TEE for diagnosing a PFO. In the same postmortem correlation study cited above (64), detection of a turbulent color jet within the atrial septum by color doppler TEE was 100% sensitive and specific for diagnosing a PFO.

Transcranial doppler

TCD is an alternative noninvasive method for diagnosing right-to-left shunt. The technique is based on the intracranial detection of intravenously injected agitated saline. In the presence of a right-to-left shunt, like paradoxical emboli, the contrast agent enters the arterial circulation and produces bubble signals in the TCD recording (68). Compared to a contrast TEE, TCD has 68% to 100% sensitivity and 92% to 100% specificity in diagnosing a PFO (65,66,68). A technical limitation of TCD is that a bilateral temporal window to the middle cerebral arteries may not always be available.

Oximetric Detection of PFO

Continuous monitoring of oxygen saturation during various maneuvers (e.g., Valsalva) has been used to detect PFO. For example, Karttunen and co-workers have shown that using TEE as a gold standard, a fall in oxygen saturation on the digitized oxygen saturation curve during Valsalva and Muller maneuvers detected PFO with 85% sensitivity and 100% specificity (69). In the same study, these investigators also examined the diagnostic performance of dye dilution techniques. Specifically,

TABLE 3. Comparative diagnostic performance of tests to detect patent foramen ovale.

Test	Number of Patients in Series	Sensitivity %	Specificity %	PPV %	NPV %
TEE(65) (with contrast)	9	89	100	100	96.2
TEE(65) (color doppler)	9	100	100	100	100
TTE(66,67)	31,49,	47–54	94–100	87.5–100	73.9–75
TCD(66,67,68)	31,49,36	68–100	92–100	100	83.3–100
Ear oximetry(69)	83	85	100	100	79
Dye dilution(69)	67	76	100	100	65

Abbreviations: TEE, transesophageal echocardiography; TTE, Transthoracic echocardiography; TCD, transcranial doppler; PPV, positive predictive value; NPV, negative predictive value.

early detection of dye due to early traversal into the left atrium (and before transit through the lungs) diagnosed PFO with 76% sensitivity and 100% specificity. Technical features of the test include the injection of indocyanine green dye with the supine patient performing Mueller and Valsalva maneuvers and detection of dye using a dichromatic ear piece densitometer.

Perfusion Lung Scanning

Perfusion lung scanning has been used to detect a right-to-left shunt because radionuclide particles bypass the lung and are trapped in other organs (e.g., brain, kidney, etc.) (74,75). Thus,

detection of 99m technetium-labeled macroaggregated albumin in other end organs can be used to suggest a right-to-left shunt, but clarification of the site by shunt source requires further testing, such as with TEE. Perfusion lung scanning has been used to quantitate the magnitude of shunt, just as shunt calculations while the patient breathes 100% oxygen.

Magnetic Resonance Imaging

Because it visualizes vascular structures well, MRI has been used to evaluate for PFO. Special techniques, such as a gradient-echo imaging, allow visualization of MRI contrast agent in its

first pass through the circulation. This capability permits seeing PFO and overcomes limitations of earlier spin-echo techniques (23). Greater availability of the gradient-echo capability will permit broader application of MRI.

Cardiac Catheterization

Noninvasive tests have largely replaced cardiac catheterization for the diagnosis of PFO. The utility of catheterization lies in the opportunity to measure pressures and to deploy devices that can close the PFO during the same intervention.

TREATMENT OF PFO

Paradoxical Embolism

Therapy for PFO has been described in detail in patients with paradoxical embolism. Antiplatelet therapy and anticoagulation have been found to be beneficial in patients with stroke and PFO when the risk of cerebral ischemia exceeded 0.8% and 1.4% per year, respectively (76). In the same study, the benefit obtained by PFO closure exceeded that of other therapeutic options.

Surgical closure can be performed with minimal morbidity and mortality (77). Pericardial effusion, postcardiotomy syndrome, and atrial fibrillation have been reported following surgery (77,78). Cerebrovascular events recur in 8.8% to 19.1% after surgery, and recurrence is more frequent in older patients and in those with multiple cerebrovascular events before PFO closure.

