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### Permalink

<https://escholarship.org/uc/item/4ww845gm>

### Journal

Texas Heart Institute Journal, 44(3)

### ISSN

0730-2347

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### Publication Date

2017-06-01

### DOI

10.14503/thij-16-6027

Peer reviewed

# Review

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**Key**

**words:**Diagnostic imaging; exercise tolerance; foramen ovale, patent/ complications/diagnoses/ diagnostic imaging/physiopathology/surgery/therapy; heart septal defects, atrial/ prevention & control; hemodynamics; hypertension, pulmonary/complications/ etiology/physiopathology; hypoxia/complications/ diagnosis/etiology; pulmonary disease, chronic obstructive/ complications/physiopathology/therapy; recovery of function; risk factors

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# Potential Role of Patent Foramen Ovale in Exacerbating Hypoxemia

## in Chronic Pulmonary Disease

*Patent foramen ovale has been associated with multiple pulmonary diseases, such as pulmonary hypertension, platypnea-orthodeoxia syndrome, and chronic obstructive pulmonary disease. A connection*

*between patent foramen ovale and chronic pulmonary disease was first described more than 2 decades ago in case reports associating patent foramen ovale with severe hypoxemia that is expected based on the severity of the primary pulmonary disease. It has been suggested that patients with both chronic pulmonary disease and patent foramen ovale are subject to severe hypoxemia because of the right-to-left shunt. Furthermore, investigators have reported improved systemic oxygenation after patent foramen ovale closure in some patients with chronic pulmonary disease. This review focuses on the association between chronic pulmonary disease and patent foramen ovale and on the dynamic of a right-to-left shunt, and it considers the potential benefit of patent foramen ovale closure in patients who have hypoxemia that is excessive in relation to the degree of their pulmonary disease. (Tex Heart Inst J 2017;44(3):189-97)*

In fetal circulation, the foramen ovale functions as a one-way valve that enables blood to flow from the right atrium (RA) to the left atrium (LA) so that oxygenated blood from the placenta can bypass the un-aerated lungs and directly enter the fetus systemic circulation. This mechanism is maintained throughout evolution; all placental mammals have a foramen ovale.<sup>1,2</sup> After birth, an infant's pulmonary vascular resistance decreases, and there is a concomitant increase in LA pressure and decrease in RA pressure. The

septum primum is forced against the LA side of the septum secundum, and the 2 septa eventually fuse, leaving behind the fossa ovalis, a depression that marks the site of the foramen ovale. Functional closure of the foramen ovale is incomplete in about 20% of the population.<sup>3-8</sup> Most people with a patent foramen ovale (PFO) remain asymptomatic. Nevertheless, interatrial shunting through a PFO can occur with strenuous effort that simulates a Valsalva maneuver, such as yelling, straining during bowel evacuation, coughing, and exercise.

Anatomic variants associated with PFOs also promote shunting. A residual eustachian valve can direct flow preferentially from the inferior vena cava toward the interatrial septum. Even with minimal interatrial communication, the size of a remnant eustachian valve appears to be an independent risk factor for a right-to-left (RL) shunt.<sup>9</sup>

<sup>11</sup>Significant tricuspid valve regurgitation in the presence of a PFO can project blood to the superior aspect of the RA and then through the interatrial communication, causing RL shunting.<sup>12</sup> An atrial septal aneurysm— a bulge in the fossa ovalis— can occur with an interatrial communication and appear to be an additional risk factor for cryptogenic stroke and hypoxemia.<sup>13</sup>

<sup>15</sup>On occasion, excessive hypoxemia is due to the opening of a PFO associated with unwinding of the aorta or with hemidiaphragmatic paralysis, the latter of which is exacerbated when a patient moves from a lying to a standing position (orthodeoxia).<sup>16,17</sup>

Patent foramen ovale has been linked with paradoxical embolic stroke, platypnea-orthodeoxia syndrome, decompression illness, exacerbation of obstructive sleep apnea,

Dr. Tob is on the steering committee of the Premium Trial of PFO closure for migraines, which is sponsored by St. Jude Medical, Inc. Dr. Aboulhosn is a proctor for St. Jude Medical for PFO closure. These authors stake responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. No funding sources were involved in the preparation, writing, or editing of this manuscript.

obesity hypoventilation syndrome, chronic pulmonary disease, and migraine headache with aura. The proposed mechanisms and clinical characteristics of PFOs associated with these conditions have been described in detail.<sup>18-</sup>

