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Patent Foramen Ovale Closure for Hypoxemia

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KEYWORDS

• Patent foramen ovale • Hypoxemia • Right-to-left shunting • COPD • Platypnea-orthodeoxia

KEY POINTS

- Hypoxemia may occur in the presence of a patent foramen ovale (PFO) caused by right-to-left shunt across the interatrial septum.
- Right-to-left shunting can be exacerbated by clinical conditions that alter the relative pressure between the right and left atria (eg, obstructive sleep apnea, chronic obstructive pulmonary disease, and pulmonary hypertension) or by changes in the anatomic relationship between the inferior vena cava and the foramen ovale caused by surgery or other conditions that may cause cardiac rotation.
- A PFO is one cause of platypnea-orthodeoxia (dyspnea and hypoxemia while upright, which improves in the recumbent position), in addition to liver and lung disease.
- PFO closure may successfully treat hypoxemia in selected cases.

INTRODUCTION

Several clinical syndromes are associated with patent foramen ovale (PFO), including stroke caused by paradoxic embolism, migraine headaches with aura, and decompression sickness. Although the link between these disorders and PFO has been studied extensively, the associations between hypoxemia-related conditions such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and the platypnea-orthodeoxia syndrome (POS) are not fully defined. Case reports linking PFO to hypoxemia that is out of proportion to the severity of lung disease have been described over the last 2 decades.[1–3] This article describes the mechanisms linking hypoxemia with the presence of a PFO, the clinical conditions in which PFO may play a role in contributing to hypoxemia, and the role of PFO closure in management.

PATENT FORAMEN OVALE AND HYPOXEMIA

In the fetal circulation, blood from the inferior vena cava (IVC) flows from the right atrium (RA) into the left atrium (LA) through the foramen ovale, which acts as a one-way valve. This valve ensures that oxygenated blood from the placenta directly enters the systemic circulation, and bypasses the nonaerated, amniotic fluid–filled lungs. The remaining oxygenated blood that gets into the right ventricle (RV) is directed through the ductus arteriosus into the descending aorta, thus also bypassing the nonfunctional lungs. The IVC is aligned with the PFO by the eustachian valve, which facilitates the IVC flow directly across the septum. Blood from the superior vena cava (SVC) meanwhile is directed down into the RA and across the tricuspid valve (Fig. 1). After birth, the pulmonary vascular resistance decreases, leading to a decrease in RA

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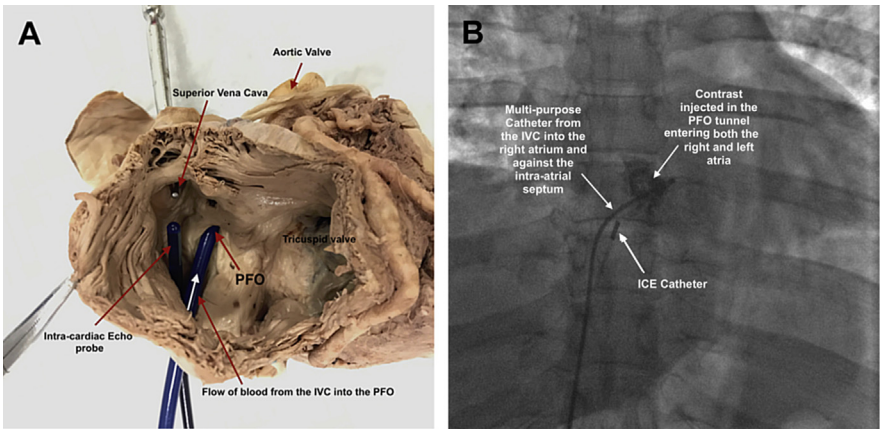

Fig. 1. (*A*) Gross anatomy showing the atrial septum from the right atrial side. The delivery catheter follows the course of the IVC and into the PFO. The SVC is angled away from the PFO and points toward the tricuspid valve. (*B*) Fluoroscopic image showing the course of a catheter as it enters the RA via the IVC and is directed toward the PFO. ICE, intracardiac echocardiography.

