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Chapter 12 Hypoxemia and PFO

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CHAPTER

12

Hypoxemia and PFO

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OUTLINE

INTRODUCTION

During the embryonic period, the foramen ovale allows oxygenated blood from the maternal placenta to bypass the unaerated lungs and directly enter the left atrium, thereby reaching the systemic fetal circulation. This right-to-left shunt in the developing fetus is due to higher right atrial pressure from elevated pulmonary vascular resistance in the unoxygenated fetal lungs [1]. After birth, pulmonary vascular resistance decreases, along with the pressure in the right atrium, while a significant rise in left atrial pressure is seen. These changes result in closure of the septum primum against the septum secundum with subsequent fusion (Fig. 12.1). However, in 20%–25% of individuals, the foramen ovale fails to completely close and remains patent (Chapter 1) [2–4]. Once thought to be rather benign, a patent foramen ovale (PFO) has now been linked to multiple relevant pathologies. Although the association between PFO and stroke has been well established (Chapters 4–7) [5,6], PFO-mediated hypoxemia remains clinically underrecognized and undertreated.

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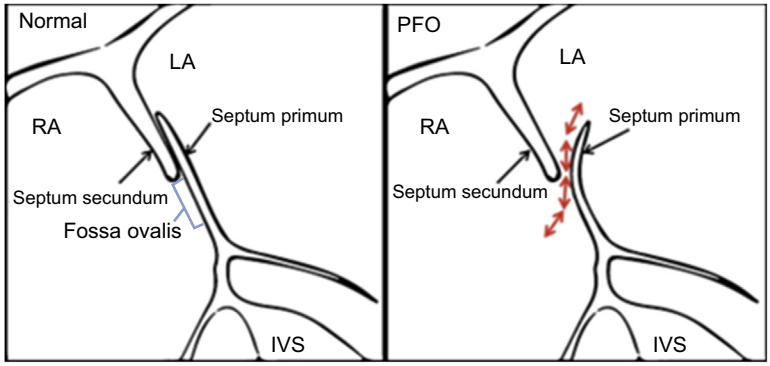

FIGURE 12.1 Patent foramen ovale. *IVS*, interventricular septum; *LA*, left atrium; *RA*, right atrium. *Adapted with permission from Ref. [82].*

PFO AND HYPOXEMIC CONDITIONS

Pathophysiological Interplay Between PFO and Hypoxemia

In patients who have a PFO with no underlying pulmonary pathology, the left atrial pressure is 5–7mm Hg higher than right atrial pressure. However, among patients suffering from pulmonary disorders such as pulmonary hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea, or obesity hypoventilation syndrome, intrathoracic pressure is often higher, resulting in right atrial pressure exceeding left atrial pressure [7,8]. This reversal of the interatrial pressure gradient results in significant shunting of blood from the deoxygenated venous to the oxygenated systemic circulation (Fig. 12.2A and B). The admixture of deoxygenated venous blood to oxygenated arterial blood may result in profound hypoxemia. In patients with pulmonary conditions causing chronic hypoxemia due to their primary lung pathology, a coexisting cardiac right-to-left shunt results in decreased arterial oxygenation out of proportion to the underlying pulmonary disease. Distinguishing the relative contribution of hypoxemia due to underlying pulmonary disease from a cardiac right-to-left shunt-induced arterial desaturation can be challenging.

PFO and Obstructive Sleep Apnea

The prevalence of obstructive sleep apnea (OSA) is estimated to be 10%–15% in adult females and 20%–30% in adult males [9]. The mechanism for hypoxemia in OSA patients includes intermittent upper airway obstruction during sleep caused by the receding tongue, resulting in disordered breathing (consisting of hypopneic and apneic episodes) and subsequent hypoxemia. Hypoxemia is also propagated by increased pulmonary arteriolar resistance, pulmonary hypertension, and fluctuations in intrathoracic pressure during periods of forced breathing against an obstructed upper airway [10]. Risk factors for OSA include male gender, diabetes, hypertension, and obesity. The presence of OSA elevates the risk for cardiovascular and all-cause mortality [11,12]. Due to conflicting results of several prior studies, the mechanistic association between PFO and OSA has been a subject of ongoing debate.