<sup>29</sup>In patients with PFO who have one of these conditions, the LA pressure is typically 5 to 8 mmHg higher than the RA pressure; however, in patients with chronic pulmonary disease, such as chronic obstructive pulmonary disease (COPD), elevated intrathoracic pressure and pulmonary artery pressure (PAP) can cause the RA pressure to surpass the LA pressure, resulting in RL shunting.<sup>30-</sup>

<sup>34</sup>Hypoxemia occurs if a large amount of deoxygenated venous blood shunts to the left side of the heart; this could explain why a patient with PFO might experience decreased arterial oxygenation to a degree greater than that expected based on the patient's underlying pulmonary disease.<sup>35-</sup>

<sup>37</sup>However, based on our own clinical observation of such patients, it is difficult to distinguish the relative contribution of the RL shunt versus the underlying pulmonary disease to the patient's hypoxemia.

In the United States, COPD affects as many as 32 million people, or 10% of the population. Moreover, at least 20% of COPD patients also have PFOs, which means that more than 6 million patients are affected by both COPD and PFO.<sup>38</sup> More than one million Medicare patients use supplemental oxygen because of COPD, and the annual cost is over \$2 billion.<sup>39,40</sup> This review takes into account the potential public health impact of eliminating RL shunts and explores the current understanding of how PFO can progress from an incidental finding to an active contributor to hypoxemia in patients with chronic pulmonary disease.

## Diagnostic Imaging Methods for Patent Foramen Ovale

Patent foramen ovale can be identified during autopsy or cardiac catheterization. However, it is most often diagnosed during contrast echocardiography. Use of agitated-saline contrast during transesophageal echocardiography (TEE), with and without the use of training, is the minimally invasive standard for PFO diagnosis.<sup>41,42</sup> The more frequently used screening method, transthoracic echocardiography (TTE) with agitated-saline contrast, is limited because it does not enable direct visualization of a PFO; instead, the images capture agitated-saline bubbles

in the LA. More recent data have suggested a role for transcranial Doppler (TCD) in PFO identification, given TCD's greater sensitivity in comparison with echocardiography and its ability to quantify the degree of RL shunting.<sup>43-45</sup>

Standardizing PFO sizing is challenging because the degree of shunting differs, depending upon whether the patient is at rest or performing a maneuver that increases intrathoracic pressure. Currently, there is no accepted grading criterion. Some investigators focus on

the anatomic size of the defect, whereas the measurement of the degree of the shunt based on the number of agitated-saline microbubbles detected in the LA or middle cerebral artery at a specific moment within a designated timeframe. The most accurate technique for measuring PFO size is to position a sizing balloon within the PFO and gently inflate it with diluted contrast medium; however, this method necessitates invasive right-sided heart catheterization.<sup>46</sup> Anatomic grading on echocardiography is determined by measuring the separation of the septum primum from the septum secundum; however, this does not always correlate with the degree of shunting. A functional method of shunt-grading involves agitated-saline contrast injections and echocardiography. The degree of shunting depends on the number of microbubbles observed in the LA over 3 s.<sup>47</sup> Agitated-saline solution is also used as a contrast agent with TCD, in which the number of saline microbubbles—or high-intensity transient signals (HITS)—reaching the middle cerebral artery are measured during an interval of 25 to 1 min. The degree of shunting is based on a logarithmic scale of 0 to 5+; in grade 5+, the bubbles form a "curtain" because they are indistinguishable and too numerous to count (Table I).<sup>48</sup> Patent foramen ovale correspond to a TCD shunt of grade 3 or higher and is confirmed by right-sided heart catheterization. Grade 1 and 2 shunts are usually caused by either the transmission of a few bubbles through the pulmonary circulation or by a very small PFO (less than 2 mm, as determined by balloon sizing).<sup>49</sup> The sensitivity of power M-mode TCD (98%) has been found to be greater than that of TEE (91%) for PFO detection.<sup>48,49</sup> However, although TCD sensitivity surpasses that of echocardiography and intracardiac echocardiography, it is also more likely to produce false-positive results.<sup>45</sup> Thus, TCD is not specific. The operator is unable to view the PFO anatomy and cannot distinguish between a PFO, a fenestrated atrial septal aneurysm, a systemic venous-to-pulmonary venous collateral fistula, or a pulmonary arteriovenous fistula. Nevertheless, because it

