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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 SaO_2 changes. The changes in SaO_2 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 SaO_2" 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 SaO_2"; they experienced improvement or complete resolution of their dyspnea and hypoxemia (improved SaO_2 from baseline 5.2 6 4.7% when recumbent and 15.6 6 3.0% 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 6 16.8 mm Hg, $P = 0.06$). 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. Vc 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 some- times 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	Pulmonarycomorbidities	*N*	Cardiaccomorbidities
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]

[a]This patient had combined cardiac and pulmonary comorbidities (hepato-pulmonary syndrome).

isunknown.Areviewofcurrent literature reveals that platypnea-orthodeoxiaismainly observedinpatientswithprominentR to Lshunting, severepulmonarydisease,hepaticfailureoracombinationofthese[2].

The pathophysiology of platypnea-orthodeoxiaiscomplex and is not yet completely explained. Atthecore of platypnea-orthodeoxia lies a severeventilation-perfusion mismatch, with or without a R to Lshunt[6,7]. It is uncommon for an isolated pulmonarypa-thology to manifest as platypnea-orthodeoxia. Patients with pulmonary disease usually have improved ventila- tion when they sit up, and therefore, increase theiroxy-gen saturation in the upright position. However, platypnea-orthodeoxia has been described in patients who have lung pathology predominantly affectingthelower 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 describetheoutcomes after PFOclosure.

METHODS

The studypopulation consistedof 683patientsreferred to theInterventional Cardiologyprogram at theUniversityofCalifornia,Los Angelesbetween2001 and 2012 for theassessmentof conditions associatedwithPFO, includingcryptogenic stroke, migraines, acephal-gicmigraines, sleepapnea,decompression illness,andplatypnea-orthodeoxia. Patientswere assessed for the presence ofplatypnea-orthodeoxia withtheinclusion criteria ofdyspneaandhypoxemia(measured by a pulse- oximeter placed on afinger)in theupright position,which was improved in the supineposition.Thosewithunderlyingpulmonary diseaseunderwent pulmonaryfunction testing to assess the degree ofpulmonarydis- ease. Thepatientswereassessedfor the presence of a R to L shunt byperformingatransesophageal echocardio-gram (TEE)bubblestudy(PhillipsiCAI, iE33xMA- TRIX, Andover Massachusetts) alone orincombinationwithatranscranial Doppler (TCD) bubble study (Spencer Technologies, Seattle, Washington).Thisprospective

observational study was approved by the Institutional Review Board.

The reason for referral was hypoxemia inallpatients. However, the preliminary diagnosis atthetime of referral varied; to help with theanalysis,patients were grouped asfollowed:

1. Those with concomitant pulmonary pathologyinadditiontoPFOatthetimeofreferral.
2. Those with cardiac comorbidity (structural cardiac anomaly in addition toPFO).
3. Those with a combination of pulmonary diseaseandcardiac anomaly (TableI).

Those patients with platypnea-orthodeoxia andPFOunderwent percutaneous PFO closure. The PFOmorphology was evaluated prior to the closure procedure using TEE. Whenever the PFO appeared to be larger than 10 mm by ultrasound imaging, PFO sizingwasperformed using a sizing balloon at the time of closure. Postclosure assessment consisted of clinical evaluation and TEE, or TEE and TCD at 3 months, exceptincases where the patient was symptomatic, whichwar-ranted earlier follow-up. If TCD indicated a residual shunt grade 3, then it was repeated at 3 monthinter-vals up to 1 year oruntil complete resolutionof the shunt, asevidencedby anegativeTCD(grade0–2).

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

- "Improvedoxygen saturation(SaO_2)": SaO_2improvedto>93% atrestin thesupine and sittingposition; supplemental oxygennolonger required whilesupine,noorlimitedoxygenrequiredwhenupright.
- "No change": Dyspnea and hypoxemia may have improved, but saturation remained<93% and the patient remained symptomatic requiring supplemen- tal oxygen when supine and upright.

STATISTICAL ANALYSIS

Continuous variables were expressed as meanval-ues±standard deviation. Nominal anddichotomous

