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The Effect of Patent Foramen Ovale Closure in Patients With Platypnea-Orthodeoxia Syndrome

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Background: Platypnea-orthodeoxia syndrome is a rare condition characterized by hypoxemia in the upright position that is improved in the supine position. Although several etiologies of platypnea-orthodeoxia exist, it is frequently associated with right- to-left shunting of blood at the cardiac or pulmonary level, usually via a patent foramen ovale (PFO). The aim of this study was to evaluate the incidence of platypnea-orthodeoxia syndrome in a select patient population with right-to-left shunting and to describe the outcomes after PFO closure. **Methods:** Patients with platypnea-orthodeoxia were prospectively identified from a population of patients who had a PFO and were referred to UCLA from 2001 to 2012. Those patients who elected to have their PFO closed were assessed for the severity of their symptoms and interval SaO₂ changes. The changes in SaO₂ before and after closure were compared in the supine and upright position. Patients were classified depending on the result of PFO closure as having “improved SaO₂” or “no change.” **Results:** Of 683 patients with PFO-associated conditions, 17 (2.5%) had platypnea-orthodeoxia and elected to close their PFO. The results in 11 of 17 patients (64.8%) were classified as having “improved SaO₂”; they experienced improvement or complete resolution of their dyspnea and hypoxemia (improved SaO₂ from baseline 5.2 ± 6.4% when recumbent and 15.6 ± 6.3% when upright, $P = 0.03$ and $P < 0.0001$, respectively). Patients with no change after PFO closure predominantly had a pulmonary etiology for their hypoxia, with elevated mean pulmonary pressures measured before closure (51.4 ± 16.8 mmHg, $P = 0.06$). **Conclusion:** PFO closure may resolve symptomatic postural dyspnea and hypoxemia and is an effective method for treating platypnea-orthodeoxia, but is not effective when the primary etiology of the hypoxemia is due to a pulmonary cause. © 2015 Wiley Periodicals, Inc.

Key words: patent foramen ovale; platypnea-orthodeoxia syndrome; right-to-left shunt

BACKGROUND

Platypnea-orthodeoxia syndrome is a rare clinical condition characterized by dyspnea and hypoxemia in the upright position that improves in the recumbent position. By definition, platypnea refers to dyspnea that is relieved by lying down, and worsened by standing or sitting upright; orthodeoxia is arterial hypoxemia that

is made worse in the upright position and improved on lying down [1,2]. The etiology of this syndrome is usually attributed to the presence of a right-to-left (R to L) shunt through a patent foramen ovale (PFO) or sometimes an atrial septal defect (ASD) or a fenestrated ASD with interatrial aneurysm [3–5]. The prevalence of platypnea-orthodeoxia among patients with R to L shunts

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TABLE I. Patients with Platypnea-Orthodeoxia Stratified by Medical Condition at the Time of Referral

N	Pulmonary comorbidities	N	Cardiac comorbidities
3	Chronic obstructive pulmonary disease, Pulmonary fibrosis	2	Pulmonic stenosis, S/p repair
4	Pulmonary hypertension, idiopathic or due to vasculitis	1	Aortic aneurysm with dissection
3	Hepato-pulmonary syndrome	2	Ebstein anomaly, S/p repair
1	S/p lung transplant with opportunistic infection	1	Idiopathic nonischemic cardiomyopathy ^a

^aThis patient had combined cardiac and pulmonary comorbidities (hepato-pulmonary syndrome).

is unknown. A review of current literature reveals that platypnea-orthodeoxia is mainly observed in patients with prominent R to L shunting, severe pulmonary disease, hepatic failure or a combination of these [2].

The pathophysiology of platypnea-orthodeoxia is complex and is not yet completely explained. At the core of platypnea-orthodeoxia lies a severe ventilation-perfusion mismatch, with or without a R to L shunt [6,7]. It is uncommon for an isolated pulmonary pathology to manifest as platypnea-orthodeoxia. Patients with pulmonary disease usually have improved ventilation when they sit up, and therefore, increase their oxygen saturation in the upright position. However, platypnea-orthodeoxia has been described in patients who have lung pathology predominantly affecting the lower lobes, resulting in severe bibasilar ventilation-perfusion mismatch [8].

The aim of this study was to evaluate the incidence of platypnea-orthodeoxia syndrome in a select patient population with R to L shunting and to describe the outcomes after PFO closure.