**TABLE I.** Methods for Grading Shunts

Shunt Grade	Microbubbles/HITS Observed	
	Transcranial Doppler (n)*	Echocardiography (n)**
1	1-10	<5
2	11-30	5-25
3	31-100	>25
4	101-300	Complete opacification of left atrium
5	>300	—
5+	"Curtain" of microbubbles	—

1	1-10	<5
2	11-30	5-25
3	31-100	>25
4	101-300	Complete opacification of left atrium
5	>300	—
5+	"Curtain" of microbubbles	—

HITS = high-intensity transient signals

\* Observed over 25–60 s

\*\* Observed over 5 s

is more comfortable for the patient than is TEE, TCD is useful as the initial screening tool for identifying an RL shunt.<sup>43,49,50</sup>

### Patent Foramen Ovale Prevalence in Hypoxemic COPD Patients

Soliman and colleagues<sup>35</sup> were the first to describe a relationship between PFO and COPD in 20 patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease stages III–IV) (Table II). With the use of contrast TEE and pressure-generating maneuvers (coughs and Valsalva maneuvers), the investigators found that the prevalence of PFO in the COPD group was twice that in control subjects (70% vs 35%;  $P < 0.05$ ). More PFOs were detected in their control group than in the control groups of most other population studies, perhaps because they defined a positive shunt as having a minimum of 5 microbubbles in the LA within 3 cardiac cycles;

this was a low cutoff compared to those used in other studies.<sup>3-8</sup> In a Turkish study similar to that of Soliman and colleagues, Haćievliyağil and associates<sup>36</sup> detected a 2-fold increase in PFO prevalence in COPD patients with hypoxemia in comparison with healthy controls. Although Kilic and colleagues<sup>51</sup> found no association between PFO and hypoxemia in COPD patients, they did detect higher PA levels in patients with a PFO. Martolini and colleagues<sup>52</sup> found a PFO in 12 of 22 patients with COPD, and more of these patients had hypoxemia in comparison with their non-PFO counterparts. Shaikh and co-authors<sup>53</sup> were unable to corroborate these findings in their study of 50 patients with COPD and 50 healthy controls; the 2 groups had a PFO prevalence of

46% and 30%, respectively ( $P=0.15$ ). They

The following 2 cases, which involve patients treated at our

etal.<sup>35</sup> (1999)

used both contrast TTE and TCD to identify PFO, and, like Soliman and colleagues, they used a relatively low cutoff for a positive RL shunt (scattered individual bubbles seen on TTE or  $\geq 3$  bubbles seen on TCD), which might account for the authors' observation that there was a higher prevalence of RL shunting in their study. Most shunts were classified as grade 1 or 2. Notably, Shaikh and co-authors did not detect a statistically significant difference in the prevalence of large PFOs (defined as

clinic, illustrate hypoxemia in the presence of PFO and the impact of PFO closure. **Patient 1.** A 61-year-old man with a history of COPD (forced expiratory volume 1 [FEV1], 56%) and tobacco dependence was referred by his pulmonologist for worsening hypoxemia thought to be disproportionate to his pulmonary disease. Resting oxygen saturation was 84% without supplemental oxygen; it improved to 97% on 6 L of supplemental oxygen and fell to as low as 70% during exercise. During a 6-minute walk

Reference	No. Pts.	Variable	Sa <sub>o</sub> <sub>2</sub> change with Valsalva maneuver
			1.5 ± 0.5 severe-COPD group (%)
			PAP (mmHg) 21 ± 2.4
Hacievliyagil SS, et al. <sup>36</sup> (2006)	102	0.002	Sa <sub>o</sub> <sub>2</sub> at rest (%) 84 ± 6
			Pa <sub>o</sub> <sub>2</sub> at rest (mmHg) 51 ± 8
			PAP at rest (mmHg) 64 ± 2
			0.006
			47 ± 14
Kilic H, et al. <sup>51</sup> (2010)	21	NS	Sa <sub>o</sub> <sub>2</sub> (%) 79 ± 3
			Pa <sub>o</sub> <sub>2</sub> (mmHg) NS 46 ± 1
			PAP (mmHg) 34 ± 5.4 42 ± 6
			0.033
Martolini D, et al. <sup>52</sup> (2014)	22	<0.01	Pa <sub>o</sub> <sub>2</sub> at rest (kPa) 10.2 ± 0.2
			Sa <sub>o</sub> <sub>2</sub> at rest (%) 96 ± 2
			0.049
Shaikh ZF, et al. <sup>53</sup> (2014)	100	NS	Pa <sub>o</sub> <sub>2</sub> (kPa) 8.6
			8.5
			57 ± 6.8
			Submaximal exercise endurance time (s) NS 570 ± 30
			534 ± 279
			NS
			Ventilation at peak exercise (L/min) 31 ± 3
			34 ± 8.8