Nonsurgical closure of PFO is an attractive alternative to surgery. Early studies using clamshell and button devices were hampered by frequent recurrence of cerebrovascular events and residual right-to-left shunting (79,80). More recently, experience and better technology have established placing catheter-deployed devices as an attractive option. For example, in a multicenter study using the atrial septal occlusion system device for percutaneous PFO closure, only 1 of 46 patients (mean age 44 years) with PFO and paradoxical embolism experienced a recurrent transient ischemic attack (TIA) within 7 months after the procedure (81). In a more recent study, percutaneous PFO closure was achieved with a success rate exceeding 95% and a periprocedural complication rate of 10% using a variety of PFO occluding

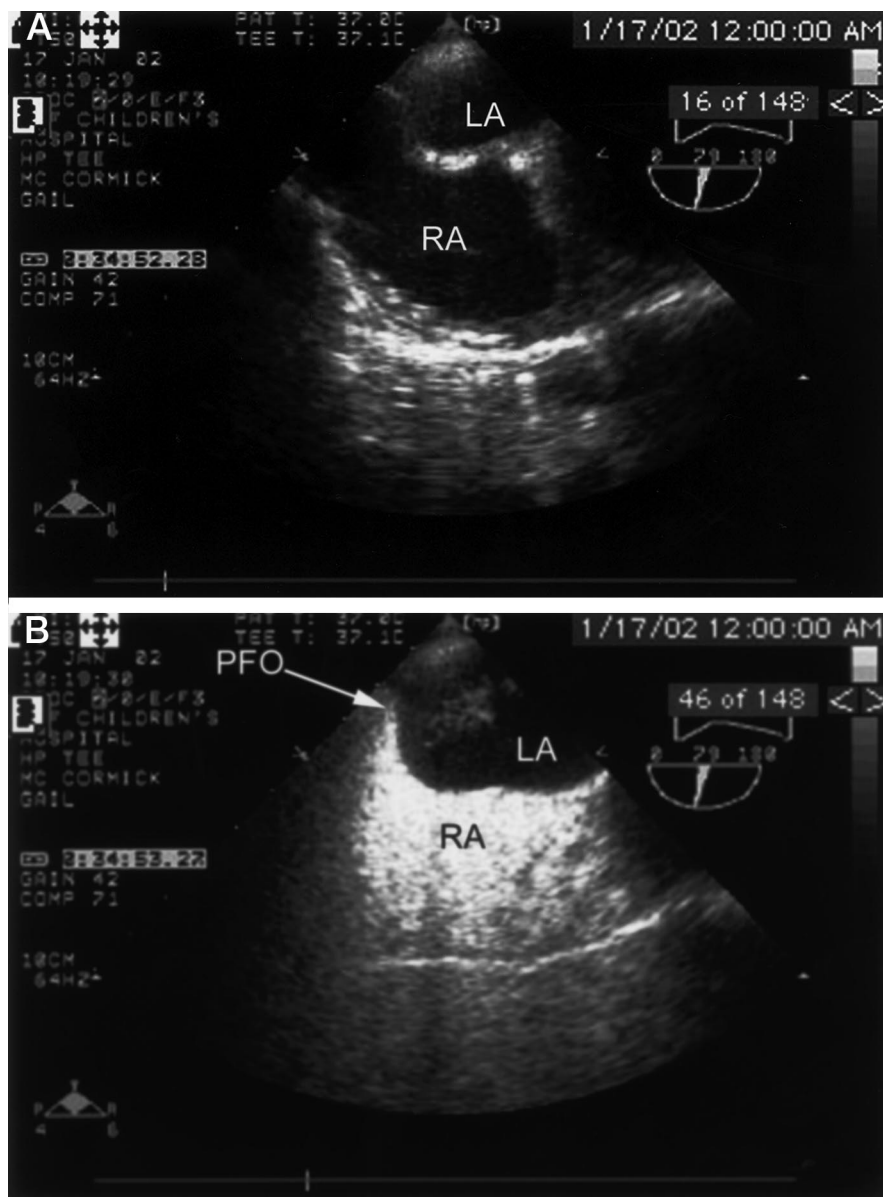


FIGURE 2. A, TEE image depicting right atrium (RA) and left atrium (LA). B, Contrast bubbles flow across the PFO from the right to the left atrium.

devices. During a mean follow-up of 1.6 ± 1.4 years, 10.3% of the patients experienced recurrent thromboembolic events. Recurrence was more common in patients in whom a shunt persisted after the procedure (82). The only device currently approved for PFO closure by the Food and Drug Administration is the CardioSEAL septal occlusion system. Approved under the Humanitarian Device exemption pathway in February 2000, this device is indicated for the closure of PFO in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a PFO after failure of conventional drug therapy (i.e., therapeutic INR on oral anticoagulants) (83). In a retrospective study involving 63 patients with a follow up of 2.6 ± 2.4 years, the CardioSEAL device was used in 13 patients while the clamshell and buttoned devices were used in 28 and 22 patients, respectively. Only one of the patients who received the CardioSEAL device had a recurrent neurologic event. Overall, the actuarial analysis revealed an annualized risk of 3.2% for recurrent stroke or TIA following transcatheter closure (84). Angiographic data from 21 consecutive patients who received the CardioSEAL device demonstrated that although the appearance of the atrial septum and the size of the defect varied widely, the CardioSEAL device appeared appropriate to the overall cardiac size in most of the patients (4).