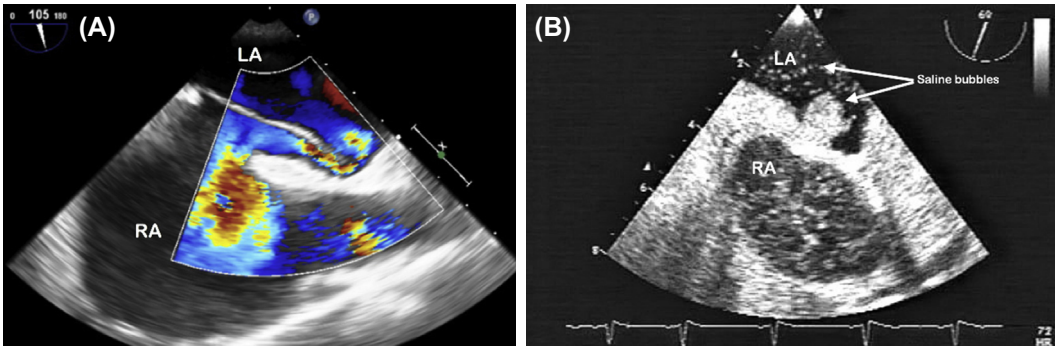

FIGURE 12.2 Transesophageal echocardiogram showing a PFO with resting bidirectional shunt. Color Doppler imaging confirms a left-to-right shunt (A) and bubble study confirms right-to-left shunting (B). *LA*, left atrium; *RA*, right atrium.

In an observational study of 72 patients (48 subjects with OSA and 24 controls), Shanoudy et al. [13] detected a higher prevalence of PFO by transesophageal echocardiography (TEE) in patients with OSA compared to controls (69% vs. 17%, $P < .0001$) [13]. Additionally, the authors also demonstrated that although baseline oxygen saturation was similar in both groups, significant systemic hypoxemia occurred with Valsalva provocation among OSA patients who had a PFO compared to subjects without a PFO (Change in O2 saturation of $-2.4\% \pm 1.5\%$ vs. $-1.3\% \pm 0.6\%$; $P = .007$). It is also noteworthy that one-third of patients had a >4 standard deviation decrease in oxygen saturation.

The ratio between oxygen desaturation index (ODI) and apnea-hypopnea index (AHI) is a metric of the severity of hypoxemia for the degree of OSA. Hypoxemia due to apneic episodes results in increased pulmonary arteriolar resistance and a transient elevation in pulmonary artery pressure. In the presence of a PFO, the increased right-sided pressure results in augmented right-to-left shunting and, thereby, worsening hypoxemia. Correlation between patients with PFO resulting in right-to-left shunt and increased ODI/AHI ratio has also been well demonstrated by several investigations [14,15]. In their study, Shaikh et al. [15] showed a higher prevalence of larger right-to-left shunts (18% vs. 6%; $P = .049$), with increased ODI/AHI in patients with a clinically significant shunt (1.05 vs. 0.86; $P = .004$). In a larger study of 100 OSA patients and 200 control subjects, the authors demonstrated a 2.2 times higher prevalence of right-to-left shunt in OSA patients as detected using a transcranial Doppler (TCD) bubble test (42% vs. 19%; $P < .001$) [14]. The authors showed that patients with a right-to-left shunt had a higher ODI/AHI ratio ($P < .0001$). OSA patients with PFO were younger and less frequently hypertensive. This led the authors to hypothesize that with a similar level of obstructive airway dysfunction, patients with right-to-left shunt become symptomatic at an earlier disease state due to more profound hypoxemia as compared to patients without a right-to-left shunt.

Several mechanisms exist which result in increased right-to-left shunting across a PFO in patients with OSA. Intermittent obstructive ventilation resulting in hypoxemia and hypercapnia predisposes patients to developing pulmonary hypertension, which occurs in roughly 15%−20% of sleep apnea patients [9]. Recurrent hypoxemia also results in reflex pulmonary vasoconstriction that can subsequently result in chronic pulmonary hypertension by long-term modification of the pulmonary vasculature. Fluctuations in intrathoracic pressure occur as patients breathe forcefully against an obstructed upper airway. This results in a negative pleural pressure which causes leftward bulging of the interatrial septum [16]. Lastly, apneic episodes result in sudden increases in pulmonary pressures, which can lead to transient reversal of the interatrial pressure gradient, thereby increasing right-to-left shunting across a PFO [17,18]. This was confirmed by a study that showed significant PFO-mediated shunting during apneic episodes while no significant shunting was detected in OSA patients while they were awake [18].

Case reports have demonstrated cessation in right-to-left shunting with the use of continuous positive airway pressure (CPAP) in OSA patients who have a PFO [19]. Pinet and Orehek showed that with the use of CPAP, right-to-left shunting was terminated and could only be provoked with a Valsalva maneuver [19]. The use of CPAP can mitigate the hemodynamic changes that occur in the pulmonary vasculature during recurrent apneic episodes in OSA patients with PFO, thereby leading to cessation of right-to-left shunting [20]. Improvement in interatrial shunting with the use of CPAP has also been attributed to beneficial changes in disordered breathing, apneic episodes, and sudden increase in intrathoracic pressures.