NS = not significant; PAP = pulmonary artery pressure; PFO = patent foramen ovale; Pts = patients; Sa<sub>o</sub><sub>2</sub> = arterial oxygen saturation; VM = Valsalva maneuver. Data are presented as mean ± SD or as a number.

grade >3 with use of TCD or TTE) in 13 of 50 COPD patients compared with 3 of

test (6 MWT) without supplemental oxygen, the patient's oxygen saturation decreased from 88% to 77%, a

50 control subjects ( $P=0.01$ ).

### Two Cases of Hypoxemia in the Presence of Patent Foramen Ovale

and his pulse rate increased from 84 to 92 beats/min (total distance, 363 m). The patient underwent TEE with agitated saline contrast, which showed a moderate-sized, interatrial RL shunt generated during the Valsalva maneuver (Figs. 1A, 1B, and 2A). Left- and

right-sided cardiac catheterization results included an RA pressure of 12 mmHg, a systolic PAP of 35 mmHg, a pulmonary vein saturation of 98%, and a pulmonary capillary wedge pressure (PCWP) of 9 mmHg. Coronary angiograms revealed only mild, nonobstructive coronary artery disease. On intracardiac echocardiography, a moderate-sized PFO (tunnel length, 6 mm) was confirmed; there was no septal aneurysm, significant tricuspid regurgitation, or prominent Eustachian valve. The RL shunt was determined to

be caused by the PFO, with shunting exacerbated by the patient's elevated RA pressure caused by COPD. The PFO was closed with a 25-mm Gore Helex® septal occluder (W.L. Gore & Associates, Inc.; Flagstaff, Ariz) and confirmed by postprocedural color-Doppler TEE (Fig. 1C) and 3-dimensional TEE with agitated saline contrast medium (Fig. 2B). After closure, oxygen saturation rose to 91% at rest without supplemental oxygen. One month after closure, TTE revealed unchanged

**TABLE II.** Comparison of Hypoxemia Markers in Studies of Patients with Chronic Obstructive Pulmonary Disease with and without PFO

Reference	No. Pts.	Variable	PFO Detected	No PFO Detected	P Value
Soliman A,	40	Sa <sub>o</sub> <sub>2</sub> at rest (%)	94 ± 2.3	NS	

pulmonary artery and RA pressures, and there were no obvious leaks around the occlusion device. In a post-procedural 6MWT without supplemental oxygen, the patient's total walking distance increased to 422 m; his oxygen saturation decreased from 92% to 84%; and his pulse rate increased from 78 beats/min to 91 beats/min. He reported symptomatic improvement of his dyspnea during exertion.