Hypoxemia

Many studies have reported successful surgical closure of PFO in the setting of right-to-left shunt and hypoxemia. In a collective review of 39 patients, 29 (64%) were managed successfully with surgical closure of the defect, sometimes associated with septal aneurysm resection or coronary revascularization. Twenty-six of the 29 patients experienced excellent immediate results while 3 patients died as a complication of the procedure (17).

Transcatheter closure of the PFO can also provide immediate and persistent relief from hypoxia. In an early case series, transcatheter closure corrected hypoxia in all eight patients in whom a clamshell device was used. Embolization of the device occurred twice and the device was reimplemented successfully during the same procedure. One

patient experienced nonsustained ventricular arrhythmia (85). A subsequent report of 11 cases further confirmed the rapid resolution of hypoxia with various devices, with one failure due to kinking of the introducer sheath (62). Complications included supraventricular arrhythmias in two patients and a stroke in one patient.

SUMMARY

PFO occurs commonly in the general population and most patients are asymptomatic. Paradoxical embolism and hypoxemia from a right-to-left shunt occur in some patients, causing considerable morbidity and mortality. Right-to-left shunting is promoted by an interatrial pressure gradient but may develop due to preferential streaming of inferior vena caval blood through the PFO. A high index of suspicion is required to make a timely diagnosis of PFO. Contrast-enhanced TEE remains the gold standard for diagnosis. Transcatheter closure is an attractive treatment for most symptomatic patients. Surgical closure may be employed when transcatheter closure is not available or has failed.

REFERENCES

- Bernstein D. Developmental biology of the cardiovascular system. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th edition. Philadelphia, PA: Saunders; 2000:1337-1340.
- Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59:17-20.
- Fisher DC, Fisher EA, Budd JH, et al. The incidence of patent foramen ovale in 1,000 consecutive patients: a contrast transesophageal echocardiography study. *Chest*. 1995;107:1504-1509.
- Marshall AC, Lock JE. Structural and compliant anatomy of the patent foramen ovale in patients undergoing transcatheter closure. *Am Heart J*. 2000;140:303-307.
- Langholz D, Louie EK, Konstadt SN, et al. Transesophageal echocardiographic demonstration of distinct mechanisms for right to left shunting across a PFO in the absence of pulmonary hypertension. *J Am Coll Cardiol*. 1991; 18:1112-1117.
- Schwerzmann M, Seiler C, Lipp E, et al. Relation between directly detected patent foramen ovale and ischemic brain lesions in sport divers. *Ann Intern Med*. 2001;134:21-24.
- Holcomb BW, Loyd JE, Byrd BF III, et al. Iatrogenic paradoxical air embolism in pulmonary hypertension. *Chest*. 2001;119:1602-1605.
- Overall JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of

