Treatment of Platypnea-Orthodeoxia Syndrome in a Patient with Normal Cardiac Hemodynamics: A Review of Mechanisms with Implications for Management

Brian S. Porter, M.D.[a]; *Bruce Hettleman,* M.D.

[a]CORE PHYSICIANS, EXETER, NEW HAMPSHIRE

ABSTRACT: Platypnea-orthodeoxia syndrome is a rare entity characterized by dyspnea and hypoxemia in the sitting position and usually resolved by lying down. Although it is not well understood, it is thought to be associated with either intracardiac or extracardiac factors. Within the group of intracardiac etiologies, it typically occurs in the presence of right heart failure or elevated right-sided filling pressures. When right heart failure is absent, platypnea-orthodeoxia is thought to be due to either anatomic changes that produce a baffle-directing flow across an atrial defect or to posture-dependent right-to-left pressure gradients.

We report this case of a patient with no prior diagnosis of heart failure who presented to our hospital with 6 months of New York Heart Association class IV dyspnea and recent paradoxical embolus across a patent foramen ovale (PFO). Platypnea-orthodeoxia syndrome was diagnosed clinically. Transesophageal echocardiography revealed bidirectional shunting across the PFO. In the catheterization laboratory, invasive hemodynamics showed normal right and left atrial pressures and normal pulmonary arterial pressures. An Amplatzer Cribiform occluder device (AGA Medical Corp.) was used to close the PFO, completely curing the patient's symptoms.

This is a novel case of subacute-onset severe platypnea-orthodeoxia associated with paradoxical embolus occurring while seated in the upright position. The cause of the patient's symptoms may have been progressive kyphosis or to increased pulmonary tidal volumes. Evaluation for platypnea-orthodeoxia is important in cases of occult dyspnea because the condition may be cured by closing the anatomic defect, as it was in this case.

CASE PRESENTATION

A 69-year-old man presented to our hospital's emergency room complaining of severe dyspnea. His medical history was notable for a stage-4 mantle cell lymphoma that had been diagnosed 5 years previously. Treatment included chemotherapy followed by total body irradiation and allogenic hematopoietic stem cell transplant. He eventually achieved complete remission although he suffered from chronic graft-versus-host disease, steroid-induced osteoporosis, and mild dilation of the ascending aorta.

He had been admitted to our hospital 5 months earlier with a similar dyspnea complaint. Evaluation at that time included normal pulmonary spirometry, moderately decreased pulmonary diffusion capacity, a low-probability ventilation–perfusion scan, normal bronchoalveolar lavage, and a normal chest computed tomography (CT) scan. No formal diagnosis was established to explain the dyspnea, and the patient was discharged home with expectant management.

Three months following the initial admission, he suffered an ischemic stroke to the left basal ganglia and left frontal lobe. This was his first lifetime stroke and occurred while driving. He was treated with alteplase with nearly complete resolution of stroke symptoms. At that time, an echocardiogram with agitated saline injection performed at another hospital revealed evidence of a patent foramen ovale (PFO) that had not been previously identified. An embolic source of stroke was suspected, and he was discharged to home on aspirin therapy.

With respect to his current presentation, the patient complained of persistent dyspnea that had steadily worsened over the preceding weeks to months. He was mildly dyspneic at rest and was almost completely unable to walk. For comparison, he had been able to shovel snow without difficulty just 12 months prior. He also volunteered the symptom of platypnea (worsening shortness of breath in the upright position). He denied chest pain, palpitations, history of chest trauma, liver disease, history of cardiac murmur, or family history of congenital heart disease and claimed he was taking his medicines as directed, including

aspirin 81 mg daily, dexamethasone, cyclosporine, and inhaled bronchodilators. A married, retired engineer, he had no history of occupational exposures and was a lifetime nonsmoker who rarely consumed alcohol and never used illicit drugs.

When he presented in our emergency room, his pulse was in the low 100s, blood pressure was 130/80, and body mass index was 22 kg/m^2. In addition, his arterial oxygen saturation was 89% by pulse oximetry while breathing ambient air in the seated position, and this improved to 94% after adding 3 liters of nasal oxygen. When lowered to the supine position, his oxygen saturation on the same supplemental oxygen improved to 99%. The patient was tachypneic in the upright position but did not appear acutely ill. Jugular venous pressure was normal. A regular S1 and normally split S2 were heard without extra heart sounds. No murmurs were appreciated, and no lift or heave was present. The carotid upstrokes and peripheral pulses were normal and the lungs were clear. No peripheral edema was present, and there were no clubbed fingers.

