Reviews

Cardiac Platypnea-Orthodeoxia Syndrome: An Often Unrecognized Malady

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ABSTRACT

Platypnea-orthodeoxia syndrome (POS) is a rare but clinically important form of dyspnea. The syndrome is characterized by dyspnea and arterial oxygen desaturation that occurs in the upright position and improves with recumbency. In cardiac POS, an atrial septal defect or patent foramen ovale allows communication between the right- and left-sided circulations. A second defect, such as a dilated aorta, prominent eustachian valve, or pneumonectomy, then contributes to right-to-left shunting through the interatrial connection. Diagnosis is made through pulse oximetry to confirm orthodeoxia and through transesophageal echocardiography with bubble study to visualize the shunt. Although data are limited for this rare syndrome, percutaneous closure has thus far proven safe and effective.

Introduction

Dyspnea is a frequently encountered symptom in medicine. Of the top 6 reasons for patients to be hospitalized through the emergency department, dyspnea is either the primary symptom or an associated symptom in all 6.[1] Dyspnea is also a complaint of nearly 4% of patients seeking treatment in the ambulatory care setting, and population samples have determined the prevalence of dyspnea to be between 17% and 38%.[2]

Unfortunately, many of the most common causes of dyspnea, such as chronic obstructive pulmonary disease and congestive heart failure, are not fully reversible. Treatments for these conditions are typically targeted toward slowing disease progression and controlling symptoms, rather than curing the underlying disease process. In this context, clinicians must be particularly aware of dyspnea syndromes that are fully reversible. Platypnea-orthodeoxia syndrome (POS) represents 1 of these entities. As detailed in this review, POS is frequently debilitating to the patients who suffer from it. However, when POS is identified, a safe and relatively simple procedure can lead to dramatic symptom improvement.

Case Report

A 46-year-old male with a past medical history significant for anaplastic large cell lymphoma was evaluated for dyspnea. A right pneumonectomy had been performed 2 months prior to the current admission, which was initially tolerated well.

He was seen at a community hospital 1 month ago complaining of increasing shortness of breath, which he attributed to noxious fumes from his furnace. The evaluation was notable for an initial oxygen saturation of 65% on room air, a negative ventilation-perfusion scan, negative lower extremity Doppler ultrasound, and a negative pulmonary angiogram. A transthoracic echocardiogram demonstrated mild right ventricular dilatation and mild left ventricular dysfunction, and a transesophageal echocardiogram showed a large patent foramen ovale (PFO) with significant right-to-left shunting. Cardiac catheterization was performed and demonstrated normal coronary arteries and normal left ventricular function. Right heart pressures and cardiac output were normal. The patient was placed on 4 L of oxygen by nasal cannula. His dyspnea improved and he was discharged.

The patient's dyspnea returned within the month, and he was readmitted for further evaluation. The transesophageal echocardiogram was repeated, and importantly, the study was performed in both the upright and supine positions. Flow across the PFO was significantly higher in the upright than the supine position, consistent with the lower oxygen saturation seen in the upright position. The patient's PFO was closed percutaneously using a 22-mm septal occluder device placed in the interatrial septum. A postprocedure echocardiographic bubble study was negative for shunting.

The patient's dyspnea immediately improved. At the time of discharge, oxygen saturations were in the upper 90s on room air, and he was able to maintain those saturations with moderate exercise.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Received: April 25, 2014
Accepted: May 13, 2014

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22301 © 2014 Wiley Periodicals, Inc.

Definition and Clinical Presentation

POS is a rare but clinically important form of dyspnea. The syndrome is characterized by dyspnea that occurs in the upright position and is relieved by recumbency (platypnea).[3] A significant drop in arterial oxygen saturation is noted when moving from the supine to the upright position (orthodeoxia), although there is often a mild hypoxemia present even while supine.[4] Due to the pathophysiology of orthodeoxia (see Mechanisms of Cardiac POS below), paradoxical embolism is a frequent coexisting condition.[5]

Since its original description by Burchell and Wood in 1949, there have been <150 case reports in the literature.[6] Although the recognition of POS does seem to be increasing, with over 80 case reports in the last decade alone, it likely remains underdiagnosed.[7] Cardiac etiologies are most frequently associated with platypnea-orthodeoxia, and will be the focus of this review.