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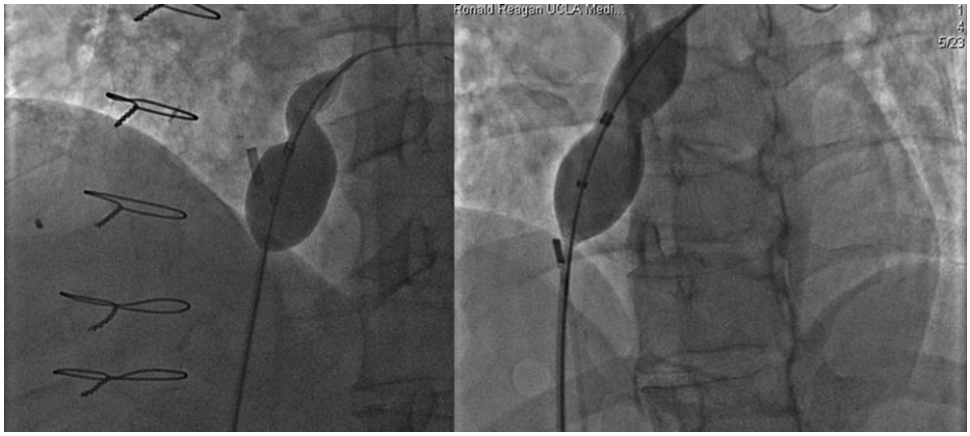

Fig. 1. Left-Fluorographic image of a measuring balloon placed across a sigmoid-shaped, long PFO canal consistent with a large ostium secundum defect with stretched walls. Right- fluoroscopic image of a measuring balloon placed across the conventional PFO of a similar size. Both patients had their PFOs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

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

RESULTS

Study Population

Of the 683 patients referred for evaluation ofPFOrelated 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 aPFOand had it closed percutaneously. The other 5 patients had primary liver or pulmonary disease with platypnea and orthodeoxia but did not have a PFO presentasdetermined by TCD or TEE. One patient was losttofollow-up, and therefore, was excluded from thefinalanalysis. The clinical descriptors of the 17 patients whose data were analyzed are presented in theSup-porting Information Table. The mean age at thetimeof referral was 62.6 13.8, and 59%were female.

The primary pathology was a pulmonary condition (i.e., COPD, idiopathic pulmonary hypertension) in10patients, a cardiac etiology existing in addition tothePFO (i.e., idiopathic cardiomyopathy, aortic aneurysm, adult congenital heart disease other than PFO) in6patients, and both a cardiac and pulmonary condition in 1 patient. In 4 of 17 patients, recent paralysis ofahemi-diaphragm, either iatrogenic or from a pathologi- cal process, contributed to sudden worsening oftheconditionand,ultimately,ledtoconsideration forPFO

closure. In 3 of 17 patients (17.6%), balloon sizingofthe PFO with the purpose of measuring it at thetimeof closure demonstrated a long tunnel (Fig. 1). In2cases, PFO closure was used as a palliative procedure to improve the patients' quality of life by attemptingtoincreaseSaO_2priortoalungorcardiactransplant.

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 foundin3patients,and1hadaprominentEustachianvalve.

Prior to PFO closure, the mean TCD grade atrestwas 3.7 0.8 and on release of Valsalva was 4.3 0.9. Initial follow-up was 2.1 1.7 months after theindexprocedure, with the final follow-up on surviving patients performed at 11.4 3.4 months. At thattime,4 of 17 (23.5%) patients had mild to moderate residual R to L shunting demonstrated on TEE or TCD,withthe mean Spencer grade of 2.5 2 at rest and 3.70.9onValsalva.

PFO Closure and Outcome

Thecomparison among patients groupedbyoutcomeispresentedinTableII. Thegroupswere notstatistically differentintermsof age,bodymassindex,PFOanat-omy,orthe typeofdeviceused for PFOclosure.Thosepatientswhoexperiencedanimprovementoraresolutionoftheir symptoms("improvedSaO_2"group)primarilyhadacardiac diagnosis; thosewithnochangeinsymp- toms and/or residual hypoxemiahadapulmonarydiag-nosis.

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

Variable		Improved Mean±SD, or *N(%)* or *N(%)*	Nochange Mean±SD,	*P*-value
Totalpatients		11(100%)	6(100%)	–
Age		59.0±12.9	69.3±14	0.1
Reasonforreferral	Pulmonarycomorbidities	5(45.4%)	5(83.3%)	0.3
	Cardiaccomorbidities	6(54.6%)	0(0%)	0.0427
	Both	0(0%)	1(16.7%)	1
BMI(kg/m^2)		30.1±5.8	29.1±7.6	0.8
PFO canal height oncath(mm)		9.3±3.0	11.5±4.9	0.3
Presence of atrials e p t a l 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 ofresidualshunt		2(18.2%)	2(33.3%)	0.6
FEV1 (%ofpredicted)		80.7±4.1	77.9±26.3	0.7
FVC (%ofpredicted)		69.3±30.7	91.9±19.3	0.1
FEV1/FVC(%)		72.5±21.2	73.9±21.7	0.9
TV (%ofpredicted)		81.3±6.5	99.5±4.9	<0.0001
TLC (%ofpredicted)		107±18.1	92.5±0.7	0.0724
Mean pulmonary pressure (mmHg,precath)		28.1±10.3	51.4±16.8	0.0028
SaO2 supine(%,preprocedure)		90.5±6.9	83.2±5.4	0.0411
SaO2 upright(%,preprocedure)		76.3±5.2	76±6.9	0.9
SaO2 supine(%,postprocedure)		95.7±2.1	87.2±3.5	<0.0001
SaO2 upright(%,postprocedure)		91.7±7.8	78.5±4.9	0.002