Other case reports describe subjective and objective clinical improvement in patients with OSA after percutaneous PFO closure. In a case report, PFO closure was performed for secondary ischemic stroke prophylaxis; the patient demonstrated a significant improvement in OSA symptoms and a decrease in AHI was observed on polysomnography [9]. The clinical improvement in this particular patient could not be explained by lifestyle, weight, or medication adjustments. Additional case reports have shown improvement in fatigue, daytime lethargy, and exercise capacity after PFO closure [21]. These findings have been confirmed by an observational study by Rimoldi et al. who investigated 40 patients with newly diagnosed OSA [10]. Among these patients, 14 (35%) were found to have a PFO and all of them underwent successful PFO closure. Compared to controls, PFO closure demonstrated a substantial decrease in AHI (ΔAHI, -7.9 ± 10.4 vs. $+4.7 \pm 13.1$ events per hour, $P = .0009$) and ODI (ΔODI, -7.6 ± 16.6 vs. $+7.6 \pm 17.0$ events per hour, $P = .01$) indices for OSA patients who underwent device closure. A significantly reduced number of patients were classified as having severe OSA after PFO closure (21% vs. 79%, $P = .007$). Subjects who underwent device closure also experienced an improvement in cardiovascular parameters which included brachial artery flow-mediated vasodilation, carotid artery stiffness, left ventricular diastolic function, nocturnal blood pressure dipping, nocturnal systolic (-7 mm Hg, $P = .009$) and diastolic blood pressure (-3 mm Hg, $P = .04$). The authors concluded that in patients with OSA and PFO, percutaneous device closure improves sleep-disordered breathing and nocturnal oxygenation, which subsequently leads to improvement in endothelial function

and vascular stiffening. On the contrary, the PFO Closure on Obstructive Sleep Apnea Syndrome (PCOSA) study showed that the prevalence of PFO in OSA was similar to that in the general population [22]. The authors of this study concluded that although PFO closure was safe, it did not improve OSA severity parameters on polysomnography. It should be noted that this study used transthoracic echocardiography (TTE) with bubble study to detect a PFO, which has inferior sensitivity and diagnostic accuracy compared to TEE and TCD (Chapter 2) [23–26]. Of the 143 OSA patients screened with a TTE bubble test, only 23 underwent PFO closure [22].

PFO and Chronic Obstructive Pulmonary Disease

The prevalence of PFO in patients with chronic obstructive pulmonary disease (COPD), and the potential improvement in hypoxemia and patients' functional capacity after PFO closure, have been a topic of multiple investigations. Based on observational studies, the approximate prevalence of PFO in COPD patients is estimated to be 45%–54% [10,27]. However, not all studies have demonstrated a statistically higher prevalence of PFO in patients with COPD when compared to controls [28]. The reported prevalence has varied among different studies due to the modality used to diagnose PFO (TTE vs. TCD) and the criteria used for a positive right-to-left shunt. TCD may be limited in identifying a PFO due to its inability to differentiate between intracardiac and transpulmonary shunts [29].

Soliman et al. demonstrated a doubling of the prevalence of PFO in patients with severe COPD versus controls when diagnosed with TEE bubble study and Valsalva provocation [27]. It was noted that roughly half of these patients had transient arterial oxygen desaturation, the degree of which correlated with the severity of underlying pulmonary hypertension secondary to COPD. Authors from another study confirmed the increased prevalence of PFO in COPD patients compared to controls when a TTE bubble study was used to make the diagnosis [30]. Compared to COPD patients without a PFO, those with a PFO were shown to have a lower arterial oxygen saturation, reduced 6-minute walk test duration, and more severe disease course.

On the contrary, Martolini et al. showed that although the prevalence of PFO is higher in patients with COPD, the functional limitations in terms of exercise capacity remained unchanged despite the presence of a right-to-left shunt [31]. Twenty-two patients enrolled in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II COPD were included in this study. PFO was identified in 54% of patients (12 out of 22 patients) using TCD. As compared to patients without a PFO, those with PFO did not have reduced exercise capacity or 6-minute walk test duration. The authors concluded that the presence of PFO, although it resulted in right-to-left shunting, had no implications in terms of functional capacity or limitations. However, the results of this study were criticized due to the lack of control subjects, small sample size, and absence of patients with large shunts.