Laboratory studies revealed mild anemia (hematocrit 32) and mild thrombocytopenia (platelets 107,000). Creatinine, liver transaminases, and international normalized ratio were all normal. An electrocardiogram showed normal sinus rhythm with left axis deviation. A chest CT with intra-arterial contrast showed no evidence of pulmonary embolus or intrapulmonary shunt. Transthoracic echocardiography confirmed the prior diagnosis of right-to-left intracardiac shunting at the atrial level, with saline bubbles seen in the left ventricle two beats after they entered the right ventricle (RV). The right atrium was not well seen, but right and left ventricular size and function appeared normal.

A PFO with right-to-left shunting in the absence of heart failure was suspected as the cause of the patient's platypnea and orthodeoxia. The following day, transesophageal echocardiography revealed the presence of a wide PFO with right-to-left flow in early ventricular systole and left-to-right flow late in systole (Figure 1). Subsequently, heart catheterization with intracardiac echo was performed with an intent to close the PFO. With the patient in a lightly-sedated supine position, catheterization revealed arterial hypertension (aortic pressure of 186/94 mm Hg), normal right atrial pressure (mean 5 mm Hg), normal RV pressure (21/6 mm Hg), normal mean pulmonary capillary wedge pressure (9 mm Hg), and normal left atrial pressure (5 mm Hg, measured directly). Cardiac output was 6 L/min and cardiac index was 3 L/min by estimated Fick measurement. Oximetry showed no significant step up in oxygen saturation in any of the entered chambers (superior vena cava 75%, inferior vena cava 85%, mid-right atrium 74%, main pulmonary artery 72%, left atrium 98%, femoral artery 99%). The PFO was measured at 13 mm by sizing balloon (Figure 2). A 25-mm Amplatzer device was

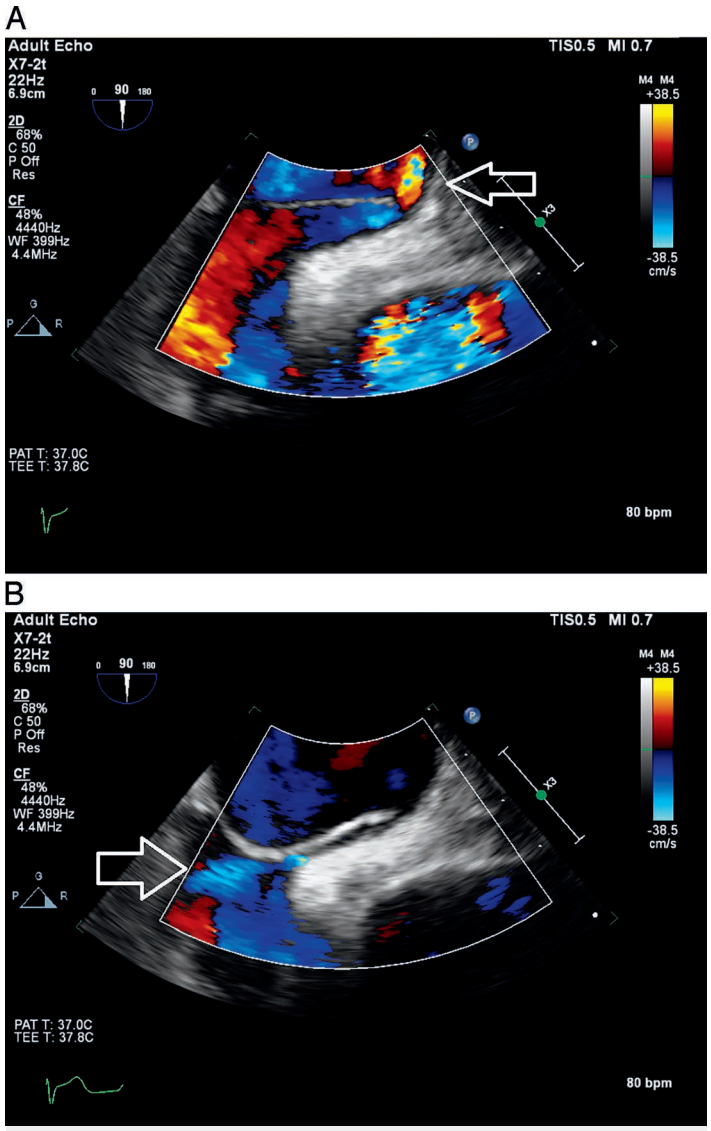

Figure 1.
Transesophageal echocardiography (TEE) still images. (A) Right-to-left flow across the patent foramen ovale (PFO) is demonstrated in early ventricular systole (arrow). (B) Left-to-right flow across the PFO is demonstrated in late ventricular systole (arrow).

placed across this lesion using standard techniques. Real-time echocardiography with agitated saline injection following device implantation revealed complete resolution of the shunt. Clopidogrel was added to his medication regimen, and he was returned to the inpatient ward.