- case-control studies. *Neurology*. 2000;55:1172-1179.
- Mas J-L, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med*. 2001;345:1740-1746.
- Schuchlenz HW, Weihs W, Horner S, et al. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med*. 2000;109:456-462.
- Dubourg O, Bourdarias JP, Farcot JC, et al. Contrast echocardiographic visualization of cough-induced right-to-left shunt through a patent foramen ovale. *J Am Coll Cardiol*. 1984; 4:587-594.
- Miller RL, Das S, Anandarangam T, et al. Relationship between patent foramen ovale and perfusion abnormalities in acute pulmonary embolism. *Am J Cardiol*. 1997;80:377-378.
- Konstantinides S, Geibel A, Kasper W, et al. Patent foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. *Circulation*. 1998;97: 1946-1951.
- Slebos D-K, Tulleken JE, Ligtenberg JJM, et al. A narrow escape: surviving massive pulmonary thromboembolism due to a persistently patent foramen ovale. *Intensive Care Med*. 2000; 26:1400.
- Burchell HB, Helmholtz Hf, Wood EH. Reflex orthostatic dyspnea associated with pulmonary hypertension. *Am J Physiol*. 1949;159:563-564.
- Schnabel TG, Ratto GB, Kirbyck TM, et al. Postural cyanosis and angina pectoris following pneumonectomy: relief by closure of an interatrial septal defect. *J Thorac Surg (J Thorac Cardiovasc Surg)*. 1956;32:246-250.
- Wihlm JM, Massard G. Late complications. Late respiratory failure. *Chest Surg Clin N Am*. 1999;9:633-654.
- Wihlm JM, Darteville P, Fuentes P, et al. Interatrial right-to-left shunt after pneumonectomy: report of 4 cases. Presented at the 3rd Annual meeting of the European Association for Cardio-Thoracic Surgery, Munich, Germany, 1989.
- Hazard PB. Post pneumonectomy right-to-left interatrial shunt: obliteration with balloon-tip vascular catheter. *Crit Care Med*. 1987;15:618-619.
- Lee KA, Conlan AA. Synchronous patent foramen ovale and bronchopleural fistula after right pneumonectomy: non operative management with survival. *J Thorac Cardiovasc Surg*. 1998;115:951-952.
- Begin R. Platypnea after pneumonectomy. *N Engl J Med*. 1975;293:342-343.
- LaBresh KA, Pietro DA, Caotes EO, et al. Dyspnea after pneumonectomy. *Chest*. 1981;79: 605-607.
- Mercho N, Stoller JK, White RD, et al. Right-to-left interatrial shunt causing platypnea after pneumonectomy. *Chest*. 1994;105:931-933.
- Van Rossum P, Plokker WM, Ascoop AP. Breathlessness and hypoxemia in the upright position after right pneumonectomy. *Eur Heart J*. 1988;9:1230-1233.
- Bakris NC, Siddiqi AJ, Fraser CD, et al. Right-to-left shunt after pneumonectomy. *Ann Thorac Surg*. 1997;63:198-201.
- Nootens MT, Berarducci LA, Kaufmann E, et al. The prevalence and significance of a PFO in pulmonary hypertension. *Chest*. 1993;104: 1673-1675.

