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LETTER TO THE EDITOR

Platypnea-orthodeoxia syndrome mimicking postural orthostatic tachycardia syndrome

Jeremy K. Cutsforth-Gregory[1] · Eduardo E. Benarroch[1] · Guillaume Lamotte[1]

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To the editor,

We present the case of a 51-year-old man who presented to our institution for evaluation of orthostatic intolerance. Autonomic evaluation revealed postural tachycardia syndrome (POTS), and the man was diagnosed with platypnea-orthodeoxia syndrome (POS).

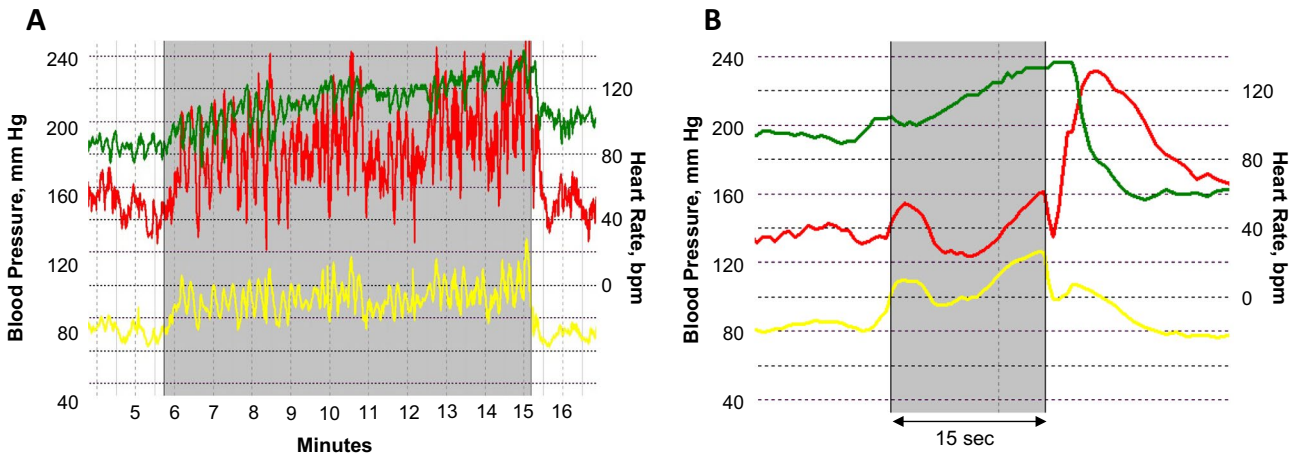
The patient's chief complaints were dizziness and spells of apparent loss of consciousness provoked by upright posture. These symptoms were accompanied by dyspnea, chest pain, palpitations, and exercise intolerance for the past year. He had a history of obstructive sleep apnea and was compliant with continuous positive airway pressure at night. His height and weight were 183 cm and 106 kg, respectively (body mass index 31.6 kg/m^2). Results of the neurologic examination were normal. Cardiac examination revealed a systolic flow murmur in the pulmonic position, without fixed splitting of the second heart sound. The remainder of the examination was otherwise unremarkable. He was not taking any medications.

Tilt table test showed symptomatic orthostatic tachycardia (supine to upright heart rate increment 48 bpm) without orthostatic hypotension, consistent with a diagnosis of POTS (Fig. 1a) [1]. Excessive blood pressure oscillations during head-up tilt and exaggerated phase IV blood pressure overshoot during the Valsalva maneuver suggested an hyperadrenergic response (Fig. 1a, b). Ambulatory 24-h blood pressure recording revealed labile hypertension. Results of the thermoregulatory sweat test were normal. Complete blood counts, electrolyte panel, creatinine, thyroid-stimulating hormone, serum protein electrophoresis, urine metanephrines, and paraneoplastic autoantibody panel (including ganglionic nicotinic acetylcholine receptor antibodies) were normal or negative. Hematocrit was 46.3%. Plasma norepinephrine rose appropriately from 241 to 581 pg/mL from the supine to standing position (Fig. 1c).