METHODS

The study population consisted of 683 patients referred to the Interventional Cardiology program at the University of California, Los Angeles between 2001 and 2012 for the assessment of conditions associated with PFO, including cryptogenic stroke, migraines, acephalgic migraines, sleep apnea, decompression illness, and platypnea-orthodeoxia. Patients were assessed for the presence

of platypnea-orthodeoxia with the inclusion criteria of dyspnea and hypoxemia (measured by a pulse oximeter placed on a finger) in the upright position, which was improved in the supine position. Those with underlying pulmonary disease underwent pulmonary function testing to assess the degree of pulmonary disease. The patients were assessed for the presence of a R to L shunt by performing a transesophageal echocardiogram (TEE) bubble study (Phillips iCAI, iE33xMA-TRIX, Andover, Massachusetts) alone or in combination with a transcranial Doppler (TCD) bubble study (Spencer Technologies, Seattle, Washington). This prospective

observational study was approved by the Institutional Review Board.

The reason for referral was hypoxemia in all patients. However, the preliminary diagnosis at the time of referral varied; to help with the analysis, patients were grouped as follows:

1. Those with concomitant pulmonary pathology in addition to PFO at the time of referral.
2. Those with cardiac comorbidity (structural cardiac anomaly in addition to PFO).
3. Those with a combination of pulmonary disease and cardiac anomaly (Table 1).

Those patients with platypnea-orthodeoxia and PFO underwent percutaneous PFO closure. The PFO morphology was evaluated prior to the closure procedure using TEE. Whenever the PFO appeared to be larger than 10 mm by ultrasound imaging, PFO sizing was performed using a sizing balloon at the time of closure. Postclosure assessment consisted of clinical evaluation and TEE, or TEE and TCD at 3 months, except in cases where the patient was symptomatic, which warranted earlier follow-up. If TCD indicated a residual shunt grade 3, then it was repeated at 3 month intervals up to 1 year or until complete resolution of the shunt, as evidenced by a negative TCD (grade 0–2).

The level of dyspnea and hypoxemia was reassessed during follow up and patients were classified into two groups:

- “Improved oxygen saturation (SaO_2)”: SaO_2 improved to $>93\%$ at rest in the supine and sitting position; supplemental oxygen no longer required while supine, nor limited oxygen required when upright.
- “No change”: Dyspnea and hypoxemia may have improved, but saturation remained $<93\%$ and the patient remained symptomatic requiring supplemental oxygen when supine and upright.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean values $\pm$ standard deviation. Nominal and dichotomous

Fig. 1. Left-Fluorographic image of a measuring balloon placed across a sigmoid-shaped, long PFO canal consistent with a large ostium secundum defect with stretched walls. Right- fluoroscopic image of a measuring balloon placed across the conventional PFO of a similar size. Both patients had their PFOs closed with a Helex 30 mm device.

variables were expressed as frequencypercentage.SPSS version 20.0 statistical software was used for the study analysis (IBM Corporation, Armonk NY). Analysis of variance and Fisher's exact test were used for comparison among the study groups; paired was used for comparison within the study groups. A p-level 0.05 was used to determine significance.

idiopathic cardiomyopathy, aortic aneurysm, adult congenital heart disease other than PFO) in 6 patients, and both a cardiac and pulmonary condition in 1 patient. In 4 of 17 patients, recent paralysis of a hemi-diaphragm, either iatrogenic or from a pathological process, contributed to sudden worsening of the condition and, ultimately, led to consideration for PFO

RESULTS

Study Population

Of the 683 patients referred for evaluation of PFO-related conditions, 23 patients (3.4%) were diagnosed with platypnea-orthodeoxia. Of the 23, 18 (78.3%) were found to have R to L shunting through a PFO and had it closed percutaneously. The other 5 patients had primary liver or pulmonary disease with platypnea and orthodeoxia but did not have a PFO present as determined by TCD or TEE. One patient was lost to follow-up, and therefore, was excluded from the final analysis. The clinical descriptors of the 17 patients whose data were analyzed are presented in the Supporting Information Table. The mean age at the time of referral was 62.6 $\pm$ 13.8, and 59% were female.