Two days following intervention, the patient denied dyspnea of any kind. Pulse oximetry was measured at 97% in the standing position, 97% in the seated position, and 95% in the supine position. At 3 weeks follow-up, he reported being able to walk

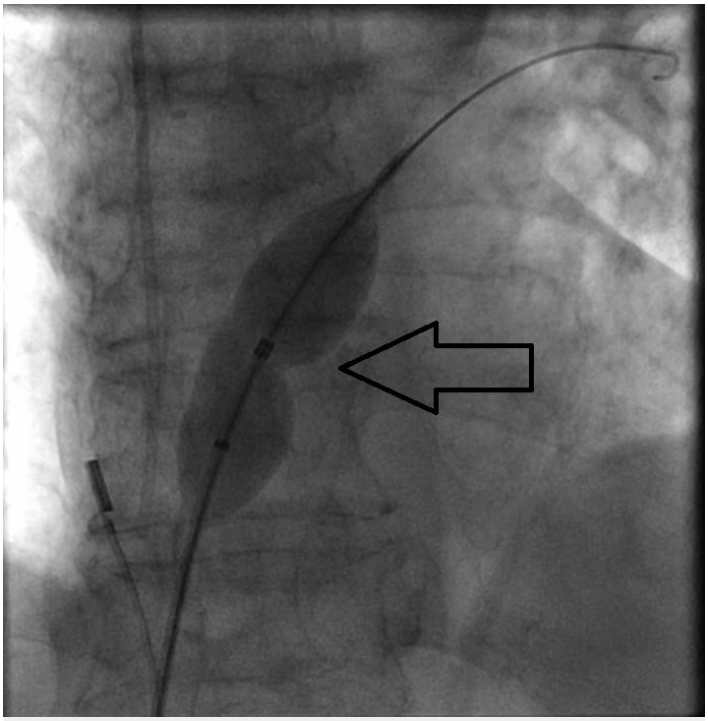

Figure 2.
Amplatzer sizing balloon in place across the patent foramen ovale. The waist (arrow) measured 13 mm.

up a flight of 12 stairs without stopping. At the final 3-month follow-up, he was able to stop clopidogrel. An echocardiogram at that time showed a well-seated closure device without evidence of shunt by saline injection.

DISCUSSION

We describe the case of a patient with platypnea-orthodeoxia syndrome secondary to a PFO without pulmonary hypertension or right heart failure that was successfully treated by catheter-based closure of the PFO. Platypnea-orthodeoxia is a rarely identified clinical syndrome that was first identified in 1949 and was initially termed "orthostatic cyanosis." The terms "platypnea" and "orthopnea" were coined in 1969 and 1976, respectively, to describe breathlessness and arterial desaturation worsening in the upright position and improving when supine.[1] However, the condition and its pathophysiology have remained somewhat mysterious. In the first half century after the condition was identified, fewer than one case per year was reported in the literature.[2] The condition is probably under-recognized because upright and supine vital signs are not routinely collected in most clinical visits. When it is detected, however, the signs and symptoms appear paradoxical and are therefore memorable to the treating physician.

Both intracardiac and extracardiac etiologies for platypnea-orthodeoxia syndrome have been described. The most common cause of orthodeoxia-platypnea in the extracardiac group of etiologies is cirrhosis leading to hepatopulmonary syndrome.[3] In hepatopulmonary syndrome, acquired pulmonary arteriovenous fistulae, which stem from liver disease, allow the requisite right-to-left shunting that is accentuated in the upright position. The reason why shunting is exacerbated in the upright position is unclear, although most patients spontaneously improve after undergoing liver transplantation. Other reported causes of intrapulmonary shunting leading to platypnea-orthodeoxia include Osler-Weber-Rendu disease and severe cases of parenchymal lung disease.[4,5] For patients with platypnea-orthodeoxia due to pulmonary disease, gravitational effects on regional pulmonary arterial flow may account for the positional changes in patients' symptoms and saturation.[1] An alternative explanation is hypovolemia that causes postural changes in ventilation-perfusion matching.[4]