PFO and Pulmonary Hypertension

In the setting of chronic pulmonary disorders, ventilation-perfusion mismatch may lead to hypoxia-induced vasoconstriction and subsequent pulmonary hypertension [32,33]. Roughly 33% of all patients with COPD are noted to have some degree of pulmonary hypertension [34,35]. Pulmonary hypertension has deleterious effects by resulting in an increase in right atrial pressure. This increase in right atrial pressure produces a reversal of the pressure gradient between the left and right atrium, thereby promoting right-to-left shunting and exacerbation of hypoxemia [36–39]. As a result, the presence of a PFO in patients with COPD and associated pulmonary hypertension may aggravate underlying hypoxemia and dyspnea. Several studies have shown that PFO-mediated right-to-left shunting can be decreased by using the same medications that decrease hypoxia-driven pulmonary vasoconstriction and pulmonary hypertension. These medications include inhaled nitric oxide, supplemental oxygen, and phosphodiesterase 5 inhibitors [14,40].

Nootens et al. evaluated the prevalence of PFO and its relation to 5-year survival, and exercise tolerance in patients with pulmonary hypertension; however, no significant differences were found as compared to the general population [3]. It has long been hypothesized that in the setting of pulmonary hypertension, a right-to-left interatrial shunt serves the purpose of a "pop off" valve that allows right atrial and ventricle pressure decompression. Therefore, clinicians have questioned the safety of PFO closure in the setting of significant pulmonary hypertension, with the concern of worsening the clinical condition due to a sudden increase in right-sided pressures following PFO closure. Experimental studies in animal models by Austen et al. showed a benefit of right-to-left shunting via creation of atrial septostomy in dogs with right ventricular hypertension [41]. Some studies have shown clinical improvement in patients with severe pulmonary hypertension after an iatrogenic right-to-left shunt was created

via an atrial septostomy [42–47]. In light of such observations, close hemodynamic monitoring is recommended during and immediately after closure of a PFO in subjects who have severe pulmonary hypertension. During PFO closure, it is recommended to place a sizing balloon or the occluder device without releasing it, so as to monitor intracardiac pressures and hemodynamic stability. If intracardiac parameters and hemodynamics remain stable after 15–20 min, the device can be placed, and closure can be finalized. The creation of atrial septostomy in pulmonary hypertension patients (especially in those with group III pulmonary hypertension) is not recommended as a routine therapeutic measure. This is due to concerns of exacerbating hypoxemia (in addition to baseline hypoxemia from underlying lung disease) via admixture of deoxygenated blood with the systemic circulation. Atrial septostomy is only infrequently used as a palliative measure of decreasing right-sided pressures.

It is well understood that right-to-left shunting via a PFO can worsen hypoxemia in patients with COPD in the presence of group III pulmonary hypertension. Whether percutaneous PFO closure results in a substantial benefit in this population remains controversial. This is primarily because studies investigating this topic have included small sample sizes and produced conflicting conclusions. An observational study consisting of 10 patients with severe pulmonary hypertension, associated with significant hypoxemia due to various etiologies, underwent PFO closure [36]. Etiologies of pulmonary disorders and pulmonary hypertension ranged from sarcoidosis to obesity hypoventilation syndrome and thromboembolic pulmonary disease. The authors observed a marked improvement in hypoxemia in all patients immediately after PFO closure. A significant improvement in mean arterial oxygen saturation was reported after device closure (87% ± 7% prior to closure vs. 96% ± 3% after closure, $P = .002$). These reassuring results were confirmed by a larger retrospective analysis of 97 patients with varying chronic lung diseases including COPD, interstitial lung disease, OSA, sarcoidosis, and reactive airway disease [46]. More than 50% of the individuals experienced ≥1 New York Heart Association (NYHA) functional class improvement ($P < .001$) after PFO closure. Nearly one-third (34%) of the patients who underwent device closure had reduced oxygen requirements, with 4 patients completely weaned off oxygen following PFO closure ($P < .001$).

Percutaneous PFO Closure for Other Chronic Pulmonary Disorders

Berger et al. reported 2 patients with PFO and hypoxemia in the absence of pulmonary arterial hypertension or other predisposing conditions like pneumonectomy or diaphragmatic weakness. In both patients, percutaneous PFO closure with an Amplatzer device (Abbott, St. Paul, Minnesota, USA) resulted in resolution of dyspnea and hypoxia [48]. Kapur et al. also reported successful treatment of refractory hypoxemia in a patient with PFO and left ventricular assist device implantation. The patient experienced significant right-to-left shunting after left ventricular assist device implantation due to a decrease in left ventricular diastolic pressure; PFO closure resulted in improvement of the postoperative hypoxemia [49]. Maraj et al. also reported improvement of oxygenation and cyanosis in a 74-year-old male who was noted to be hypoxic and cyanotic during a gastrointestinal endoscopy. He was found to have PFO-mediated right-to-left shunting without pulmonary hypertension. Due to the presence of severe multivessel coronary artery disease, the patient underwent coronary artery bypass surgery with surgical PFO closure that resulted in improvement of hypoxemia and resolution of cyanosis [50].

