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Patent Foramen Ovale and Hypoxemia

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Abstract: Patent foramen ovale (PFO), an embryonic remnant of the fetal circulation, is present in 20–25% of adults. Although recent observational studies and clinical trials have established the link between PFO-mediated right-to-left shunting with cryptogenic stroke and migraine with aura, the role of a PFO in exacerbating hypoxemic medical conditions (ie, sleep apnea, chronic obstructive pulmonary disease, pulmonary hypertension, platypnea–orthodeoxia, pulmonary arteriovenous malformation, high-altitude pulmonary edema, and exercise desaturation) remains less understood. PFO-mediated hypoxemia occurs when deoxygenated venous blood from the right atrium enters and mixes with oxygenated arterial blood in the left atrium. Patients with an intracardiac right-to-left shunt may have profound hypoxemia out of proportion to underlying primary lung disease, even in the presence of normal right-sided pressures. The presence of right-to-left cardiac shunting can exacerbate the degree of hypoxemia in patients with underlying pulmonary disorders. In a subset of these patients, percutaneous PFO closure may result in marked improvement in dyspnea and hypoxemia. This review discusses the association between PFO-mediated right-to-left shunting with medical conditions associated with hypoxemia and explores the role of percutaneous PFO closure in alleviating the hypoxemia.

Key Words: patent foramen ovale, hypoxemia, right-to-left shunt, chronic obstructive pulmonary disease, sleep apnea, platypnea–orthodeoxia

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During the embryonic period, the foramen ovale acts as a conduit for shunting oxygenated blood from the placenta directly to the fetal systemic circulation[1] by allowing passage of blood from the inferior vena cava into the left atrium, thus bypassing the functionally inert and high-resistance pulmonary circulation. After birth, the decrease in pulmonary vascular resistance within the now aerated lungs and the increase in left atrial pressure lead to functional closure of the foramen ovale. This normally engenders fusion of the septum primum flap against the septum secundum, forming a solid fossa ovalis. In 20–25% of the population, the foramen remains patent, or more precisely, able to open.[2,3]

Recent observational studies and clinical trials have described the efficacy and safety of percutaneous patent foramen ovale (PFO) closure for secondary prevention of cryptogenic stroke[4–6] and possibly for treating migraine with aura.[7–9] Although the connection between PFO and these neurologic conditions has been established, the role of PFO-mediated right-to-left shunting in exacerbating hypoxemic medical conditions [eg, chronic obstructive pulmonary disease (COPD), platypnea–orthodeoxia (POD), obstructive sleep apnea (OSA)] remains inadequately studied.

IMAGING ASSESSMENT OF A PFO

Short of an autopsy or confirmation during cardiac surgery, a right heart catheterization with guidewire passage across the atrial septum under fluoroscopy is the most accurate method for diagnosing a PFO.[10] Transesophageal echocardiography (TEE) with agitated saline bubble study is the accepted minimally invasive reference for the detection and quantification of PFO-mediated shunts. TEE allows direct visualization of the atrial septal anatomy and differentiates between a PFO, atrial septal defect, and pulmonary shunt.[11,12] However, a TEE can miss or misdiagnose a PFO in 10% of patients if not complemented by another imaging modality.[13] TEE is limited by its need for sedation, discomfort for the patient, and entails high risk or is contraindicated in various esophageal pathologies. Due to these limitations, a noninvasive screening test is often the first modality of choice, which involves an agitated saline bubble study with a provocative test (typically a prolonged Valsalva maneuver) to detect embolic bubbles at the level of the left atrium [transthoracic echocardiography (TTE)] or the middle cerebral arteries [transcranial Doppler (TCD)].[14] TTE with fundamental imaging carries a sensitivity of 46% with improved sensitivity up to 90% using harmonic imaging mode.[15,16] A TCD has a sensitivity of 97% and specificity of 93% when compared with TEE, but is unable to differentiate cardiac from pulmonary shunts.[17] Additionally, TCD is highly sensitive to quantify post-PFO closure residual right-to-left shunting.[18–20] Intracardiac echocardiography may be used to detect a residual shunt at the end of an implantation and is also useful to guide the procedure. Finally, indirect assessment for a right-to-left shunt has been described using ear oximetry measurements; demonstration of arterial oxygen desaturation during the release phase of repetitive Valsalva maneuvers has been found to be a sensitive and safe screening method compared to TEE as the reference[21,22]; however, it still lacks clinical validation. The main difficulty with the methods to diagnose a right-to-left shunt is that none of the current methods are able to quantitate the amount of shunted blood in terms of milliliter per minute.