The patient's complaint of dyspnea with standing (platypnea) prompted further evaluation for possible orthostatic changes in oxygenation. Radial artery blood gases while breathing room air in the supine position were normal; upon standing for 8 min, oxygen saturation and partial pressure of oxygen declined while the alveolar-arterial gradient rose, consistent with orthodeoxia. Analysis of blood gases in the upright position also revealed respiratory acidosis with decreased pH, increased partial pressure of carbon dioxide and mild increase in bicarbonate (Fig. 1c). No abnormalities were seen on the transthoracic echocardiogram in the supine position, nor on the transesophageal echocardiogram, with the latter showing no right-to-left shunt despite agitated saline injections at rest and with Valsalva release performed in the supine position and at 45° and 80° upright. The cardiopulmonary exercise test with right heart catheterization was performed in both the supine and upright positions (cycle ergometer with stepwise increment in intensity). Exercise was terminated at 140 watts due to symptoms of presyncope. The calculated shunt equation showed a non-significant shunt of 10.3% in the supine position and 11.6% during maximal upright exercise. Therefore, there was no evidence of right-to-left or left-to-right shunt during the cardiopulmonary stress test during right heart catheterization, although episodes of desaturation were detected during exercise in the upright position. Pulmonary function tests showed a substantial obstructive component that improved upon bronchodilation (forced expiratory volume capacity in the first second [FEV1] increased from 69 to 99% with albuterol). Computed tomography (CT) scan of the chest showed normal lung parenchyma. A supine ventilation-perfusion (V/Q)

✉ Jeremy K. Cutsforth-Gregory
cutsforthgregory.jeremy@mayo.edu

[1] Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA



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Arterial Blood Gas	Normal Range	Sitting, Rest	Standing, Exercise
pH	7.35-7.45	7.44	7.35
PO_2	73-97 mmHg	90	55
PCO_2	35-45 mmHg	34	45
O_2 saturation	> 92 %	97	88
A-a gradient	5 - 15 mmHg	13	36
Hematocrit	38.8 - 50.0%	46.3	46.3
Lactate (exercise)	0.6 - 2.3 MEQ/L	1.7	4.8
Bicarbonate / base excess	22 - 26 MEQ/L	23 / -1	25 / -1

Fig. 1 Autonomic testing showing postural orthostatic tachycardia syndrome (POTS) and results of supine and orthostatic blood gases. **a** Head-up tilt provoked excessive rise in heart rate (green line) and symptoms of dizziness, confusion, chest tightness, diaphoresis, and acral paresthesias, consistent with POTS. The accompanying rise in blood pressure (systolic, red line; diastolic, yellow line) suggests a hyperadrenergic state. **b** Beat-to-beat blood pressure and heart rate monitoring during the Valsalva maneuver showed exaggerated phase IV overshoot, another hyperadrenergic feature. **c** Orthostatic blood gas testing demonstrating orthodeoxia. *A-a* Alveolar-arterial, O_2 oxygen, PO_2 partial pressure of oxygen, PCO_2 partial pressure of carbon dioxide

scan showed normal perfusion and ventilation to both lungs. There was evidence of diffuse fatty infiltration of the liver on CT abdomen. An exhaled nitric oxide test was normal at 25.5 parts per billion (upper limit of normal 39.9 parts per billion). Carotid ultrasound revealed normal anatomy without significant stenosis.

The autonomic evaluation was consistent with a diagnosis of POTS; however, the patient's orthostatic shortness of breath (platypnea) and orthostatic oxygen desaturation (orthodeoxia) led to the diagnosis of POS secondary to chronic lung disease causing a V/Q mismatch. The recommended symptomatic management included reconditioning with graded exercise with an emphasis on recumbent exercise and treatment of underlying obstructive lung disease. During a phone follow-up assessment 10 days after discharge, the patient reported improvement of the platypnea but worsening tachycardia with the use of beta-adrenergic receptor agonist bronchodilators. Inhaled corticosteroids were then recommended. Subsequent follow-up data were not available. Further evaluation of the liver disease was also recommended (e.g., hepatitis serologies, abdominal sonography); however, the suspicion for cirrhosis and/or hepatopulmonary syndrome was low as the patient had no history of taking medications, supplements, chemicals, solvents, or alcohol that could cause hepatotoxicity, as well as a normal exhaled nitric oxide test.