Mechanisms of Cardiac POS

Though a unifying mechanism has yet to be determined, position-dependent right-to-left shunting appears to underlie POS. This shunting requires both an anatomic and functional defect.[8] Anatomic defects allow communication between the right- and left-sided circulation. In cardiac POS, the anatomic defect is either a PFO (more common) or an atrial septal defect (ASD). Although interatrial right-to-left shunting is expected in the setting of elevated pulmonary pressures, these pressures are usually normal in POS.[9] For this reason, a second, functional, defect is required to shunt deoxygenated blood into the higher pressure systemic circulation (Table 1). These functional defects can generally be classified into 2 groups: (1) those that preferentially direct blood flow through the interatrial communication and (2) those that cause a transient increase in right atrial pressure resulting in a transient right-left atrial gradient.[10] Even though it is possible for several functional defects to be present, the majority of patients reported in the literature have only 1 anatomic and 1 functional defect.

The first group of functional defects are those that preferentially direct blood flow through the interatrial communication. The normal pattern of venous blood return from the superior vena cava is downward in the anterior half of the right atrium, whereas blood from the inferior vena cava flows upward in the posterior half.[11] In most patients with ASDs or PFOs, neither of these streams is aimed directly at the interatrial communication. However, when a second, functional defect distorts the usual cardiac anatomy, a change in position can allow deoxygenated blood (typically from the inferior vena cava) to flow directly across the ASD or PFO into the left atrium.[8] These functional defects can either reposition the atrial septum (aortic dilation/aneurysm, atrial septal aneurysm, intracardiac lipoma, cardiac surgeries) or redirect the blood flow from the inferior vena cava (prominent eustachian valve). Occasionally, a tricuspid regurgitant jet can also be projected directly through the interatrial communication.[12]

The other group of functional defects act through transient reversal of the left-to-right pressure gradient.[11] These conditions elevate right atrial pressures to the point that the left-to-right pressure gradient reverses for certain parts of the cardiac cycle, particularly when the patient is in the upright position. These conditions either increase pulmonary vascular resistance (pneumonectomy, pulmonary embolism, chronic obstructive pulmonary disease, pulmonary hypertension), require high right-sided filling pressures to maintain cardiac output (constrictive pericarditis, pericardial effusion), or lead to decreased right-sided compliance (right ventricular ischemia).

Table 1. Functional Defects Associated With Cardiac Platypnea-Orthodeoxia Syndrome

Group A: Direction of Blood Flow Through Interatrial Communication	Group B: Transient Reversal of Left-to-Right Pressure Gradient
Absent superior vena cava	Chronic obstructive pulmonary disease
Aortic valve replacement	Constrictive pericarditis
Ascending aorta repair	Pericardial adipose deposition compressing right ventricle inflow tract
Ascending aortic aneurysm	Pericardial effusion
Atrial septal aneurysm	Pneumonectomy
Atrial switch procedure	Pulmonary embolism
Cardiac cyst/mass	Pulmonary hypertension
Coronary sinus dilatation	Right ventricular ischemia
Ebstein's anomaly	
Eosinophilic endomyocardial disease	
Fontan procedure	
Hepatic cyst distorting right atrium	
Lipomatous hypertrophy of the interatrial septum	
Paraesophageal hernia repair	
Partial anomalous venous return	
Persistent left superior vena cava	
Prominent eustachian valve	
Tortuous ascending aorta	
Transposition of the great vessels	
Tricuspid regurgitation	
Tricuspid stenosis	
Unroofed coronary sinus	

Mimics of Cardiac POS

Patients can present with symptoms of platypnea and orthodeoxia without a specific underlying cardiac etiology. Nonetheless, similar anatomic and functional defects must be present. Instead of an ASD or PFO permitting right-to-left