pressure. As the LA pressure exceeds the RA pressure, the septum primum closes against the septum secundum. With time, the septum primum and secundum fuse leaving behind the fossa ovalis. For approximately 20% of the population this fusion remains incomplete, resulting in a PFO.[4–6] In most people who have a PFO, it is an incidental finding and not associated with symptoms or hypoxemia. However, right-to-left shunting (RLS) of blood can occur during any activity that increases venous return and right atrial pressure, such as the release of the Valsalva maneuver. It is estimated that a cryptogenic stroke occurs in 1 in 1000 people per year who have a PFO. Of the patients with PFO who have some related symptom, only 3% present with symptomatic hypoxemia.

Although RLS causing hypoxemia is rare in patients without increased right-sided pressures, there have been reports of significant hypoxemia in patients with normal right-sided pressures.[7] Godart and colleagues[7] report a series of 11 patients with PFO who presented with significant dyspnea and cyanosis, which subsided after percutaneous closure of the atrial defect. Six of the 11 patients also had POS, in which the hypoxemia occurs on sitting or standing up. Various theories exist to explain RLS in patients with normal right-sided pressures. These theories include preferential blood flow streaming from the IVC to the LA because of the presence of a large eustachian valve.[8,9] Another theory describes the presence of a systolic right-to-left atrial pressure gradient in conditions such as RV infarction, right atrial myxoma, and mechanical ventilation.[10,11] In these cases, inspiration, the Valsalva maneuver, and changes in posture exacerbate RLS. In the 11 patients described earlier, the investigators observed that all of the patients had rotated atrial septa toward the horizontal axis such that the PFO was more directly in line with the blood flow from the IVC. Note that this phenomenon has also been noted in patients with ascending aortic aneurysms that may distort the septum, or after pneumonectomy and abdominal surgery, which are thought to alter the anatomic orientation or opening height of the PFO. The incidence and degree of shunting also increase when the septum primum is aneurysmal or highly mobile (Fig. 2).[9,12]

Establishing that an RLS through a PFO is primarily responsible for hypoxemia or cyanosis in patients without increased right-sided pressures can be challenging. Persistent desaturations despite administration of 100% oxygen therapy should alert clinicians to the possibility of an RLS. A transesophageal echocardiogram (TEE) showing cross-septal flow on color Doppler or contrast administration can help confirm the diagnosis. In addition, on cardiac catheterization, there is a step-down in the oxygen saturation levels in the LA compared with the pulmonary veins, with return to normal blood saturation after occlusion of the PFO using a soft balloon sizing catheter.[7] Once identified, quantifying the degree of hypoxemia caused by RLS can be difficult. A low pulmonary vein oxygen saturation might indicate a mixed picture in which pulmonary disease is a contributor to hypoxemia, whereas a step-down of saturations in the LA compared with the pulmonary veins should indicate that an RLS through the PFO plays a larger role. Crossing the PFO to obtain