Orthostatic hypertension, defined as a postural increase of at least 20 mmHg systolic blood pressure upon standing, should also be considered in the differential diagnosis [2]. Clinical manifestations of orthostatic hypertension include chest pain, dyspnea, and syncope, and postural tachycardia may coexist on testing [2]. The pathophysiology of orthostatic hypertension is not fully understood, and proposed mechanisms include excessive venous pooling and increased peripheral vascular resistance [2]. Orthostatic hypertension is an important condition to recognize because symptoms

may be reduced by medications such as alpha- or beta-blockers. As orthodeoxia with a measurable reduction in oxygen saturation from supine to standing is not a feature of orthostatic hypertension, the diagnosis of POS seems more appropriate in this patient.

POS is characterized by dyspnea and hypoxemia in the upright position that resolve in recumbency [3]. Patients develop variable combinations of symptoms, including orthostatic dyspnea, tachypnea, tachycardia, chest tightness, and cyanosis upon standing [3]. Although platypnea is classically the cardinal manifestation of POS, the present case highlights the fact that symptoms of cerebral hypoperfusion or sympathetic activation and excessive heart rate rise may be seen in this disorder, mimicking POTS. The postural tachycardia in POS is thought to be compensatory for the hypoxemia. In 258 patients with pulmonary arteriovenous malformations evaluated prospectively, 30% of patients had orthodeoxia, and orthostatic tachycardia was more pronounced compared to controls [4]. Furthermore, the authors demonstrated a significant correlation between the orthostatic pulse rise and the drop in oxygen saturation [4]. In the present case, the hypoxemia was moderate and other factors, such as deconditioning and anxiety, likely contributed to the postural tachycardia.

The distinguishing feature of POS is the measurable reduction in oxygen saturation from supine to standing [5]. The gold standard for the diagnosis of POS is cardiac catheterization, which shows a drop in the oxygen saturation between the pulmonary vein and the aorta and excludes concurrent pulmonary hypertension [6]. The mechanism of POS is thought to be orthostatic accentuation of a right-to-left shunt, and etiologies generally fit into one of three categories: right-to-left intra-atrial shunt, pulmonary V/Q mismatch, or pulmonary vascular shunting [6]. POS has also been reported with other types of intracardiac shunt, pulmonary or intrahepatic shunt, and V/Q mismatch due to pulmonary parenchymal disease [3, 5, 7, 8]. Recently, POS has been reported during the acute phase of severe 2019 novel coronavirus disease (COVID-19) and after fibrotic evolution of COVID-19 interstitial pneumonia associated with pulmonary embolism [9, 10]. The predominantly basal distribution of pulmonary parenchymal changes associated with COVID-19 pneumonia and the hypercoagulable state and microthrombi that can be seen in COVID-19 disease may explain the development of POS secondary to pulmonary V/Q mismatch [9, 10]. The cause of POS in our patient remains speculative—primarily obstructive lung disease causing V/Q mismatch and possible hepatic disease with or without occult intrapulmonary shunting. With regards to the patient's arterial blood gas testing, the upright position induced moderate hypoxemia. The rise in partial pressure of carbon dioxide from 34 to 45 mmHg suggested hypoventilation; however, the increase in alveolar-arterial gradient indicated the likely contribution of a ventilation/perfusion mismatch and no shunt or impaired pulmonary diffusion could be identified. The normal V/Q scan may reflect the effects of body position on V/Q matching as the recumbent position has been shown to reduce the V/Q mismatch [11].

Atypical features of our patient with respect to POTS were the male sex and mature age. Breathlessness that worsens in the upright position is a common symptom in patients with POTS and may be related to dysfunctional breathing/hyperventilation syndrome [12]. Orthodeoxia, however, is not a feature of POTS and the unusual severity of the respiratory symptoms during orthostatic challenge in our patient prompted further testing.

Clinicians should be aware that POS may mimic POTS. In patients presenting with platypnea, measurement of oxygen saturation in the supine and standing positions should be performed. A measurable drop in arterial oxygen saturation of > 5% should prompt further investigation with analysis of supine and standing arterial blood gases as well as testing for intracardiac shunts and lung or liver disease. If an intracardiac anatomical defect is present, the condition is potentially curable with surgical intervention.

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Declarations

Conflicts of interest The Corresponding Author affirms that none of the authors has a conflict of interest.

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