27. Gorcsan J, Edwards TD, Ziady GM, et al. Transesophageal echocardiography to evaluate patients with severe pulmonary hypertension for lung transplantation. *Ann Thorac Surg.* 1995;59:717-722.
28. Ghamande S, Ramsey R, Rhodes JF, et al. Right hemidiaphragmatic paralysis causing a right-to-left interatrial shunt: a case report and literature review. *Chest.* 2001;120:2094-2096.
29. Murray KD, Kalanges LK, Weiland JE, et al. Platypnea-orthodeoxia: an unusual indication for surgical closure of a PFO. *J Card Surg.* 1991;6:62-67.
30. Cordero PJ, Morales P, Mora V, et al. Transient right-to-left shunting through a PFO secondary to unilateral diaphragmatic paralysis. *Thorax.* 1994;49:933-934.
31. Begin R, Gervais A, Guerin L, et al. Patent foramen ovale and hypoxemia in chronic obstructive pulmonary disease. *Eur J Respir Dis.* 1981;62:373-375.
32. Soliman A, Shanoudy H, Jing L, et al. Increased prevalence of PFO in patients with severe COPD. *J Am Soc Echocardiogr.* 1999;12:99-105.
33. Boon ES, Maesen BL, Valcke Y, et al. Fatal asthma attributed to patent foramen ovale. *Eur Respir J.* 1993;6:1567-1568.
34. Cujec B, Polasek P, Mayers I, et al. Positive end-expiratory pressure increases the right-to-left shunt in mechanically ventilated patients with patent foramen ovale. *Ann Intern Med.* 1994;119:887-894.
35. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001;345:568-573.
36. Lamm WJE, Graham MM, Albert RK. Mechanism by which prone positioning improves oxygenation in acute lung injury. *Am J Respir Crit Care Med.* 1994;150:184-193.
37. Legras A, Dequin P-F, Hazouard E, et al. Right-to-left interatrial shunt in ARDS: dramatic improvement in prone position. *Intensive Care Med.* 1999;25:412-414.
38. Dewan NA, Gayasaddin M, Angelillo VA, et al. Persistent hypoxemia due to patent foramen ovale in a patient with adult respiratory distress syndrome. *Chest.* 1986;89:611-613.
39. Levine BD, Grayburn PA, Voyles WF, et al. Intracardiac shunting across a patent foramen ovale may exacerbate hypoxemia in high-altitude pulmonary edema. *Ann Intern Med.* 1991;114:569-570.
40. Shanoudy H, Soliman A, Raggi P, et al. Prevalence of patent foramen ovale and its contribution to hypoxemia in patients with obstructive sleep apnea. *Chest.* 1998;113:91-96.
41. Bone RC, Dantzker DR, George RB, et al. *Pulmonary and Critical Care Medicine*, Vol. 2. Chicago: Mosby; 1995.
42. Douglas NJ. The sleep apnea/hypopnea syndrome. *Eur J Clin Invest.* 1995;25:285-290.
43. Parish JM, Shepard JW. Cardiovascular effects of sleep disorders. *Chest.* 1990;97:1220-1226.
44. Dear WE, Chen P, Barasch E, et al. Sixty-eight-year-old woman with intermittent hypoxemia. *Circulation.* 1995;91:2284-2289.
45. Rietveld AP, Mermman L, Essed CD, et al. Right-to-left shunt with severe hypoxemia at the atrial level in a patient with hemodynamically important right ventricular infarction. *JACC.* 1983;2:776-779.
46. Fraker JD Jr. Atrial level right-to-left shunt abolished by relief of pericardial tamponade. *Am J Cardiol.* 1984;53:646-648.
47. Gallerstein PE, Belluscio RL, Berger M, et al. Right-to-left intracardiac shunt: a unique presentation of metastatic cardiac disease. *JACC.* 1984;3:865-867.
48. Rosso J, Lemaire F, Geschwind H, et al. Right atrial myxoma: an unusual case of intracardiac right-to-left shunt. *Bulletin Europeen de Physiopathologie Respiratoire* 1985;21:109-182.
49. Strunk BL, Cheitlin MD, Stulberg MS, et al. Right-to-left shunting through a PFO despite normal intracardiac pressures. *Am J Card.* 1987;60:413-415.
50. Inoue T, Yamauchi H, Hayashi T, et al. Right-to-left shunting through a PFO caused by pulmonary hypertension associated with rheumatoid arthritis and Sjogren's syndrome: a case report. *Angiology.* 1990;4:1082-1085.
51. Gudipati CV, Nagelhout DA, Serota H, et al. Transesophageal echocardiographic guidance for balloon catheter occlusion of PFO complicating right ventricular infarction. *Am Heart J.* 1991;121:919-922.
52. Baldwin RT, Duncan JM, Frazier OH, et al. PFO: a cause of hypoxemia in patients on left ventricular support. *Ann Thorac Surg.* 1991;52:865-867.
53. Adolph EA, Lacy WO, Hermoni YI, et al. Reversible orthodeoxia and platypnea due to right-to-left intracardiac shunting related to pericardial effusion. *Ann Intern Med.* 1992;116:138-139.
54. Thompson RC, Finck SJ, Leventhal JP, et al. Right-to-left shunt across a PFO caused by cardiac tamponade: diagnosis by transesophageal echocardiography. *Mayo Clin Proc.* 1992;66:391-394.
55. Laybourn KA, Martin ET, Cooper RA, et al. Platypnea and orthodeoxia: shunting associated with an aortic aneurysm. *J Thorac Cardiovasc Surg.* 1997;113:955-956.
56. Popp G, Melek H, Garnett AR. Platypnea-orthodeoxia related to aortic elongation. *Chest.* 1991;112:1682-1684.
57. Ouseph R, Stoddard MF, Lederer ED. PFO presenting as refractory hypoxemia after heart transplantation. *J Am Soc Echocardiography.* 1997;10:973-976.