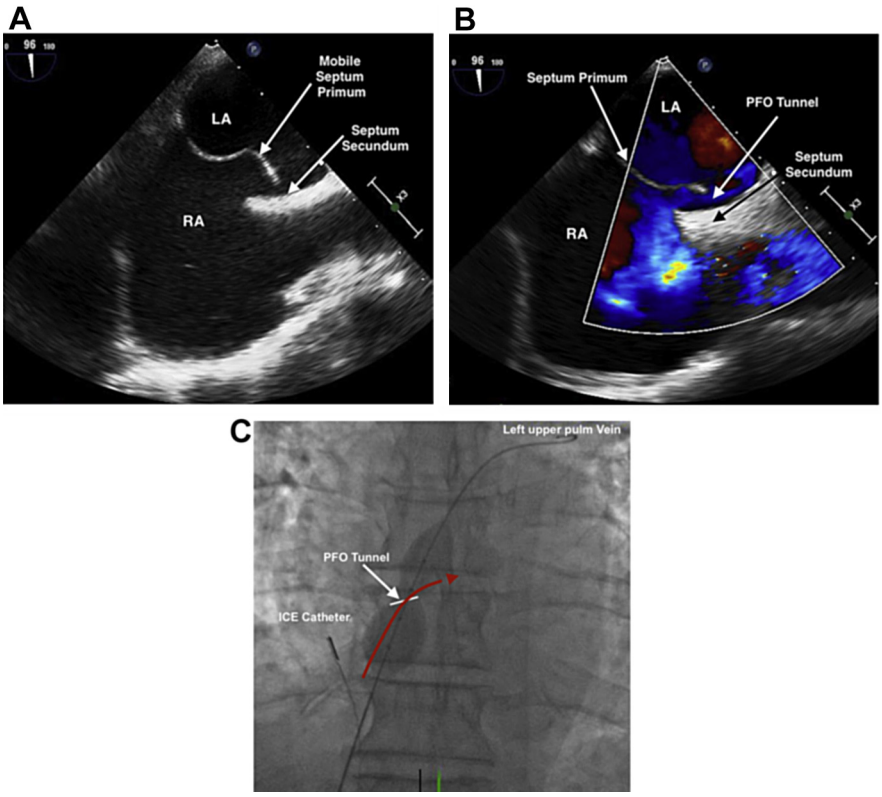

Fig. 2. (*A*) Large PFO with an aneurysmal septum primum. (*B*) Color-flow echocardiogram showing significant flow across PFO caused by a mobile septum primum. (*C*) Fluoroscopic image showing a sizing balloon in the PFO. The sizing balloon shows a wide-diameter (12 mm) PFO tunnel (*white line*). The red arrow indicates the shunt pathway if the balloon was not present.

saturation samples in the LA and pulmonary veins is usually straightforward and can be performed using a multipurpose catheter and a J-tipped guidewire. Once in the left atrium, it is important to be meticulous with catheter manipulation and aspiration so as to prevent clots or air from entering the LA (see Fig. 2; Fig. 3).

PATENT FORAMEN OVALE AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with COPD have been noted to have a higher prevalence of PFO. Soliman and colleagues[2] evaluated the prevalence of PFO in patients with severe COPD (forced expiratory volume in 1 second [FEV_1] <50%, and FEV_1/forced vital capacity ratio <50%) compared with control subjects without COPD by means of contrast TEE and cough or Valsalva maneuvers. The prevalence of PFO in patients with COPD was twice that of normal controls (70% vs 35%). In addition, the investigators also noted transient systemic arterial desaturations in half of these patients, the severity of which was proportional to the degree of pulmonary hypertension. Note that the prevalence of PFO in this study was much higher compared with other population-based studies. The prevalence of diagnosing a PFO depends on the threshold used during the contrast study. Hacievliyagil and colleagues[13] similarly found a higher prevalence of PFO in patients with COPD (23 out of 52 compared with 10 out of 50 controls). The investigators used transthoracic echocardiography (TTE) with contrast at rest and with Valsalva to detect PFO. They also found that patients with COPD with PFO had lower oxygen saturations, shorter 6-minute walk test (6MWT) durations, and longer duration of disease compared with patients with COPD without PFO. In contrast, a study by Shaikh and colleagues[14] did not find a statistically significant increase in the prevalence of PFO in 50 patients with COPD compared with 50 controls (46% vs 30%; $P = .15$). The investigators did find that large shunts were more common in patients with COPD. They used both contrast TTE and transcranial Doppler (TCD) to make the diagnosis of PFO, with most shunts