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DOI:10.1002/clc.22301 © 2014 Wiley Periodicals, Inc.

communication, the anatomic defect is typically a pulmonary arteriovenous malformation, or severe ventilation-perfusion mismatching. Functional defects (Table 2) increase blood flow through the pulmonary arteriovenous malformations or increase the severity of ventilation-perfusion mismatching. A particularly interesting association is seen with chronic liver disease, whereby worsening liver disease has been shown to correlate with worsening oxygen desaturation on standing,[13] most likely related to the development of pulmonary arteriovenous malformations through the hepatopulmonary syndrome.

Diagnosis

POS should be suspected in any patient with dyspnea that worsens in the upright position and improves with recumbency. An insufficient rise in arterial oxygen saturation despite the patient breathing 100% oxygen also increases suspicion.[5] The confirmatory finding for POS is a position-dependent drop in arterial oxygen saturation, with or without the use of a tilt table.

Once the diagnosis of POS has been established, an attempt should be made to determine the underlying etiology. Intracardiac shunting has been the most frequently implicated finding in reports of POS. Transesophageal echocardiography is the preferred diagnostic modality, providing good visualization of any defects or aneurysms that may be present in the atrial septum.[4] An intravenous agitated bubble study should be done to assess for the presence of right-to-left shunting.[4] The test is considered positive for shunt if any bubbles appear within the left atrium, and suggests an intracardiac shunt if those bubbles appear within 3 cardiac cycles.[14] Intravenous fluid replacement or performance of the Valsalva maneuver can significantly increase the sensitivity of the bubble study, and should be considered if no shunt is detected despite a strong clinical suspicion.[5,15] Other modalities for assessing intracardiac defects include right-heart catheterization, ventilation-perfusion scan demonstrating early extrapulmonary uptake,[16] and transcranial Doppler[4]; however, these tests should typically be employed only in the setting of an inconclusive echocardiographic study. Cardiac magnetic resonance imaging can also be used to search for distortions in normal cardiac anatomy, which may explain the right-to-left shunting.[17] If no intracardiac lesion is identified, pulmonary, abdominal, or other conditions known to cause POS should be investigated.

Table 2. Noncardiac Conditions Associated With Platypnea-Orthodeoxia Syndrome

Pulmonary	Abdominal	Other
Acute respiratory distress syndrome	Bowel obstruction or ileus	Chest wall trauma
Chronic obstructive pulmonary disease	Hepatopulmonary syndrome	Diabetic autonomic neuropathy
Cryptogenic fibrosing alveolitis	Alcoholic liver cirrhosis	Kyphoscoliosis
Fat embolism	Autoimmune hepatitis	Organophosphate poisoning
Hemidiaphragmatic dysfunction	Hepatitis A	Paraesophageal hernia repair
Pleural effusion	Noncirrhotic portal hypertension	Parkinson's disease
Pneumocystis and cytomegalovirus pneumonia	Schistosomiasis	Propafenone overdose
Pneumonectomy		Vertebral fractures
Pulmonary arteriovenous malformations		
Pulmonary embolism		
Radiation-induced bronchial stenosis		
Traumatic bronchial rupture		
Ventilation/perfusion mismatching		

Treatment

Definitive treatment for POS secondary to intracardiac shunting involves closure of the interatrial defect. The decision to pursue definitive treatment must be made with careful consideration of not only the severity of the patient's symptoms, but also the patient's underlying medical conditions and ability to tolerate an invasive procedure. Recently, percutaneous closure has supplanted cardiac surgery for treatment of ASDs and PFOs, given its decreased morbidity, mortality, and expense.[3] Percutaneous intervention has also been successful in the specific setting of ASD or PFO closure in patients with POS. Table 3 shows results from all available case series.[18–29]