The positive data on PFO closure and improvement in hypoxemia have been equally matched with conflicting data that suggest no improvement in objective hypoxemia or subjective dyspnea in some patients. In their observational retrospective analysis of 9 subjects, El Tahlawi et al. found no significant improvement in NYHA functional class after PFO closure in patients with various chronic pulmonary processes such as COPD, pneumoconiosis, chronic thromboembolic pulmonary disease, and interstitial lung disease [51].

PFO and Platypnea-Orthodeoxia Syndrome

Platypnea-orthodeoxia (POD) is a rare entity that is characterized by dyspnea and accompanying hypoxemia in the upright position. Dyspnea and hypoxemia occur when the patient is sitting upright or standing with an improvement in dyspnea and hypoxemia in the recumbent positioning [52]. Initially these constellations of symptoms were thought to be unrelated, but in 1969 the association between POD and right-to-left intracardiac shunting was described [45]. Other scenarios where POD is seen (besides in patients with PFO or ASD) are in individuals with advanced liver disease and various pulmonary disorders leading to a ventilation-perfusion mismatch. With advancing age, anatomical changes take place such as elongation of the aorta, atrial septum stretching, and diaphragmatic paralysis, all of which can yield pronounced right-to-left shunting and arterial desaturation in the upright position through a preexisting PFO [53,54]. Similar anatomical changes have also been described in

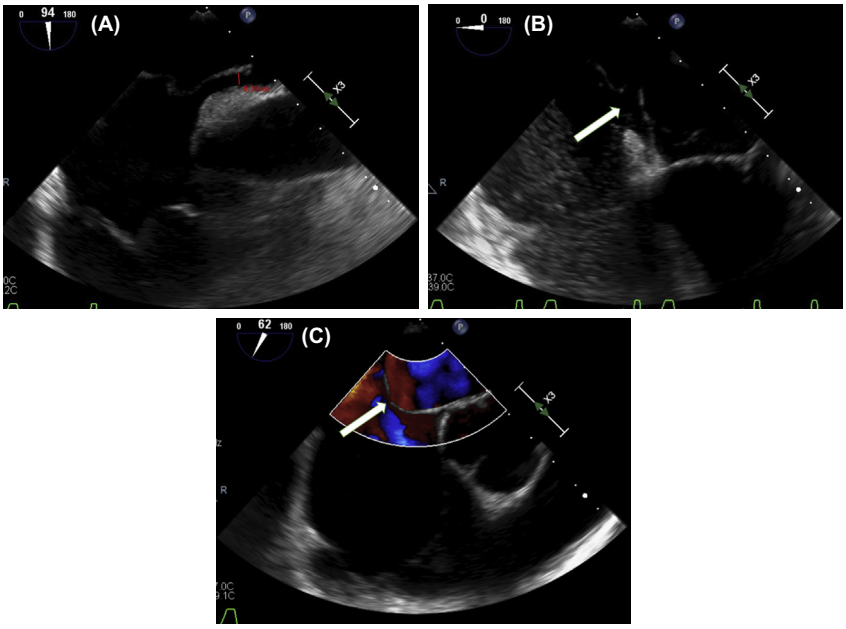

FIGURE 12.3 A 28-year-old female presented with both platypnea-orthodeoxia syndrome and exercise desaturation. Transesophageal echocardiography revealed a PFO, atrial septal aneurysm, and a small atrial septal defect. All 4 heart chamber sizes were normal on cardiac magnetic resonance imaging. (A) Transesophageal echocardiogram demonstrating a PFO with an atrial septal aneurysm. (B) Positive bubble study demonstrating right-to-left shunting via PFO. (C) Color flow Doppler through a small co-existing atrial septal defect.

postoperative patients with pneumonectomy or upper abdominal surgeries such as laparoscopic Nissen fundoplication or cholecystectomy. These anatomical changes may be due to rotation of the heart during diaphragmatic surgical manipulation, or possibly from a new right hemidiaphragmatic paralysis [55–57], resulting in opening of the preexisting PFO and exacerbation of right-to-left shunting. It is important to consider that PFO-mediated right-to-left shunting is 1 of the mechanisms for new-onset postoperative dyspnea and hypoxemia in patients with normal right-sided pressures and radiologic chest imaging.