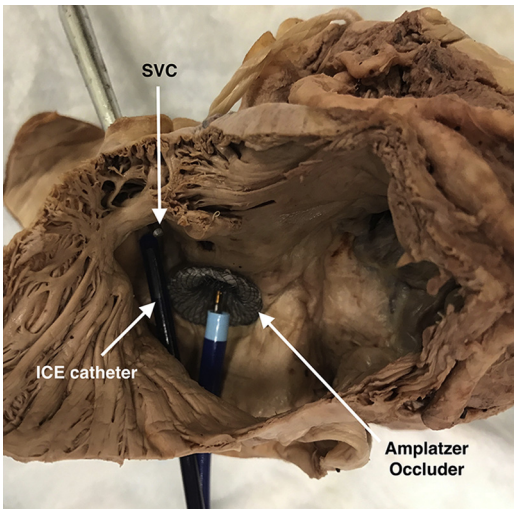

Fig. 3. The direct access of a guiding catheter from the IVC into the PFO and deployment of an Amplatzer device within the septum.

being grade 2 or less (grade 0, up to 3 microbubbles; grade 1, 3–10; grade 2, 11–30; grade 3, 31–100; grade 4, >100; grade 5, microbubbles filling the spectrum for more than 3 cardiac cycles). Note that TCD is a more sensitive tool for the detection of PFO than TTE. The ultimate standard for diagnosing a PFO is to perform a right heart catheterization (RHC) and show that a guidewire can cross the atrial septum. With RHC as the standard, a TCD grade 3 or greater correlates to the presence of a PFO. TCD grades 1 or 2 are unlikely to be caused by a PFO and are ascribed to pulmonary passage of microbubbles.

Martolini and colleagues[15] evaluated patients enrolled in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II COPD study to assess the effects of PFO on arterial oxygen saturation and exercise tolerance, and whether the RLS through the PFO increased during exercise. Twenty-two patients were enrolled in the study, and contrast-enhanced TCD was used to diagnose PFO in these patients. A PFO was identified in 12 of the 22 patients (54%). Furthermore, although the prevalence of PFO was higher in this population than in the general population, patients with PFO did not have a decreased exercise tolerance or a reduced 6MWT duration compared with those without a PFO. Although there was an increase in RLS during exercise, there were no functional consequences from a PFO in this group of patients. The limitations of the study include a small sample size, very few large PFOs, and absence of a control group. In addition, inaccuracies may arise during TCD to determine the presence of a PFO in patients with COPD, because TCD cannot accurately distinguish between intracardiac and intrapulmonary shunting, and patients with COPD can have significant intrapulmonary shunting. Differentiating between the two depends on timing of the bubbles and operator experience.

PATENT FORAMEN OVALE AND PULMONARY HYPERTENSION

Up to one-third of patients with COPD have associated pulmonary hypertension.[15–17] COPD is characterized by ventilation-perfusion mismatch, which results in blood flowing to capillaries supplying diseased or nonfunctional alveoli. This condition causes a progressive increase in pulmonary artery pressure (PAP) caused by hypoxia-induced pulmonary vasoconstriction.[18,19] An increase in PAP leads to an increase in RA pressure, which can lead to increased RLS in the presence of a PFO. Patients with COPD and PFO therefore can have an RLS as an additive cause for hypoxemia.

The phenomenon of clinical deterioration following shunt closure in patients with congenital heart disease and Eisenmenger syndrome is described in the early surgical literature.[20] This phenomenon led to the hypothesis that an RLS may be necessary to release the excessive PAP in patients with pulmonary hypertension. Austin and colleagues[21] showed improvement in systemic pressures and exercise tolerance with creation of an RLS via atrial septostomy in dogs with experimental RV hypertension. Similarly, in patients with severe pulmonary hypertension, the creation of an RLS via atrial septostomy has been shown to provide symptomatic benefit.[22–24] Nootens and colleagues[4] studied the prevalence and significance of PFO in patients with pulmonary hypertension and found no difference in the prevalence of PFO in these patients compared with the general population (25%–30%). In addition, they did not find any difference in 5-year survival or exercise tolerance.