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

	SaO_2supine(%)			SaO_2upright(%)		
Group	Preclosure	Postclosure	*P*-value	Preclosure	Postclosure	*P*-value
Improved (*N*¼11)	90.5±6.9	95.7±2.1	0.03	76.3±5.2	91.7±7.8	<0.0001
Nochange (*N*¼6)	83.2±5.4	87.2±3.5	0.2	76.0±6.9	78.5±4.9	0.4

Lung function as assessed by pulmonary function testing (PFT), in those with no symptom changeafterPFO closure, was similar to the rest of the studypopu-lation. However, their mean pulmonary pressuresweresignificantly higher compared with the otherstudy group ($p<0.05$). Of the 4 patients with PFO receiving bosentan or sildenafil treatment for their pulmonary hypertension,3experiencednochangeins ymptomsor SaO_2after PFO closure, and 1 experienced complete resolution of playpnea-orthodeoxia.

Ofthe 17patientswithplatypnea-orthodeoxia, 11(65%)experienceda“positive change” afterPFOclo- sure,with the SaO_2improvingto>93% inthe supine andsitting position. These patientsnolonger required supplementaloxygen while supineandrequiredeitherno orverylimited oxygenuse whenupright (TableII).Ofthe 11patientswho wereinthe“improved SaO_2” group,6(54%) hadcomplete resolutionoftheirsymptoms.

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 SaO_2 of patients before and after PFO closure. Following PFO closure, the patients from the "improved SaO_2" group experienced an increase in the mean supine SaO_2 by 5.2 4.7%, (p 0.03). Similarly, the mean SaO_2 in the upright position improved by 15.6 3.0% (p < 0.0001). Of the 11 patients, 6 no longer required use of supple- mental oxygen, and 5 required limited oxygen only when upright and during physical exertion.

In contrast, the increase in mean SaO_2observed among patients from the “no change” group wasnotsignificant; all 6 patients continued to require supple- mental oxygen after PFOclosure.

Due tosignificant comorbiditiespresent in several of the patients, percutaneous PFOclosure,thoughsuccess-ful,didnotimprove the overall outcome.Fourpatientsdied. One patient died 7 weeks after the procedure due to heart failure fromrapidly progressing idiopathiccar-diomyopathy;anotherpatientdied after 8monthsdue to anunresectable pancreatic cancer.The third patient died as a result ofinvasive aspergillosisin asingletrans-planted lung andesophagealcarcinoma; the fourth patient died from amassive pulmonaryembolism.

DISCUSSION

Platypena-orthodeoxia is a complex medical condi- tion where patients often present with comorbidities that alone, or in combination with PFO, may be responsible for severe postural desaturation. R toLshunting through an interatrial defect (e.g., a PFOoran atrial septal defect) is the most frequent etiologyofplatypnea-orthodeoxia [5,10]. The associationwithatrial 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 Amplatzerdevicewas found to be sitting on the anterior wall of the infe- rior vena cava. The incorrect placement of theASDdevice over the inferior vena cava orifice directedtheinferior vena caval blood into the left atrium[14].Although PFO is present throughout a patient’slife-time, platypnea-orthodeoxia occurs later in life.Theonset of symptoms is usually linked to another cardiac or extracardiac event that changes the configurationofthe interatrial septum, thereby significantly increasing the degree of shunting. Some examples of theseeventsare pneumonectomy with a mediastinal shift, aortic root elongation, aortic root aneurysm, kyphosis, unilat- eral paralysis of the diaphragm, and a localizedperi-cardial effusion. It is hypothesized that theseeventsmay cause rotation of the heart with stretching oftheinteratrial septum and opening of the PFO flap, provid- ing a greater degree of deoxygenated blood toenterthe left atrium. When the correction of the concomitant pathology leading to platypnea-orthodeoxia is notpos-sible (e.g., kyphoscoliosis, pneumonectomy, aorticrootdilation), PFO closure can be an effective waytoresolve orthostatic dyspnea and hypoxemia[15].

The concept of a postural change affecting the RtoLshuntisnotnew.Acorrelationbetweenthemagni-

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 theamountof shunted blood from the recumbent tostanding position, possiblydue tostretchingof the PFO[17].The prevailing theory is thatplatypnea-orthodeoxia resultsfrom a positionalmodificationof the PFOanatomysuch that a change from supine to theuprightposition pro- ducesstretchingof theinteratrial communication,lead- ing to increaseddeoxygenatedblood flow from the right atriumthroughthe defect [10]. Thisphenomenonhas beendemonstratedusing TEE and TTEwith patientsmoving from the supine tosittingpositionduringthe study or using atilt-table[18–20].