Symptomatic improvement is seen in >95% of patients treated with percutaneous closure. There is also an average increase in upright arterial oxygen saturation of 10% to 20%. Major adverse events are rare, and are typically attributable to a severe preexisting illness (eg, septic shock), rather than the procedure itself. In the only series that consisted of both percutaneous and surgical intervention, decreased morbidity and shortened hospital stay in the percutaneous group were the only significant differences observed, although the number of patients was small.[19] When weighing surgical and percutaneous closure, it should be noted that septal hypermobility does not preclude a patient from percutaneous treatment.[30]

Prognosis

There have been limited long-term follow-up results of POS patients published to date (Table 3). However, these data do suggest a good prognosis, both for shunt correction and symptom improvement. The 78-patient series by Guerin et al in 2005 has been the largest to date.[20] At a mean 15-month follow-up, only 1 patient required reintervention. At 6 months, a small shunt was observed on echocardiogram in only 6 patients, none of which were

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Table 3. Reported Case Series Regarding Treatment of Cardiac Platypnea-Orthodeoxia Syndrome

Author	Year	No. of Patients	Treatment	Closure Success or Symptom Resolution (%)	Absolute Increase in SpO_2	Major In-Hospital Complications	Follow-up Period	Follow-Up Results
Takaya	2014	3	Perc	100	10	None	—	—
Zavalloni	2013	6	Perc	100	17	1 death (unrelated septic shock)	Mean 3 months	1 cardioembolic TIA, 3 repeat interventions
Blanche	2013	5	Perc	100	10	None	Median 6 months	No late complications or repeat procedures
Sanikommu	2009	7	Perc	100	—	None	—	—
Toffart	2008	8	6 (Perc)/2 (Surg)	83 (Perc)/100 (Surg)	—	1 unrelated death in percutaneous group	Mean 2.3 years	2 unrelated deaths, 1 repeat intervention
Guerin	2005	78	Perc	97	10	2 deaths (unrelated to procedure)	Mean 1.3 years	7 late deaths unrelated to procedure
Delgado	2004	18	Perc	100	13	None	Mean 2.9 years	2 shunts requiring intervention, 1 POS recurrence
Rao	2001	10	Perc	100	19	None	Median 1 year	1 residual shunt requiring intervention
Godart	2000	6	Perc	91	—	1 death (unrelated septic shock), 1 CVA	Up to 2.5 years	No late complications or repeat procedures
Waight	2000	4	Perc	100	16	None	—	—
Bakris	1997	4	Surg	100	—	None	—	—
Landzberg	1995	8	Perc	100	—	2 device embolizations, retrieved successfully	Mean 2.3 years	2 deaths from cancer, 1 from nonembolic CVA

Abbreviations: CVA, cerebrovascular accident; Perc, percutaneous intervention; POS, platypnea-orthodeoxia syndrome; SpO_2, oxygen saturation; Surg, surgical intervention; TIA, transient ischemic attack.

symptomatic. Importantly, there were no major adverse events related to the procedure.

The longest follow-up period to date has been a mean of 2.9 years, from the 18-patient series reported by Delgado et al in 2004.[21] During follow-up, moderate shunt recurred in 2 patients, only 1 of which was symptomatic. There were no deaths during follow-up. At 2.9 years, the actuarial risk of recurrent POS was 4.6%, and the actuarial risk of reintervention was 9.2%. Larger series looking at PFO closure in general have reported even lower rates of shunt recurrence, suggesting that the positive results of percutaneous POS treatment should be durable.[31]

Summary

POS is a rare but clinically important syndrome characterized by dyspnea and arterial oxygen desaturation that is worsened by standing and relieved by recumbency. In cardiac POS, an ASD or PFO connects the right and left circulations. A second defect, such as a dilated aorta, prominent eustachian valve, or pneumonectomy then allows right-to-left shunting through the interatrial communication. Diagnosis is made through pulse oximetry to confirm orthodeoxia and through transesophageal echocardiography with bubble study to visualize the shunt. Although data are limited for this rare syndrome, percutaneous closure has thus far proven safe and effective.

Acknowledgments

The authors thank Dr. Peter Block for his guidance in submitting this manuscript.

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DOI:10.1002/clc.22301

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