ROLE FOR PATENT FORAMEN OVALE CLOSURE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Although PFO with RLS, particularly in the presence of pulmonary hypertension, can contribute to hypoxemia in patients with COPD, it is unclear whether there is any benefit to PFO closure in this subgroup of patients. Ilkhanoff and colleagues[25] studied patients referred for percutaneous

closure of a PFO at a single center. Ten patients underwent PFO closure for hypoxia; of those patients, 4 had persistent hypoxemia at rest, 6 had intermittent hypoxemia, and 2 had platypnea-orthodeoxia. The mean PAP in the group was 45 mm Hg. Of note, the patients in this study had significant pulmonary disease in the forms of sarcoid, obesity-hypoventilation syndrome, and thromboembolic lung disease. There was an improvement in the mean arterial oxygen saturation level after PFO closure (87% ± 6.5% preprocedure to 96% ± 2.9%). One patient had a transient ischemic attack (TIA) after an initially unsuccessful closure attempt. A retrospective study by Tahlawi and colleagues[26] studied the effects of PFO closure in 9 patients with chronic pulmonary disease and found no significant improvement in New York Heart Association (NYHA) functional class after PFO closure. A more recent, larger, single-center, retrospective study of PFO closure in 97 patients with chronic lung disease showed decrease in oxygen requirement and improvement in NYHA class after closure (51% of patients had improved NYHA class >1, $P<.001$; 34% of patients experienced a decrease in O_2 requirements, $P<.001$).[27] The study used contrast TTE and found that patients with a substantial RLS experienced significantly more symptom relief with PFO closure. Fenster and colleagues[27] described a 5-year single-center experience in which a large cohort of patients with chronic respiratory insufficiency underwent transcatheter PFO closure for dyspnea and hypoxia. All patients were assessed using TTE and, in those without a resting RLS, provocative maneuvers were used to elicit transseptal shunting. PFO closure was performed only if the patient had symptomatic hypoxemia, clear RLS on intracardiac echocardiography (ICE), and no significant pulmonary hypertension. Repeat saline contrast TTE was performed at 1 month and 6 months after the procedure; exercise testing, supplemental O_2 requirements, and NYHA class were assessed before and after the closure. At baseline, 54% of patients had NYHA class 3 symptoms, and 67% of the patients had coexisting pulmonary disease. Seventy-seven percent of patients had a resting shunt and an atrial septal aneurysm was present in 39% of patients. Procedural success was achieved in 99% of the patients and clinical success was observed in 70% of patients. NYHA class improvement was seen in a little more than half of the patients and 34% of patients were able to decrease their O_2 requirements. Male gender and coexisting pulmonary disease were associated with a lower rate of clinical improvement.

PATENT FORAMEN OVALE AND SLEEP APNEA

OSA is present in 24% of men and 9% of women in the general population, with increasing prevalence of this disorder caused by the increasing rates of obesity. Studies have indicated that a higher prevalence of PFO may be seen in people with OSA, with some suggesting that the prevalence may be as high as 65%.[1,28] OSA is characterized by collapse of the pharyngeal smooth muscles during exhalation resulting in airway obstruction during sleep in the recumbent position and subsequent decrease in arterial oxygen saturation. Shanoudy and colleagues[1] studied the prevalence of PFO in 48 patients with known sleep apnea and 24 control subjects. A greater proportion of patients with OSA had PFOs compared with the controls (69% vs 17%; $P<.0001$). The investigators also observed that the baseline oxygen saturations were similar in all patients with sleep apnea regardless of the presence or absence of a PFO (93.9% + 1.7% vs 95% + 0.6%; $P = .007$). However, a significantly greater decrease in O_2 saturation was noted in the PFO group compared with patients with OSA without a PFO. In another study of 78 patients with OSA and 89 without OSA,[29] TCD showed a statistically significant higher prevalence of PFO in the OSA group (27% vs 15%; $P<.05$). Mojadidi and colleagues[30] studied the prevalence of RLS in 100 patients with diagnosed OSA compared with 200 control subjects without OSA using TCD. They observed a much higher prevalence of RLS in patients with OSA compared with those without diagnosed sleep apnea (42% vs 19%; $P<.0001$). These findings suggest that OSA alters the pressure gradient across the atrial septum, which predisposes to opening of the septal foramen and increases RLS.