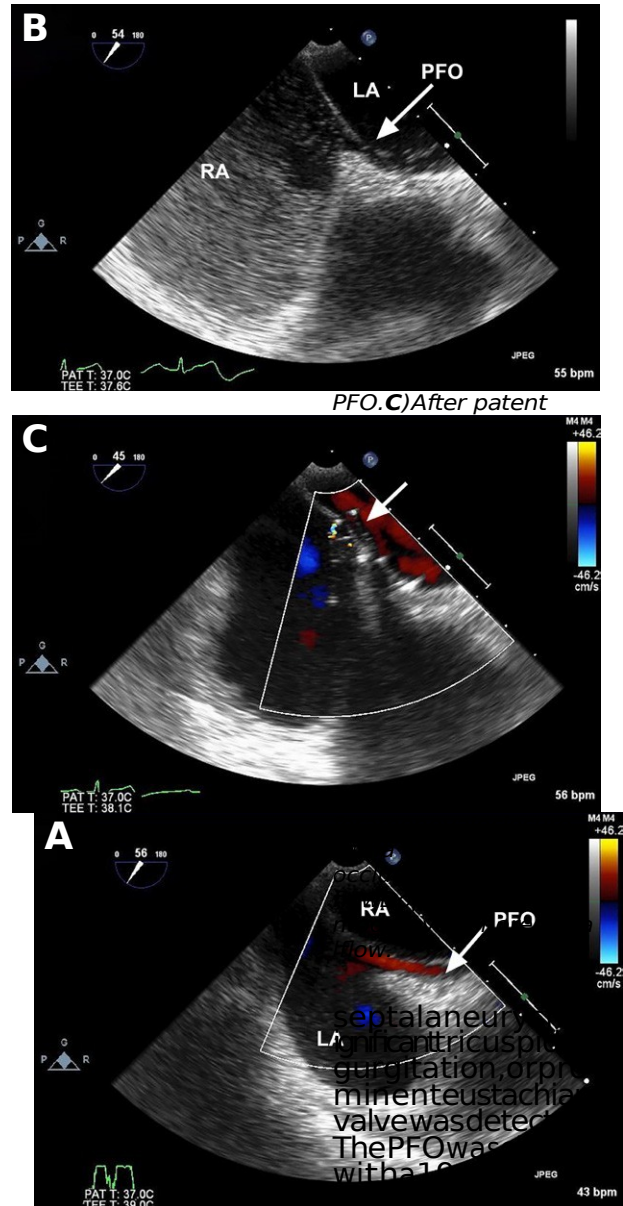
**Patient 2.** A 59-year-old man was referred to our clinic by his pulmonologist to be considered for percutaneous PFO closure in the presence of progressive, exercise-induced hypoxemia. The patient's medical history was significant for diabetes mellitus, obstructive sleep apnea (treated with noninvasive positive-pressure ventilation at night), asthma with COPD (FEV1, 55%) and morbid obesity (body mass index, 44 kg/m<sup>2</sup>).

The patient reported no history of tobacco use and had no known coronary artery disease. He had experienced gradually worsening hypoxemia; his resting oxygen saturation was 94%, and it fell to 87% with only mild exertion. In the presence of an unchanged pulmonary function test, the pulmonologist was concerned that the patient's hypoxemia seemed excessive for the extent of

his chronic pulmonary dysfunction. A TEE from the referring center, which had been performed with agitated-saline contrast medium, showed an interatrial RLS shunt; normal atrial pressures and normal PAP were noted. Results of left- and right-sided cardiac catheterization included a systolic PAP of 40 mmHg, normal PCWP, and no coronary artery disease. The patient's worsening hypoxemia was attributed to the increased RLS shunt through the PFO in the presence of obstructive sleep apnea, COPD, and morbid obesity. His pulmonologist and cardiologist decided that PFO closure might improve his oxygenation. During right-sided heart catheterization with intracardiac echocardiographic imaging, an 18-mm PFO (measured through balloonsizing) was revealed (Fig. 3); no

whose hypoxemia was out of proportion to his chronic obstructive pulmonary disease. **A)** Color-flow Doppler modes show flow

across the patent foramen ovale (PFO) from the right atrium (RA) to the left atrium (LA). **B)** Agitated-saline contrast injection reveals shunting of bubbles from the RA to the LA through the

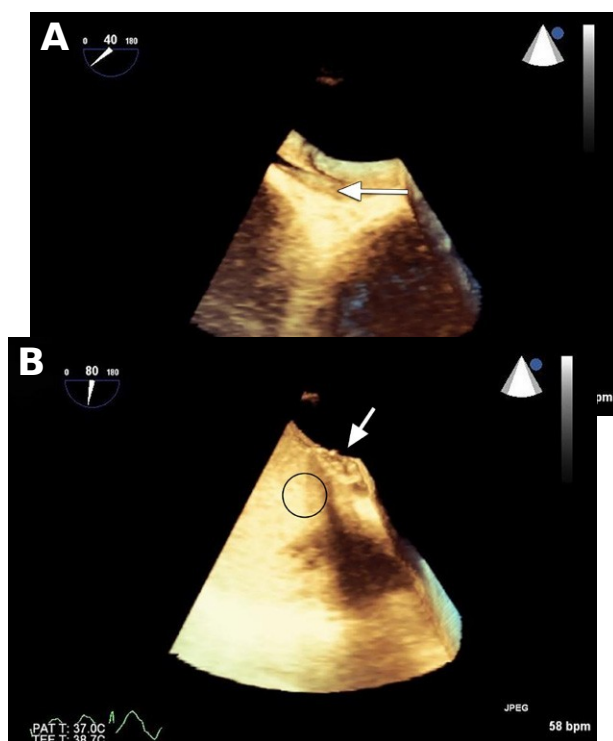


**Fig. 1.** Patient 1. Transesophageal echocardiogram (mid-esophageal, bicaval view) shows an interatrial right-to-left shunt in a patient