The degree of intermittent right-to-left shunting can be posture dependent, with an increased contrast bubble load reportedly occurring in 42% of patients in the upright position compared to recumbence.[23] Thus, PFO testing in the upright position may be warranted

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when in doubt, or with inconclusive tests that are obtained in the recumbent position (Fig. 1).

PFO AND HYPOXEMIC CONDITIONS

The association between PFO-facilitated right-to-left shunting and hypoxemia-associated pathologies, such as COPD, POD syndrome, and OSA, has become a subject of recent interest.[3,24–28] PFO-mediated hypoxemia occurs when deoxygenated venous blood from the right atrium passes across the atrial septum and mixes with oxygenated blood in the left atrium. In case reports, patients with an intracardiac right-to-left shunt have been described to have profound hypoxemia out of proportion to underlying primary lung disease,[29–32] even in the presence of normal right-sided pressures.[33] However, it is often difficult to quantitate the relative contribution of the right-to-left shunt in causing a patient's hypoxemia compared to the coexisting pulmonary process.

This review describes the association between PFO-mediated right-to-left shunting with medical conditions that may produce hypoxemia, and explores the role of percutaneous PFO closure in alleviating the hypoxemia.

Patent Foramen Ovale and Obstructive Sleep Apnea

OSA, present in 20–30% of males and 10–15% of females, is characterized by intermittent upper airway obstruction during sleep caused by the receding tongue and encroachment of the narrow upper airway during breathing, resulting in hypoxemia. Risk factors for OSA include male gender, obesity, diabetes, and hypertension; in addition, OSA is a contributing factor to increased cardiovascular and all-cause mortality.[34,35] The association between PFO and OSA has been a subject of ongoing debate as there have been conflicting results of various studies.

Shanoudy et al[30] described the prevalence of TEE-confirmed PFO in 48 subjects with OSA and 24 controls. The study found a significantly higher prevalence of PFO in the OSA group (69% vs 17%; $P < 0.0001$). Although the patients' baseline oxygen saturation was similar in both groups, provocation with Valsalva maneuver resulted in a significant decrease in O_2 saturation only in those who had a PFO −2.4% ± 1.5% versus −1.3% ± 0.6%; $P = 0.007$; one third of patients had a >4 SD drop in O_2 saturation.[30] Shaik et al[36] demonstrated a higher prevalence of larger right-to-left shunts (18% vs 6%; $P = 0.049$), with increased oxygen desaturation index (ODI)/apnea–hypopnea index (AHI) in those with a clinically significant shunt (1.05 vs 0.86; $P = 0.004$).[36]

A larger study involving 100 patients with OSA and 200 gender- and age-matched controls found a 2.2 times higher prevalence of right-to-left shunt in OSA patients using TCD (42% vs 19%; $P < 0.0001$). The study found that patients with a right-to-left shunt had a higher ODI/AHI ratio ($P < 0.0001$), which is a measure of the severity of hypoxemia for the degree of OSA.[26] Hypoxemia due to the apnea is thought to lead to increased pulmonary arteriolar resistance and a transient elevation in pulmonary artery pressure. In the presence of a PFO, the increased right-sided pressure opens the foramen ovale flap, increasing the right-to-left shunt, and therefore exacerbating hypoxemia. Because OSA patients with PFO were younger and had less hypertension, it was hypothesized that patients become symptomatic at an earlier OSA disease stage due to more prominent hypoxemia at a similar level of OSA dysfunction when compared to those without a right-to-left shunt.