The prevalence of pulmonary hypertension in patients with OSA is approximately 15% to 20%.[31] The development of pulmonary hypertension can be associated with obstructive ventilation patterns, daytime hypoxemia, and hypercapnia. There are large intrathoracic pressure swings caused by forced expiration and inspiration against an obstructed upper airway. These pressure swings can lead to negative pleural pressures of up to −80 cm H_2O, and even pulsus paradoxus with leftward shift of the interatrial septum.[32] In addition, recurrent hypoxemia leads to reflex pulmonary vasoconstriction and long-standing pulmonary vasoconstriction, which in turn leads to chronic changes in pulmonary vasculature and pulmonary hypertension. Systolic transmural PAP increases acutely by 10 mm Hg

or more during episodes of sleep apnea.[33] This acute effect on PAP may lead to increased RA pressure and exacerbation of RLS through a PFO. These changes in hemodynamics potentially cause greater levels of desaturation during episodes of sleep apnea. Beelke and colleagues[34] studied patients with OSA with a PFO during sleep with a TCD. These patients did not have any shunting across the PFO while awake, but significant RLS occurred during episodes of apnea while asleep. Therefore, there are multiple mechanisms that lead to increased RLS through a PFO in patients with OSA.

Pinet and colleagues[35] describe the case of a patient with OSA and a large PFO with baseline RLS in which treatment with continuous positive airway pressure for 1 week led to cessation of the baseline RLS with shunting present only during Valsalva. It has been hypothesized that recurrent episodes of sleep apnea can cause long-term hemodynamic changes resulting in increased right atrial pressures and chronic RLS.[28] There are case reports that describe improvement in sleep apnea symptoms and the number of apneic and hypopneic episodes after PFO closure in patients with OSA.[36,37] Silver and colleagues[36] reported the case of a 51-year-old man with severe OSA who underwent PFO closure following an ischemic stroke. Polysomnographic studies done before and after the PFO closure showed a clear decrease in the number of apnea episodes and the patient reported improvement in symptoms. This improvement was not explained by weight loss, medications, or changes in sleep duration and was attributed to the PFO closure. In another case, significant improvements in daytime sleepiness, fatigue, and exercise were seen in a 42-year-old man following PFO closure.[37] The mechanism underlying this improvement is unclear and, although the reduction in desaturation likely plays a role, there are potentially other unidentified mechanisms that may be responsible (Fig. 4).

PATENT FORAMEN OVALE AND PLATYPNEA-ORTHODEOXIA

POS is a rare clinical entity in which patients experience dyspnea and hypoxemia while upright, which improve in the recumbent position. Platypnea (flat breathing), first described in 1949, refers to shortness of breath in the upright position, whereas orthodeoxia refers to arterial hypoxemia that is worse with standing and made better by lying down.[38] Blood shunting through a PFO or atrial septal defect is the most common cause for this condition. Other causes include liver disease and severe pulmonary disorders.[38,39] The role of PFO closure in this disorder has been evaluated in small studies. Mojadidi and colleagues[40] examined 683 patients referred for conditions associated with PFO, of whom 17 (2.5%) had POS and underwent PFO closure. Eleven of 17 patients (65%) in whom the PFO was closed experienced improvement in hypoxemia and dyspnea in the upright position. It was noted that patients who did not experience improvement in symptoms or oxygen levels had primary lung disease with pulmonary hypertension. In another single-center study, PFO closure was evaluated in 52 patients with POS.[41] Associated conditions included pneumonectomy, ascending arch dilatation, and arch surgery, although approximately 38% of patients did not have any associated condition to explain the POS. There was a significant improvement in hypoxemia and symptoms after PFO closure. Although a residual shunt was found in 20% of patients, even those patients experienced significant relief in symptoms.