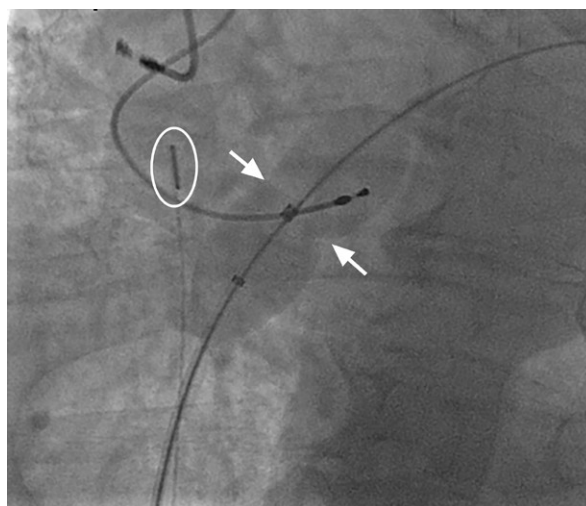
with a patent foramen ovale (PFO). The PFO was closed with a transcatheter septal defect occluder (St. Jude Medical, part of Abbott Laboratories; St. Paul, Minn) (Fig. 4). A postdeployment color-

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**Fig. 2** Patient 1. Three-dimensional, volume-rendered, trans-esophageal echocardiograms show **A**) the interatrial shunt before closure of the patent foramen ovale (arrow), and **B**) no residual shunting after closure with a GoreHalex septal occluder (arrow), upon agitated-saline contrast injection (oval).



**Fig. 3** Patient 2. Fluoroscopic images show balloonsizing for patent foramen ovale (PFO) closure. The balloon catheter was placed over a guidewire and passed across the PFO and into the left atrium. The balloon was inflated gently until an indentation was seen at the level of the PFO (arrows) and there was no flow around the balloon, as determined by Doppler-flow imaging through an intracardiac echocardiographic catheter (oval). As COPD progresses, PAP rises because of hypoxia-induced pulmonary vasoconstriction, and RA pressure subsequently increases.<sup>58,59</sup> If PFO is present, elevated RA pressure can increase the degree of RL shunting, worsening hypoxemia beyond the level expected based on the patient's degree of pulmonary disease.<sup>11,60-62</sup> Conversely,

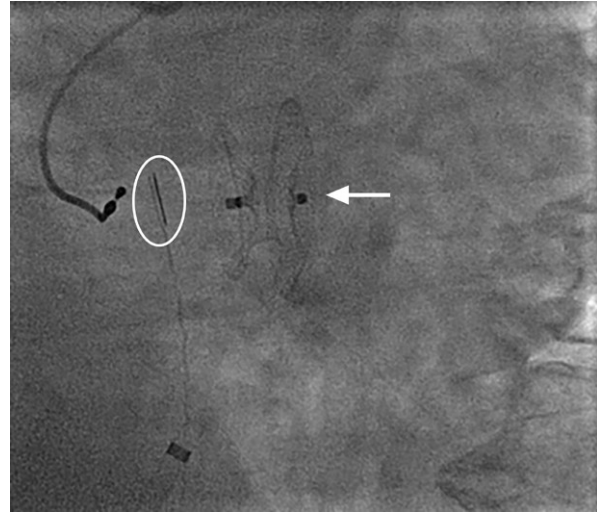
of closure, the patient reported subjective improvement in dyspnea and exercise capacity. His oxygen saturation remained at 94% at rest and during exertion.

### Pulmonary Hypertension and COPD with Patent Foramen Ovale

Patients classified by the World Health Organization as having group 3 pulmonary hypertension (PH), which includes PH associated with lung disease and sleep-related breathing disorders, are more likely to have severe COPD, and up to 30% of patients with moderate-to-severe COPD have elevated pulmonary pressures that correlate with lower 5-year survival rates when the mean PAP exceeds 25 mmHg.<sup>54-57</sup> Hypoxemia in COPD is thought to be caused by a ventilation-perfusion mismatch, in which unoxygenated blood is directed through capillaries that feed nonfunctional

**Fig. 4** Patient 2. Fluoroscopic images shows a 19-mm *AmpAzer* Atrial Septal Defect Occluder (arrow) in place across the interatrial septum, after release from the delivery cable. An intracardiac echocardiographic catheter (oval) is also seen.