Given the rarity of this syndrome, clinical data regarding POD and its association with PFO and the benefit of therapeutic PFO closure are only limited to case series and observational studies (Fig. 12.3A–C). For example, Blanche et al. reported a case series of 5 patients who experienced immediate improvement in their symptomology after a successful PFO closure [58]. Another case series of 8 patients with PFO and significant POD also described that PFO closure resulted in significant improvement in dyspnea and hypoxemia [59]. The authors reported that average oxygenation improved from 83% ± 3% prior to closure to 93% ± 2% after PFO closure. A larger observational study consisting of 17 patients with POD and PFO also showed positive results [52]. After percutaneous PFO closure, 11 out of 17 patients were noted to have significant improvement or complete resolution of POD, even when followed 1 year after device closure. In these patients, the upright oxygen saturation improved from 76% ± 5% prior to closure to 92% ± 8% after PFO closure ($P < .0001$). The patients who did not observe improvement in their symptoms were noted to have a preexisting primary lung pathology associated with severe pulmonary hypertension (mean pulmonary pressure >50 mm Hg). The largest observational investigation consisted of 52 patients and demonstrated an average of 14% increase in oxygen saturation over baseline after PFO closure in patients with POD [60].

PFO and Pulmonary Arteriovenous Malformation

Pulmonary arteriovenous malformations (AVMs) are atypical communications between a pulmonary artery and pulmonary vein (Fig. 12.4A and B, Video 12.1). AVMs, including pulmonary AVMs, are associated with hereditary hemorrhagic telangiectasia whereby growth of these vascular malformations is stimulated by the upregulation of vascular endothelial growth factor. Several case reports have illustrated that although pulmonary AVMs are a

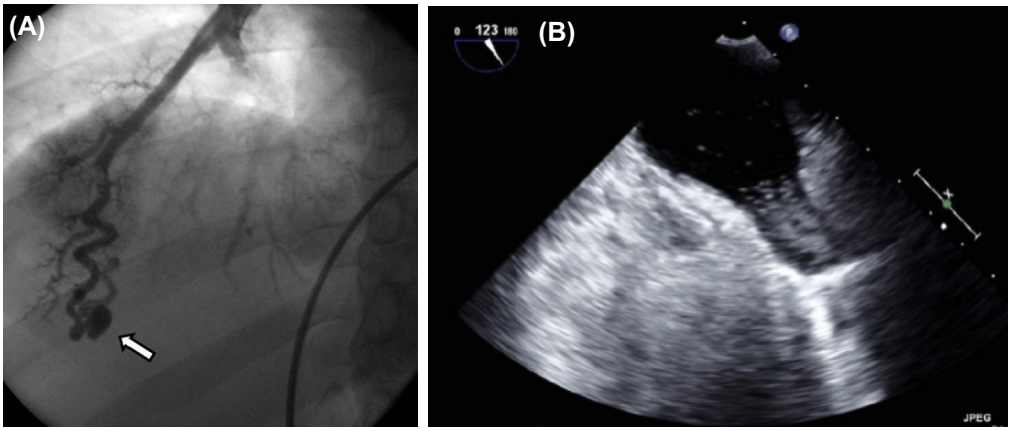

FIGURE 12.4 Pulmonary arteriovenous malformation (AVM) causing right-to-left shunting in the absence of a PFO. (A) Fluoroscopic image showing pulmonary AVM (*arrow*). (B) Transesophageal echocardiogram showing bubbles in a pulmonary vein indicating a pulmonary AVM. There is no PFO.

rare entity, they can coexist with PFO and contribute to hypoxemia secondary to right-to-left shunting [61–63]. Kijima et al. published a case of a 71-year-old woman who underwent PFO closure after experiencing 2 cryptogenic strokes [64]. Even after PFO closure, the patient was noted to have a large residual right-to-left shunt, which on further assessment was found to be secondary to a pulmonary AVM. This was subsequently closed using an Amplatzer Vascular Plug IV (Abbott, St. Paul, Minnesota, USA).