The primary pathology was a pulmonary condition (i.e., COPD, idiopathic pulmonary hypertension) in 10 patients, a cardiac etiology existing in addition to the PFO (i.e.,

closure. In 3 of 17 patients (17.6%), balloon sizing of the PFO with the purpose of measuring it at the time of closure demonstrated a long tunnel (Fig. 1). In 2 cases, PFO closure was used as a palliative procedure to improve the patients' quality of life by attempting to increase SaO_2 prior to a lung or cardiac transplant.

PFO Parameters and Follow-up

Based on TEE assessment, the mean length of the PFO was 9.0 ± 5.3 mm, with a mean height 9.8 ± 3.3 mm. An atrial septal aneurysm was found in 3 patients, and 1 had a prominent Eustachian valve.

Prior to PFO closure, the mean TCD grade at rest was 3.7 ± 0.8 and on release of Valsalva was 4.3 ± 0.9 . Initial follow-up was 2.1 ± 1.7 months after the index procedure, with the final follow-up on surviving patients performed at 11.4 ± 3.4 months. At that time, 4 of 17 (23.5%) patients had mild to moderate residual R to L shunting demonstrated on TEE or TCD, with the mean Spencer grade of 2.5 ± 2 at rest and 3.7 ± 0.9 on Valsalva.

PFO Closure and Outcome

The comparison among patients grouped by outcome is presented in Table II. The groups were not statistically different in terms of age, body mass index, PFO anatomy, or the type of device used for PFO closure. Those patients who experienced an improvement or a resolution of their symptoms ("improved SaO_2 " group) primarily had a cardiac diagnosis; those with no change in symptoms and/or residual hypoxemia had a pulmonary diagnosis.

TABLE II. Comparison of Patients Who Improved Versus Had No Change in Symptoms After Patent Foramen

Ovale Closure		Improved Mean±SD, orN(%) orN(%)	Nochange Mean±SD,	P-value
Total patients		11(100%)	6(100%)	-
Age		59.0±129	69.3±14	0.1
Reason for referral	Pulmonary comorbidities	5(45.4%)	5(83.3%)	0.3
	Cardiac comorbidities	6(54.6%)	0(0%)	0.0427
	Both	0(0%)	1(16.7%)	1
BMI(kg/m ²)		30.1±58	29.1±76	0.8
PFO canal height on cath(mm)		9.3±30	11.5±49	0.3
Presence of atrial septal aneurysm		1(9%)	2(33.3%)	0.5
Device	Amplatzer	6(54.6%)	5(83.3%)	0.3
	Helex	3(27.3%)	1(16.7%)	1
	CardioSeal	1(9%)	0(0%)	1
	Roboticsurgery	1(9%)	0(0%)	1
Presence of residual shunt		2(18.2%)	2(33.3%)	0.6
FEV1 (% of predicted)		80.7±41	77.9±263	0.7
FVC (% of predicted)		69.3±307	91.9±193	0.1
FEV1/FVC(%)		72.5±212	73.9±217	0.9
TV (% of predicted)		81.3±65	99.5±49	
TLC (% of predicted)		<0.0001		
Mean pulmonary pressure (mmHg, precath)		107±181	92.5±07	0.0724
SaO ₂ supine(% , preprocedure)		28.1±103	51.4±168	0.0028
SaO ₂ upright(% , preprocedure)		90.5±69	83.2±5.4	0.0411
SaO ₂ supine(% , postprocedure)		76.3±52	76±69	0.9
SaO ₂ upright(% , postprocedure)		95.7±21	87.2±35	
		<0.0001		
SaO ₂ upright(% , postprocedure)		91.7±78	78.5±49	0.002

TABLE III. Comparison of Oxygen Saturation Before and After PFO Closure in the Supine and Upright Position in Patients with Platypnea-Orthodeoxia

Group	SaO ₂ supine(%)		P-value	SaO ₂ upright(%)		P-
	Preclosure	Postclosure		Preclosure	Postclosure	
Improved	90.5±69	95.7±21	0.03	76.3±52	91.7±78	
(N=11)	<0.0001					
Nochange	83.2±54	87.2±35	0.2	76.0±69	78.5±49	0.4
(N=6)						

Lung function as assessed by pulmonary function testing (PFT), in those with no symptom change after PFO closure, was similar to the rest of the study population. However, their mean pulmonary pressures were significantly higher compared with the other study group ($p < 0.05$). Of the 4 patients with PFO receiving bosentan or sildenafil treatment for their pulmonary hypertension, 3 experienced no change in symptoms or

SaO₂ after PFO closure, and 1 experienced complete resolution of platypnea-orthodeoxia. Of the 17 patients with platypnea-orthodeoxia, 11 (65%) experienced a "positive change" after PFO closure, with the SaO₂ improving to >93% in the supine and sitting position. These patients no longer required supplemental oxygen while supine and required either no or very limited oxygen use when upright (Table II). Of the 11 patients who were in the "improved SaO₂" group, 6 (54%) had complete resolution of their symptoms.