The role of intracardiac right-to-left shunting in platypnea-orthodeoxia was recognized as early as 1956, and both PFO and atrial septal defects have been implicated. Platypnea-orthodeoxia secondary to intracardiac shunting has been reported most often in the setting of elevated RV filling pressure with a concomitant pressure gradient from the right-to-left atrium. Such physiology has been described in cases of pneumonectomy, pulmonic valve stenosis, Eisenmenger syndrome, tamponade following cardiac surgery, pulmonary embolism, or RV infarction and severe tricuspid insufficiency.[4,6-11] In fact, clinical evidence of right heart failure accompanying the orthodeoxia-platypnea in such cases is expected. In the absence of right heart failure, cardiac tumors that obstruct RV inflow and lead to elevated right atrial pressures have also been implicated.[12] Our case is highly unusual in that both right heart failure and pulmonary hypertension were absent, both right atrial pressure and pulmonary capillary wedge pressure were low, and RV function was normal by transthoracic and transesophageal echocardiography.

It is clear, then, that when an intracardiac anatomic defect is present at the atrial level, platypnea-orthodeoxia can occur even in the absence of elevated right-sided filling pressures. Yet most patients with atrial shunts do not seem to suffer from platypnea-orthodeoxia. Why is that so? Various explanations exist in the medical literature. One hypothesis suggests that the interatrial septum and foramen ovale may acquire a conformational change during adult life that causes blood flow to preferentially route from the right atrium to the left when the patient is seated upright, even in the absence of a significant pressure gradient.[2,11,13] Presumably, the effects of this anatomic change are dynamic such that the baffling effect resolves once the patient returns to a supine position. Although the specific anatomical changes to the septum and the mechanism for its dynamic effects have

not been well described, many underlying factors have been implicated, including kyphoscoliosis, aortic dilatation, right hemidiaphragmatic ascension, aortic ectasia, or pulmonary fibrosis.[13-19] Other hypotheses include the notion that either a persistent Eustachian valve or pericardial compression may create a physiologic baffle to direct flow from the inferior vena cava to the left atrium through a PFO when the patient sits upright.[20]

In addition to the presence of any specific anatomic factor, it has also been shown that right-to-left atrial shunting can exist in patients with normal right and left atrial pressures in early ventricular systole, especially during inspiration, when venous return to the right heart is greater than the left.[21] It seems plausible, therefore, that patients with atrial septal defects and particularly large pulmonary tidal volumes (such as patients suffering from primary lung disease or with elevated circulating catecholamine levels) might be at increased risk for developing platypnea-orthodeoxia because tidal volumes are typically larger in the upright position than the supine position.[22] Simultaneous measurement of right and left atrial pressures in patients presenting with platypnea-orthodeoxia in both supine and upright positions would be necessary to clarify this physiology, and we did not perform these measurements in our patient.

Ultimately, there is no clear mechanism to explain our patient's dramatic platypnea and orthodeoxia. Transesophageal echocardiography clearly showed right-to-left flow in early ventricular systole that reversed in late systole. Because mean left atrial pressures were slightly low due to hypovolemia, this suggests that a transient but meaningful right-to-left atrial pressure gradient existed during early ventricular systole, particularly during inspiration. Additionally, our patient had had significant kyphosis (Figure 3) due to steroid-associated osteoporosis, and this may have contributed to an acquired conformational change in the interatrial septum that allowed the requisite shunt. The rapid onset of his orthodeoxia-platypnea, along with the occurrence of paradoxical embolic stroke while in the seated position, also suggests that the anatomic insult had developed rather suddenly late in life, perhaps due to the kyphosis reaching a breaking point.