A number of mechanisms can lead to increased right-to-left shunting across a PFO in OSA patients. Pulmonary hypertension complicates 15–20% of patients with OSA, often predisposed by intermittent obstructive ventilation causing hypoxemia and hypercapnia.[37] Forced breathing against an obstructed upper airway can cause large fluctuations in intrathoracic pressure, resulting in negative pleural pressures and pulsus paradoxus with leftward bulging of the atrial septum.[38] Additionally, recurrent hypoxemia can result in reflex pulmonary vasoconstriction, which can subsequently cause long-term modification of the pulmonary vasculature and chronic pulmonary hypertension. Acute increases in pulmonary pressures during episodes of OSA may lead to transient reversal of the interatrial pressure gradient, triggering right-to-left shunting across a PFO.[39,40] One study found no significant PFO-mediated shunting in

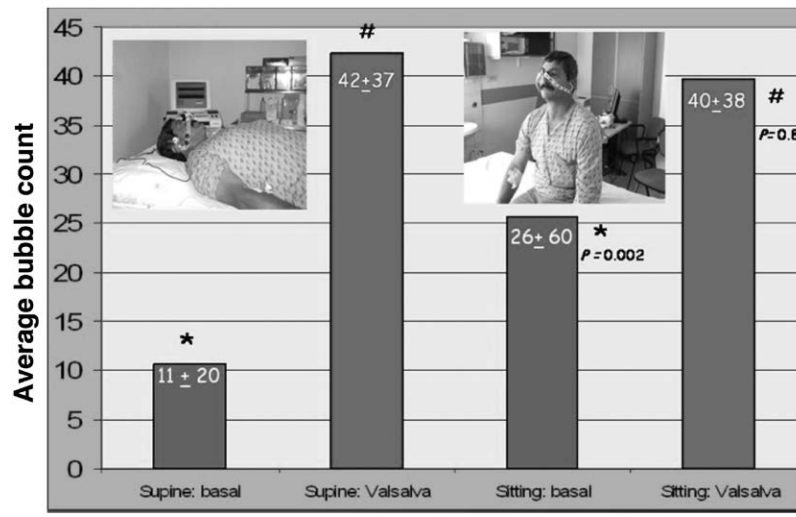

FIGURE 1. Posture dependence of right-to-left shunting across the patent foramen ovale. The graph demonstrates an increase in average bubble counts from the supine to sitting position during normal breathing (TCD bubble count from 11 ± 20 to 26 ± 60; $P = 0.002$) but minimal change from the supine to sitting position during Valsalva provocation (TCD bubble count from 42 ± 37 to 40 ± 38; $P = 0.8$).[23] A patient is visualized wearing a modified TCD headset that attaches bitemporal ultrasound probes, with bubble study performed in the supine (left image of patient) and sitting (right image of patient) positions. Image based on study by Caputi et al.[23] TCD indicates transcranial Doppler.

OSA patients while they were awake, but significant shunting during apneic episodes of sleep.[40]

Pinet et al[41] demonstrated cessation of baseline right-to-left shunting in an OSA patient who had a large PFO after treatment with continuous positive airway pressure; shunting only remained with provocative Valsalva maneuvers. This case is consistent with the understanding that recurrent apneic episodes during sleep result in chronic hemodynamic changes of the pulmonary vasculature, causing more right-to-left shunting in OSA patients who also have a PFO.[42]

A number of case reports have described improved symptoms of OSA and decreases in apnea and hypopnea episodes after PFO closure. Silver et al[37] reported a significant improvement in symptoms and a decrease in apneic episodes on polysomnography in a 51-year-old male who underwent percutaneous PFO closure for secondary prevention of ischemic stroke. This relief could not be explained by lifestyle, weight, or medication changes. Other case reports have demonstrated marked improvements in fatigue, daytime sleep habits, and exercise after PFO closure.[43] In a nonrandomized observational study, Rimoldi et al[28] assessed 40 patients with a new diagnosis of OSA. A PFO was present in 35% (14/40) of OSA patients and all underwent PFO closure. Compared to the controls, PFO closure substantially ameliorated the AHI (ΔAHI, -7.9 ± 10.4 vs $+4.7 \pm 13.1$ events per hour; $P = 0.0009$) and the ODI (ΔODI, -7.6 ± 16.6 vs $+7.6 \pm 17.0$ events per hour; $P = 0.01$). Additionally, fewer patients had severe OSA after closure (79% vs 21%; $P = 0.007$). Although remaining unchanged in the control group, patients who underwent PFO closure had improvement in cardiovascular parameters, including the brachial artery flow-mediated vasodilation, carotid artery stiffness, nocturnal systolic and diastolic blood pressure (−7 mm Hg, $P = 0.009$ and −3 mm Hg, $P = 0.04$, respectively), left ventricular diastolic function, and nocturnal blood pressure dipping. The study concluded that in OSA patients, PFO closure improves sleep-disordered breathing and nocturnal oxygenation, which in turn improves endothelial function and vascular stiffening, with additional benefits of decreased nighttime blood pressure and improvement in left ventricular diastolic function.