Of the 17 patients, 6 (35.3%) had no change in the severity of their symptoms after closing their PFO. One patient had an initial exacerbation of hypoxemia due to the presence of a significant residual R to L shunt following use of a Helex device. One month after the index procedure, this patient had a second closure procedure using an Amplatzer ASD device with reduction of R to L shunting and improvement in dyspnea and hypoxemia [9].

Table III presents the data on the SaO₂ of patients before and after PFO closure. Following PFO closure, the patients from the "improved SaO₂" group experienced an increase in the mean supine SaO₂ by 52.4.7%, ($p=0.03$). Similarly, the mean SaO₂ in the upright position improved by 15.6.3.0% ($p<0.0001$). Of the 11 patients, 6 no longer required use of supplemental oxygen, and 5 required limited oxygen only when upright and during physical exertion.

±

±

In contrast, the increase in mean SaO₂ observed among patients from the “no change” group was not significant; all 6 patients continued to require supplemental oxygen after PFO closure.

Due to significant comorbidities present in several of the patients, percutaneous PFO closure, though successful, did not improve the overall outcome. Four patients died. One patient died 7 weeks after the procedure due to heart failure from rapidly progressing idiopathic cardiomyopathy; another patient died 8 months later due to an unresectable pancreatic cancer. The third patient died as a result of invasive aspergillosis in a single transplanted lung and esophageal carcinoma; the fourth patient died from a massive pulmonary embolism.

DISCUSSION

Platypnea-orthodeoxia is a complex medical condition where patients often present with comorbidities that alone, or in combination with PFO, may be responsible for severe postural desaturation. R to L shunting through an interatrial defect (e.g., a PFO or an atrial septal defect) is the most frequent etiology of platypnea-orthodeoxia [5,10]. The association with atrial septal aneurysm, Chiari network or a persistent Eustachian valve accentuates the degree of shunting and may also potentiate a paradoxical embolism through the interatrial defect [11–13]. Platypnea-orthodeoxia has been described after an unsuccessful ASD closure where the rim of the Amplatzer device was found to be sitting on the anterior wall of the inferior vena cava. The incorrect placement of the ASD device over the inferior vena cava orifice directed the inferior vena caval blood into the left atrium [14]. Although PFO is present throughout a patient's life-time, platypnea-orthodeoxia occurs later in life. The onset of symptoms is usually linked to another cardiac or extracardiac event that changes the configuration of the interatrial septum, thereby significantly increasing the degree of shunting. Some examples of these events are pneumonectomy with a mediastinal shift, aortic root elongation, aortic root aneurysm,

kyphosis, unilateral paralysis of the diaphragm, and a localized pericardial effusion. It is hypothesized that these events may cause rotation of the heart with stretching of the interatrial septum and opening of the PFO flap, providing a greater degree of deoxygenated blood to enter the left atrium. When the correction of the concomitant pathology leading to platypnea-orthodeoxia is not possible (e.g., kyphoscoliosis, pneumonectomy, aortic root dilation), PFO closure can be an effective way to resolve orthostatic dyspnea and hypoxemia [15].

The concept of a postural change affecting the R to L shunt is not new. A correlation between the magni-

tude of R to L shunting with the position of the body during TCD was described by Lao et al in 2007 [16]. The authors postulated that this postural dependence is likely due to buoyancy of bubbles and the anterior superior location of the PFO, and possibly due to a larger opening of the PFO flap in the sitting position. Caputi et al. in 2008 postulated that the higher Spencer grade on TCD may be due to an increase in the amount of shunted blood from the recumbent to standing position, possibly due to stretching of the PFO [17]. The prevailing theory is that platypnea-orthodeoxia results from a positional modification of the PFO anatomy such that a change from supine to the upright position produces stretching of the interatrial communication, leading to increased deoxygenated blood flow from the right atrium through the defect [10]. This phenomenon has been demonstrated using TEE and TTE with patients moving from the supine to sitting position during the study or using a tilt-table [18-20].