58. Boglioli LR, Gardiner J, Gerstenblith G, et al. Carcinoid heart disease with severe hypoxia due to interatrial shunt through PFO. *Texas Heart Inst J.* 1997;24:125-128.
59. Allan JJ, Marinelli C, Dellsperger KC, et al. Percutaneous balloon catheter closure of a PFO in a patient with pulmonary disease, profound hypoxemia, and normal right heart pressures. *Clin Cardiol.* 1997;20:307-309.
60. Saito H, Tsuchiya K, Osawa H, et al. Surgical removal of right atrial myxoma with severe hypoxemia caused by right-to-left shunt through persistent foramen ovale. *Japanese J Thorac Surg.* 1998;51:1135-1136.
61. Patakas D, Pitsiou G, Philippou D, et al. Reversible platypnea and orthodeoxia after surgical removal of an hydatid cyst from the liver. *Eur Respir J.* 1999;14:725-727.
62. Godart F, Ray C, Prat A, et al. Atrial right-to-left shunting causing severe hypoxemia despite normal right-sided pressures: report of 11 consecutive cases corrected by percutaneous closure. *Eur Heart J.* 2000;21:483-489.
63. Faller M, Kessler R, Chaouat A, et al. Platypnea-orthodeoxia syndrome related to an aortic aneurysm combined with an aneurysm at the atrial septum. *Chest.* 2000;118:553-557.
64. Kilger E, Strom C, Frey L, et al. Intermittent atrial level right-to-left shunt with temporary hypoxemia in a patient during support with a left ventricular assist device. *Acta Anaesthesiol Scand.* 2000;44:125-127.
65. Schneider B, Zienkiewicz T, Jansen V, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and correlation with autopsy findings. *Chest.* 1996;77:1202-1209.
66. Nemeck JJ, Marwick TH, Lorig RJ, et al. Comparison of transcranial doppler ultrasound and transesophageal contrast echocardiography in the detection of interatrial right-to-left shunts. *Am J Cardiol.* 1991;68:1498-1502.
67. Di Tullio M, Sacco RL, Venketasubramanian N, et al. Comparison of diagnostic techniques for the detection of a patent foramen ovale in stroke patients. *Stroke.* 1993;24:1020-1024.
68. Karnik R, Stöllberger C, Valentin A, et al. Detection of patent foramen ovale by transcranial Doppler ultrasound. *Am J Cardiol.* 1992;69:560-562.
69. Karttunen V, Ventila M, Ikaheimo M, et al. Ear oximetry: a noninvasive method for detection of patent foramen ovale: a study comparing dye dilution method and oximetry with contrast transesophageal echocardiography. *Stroke.* 2001;32:448-453.
70. Hausmann D, Mugge A, Becht I, et al. Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol.* 1992;70:668-672.
71. Pearson AC, Labovitz AJ, Tatineni S, et al. Superiority of transesophageal echocardiography in detecting cardiac source of embolism in patients with cerebral ischemia of uncertain etiology. *J Am Coll Cardiol.* 1991;17:66-72.
72. Movsowitz C, Podolsky LA, Meyerowitz CB, et al. Patent foramen ovale: a nonfunctional embryological remnant or a potential cause of significant pathology? *J Am Soc Echocardiography.* 1992;5:259-270.
73. Lechat PH, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. *N Engl J Med.* 1988;318:1148-1152.
74. Durand E, Bussy E, Gaillard JF. Lung scintigraphy in postpneumonectomy dyspnea due to a right-to-left shunt. *J Nucl Med.* 1997;38:1812-1815.
75. Dogan AS, Rezaei K, Kirshner PT, et al. A scintigraphic sign for detection of right-to-left shunts. *J Nucl Med.* 1993;34:1607-1611.
76. Nendaz MR, Sarasin FP, Junod AF, et al. Preventing stroke recurrence in patients with patent foramen ovale: antithrombotic therapy, foramen closure, or therapeutic ablation? A decision analytic perspective. *Am Heart J.* 1998;135:532-541.
77. Dearani JA, Ugurlu BS, Danielson GK. Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events. *Circulation* 1999;100 (Suppl):171S-175S.
78. Homma S, Di Tullio M, Sacco RL, et al. Surgical closure of patent foramen ovale in cryptogenic stroke patients. *Stroke.* 1997;28:2376-2381.
79. Bridges ND, Hellenbrand W, Latson L, et al. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. *Circulation.* 1992;86:1902-1908.

-
80. Ende DJ, Chopra PS, Rao PS. Transcatheter closure of atrial septal defect or patent foramen ovale with the buttoned device for prevention of recurrence of paradoxical embolism. *Am J Cardiol*. 1996;78:233–236.
81. Sievert H, Babic UU, Hausdorf G, et al. Transcatheter closure of atrial septal defect and patent foramen ovale with ASDOS device (a multi-institutional European trial). *Am J Cardiol*. 1998;82:1405–1413.
82. Windecker S, Wahl A, Chatterjee T, et al. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000;101:893–898.
83. Food and Drug Administration Web site. Available at: <http://www.fda.gov/cdrh/ode/h990011sum.html>. Accessed 2000.
84. Hung J, Landzberg MJ, Jenkins KJ, et al. Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement. *J Am Coll Cardiol*. 2000;25:1311–1316.
85. Landzberg MJ, Sloss LJ, Faherty CE, et al. Orthodeoxia-platypnea due to intracardiac shunting-relief with transcatheter double umbrella closure. *Cathet Cardiovasc Diagn* 1995;36:247–250.