

Platypnea-orthodeoxia syndrome related to the patent foramen ovale and atrial septal aneurysm

Sindrom platipneje-ortodeoksije, povezan s otvorenim foramenom ovale i aneurizmom interatrijskog septuma

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Summary

The platypnea-orthodeoxia syndrome is a rare condition characterized by postural dyspnea and hypoxemia that disappear or diminish in lying position, so it can be difficult to recognize without close assessment of the patient's pattern of dyspnea. The syndrome is commonly associated to an intra-cardiac right-to-left shunt through a patent foramen ovale as the most frequently reported site of the shunt. Platypnea-orthodeoxia syndrome can be the cause of refractory hypoxemia leading to pulmonary hypertension, whereby, if suspected, contrast echocardiography in supine as well as in upright position should be performed. We are presenting a case of an unrecognized platypnea-orthodeoxia syndrome because of a patent foramen ovale and atrial septal aneurysm, with developed chronic complications due to long-standing hypoxemia. This case highlights the need of a high index of suspicion to diagnose the syndrome on time and the necessity of careful echocardiographic evaluation.

Key words: Platypnea-orthodeoxia syndrome, shunt, hypoxemia, patent foramen ovale, atrial septal aneurysm

Sažetak

Sindrom platipneje-ortodeoksije je rijetko stanje koje je karakterizirano položajnom dispnejom i hipoksemijom koja nestaje ili se smanjuje u ležećem položaju, te ga je stoga teško dijagnosticirati ukoliko se pažljivo ne procijeni bolesnikov obrazac dispneje. Često je povezan s intrakardijalnim šantom i to kroz otvoreni foramen ovale, koji predstavlja najčešću lokaciju šanta. Sindrom platipneje-ortodeoksije može biti uzrokom refrakterne hipoksemije koja dovodi do plućne hipertenzije, pa je potrebno, ukoliko sumnjamo na ovaj sindrom, učiniti kontrastni ehokardiografski pregled, kako u ležećem, tako i u povišenom položaju bolesnika. U ovom prikazu slučaja predstaviti ćemo dugo neprepoznati sindrom platipneje-ortodeoksije koji je nastao kao posljedica otvorenog foramena ovale, uz prisutnu aneurizmu interatrijskog septuma i razvijene kronične komplikacije dugotrajne hipoksemije. Cilj ovoga prikaza je naglasiti kako je potrebna visoka razina sumnje i pomna ehokardiografska evaluacija da bismo na vrijeme prepoznali i dijagnosticirali ovaj sindrom.

Ključne riječi: Sindrom platipneje-ortodeoksije, šant, hipoksemija, otvoreni foramen ovale, aneurizma interatrijskog septuma

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Introduction

The platypnea-orthodeoxia syndrome (POS) is characterized by postural dyspnea (platypnea) and hypoxemia (orthodeoxia) which disappear or diminish in a lying position. It is defined as PaO₂ decline \geq 5% or 4 mmHg when upright.^{1,2} The syndrome can occur with various intra-cardiac or extra-cardiac abnormalities, but the exact pathophysiological mechanism underlying this entity has not yet been defined. The most common etiologic association is an intra-cardiac right-to-left shunt through a patent foramen ovale (PFO), an atrial septal defect (ASD) or an atrial septal aneurysm (ASA).³ A small number of cases of POS have been reported so far, especially dealing with its complications. We present a case of an unrecognized POS because of a PFO and ASA, with developed chronic complications, as severe pulmonary hypertension and *cor pulmonale*, due to long-standing hypoxemia.

Case presentation

A 67-year-old male patient was hospitalized due to progression of dyspnea and hoarseness. Several years earlier, the patient became dyspneic and noted that his lips and tongue turned blue. He was diagnosed with COPD with partial respiratory insufficiency two years before admission in another institution and was discharged with a long-term oxygen therapy with the flow of 8 L per minute. One year prior to admission, on routine transthoracic echocardiography (TTE) in another hospital, elevated systolic pressure in the right ventricle was recorded (40 mmHg) but no anatomical defect was described. He also had arterial hypertension for many years and stable coronary artery disease.

At the moment of admission, he was dyspnoeic at rest, plethoric and centrally cyanotic with heart rate of 100 min⁻¹ and a blood pressure of 140/90 mmHg. We suspected that the possible causes of deterioration were as follows: acute COPD exacerbation, pneumonia (possibly interstitial), pulmonary embolism or heart failure. Oxygen was immediately delivered via a mask with a reservoir bag with the flow of 15 L per minute. Despite the treatment, his blood oxygen saturation was not satisfying (85-88%) without CO₂ retention. We started with diagnostic workup to reach the final diagnosis, and, meanwhile, with standardized COPD exacerbation supportive treatment (intravenous glucocorticoids, inhaled bronchodilators, empirical parenteral antibiotic therapy).

Laboratory findings showed polyglobulia (hemoglobin 182 g/L, hematocrit 0.527) with slightly elevated markers of inflammation. A chest X-ray

revealed mild congestive changes in the basal parts of the lungs and a myopatic cardiac silhouette (Picture 1).