Dyspneaexacerbated in theuprightposition mayalsobe seen inpatients with hepato-pulmonarysyndrome who havemultiple pulmonary arterio-venousfistulae secondary to liver failure [2,5,21].Hepato-pulmonary syndrome withsymptoms ofplatypnea-orthodeoxiais often associatedwith ascitesand hydrothorax with pleu- ral effusion. In these patients, the supineposition allowsanyintrathoraciceffusion to spread diffuselyacrosstheposteriorthorax,whereasth euprightposition causes thisfluidtoaccumulatein the lung bases. The accumu-lated fluid prevents expansionof the lungs and aggra- vates hypoxemia. In addition to thismechanism,hepato-pulmonarysyndromeis also associated with diffusearteriovenous fistulaeinthe pulmonary circulation. The deoxygenatedvenous blood shunts directly into the pul- monary veins without being oxygenated in thealveoli.In thesepatients, sittinguprightresultsin shifting of blood to the dilatedpre-capillarybeds of the lung bases, causing increasedhypoxemicdyspnea [22–25]. This postural dyspnea isobservedin 5% ofcirrhotic patients[25]. Other pulmonarydisordersthat have beenassoci-atedwith platypnea-orthodeoxiainclude chronic obstruc-tivepulmonary disease (COPD),pulmonaryembolism,upper airwaytumorandacute respiratory distresssyn-drome, oftenwithno evidence ofintracardiacR to Lshunting[6,26].

In ourpatient population,PFOclosure resulted in complete resolutionoforthostatic dyspneaandhypoxe-miain6/17(35.3%) patientswithplatypnea-orthodeoxia,andsignificant improvementinanother5/17 (29.4%)patientsforatotalof11/17 (64.7%) patients who improved followingPFOclosure.Theresolutionofsymptoms and theabsenceofresidualR to Lshuntingonfollow-upTCDdemonstratethattranscutaneous PFO closuremaybenefitasubsetofpatientsbyprevent ing

deoxygenated venous blood from getting mixed with oxygenated systemic blood.

While the etiology of platypnea-orthodeoxia isusu-ally attributed to a R to L shunt [1–5,10], 6 of the23patients referred to us with a clinical diagnosisofplatypnea-orthodeoxia did not have a R to L shuntbynoninvasive testing. In addition, 35.3% of our patients diagnosed with platypnea-orthodeoxia did not experi- ence any change in their subjective symptomsand/orhypoxemia following PFO closure. Although itwouldbe 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 patientswhohave 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 hypox-emiaisduetointracardiacRtoLshunting.

Since platypnea-orthodeoxia is a rare disorderandnot commonly seen by clinicians, it is often misdiag- nosed [27]. In our study there were 4 patients whohadsevere platypnea-orthodeoxia despite having a grade3R to L shunt by TCD, which represents a small amount of blood flow. It is possible that these patientshavegreater shunting from the inferior vena cava andaTCD with agitated saline injection from the legmayhaveproducedahighershuntgrade[28].

In our study, half of the patients with pulmonary comorbidities experiencedsignificant improvementoftheir symptoms afterPFOclosure,asdocumentedby improved oxygen saturation anddecreasedneedforsupplemental oxygen. The anatomicparametersof the PFO(lengthof thecanal, presenceof ASA)weresimilar between those who experiencedimprovementand those who did not. Those who did notexperienceany change from PFO closure weresignificantlyolder (74.7 4.7 vs. 59.5 9.9, p 0.015). The base-line pulmonary function testsdid notdiffersignifi-cantly between groups, makingPFT anunreliable predictorofsuccessafter PFO closure.Therefore,PFOclosure shouldbeconsideredforthesepatients,with concomitant pharmacological therapy withsilde- nafil or bosentan to alleviate any reversiblecompo-nent ofpulmonary hypertension.Toanticipate theeffect of PFO closure on pulmonary pressures,thepressure change may be measured in the rightatriumorpulmonary arteryaftertemporary occlusionofthePFO with an inflated balloon [29]. Our study demon-strated thatthe twodescriptors which predicteda poor outcome after PFO closure in patientswithplatypnea-orthodeoxia were a) the presence of severeCOPDat thetimeofreferral associatedwithmarkedpulmonaryhypertensio nand b) othersevere co-morbidities present at the time of the procedure(suchashepato-pulmonarysyndrome).

CONCLUSION

In patients with platypnea-orthodeoxia who havealarge intracardiac R to L shunt, successful closureofthe PFO may resolve symptomatic posturaldyspneaand profound hypoxemia. PFO closure is not effective when the primary etiology of the hypoxemia is duetoa pulmonarycause.

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