y. In the first patient, the PFO was initially undetected on echocardiography,



RL shunting in a patient with PFO can be minimized with the use of supplemental oxygen, inhaled nitrous oxide, or phosphodiesterase (PDE)-5 inhibitor, which reduces the hypoxia-driven rise in PAP. Boerrigter and colleagues<sup>62</sup> reported this phenomenon in 2 hypoxemic patients with PFO and PH secondary to COPD. When these patients were given supplemental oxygen, their PAP and arterial oxygenation improved substantially

when the patient was not receiving supplemental oxygen. After percutaneous PFO closure, oxygen saturation improved from 71% with exertion to above 90%. This second patient did not undergo PFO closure.

Boerrigter and colleagues report is consistent with those of earlier investigators who have identified an association between elevated PAP in COPD and RL shunting through a PFO.<sup>35,36,51,53,62</sup> These findings indicate the need for further investigation of PFO closure in the presence of PH. In patients who are unsuitable for PFO closure, PDE-5 inhibitor therapy and inhaled nitrous oxide are promising; several cases report have described improved arterial oxygenation after initiation of these therapies.<sup>62</sup> Larger studies are warranted to elucidate their potential benefit.

### Hypoxemia with Patent Foramen Ovale

There appears to be an association between PFO and hypoxemia in certain chronic pulmonary diseases; however, the challenge is separating the degree of hypoxemia caused by an intracardiac shunt from that caused by a pulmonary shunt. Theoretically, these 2 causes can be distinguished from one another by calculating the shunt fraction while a patient is on 100% supplemental oxygen. In reality, though, the dynamic nature of an RL shunt—which might be present only during the Valsalva maneuver or throughout the respiratory cycle—makes it challenging to quantify what degree of shunting causes clinically noticeable hypoxemia.

With the increased use of cardiac magnetic resonance imaging, the shunt fraction can be estimated by measuring the ratio of pulmonary blood flow to sys-

temic blood flow (often measured in the pulmonary artery and aorta, respectively).<sup>66</sup> Hypoxemia produced by an intracardiac RL shunt can be confirmed using right-sided heart catheterization. The oxygen saturation in the pulmonary veins, measured by crossing the PFO, can be compared to the systemic arterial oxygen saturation. In the presence of systemic hypoxemia, low pulmonary venous oxygen saturation levels would indicate pulmonary disease as the main culprit, whereas normal pulmonary venous oxygen saturation would indicate that the intracardiac RL shunt is the cause of hypoxemia.<sup>51</sup> Alternatively, the partial pressure of oxygen in arterial blood can be compared at rest and after balloon occlusion of the PFO. If the cardiac RL shunt is the main contributor to hypoxemia, balloon occlusion of the PFO should raise systemic oxygen levels.

Although an RL shunt through a PFO can alter systemic oxygen levels, its effect on exercise tolerance is unclear. Hacievliyagil and colleagues<sup>36</sup> reported lower systemic and pulmonary oxygen saturation levels, higher dyspnea scores, shorter distances walked during a 6MWT, and higher desaturation rates in COPD patients with a PFO compared to those without a PFO. Martolini and colleagues<sup>52</sup> also found an association

between a PFO and hypoxemia during exercise. Although an RL shunt through a PFO can alter systemic oxygen levels, its effect on exercise tolerance is unclear. Hacievliyagil and colleagues<sup>36</sup> reported lower systemic and pulmonary oxygen saturation levels, higher dyspnea scores, shorter distances walked during a 6MWT, and higher desaturation rates in COPD patients with a PFO compared to those without a PFO. Martolini and colleagues<sup>52</sup> also found an association

between PFO and reduced systemic and pulmonary oxygen levels, although they observed preserved exercise tolerance in patients with PFO, noting that RL shunting, recorded as the number of HITS observed, was greater in PFO patients during a 6MWT. Similarly, Shaikhand colleagues<sup>53</sup> reported increased shunting in PFO patients during exercise, but the patients' functional capacities were preserved. Future studies should not only measure shunting and oxygen saturations in PFO patients, but also evaluate functional testing as a primary metric, because the severity of RL shunting might not necessarily correlate with clinical symptoms. There remains a paucity of prospective data for oxygen saturation status before and after PFO closure in patients with chronic pulmonary disease. Ilkhanoff and colleagues<sup>67</sup> found that, in the first study of patients with interatrial septal defects (including PFO), mean arterial oxygen saturation improved from 86.7% to 95.9% ( $P=0.002$ ) after closure. Although the immediate post-procedural improvement of hypoxemia in these patients is encouraging, the short follow-up period and lack of pre- versus postprocedural clinical metrics makes extrapolating the outcome to other patients challenging. In their retrospective study of 9 patients with chronic pulmonary disease, EITahlawi and co-authors<sup>68</sup> found no significant improvement in New York Heart Association (NYHA) functional class after PFO closure and concluded that