Patent Foramen Ovale and Chronic Obstructive Pulmonary Disease

A number of studies have evaluated the prevalence of PFO in patients with COPD, and the added effect of PFO on hypoxemia and patients' functional status. PFO has been found to occur in 44–54% of patients with COPD.[28,29,44–47] However, not all of the studies have found a statistically higher prevalence of PFO in COPD patients compared to controls.[44] The prevalence obtained can vary depending on the diagnostic method employed (TCD vs TTE), and the different criteria used for diagnosing a right-to-left shunt. TCD may be limited in assessing the presence of a PFO in COPD patients given its inherent inability to distinguish intracardiac from transpulmonary shunts.[24]

Using TEE bubble studies with provocative maneuvers (Valsalva and cough), Soliman et al[29] first described a 2-fold increased prevalence of PFO in severe COPD patients compared to a control group. Half of these patients had transient arterial oxygen desaturations, the severity of which correlated with the severity of pulmonary hypertension. Another study also found a higher prevalence of PFO in COPD patients compared to controls as assessed by TTE bubble studies.[46] The authors demonstrated that COPD patients with a PFO had a lower arterial oxygen saturation, a reduced 6-minute walk test duration, and a longer disease course compared to COPD patients without a PFO.

Martolini et al[45] studied patients enrolled in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II COPD study to evaluate the influence of PFO on oxygenation and exercise capacity. PFO was identified in 12/22 (54%) of patients using TCD. Although the study found a higher prevalence of right-to-left shunts in COPD patients versus the general population, those with a shunt did not have less exercise capacity or 6-minute walk test duration compared to patients without a shunt. Although it was demonstrated that right-to-left shunting increased with exercise, the presence of a PFO had no functional implications. The study was limited by a small sample size, few patients with large shunts, and an absence of controls.

PFO and Pulmonary Hypertension

In patients with COPD, chronic ventilation-perfusion mismatch can lead to hypoxia-induced pulmonary vasoconstriction and pulmonary hypertension.[48–50] Pulmonary hypertension complicates up to 33% of patients with COPD.[51,52] The development of pulmonary hypertension can then lead to an increase in right atrial pressure that may reverse the interatrial pressure gradient, promote PFO-mediated right-to-left shunting, and exacerbate underlying hypoxemia.[53–56] Thus, the presence of a PFO may be associated with worsening of dyspnea and hypoxemia with progression of pulmonary hypertension in COPD patients. Studies have found that PFO-mediated right-to-left shunting can be decreased with certain medications such as inhaled nitric oxide, supplemental oxygen, and phosphodiesterase 5 inhibitors, which target hypoxia-driven vasoconstriction and pulmonary hypertension.[25,56]

Nootens et al[3] found no difference in the prevalence of PFO, 5-year survival, and exercise tolerance in pulmonary hypertension patients compared to the general population. In fact, it is hypothesized that a right-to-left shunt may be necessary to relieve excessive pulmonary artery pressures in patients with pulmonary hypertension. A PFO can function as a pop-off valve to unload the pressure overload from the right atrium and right ventricle; in certain conditions (e.g. Eisenmenger syndrome), PFO closure can lead to worsening of symptoms and clinical decline. In experimental models, Austen et al[57] observed this phenomenon where a right-to-left shunt was created by an atrial septostomy in dogs with right ventricular hypertension. Clinical improvement was observed in some studies where patients with severe pulmonary hypertension had an iatrogenic right-to-left shunt created via an atrial septostomy.[58–61] Due to these observations, some clinicians advocate hemodynamic monitoring of patients undergoing PFO or atrial septal defect closure with occluder devices; this includes placing the occluder device without releasing it to monitor intracardiac pressures and hemodynamic stability for a limited amount of time. If hemodynamic parameters remain unchanged after 15 minutes, the device can be released and closure finalized; if the right atrial pressure increases, the device should be retrieved or fenestrated, which gives time for the right heart to adjust to the increased volume load.[62] Although atrial septostomy can be used as a potential salvage option for pulmonary arterial hypertension (World Health Organization group I), it is not considered an option for pulmonary hypertension patients with underlying hypoxemic lung disease (World Health Organization group III) as their already profound hypoxemia from lung disease cannot tolerate the admixture of deoxygenated blood with the arterial circulation.