Dyspnea exacerbated in the upright position may also be seen in patients with hepatopulmonary syndrome who have multiple pulmonary arterio-venous fistulae secondary to liver failure [2,5,21]. Hepatopulmonary syndrome with symptoms of platypnea-orthodeoxia is often associated with ascites and hydrothorax with pleural effusion. In these patients, the supine position allows any intrathoracic effusion to spread diffusely across the posterior thorax, whereas the upright position causes this fluid to accumulate in the lung bases. The accumulated fluid prevents expansion of the lungs and aggravates hypoxemia. In addition to this mechanism, hepatopulmonary syndrome is also associated with diffuse arteriovenous fistulae in the pulmonary circulation. The deoxygenated venous blood shunts directly into the pulmonary veins without being oxygenated in the alveoli. In these patients, sitting upright results in shifting of blood to the dilated pre-capillary beds of the lung bases, causing increased hypoxemic dyspnea [22-25]. This postural dyspnea is observed in 5% of cirrhotic patients [25]. Other pulmonary disorders that have been associated with platypnea-

orthodeoxia include chronic obstructive pulmonary disease (COPD), pulmonary embolism, upper airway tumor and acute respiratory distress syndrome, often with no evidence of intracardiac R to L shunting [6,26].

In our patient population, PFO closure resulted in complete resolution of orthostatic dyspnea and hypoxemia in 6/17 (35.3%) patients with platypnea-orthodeoxia, and significant improvement in another 5/17 (29.4%) patients for a total of 11/17 (64.7%) patients who improved following PFO closure. The resolution of symptoms and the absence of residual R to L shunting on follow-up TCD demonstrate that transcatheter PFO closure may benefit a subset of patients by preventing

deoxygenated venous blood from getting mixed with oxygenated systemic blood.

While the etiology of platypnea-orthodeoxia is usually attributed to a R to L shunt [1-5,10], 6 of the 23 patients referred to us with a clinical diagnosis of platypnea-orthodeoxia did not have a R to L shunt by noninvasive testing. In addition, 35.3% of our patients diagnosed with platypnea-orthodeoxia did not experience any change in their subjective symptoms and/or hypoxemia following PFO closure. Although it would be ideal to rule out other etiologies as the primary cause of the orthostatic dyspnea prior to PFO closure, clinically this may not be possible. In patients who have both a pulmonary shunt as well as a cardiac shunt, PFO closure may be necessary as a therapeutic trial to determine if the primary etiology of the hypoxemia is due to intracardiac R to L shunting.

Since platypnea-orthodeoxia is a rare disorder and not commonly seen by clinicians, it is often misdiagnosed [27]. In our study there were 4 patients who had severe platypnea-orthodeoxia despite having a grade 3 R to L shunt by TCD, which represents a small amount of blood flow. It is possible that these patients have greater shunting from the inferior vena cava and a TCD with agitated saline injection from the leg may have produced a higher shunt grade [28].

In our study, half of the patients with pulmonary comorbidities experienced significant improvement of their symptoms after PFO closure, as documented by improved oxygen saturation and decreased need for supplemental oxygen. The anatomic parameters of the PFO (length of the canal, presence of ASA) were similar between those who experienced improvement and those who did not. Those who did not experience any change from PFO closure were significantly older (74.7 ± 4.7 vs. 59.5 ± 9.9, $p = 0.015$). The base-line pulmonary function tests did not differ significantly between groups, making PFT an unreliable predictor of success after PFO closure. Therefore, PFO closure should be considered for these patients, with concomitant pharmacological therapy

with sildenafil or bosentan to alleviate any reversible component of pulmonary hypertension. To anticipate the effect of PFO closure on pulmonary pressures, the pressure change may be measured in the right atrium or pulmonary artery after temporary occlusion of the PFO with an inflated balloon [29]. Our study demonstrated that the two descriptors which predicted a poor outcome after PFO closure in patients with platypnea-orthodeoxia were a) the presence of severe COPD at the time of referral associated with marked pulmonary hypertension and b) other severe co-morbidities present at the time of the procedure (such as hepato-pulmonary syndrome).

CONCLUSION

In patients with platypnea-orthodeoxia who have a large intracardiac R to L shunt, successful closure of the PFO may resolve symptomatic postural dyspnea and profound hypoxemia. PFO closure is not effective when the primary etiology of the hypoxemia is due to a pulmonary cause.

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