chronic pulmonary disease and PFO. A study of this magnitude would need to take several key factors into consideration: for example, determining whether PFO closure is suitable only in patients with larger grades of RL shunting ( $\geq$  grade 4 as established by TCD).<sup>53,61</sup> Restricting PFO closure to this group would prevent unnecessary procedures in patients whose PFOs are unlikely to produce hypoxemia. Patients with anatomic variants—including shunts of various sizes, atrial septal aneurysms, tricuspid regurgitation, and residual eustachian valves—might also benefit from screening and RL shunt correction. In future clinical trials, the preferred imaging method for initial PFO screening should also be established. Because the quality of TTE images is often poor in COPD patients who have hyperinflated lu-

hypoxemia in this patient group was more likely related to pulmonary shunting than to intracardiac shunting. Conversely, Deven-dra and associates<sup>37</sup> reported improved oxygen saturation (10.1% average improvement;  $P<0.001$ ) and NYHA functional class (1.5 median improvement in class;  $P=0.008$ ) in 10 patients with PFO and exercise-induced hypoxemia after PFO closure. More recently, a larger study of 97 patients with underlying chronic pulmonary disease showed that patients had an improvement  $\geq$  1 in NYHA functional class (51% of patients;  $P<0.001$ ) and reduced supplemental oxygen requirements (34% of patients;  $P<0.001$ ) after PFO closure. Using contrast TTE, the authors of the study determined that having a larger RL shunt was associated with a greater likelihood of clinical improvement after closure ( $P<0.0087$ ).<sup>61</sup> Although limitation exists in this single-arm study, its finding that there is the potential for improved functional status after PFO closure suggests that a prospective, randomized study using similar metrics would be instructive.

### Evaluating the Role of Patent Foramen Ovale Closure

Which chronic pulmonary disease patients would benefit from PFO closure remains unclear. Fenster and Carroll<sup>60</sup> outlined the discrepancies of hypoxemia in RL shunting and called for a multidisciplinary study to adequately address the management of patients with

for intervention, we hypothesize that, in certain chronic pulmonary disease patients with hypoxemia, PFO closure might result in substantial improvements in quality of life.

### References

ngs, TCD, which is more sensitive, might prove more useful for initial screening.<sup>48</sup> Patients suspected of having a large RL shunt could then undergo TEE to confirm the presence of a PFO, which could finally be verified by right-sided heart catheterization. Care must be taken to differentiate between patients with hypoxemia due to intracardiac shunting as opposed to other pulmonary diseases. Echocardiography in

tandem with cardiac magnetic resonance could be another option to screen for PFO, enabling shunt fraction to be calculated and a diagnosis of PFO to be ruled out in patients with intrapulmonary shunts. Cardiac magnetic resonance would also be helpful in conducting further research to quantify the relationship between the degree of shunting and onset of clinically significant hypoxemia.

Closure of PFO in patients with PH is controversial. Although elevated PAP in the presence of PFO can exacerbate hypoxemia, closing a PFO in patients with PH might be detrimental, because the RL shunt might act as a "pop-off" valve, diminishing the effect of high PAP on the right side of the heart. Prior reports of PFO closure in PH have not described any incidents of right ventricular failure.<sup>27,62</sup> In general, however, PFO closure in a patient with PH is considered unsafe and is not advised until more outcome data are available. In the meantime, pharmacologic intervention with inhaled PDE-5 inhibitors or nitrous oxide has shown promising results in these patients.

Clinical metrics to analyze, before and after PFO closure, include submaximal exercise capacity (6 MWT) and maximal exercise capacity with use of cardiopulmonary exercise variables (oxygen consumption and anaerobic thresholds). The long-term consequences of PFO closure on patient functional capacity, quality of life, supplemental oxygen use, likelihood of hospitalization, and need for lung transplantation should also be considered. Given the potential impact of interventional PFO closure on public health, the cost-to-benefit ratio of this treatment deserves focused attention. Although it is still challenging to identify the appropriate cohort

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