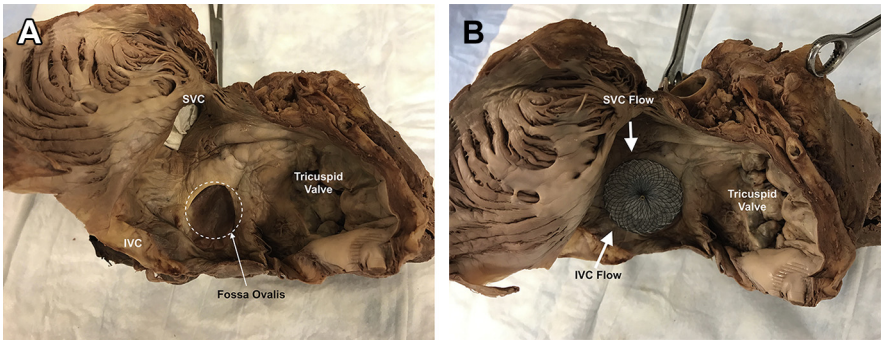

Fig. 4. (*A*) A large PFO within the fossa ovalis. (*B*) Closure device occluding the large PFO and most of the fossa so as to prevent shunting from the IVC across the septum.

POS can also develop following pneumonectomy, although this is an uncommon occurrence.[42] More common causes of dyspnea after pneumonectomy include loss of alveoli, postoperative pain, and diaphragmatic paralysis. Barkis and colleagues[42] reported the development of POS in 4 patients following pneumonectomy. The investigators highlight the importance of considering RLS through a PFO in the setting of postoperative dyspnea and low oxygen saturations along with normal radiological findings in the remaining lung. In these situations, RLS leading to systemic desaturation develops despite normal right-sided pressures, possibly because the pneumonectomy affects the cardiac position such that the PFO opens further.

PATENT FORAMEN OVALE AND PULMONARY ARTERIOVENOUS MALFORMATION

A pulmonary arteriovenous malformation (PAVM) is defined as an abnormal connection between a pulmonary artery and a pulmonary vein. The incidence in the general population is around 0.04%. This condition is associated with hereditary hemorrhagic telangiectasia in which excess vascular endothelial growth factor is thought to stimulate the growth of arteriovenous malformations. Kijima and colleagues[43] described the case of a 52-year-old man with hereditary hemorrhagic telangiectasia who presented with multiple TIAs and was found to have multiple small PAVMs, as well as a PFO. The PFO was successfully closed percutaneously using a 25-mm Gore Helex Septal Occluder (WL Gore and Associates, Inc, Flagstaff, AZ). The investigators also describe a case of a 71-year-old woman with a PFO and 2 prior strokes referred for PFO closure. Immediately after PFO closure, a large residual RLS was noted on ICE imaging. Pulmonary artery angiography revealed a large PAVM that was subsequently closed using an Amplatzer Vascular Plug IV (St. Jude Medical, St Paul, MN). These cases highlight that either a PFO or a PAVM may cause a large RLS and that both entities can coexist.

SUMMARY

A PFO is a common anatomic finding in 20% of the normal population. Although most people with a PFO are not symptomatic, significant hypoxemia can occur in circumstances in which hemodynamic or anatomic changes predispose to increased right-to-left intra-atrial shunting. The subsequent hypoxemia produces substantial dyspnea that may affect the patient's quality of life, independent of underlying pulmonary disease. Profound hypoxemia caused by right-to-left shunt across the interatrial septum usually responds to percutaneous PFO closure. An important impediment to successful treatment is the lack of awareness of the potential role of a PFO in this condition.

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