PFO and High-Altitude Pulmonary Edema

Being in a high-altitude environment may result in hypoxemia-driven pulmonary vasoconstriction. At high altitudes, patients with a PFO may experience pulmonary vasoconstriction, which results in increased right-sided pressures and subsequent worsening of right-to-left shunting. The increased right-to-left shunt results in exacerbation of hypoxemia, alteration in alveolar-arterial gradients, and capillary leakage, producing pulmonary edema. A study by Allemann et al. [65] showed that compared to resistant mountain climbers, those who had developed high-altitude pulmonary edema were more likely to have an occult PFO. The authors showed a fourfold increase in incidence of PFO (56% vs. 11% at low altitude of 550 m, $P = .004$ and 69% vs. 16% at high altitude of 4559 m, $P = .001$) as detected by TEE in patients who developed high-altitude pulmonary edema compared to those who did not. Climbers with a large PFO had more severe arterial hypoxemia (mean oxygen saturation 73% vs. 83%, $P = .001$). Additionally, in climbers who were noted to have high-altitude pulmonary edema and PFO, the size of the PFO was directly proportional to the severity of pulmonary edema and hypoxemia. Although the association between high-altitude pulmonary edema, hypoxemia, and presence of PFO is clear, there is a paucity of data regarding the clinical benefit of percutaneous PFO closure for treating high-altitude pulmonary edema. Based on a few studies, it is hypothesized that closure of PFO in patients with high-altitude pulmonary edema may be beneficial in ameliorating underlying hypoxemia by eradicating the offending right-to-left shunt [65,66].

PFO and Exercise Desaturation

Exercise-induced dyspnea and hypoxemia, although an uncommonly recognized phenomenon, has been described in case studies and anecdotal reports (Fig. 12.5A). Exercise-induced hypoxemia is defined as arterial desaturation of at least 8% from baseline or to a level of <90%. In a prospective single-center study of 50 individuals with newly diagnosed PFO, patients were evaluated for arterial oxygen desaturation with postural changes and with exertion by stair climbing [47]. Exercise desaturation was detected using pulse oximetry and compared to patients' baseline. Of 50 patients included, 17 had exercise-induced hypoxemia. After percutaneous PFO closure, these subjects experienced a significant improvement in oxygen saturation (on average by 10.1% ± 4.2%; $P < .001$) as well as NYHA functional class by a median of 1.5 classes (interquartile range: 0.75–2.00; $P < .008$). Given that the prevalence

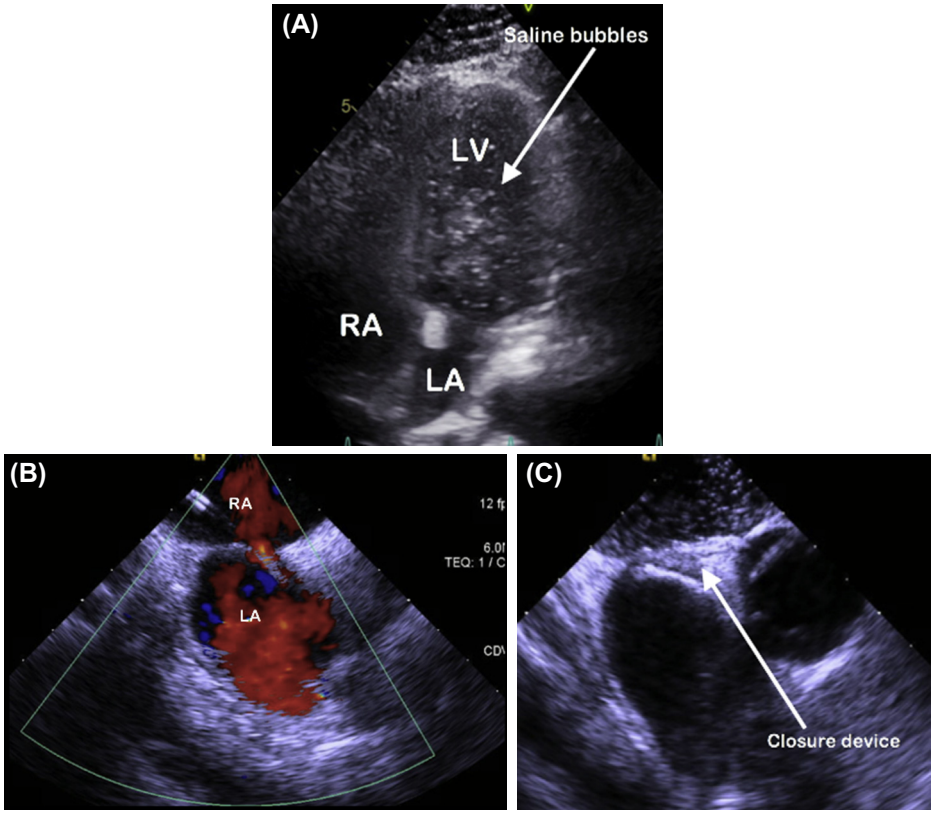

FIGURE 12.5 A 42-year-old female who worked as a health gymnastics teacher presented with gradual onset dyspnea on exertion during routine physical activity. Transthoracic echocardiography with bubble study revealed a large intracardiac right-to-left shunt which was pronounced with Valsalva provocation (A). The patient underwent successful percutaneous PFO closure using a 30 mm Gore Cardioform device (W.L. Gore and Associates; Flagstaff, Arizona) and intracardiac echocardiography (B) with no residual interatrial shunting postclosure (C). The patient experienced resolution of her dyspnea and hypoxemia, with improvement in exercise capacity.

of PFO in patients with exercise desaturation was nearly 30%, this association may not be as rare as initially perceived.