Percutaneous PFO Closure for Various Chronic Pulmonary Diseases

Although it has been shown that PFO-mediated right-to-left shunting, especially in the presence of pulmonary hypertension, may worsen hypoxemia in COPD patients, the benefit of percutaneous PFO closure remains controversial. To date, only small studies have been undertaken with conflicting results. One study investigated 10 patients with severe pulmonary hypertension who underwent

percutaneous PFO closure due to significant hypoxemia. The pathology of pulmonary disease varied from sarcoidosis to obesity hypoventilation syndrome and thromboembolic pulmonary disease. The study found a marked improvement in hypoxemia immediately after PFO closure (mean arterial oxygen saturation improved from 87% ± 7% to 96% ± 3%; $P = 0.002$).[53] In a larger retrospective study,[63] 97 patients with different chronic pulmonary diseases (ie, COPD, interstitial lung disease, reactive airway disease, OSA, or sarcoidosis) underwent percutaneous PFO closure; postclosure, over half the patients had a ≥1 New York Heart Association (NYHA) functional class improvement ($P < 0.001$) with 34% of patients having significantly reduced oxygen requirement, including 4 patients who no longer needed oxygen ($P < 0.001$). In another single-center observational study of 50 diverse consecutive patients (including those with COPD, OSA, or pulmonary hypertension)[64] with newly diagnosed PFO, exercise-induced hypoxemia was found in one third of patients. PFO closure improved oxygen saturation by an average of 10.1% ± 4.2% ($P < 0.001$), with improvement in NYHA functional class by a median of 1.5 classes (interquartile range, 0.75–2.00; $P < 0.008$).

In contrast, El Tahlawi et al[48] performed an observational retrospective study that showed different results with PFO closure in 9 patients with various chronic lung diseases (ie, 5 with COPD, 2 with pneumoconiosis, 1 with interstitial pulmonary disease, and 1 with chronic thromboembolic pulmonary disease), and found no significant improvement in NYHA functional class after PFO closure.

PFO and Platypnea-Orthodeoxia Syndrome

POD is a rare clinical condition characterized by positional dyspnea (platypnea) and hypoxemia that is made worse by standing or sitting upright (orthodeoxia) and improves in the recumbent position.[27] Initially, the terms platypnea and orthodeoxia were used to represent what were thought to be different conditions, but in 1969, Altman and Robbins[61] combined the 2 to represent a cluster of rare syndromes thought to be derived from a common root. POD is usually caused by intracardiac right-to-left shunting through a PFO or atrial septal defect, but may also occur due to ventilation-perfusion mismatch in severe pulmonary disorders and chronic liver disease. It is thought that age-related anatomical changes such as elongation of the aorta, atrial septum stretching, and diaphragmatic paralysis yield increased right-to-left shunting through a preexisting PFO by altering the anatomical orientation or opening height of the PFO; this, in turn, results in significant arterial desaturation in the upright position.[65,66] Such anatomical changes that exacerbate right-to-left shunting across a preexisting PFO have been described after certain surgeries such as pneumonectomy[67] or upper abdominal surgery (eg, laparoscopic Nissen fundoplication or cholecystectomy). The anatomical change may be due to a new right hemidiaphragmatic paralysis.[67–69] These cases emphasize the importance of considering PFO-mediated right-to-left shunting in the setting of postoperative dyspnea and hypoxemia in patients with normal right-sided pressures and radiologic findings.

Due to the rarity of POD, most studies showing therapeutic benefit of PFO closure have been limited to case reports and case series. The long-term relief of symptoms in 8 POD patients who underwent PFO closure was described in 1995.[70] Later, Blanche et al[71] reported 5 patients with POD who underwent successful PFO closure with immediate and sustained improvement in symptoms and oxygenation (oxygen saturation increased from 83% ± 3% to 93% ± 2%). A larger observational study investigated the effect of PFO closure in 17 POD patients who were followed for up to 1 year.[27] Percutaneous PFO closure improved or completely resolved orthostatic hypoxemia and dyspnea in 11/17 (65%) patients who had POD (upright SaO_2 increased from 76% ± 5% to 92% ± 8%; $P < 0.0001$). It was observed that patients who did not experience improvement had coexisting primary lung disease with severe pulmonary hypertension (mean pulmonary pressure, >50 mm Hg). Most recently, Shah et al[72] demonstrated an average of 14% increase in O_2 saturation in 52 patients with POD after PFO closure.