It is uncertain if platypnea-orthodeoxia occurs primarily due to an inducible pressure gradient occupying only a fraction of the cardiac cycle or as a flow phenomenon secondary to anatomical factors. While platypnea-orthodeoxia is rare, stroke due to "paradoxical" embolism across a PFO is much more common, even in the absence of pulmonary hypertension, right heart failure, or elevated right atrial pressures. Indeed, a review of our catheterization lab database showed that among the 171 adult PFO closure procedures performed between 2003 and 2015, only this one case was for documented platypnea-orthodeoxia, and the majority of the remaining cases were performed for

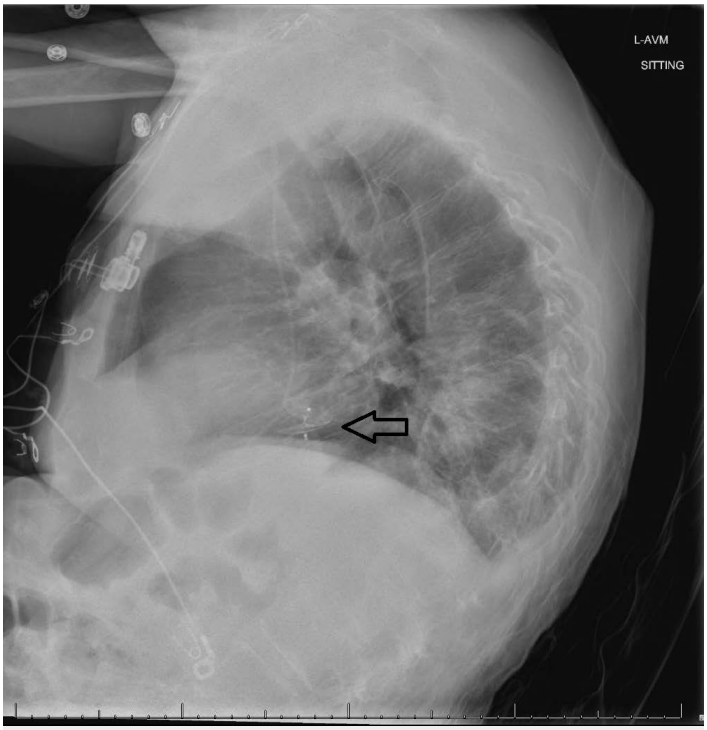

Figure 3.
Significant kyphosis on postprocedural lateral chest film. Note the presence of the Amplatzer device (arrow).

secondary stroke or transient ischemic attack prevention. If transient interatrial pressure gradients driving right-to-left flow are responsible for many of these "paradoxical" embolic events, then it could be prudent to advise patients with PFO to avoid circumstances that may exacerbate such a gradient (such as excessive hyperventilation). On the other hand, if geometric mechanisms are responsible for many of these events, then more aggressive treatment of PFO in patients with kyphosis or prominent Eustachian valves might be warranted.

Finally, given the prevalence of PFO, it is reasonable to consider platypnea-orthodeoxia in the workup of patients presenting with otherwise unexplained shortness of breath, especially in those with comorbid conditions such as kyphosis, severe lung disease, or history of prior embolic stroke. The history may suggest the diagnosis with a simple question (e.g., "Does your breathing feel more comfortable sitting up or lying flat in bed?"). Bedside examination is also relatively simple, since the patient's respiratory effort can be observed and pulse oximetry measured in supine, sitting, and upright postures. By including blood pressure and heart rate measurements in each position, evaluation for comorbid orthostasis can be performed simultaneously to better assess the patient's hemodynamic state. This is particularly relevant as hypovolemia may potentially

exacerbate the platypnea symptoms. A comprehensive history and exam to evaluate for platypnea-orthodeoxia should take no longer than 10 minutes and confers no risk to the patient. The time spent in careful diagnostic assessment is worthwhile since, unlike many other causes of dyspnea, platypnea-orthodeoxia due to intracardiac shunting is very likely curable with catheter-based therapy.[23]

CONCLUSION

We describe a case of PFO-induced platypnea-orthodeoxia syndrome with concomitant bidirectional shunting occurring in the setting of kyphosis but in the absence of pulmonary hypertension, heart failure, or elevated filling pressures. The condition produced NYHA class IV symptoms and eluded diagnosis for several months but was ultimately cured by catheter-based closure of the foramen ovale. The exact mechanism by which platypnea-orthodeoxia can develop in the presence of a PFO or ASD remains somewhat unclear; however, it may involve either acquired anatomical factors producing a baffling effect, preferentially shunting blood from right to left even in the absence of marked pressure gradients, or hemodynamic factors producing meaningful right-to-left pressure gradients under certain postural and loading conditions. Evaluation for platypnea-orthodeoxia is reasonable in patients with unexplained dyspnea since the condition is potentially curable with closure of the anatomic defect.

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Conflict of Interest Disclosure:
The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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orthodeoxia, platypnea, patent foramen ovale, dyspnea

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