The benefit of PFO closure (Fig. 12.5B and C) in such patients was also demonstrated by a recent case report of a 56-year-old physically active patient who underwent extensive workup for decompression illness and was found to have a PFO. This patient had also reported significant dyspnea during exercise. After successful percutaneous PFO closure with a 25-mm Amplatzer PFO Occluder, the patient experienced an abrupt improvement in his exercise capacity with jogging, along with no recurrent episodes of decompression illness with diving [67].

PFO and Left Ventricular Assist Device Implant

Among patients with congestive heart failure, chronically elevated left atrial filling pressures may falsely mask the presence of PFO by closing the foramen ovale (pressing the septum primum against the septum secundum). Thus, contrast echocardiography may be falsely negative in these patients, even with a Valsalva maneuver.

Implantation of a left ventricular assist device (LVAD) can provide hemodynamic mechanical support for individuals with end-stage heart failure [68]. Cannulation of the left ventricle results in an abrupt and marked decrease in left-sided diastolic filling pressures; this can potentially induce right-to-left shunting and hypoxemia across a preexisting interatrial septal defect. There have been at least 3 reported cases of successful percutaneous PFO device closure for treatment of significant postoperative hypoxemia following LVAD implantation surgery. In all cases, PFO closure resulted in profound improvement in underlying postoperative hypoxemia [49,69,70]. Such reports indicate that device closure should be considered for PFO-mediated hypoxemia after LVAD implantation; patients with a known PFO may also get their septal defect closed surgically at the time of LVAD implant. Considering that many end-stage heart failure patients have pacemakers or defibrillators with an atrial lead (a potential site of thrombus formation), percutaneous PFO closure can also be used to prevent paradoxical

embolism in LVAD patients at high risk of paradoxical embolism (e.g., an atrial lead with visible thrombus attached on echocardiography) [71].

SOCIETY GUIDELINES ON PFO CLOSURE

Given the conflicting data from some of the observational studies and the lack of randomized controlled trials of PFO closure for hypoxemia, it is not surprising that the current society guidelines shy away from recommending percutaneous PFO closure for hypoxemia. In the realm of PFO-associated stroke, although the society guidelines have made recommendations, these have now become outdated in light of recent data from randomized clinical trials and their meta-analyses, showing benefit of PFO closure for stroke of no other identifiable cause when compared to standard of care medical therapy [5,6,72–76]. In line with the outdated 2014 American Heart Association/American Stroke Association (AHA/ASA) Stroke guidelines, closure of PFO carries a Class IIb, Level of Evidence C recommendation in the setting of an ischemic stroke associated with a deep venous thrombosis [77]. Updated recommendations have already been approved by the German, European, and Canadian stroke guidelines [78–80].

In the absence of severe pulmonary hypertension, percutaneous PFO closure in patients with right-to-left shunting may result in significant improvement in dyspnea, hypoxemia, and overall quality of life. Currently, there exist no randomized clinical trials evaluating the effect of PFO closure in hypoxemic conditions. However, the PFO Closure for Obstructive Sleep Apnea (PCOSA-1; NCT 02771561) trial is an ongoing study in the United Kingdom that aims to evaluate PFO closure and its effects on hypoxemia in patients with OSA. Similarly, the Decompression Sickness in Divers With or Without PFO (DIVER-PFO) study (NCT 02432131) is an ongoing trial that is evaluating the incidence of decompression sickness in divers with or without PFO (Chapter 13). The 2008 American College of Cardiology/American Heart Association guidelines for management of adults with congenital heart disease give percutaneous atrial septal defect closure a Class IIa, Level of Evidence B recommendation for patients with documented POD [81]. Given the rarity of POD, it is unlikely that a randomized controlled trial will be conducted evaluating the effects of PFO closure in patients with POD. The relationship between PFO and the aforementioned clinical conditions have reinvigorated the topic of device closure for PFO-associated stroke. This has in turn resulted in multiple randomized clinical trials, observational studies, and meta-analyses, which demonstrate not only reduced risk of future cerebral events, but also improvement in other symptoms and hemodynamics after PFO closure. This reminds us that closure of PFO for hypoxemia entails complementary benefits in terms of reduced risk of paradoxical cerebral events.

SUPPLEMENTARY MATERIALS

Supplementary data related to this article can be found online at https://doi.org/10.1016/B978-0-12-816966-7.00012-9.

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