PFO and Pulmonary Arteriovenous Malformation

Pulmonary arteriovenous malformations are abnormal communications between a pulmonary artery and vein. They are linked to hereditary hemorrhagic telangiectasia where growth of these malformations is stimulated by vascular endothelial growth factor.

Kijima et al[73] reported a case of a 71-year-old woman with a history of 2 strokes, who, after PFO closure, had a residual right-to-left shunt on intracardiac echocardiography. Further assessment revealed a large pulmonary arteriovenous malformation that was subsequently closed using an Amplatzer Vascular Plug IV (Abbott, Chicago, IL). Similar cases of coexisting PFO and pulmonary arteriovenous malformations have been reported in other patients who presented with ischemic stroke or profound hypoxemia.[74–76] Such reports illustrate that both a PFO and pulmonary arteriovenous malformations may cause substantial right-to-left shunting and that the 2 can occur together.

PFO and High-Altitude Pulmonary Edema

A patient with a PFO may experience pulmonary vasoconstriction when in the hypoxic environment of high altitude, leading to increased right-sided pressures and exacerbation of the right-to-left shunt, which produces more hypoxemia, altered alveolar-arterial gradients, and capillary leakage resulting in pulmonary edema. Allemann et al[32] reported that compared to resistant mountain climbers, those who had a history of high-altitude pulmonary edema had a 4-fold increased incidence of TEE-confirmed PFO [56% vs 11%, $P = 0.004$ when measured at lower altitudes (550 m) and 69% vs 16% at high altitude (4559 m), $P = 0.001$]. Patients with a large PFO had more severe arterial hypoxemia (mean O_2 saturation, 73% vs 83%; $P = 0.001$). In patients with a history of high-altitude pulmonary edema who had a PFO, the size of the shunt directly correlated with the severity of hypoxemia. Although there is a paucity of data on percutaneous PFO closure for treating high-altitude pulmonary edema, it is hypothesized that some patients may have relief of symptoms and hypoxemia by eliminating the right-to-left shunt.[32,33]

PFO and Exercise Desaturation

A recent report described a 56-year-old physically active patient who participated in deep-sea diving; he was worked up for recurrent decompression illness and found to have a PFO. He also had been experiencing increased dyspnea during exercise. After percutaneous PFO closure with a 25-mm Amplatzer occluder (Abbott, Chicago, IL), exercise capacity with jogging improved immediately and durably, and diving subsequently remained uneventful.[77]

In a prospective single-center study, 50 patients with newly diagnosed PFO underwent uniform assessment for arterial oxygen saturation using pulse oximetry during postural changes and exercise (stair climbing).[63] Exercise-induced hypoxemia (defined as desaturation of at least 8% from baseline, or to a level <90%) was found in 34% (17/50) of patients. PFO closure improved oxygen saturation (average increase of 10.1% ± 4.2%; $P < 0.001$) and NYHA functional class by a median of 1.5 classes (interquartile range, 0.75–2.00; $P < 0.008$). Although positional hypoxemia (such as in patients with POD) and exercise desaturation had been described in previous anecdotal reports (Fig. 2), this observational study suggested that exercise-induced hypoxemia may be much more common than previously thought, as the investigators found it in every third patient with a PFO.

CONCLUSIONS AND OUTLOOK

The presence of right-to-left shunting can exacerbate the degree of hypoxemia in patients with underlying pulmonary

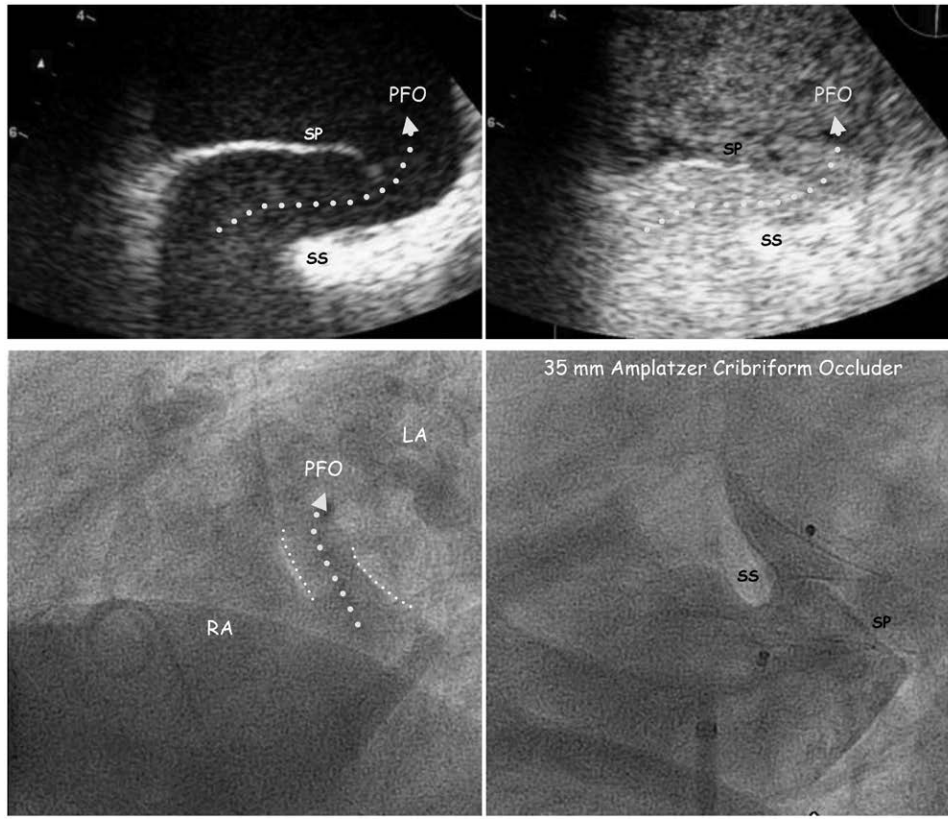

FIGURE 2. TEE images of a 67-year-old man with a large PFO canal (top left), with agitated saline bubble study demonstrating a significant right-to-left shunt (top right). The patient had a 1-year history of progressive exercise intolerance due to arterial oxygen desaturation. He underwent PFO closure with a 35-mm Amplatzer Cribriform occluder with immediate and sustained resolution of exercise intolerance. TEE at 6 months showed a well-seated occluder device with minimal residual shunting. Fluoroscopic images of the PFO canal pre- (bottom left) and postclosure (bottom right) are demonstrated. LA indicates left atrium; PFO, patent foramen ovale; RA, right atrium; SP, septum primum; SS, septum secundum; TEE, transesophageal echocardiography.

disorders. In a subset of these patients, especially in the absence of severe pulmonary hypertension, percutaneous PFO closure may result in marked improvement in dyspnea and hypoxemia. Although a PFO is present in 20–25% of the general population and most individuals remain asymptomatic,[2,3] anatomic and physiologic changes may increase right-to-left shunting which results in more severe hypoxemia. Internists, pulmonologists, and cardiologists should be aware of the link between right-to-left shunting and hypoxemia, as cessation of the shunt may result in decreased oxygen requirement, improvement of symptoms, and overall quality of life.[27,37,43,77]

Current randomized clinical trials do not exist to evaluate the effect of PFO closure in hypoxemic medical conditions. The PFO Closure for Obstructive Sleep Apnea (PCOSA 1) trial (NCT02771561) is studying PFO closure in patients with OSA in the United Kingdom and was scheduled to finish data collection in December of 2017. The Decompression Sickness in Divers With or Without Patent Foramen Ovale (DIVER-PFO) trial (NCT02432131) is investigating the incidence of decompression sickness in divers with or without a PFO. It is unlikely that a randomized trial will be performed to evaluate the effect of PFO closure in patients with POD, given the rarity of this syndrome. The link between PFO closure and associated clinical problems has resurged as a topic of interest with results of randomized clinical trials for stroke or migraine,[4–6,8,78] meta-analyses,[79,80–83] and observational studies on patients with migraine[7,9] or patients undergoing surgery.[84] These studies demonstrate that percutaneous PFO closure improves symptoms and reduces stroke in selected patients. This evokes the hypothesis that closure of a PFO for hypoxemia may convey collateral benefits such as reduced risk of paradoxical cerebral events.

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