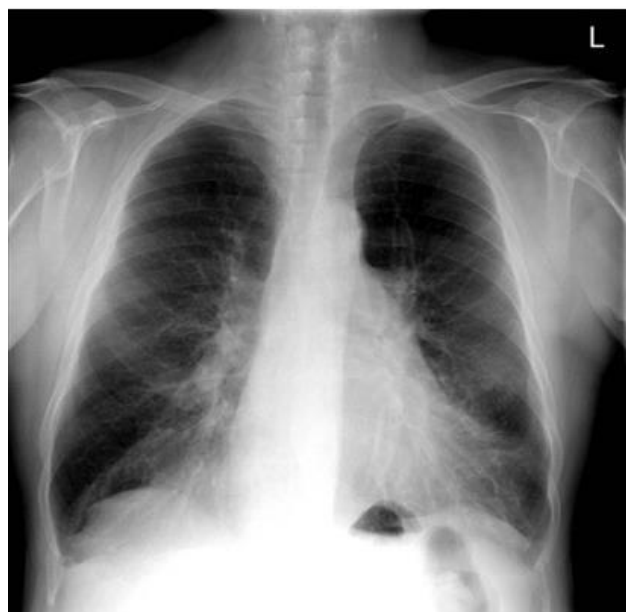


Figure 1 Chest X-ray

Slika 1. Rendgenska snimka srca i pluća

Electrocardiography showed normal sinus rhythm without signs of ischemia. Spirometry revealed obstructive airflow limitation of mild degree (forced vital capacity (FVC) 2.69 L, 69.7% predicted; forced expiratory volume in one second (FEV₁) 1.79 L, 59.7% predicted; FEV₁/FVC, 0.66) with a negative bronchodilator (salbutamol) test. Diffusing capacity of the lungs for CO (DL_{CO}) was very low at the level of alveocapillar membrane (DL_{CO}, 15.1%; transfer coefficient (K_{CO}), 17.5% predicted; alveolar volume (VA), 88.5% predicted). The patient underwent MSCT pulmonary angiography and perfusion scintigraphy to exclude pulmonary embolism. The HRCT scan also excluded interstitial pathology. Since lymphadenopathy of the right cervical lymph nodes was noticed during clinical examination, needle biopsy for cytology was also done revealing metastatic planocellular cell carcinoma of the larynx. Furthermore, bronchoscopy was performed after a week and revealed a supraglottic arc formation in the ventricular folds which did not significantly narrow the airway. Bronchial anatomy was normal with no endobronchial lesions. Surprisingly, larvae of *Strongyloides stercoralis* were isolated in bronchial aspirate and, immediately after the isolation, albendazole was introduced followed by ivermectin. Glucocorticoids were withdrawn due to *Strongyloides* infection according to current literature.⁴ Despite the treatment attempts, no dyspnea amelioration occurred.

During the clinical rounds, we noticed a regression of cyanosis in a horizontal position which prompted us to suspect about POS. Consequently, blood gas analysis in both lying and sitting position was performed. In lying position, in room air, the patient had partial respiratory failure with respiratory alkalosis – PaO₂ 38 mmHg, PaCO₂ 33 mm Hg, pH 7.49, bicarbonates 25, BE + 3, SaO₂ 78%, while in a sitting position – PO₂ 34 mmHg, PaCO₂ 32 mm Hg, pH 7.49, bicarbonates 24, BE + 2, SaO₂ 72%. With oxygen therapy, saturation increased by 11% in lying position, while in sitting position it increased only by 2%. The criteria for POS were fulfilled so we proceeded with further investigations to identify its underlying mechanism. On TTE left ventricle ejection fraction was normal but the right atrium and ventricle were markedly dilated with paradoxical movements of interventricular septum due to the pressure overload of the right ventricle (Figure 2). Moderate tricuspid valve regurgitation was found with systolic pressure in the pulmonary artery of 80 mmHg. To evaluate for interatrial shunts, saline contrast study (bubble study) was done. It revealed no shunt while lying down, but in a sitting position it confirmed the presence of contrast in the left ventricle within three heartbeats which was indicative for an intra-cardiac shunt. In order to be able to directly visualize the cardiac defect, transoesophageal contrast ultrasound both in

recumbent and elevated position was done and it ultimately demonstrated wide-open PFO with ASA (Figure 3). Right heart catheterization revealed precapillary pulmonary hypertension: SaO₂ of 48% in the right atrium, 45% in the superior caval vein, and 47% in the inferior caval vein, pulmonary capillary wedge pressure 12 mmHg, pulmonary artery pressure 88/60/40 mmHg, right ventricle pressure 89/9 mmHg, right atrium pressure 10 mmHg and pulmonary vascular resistance 12 Wood units. We were not able to pass through PFO so the blood from the lung veins was not taken for analysis. After the demonstration of severe pulmonary hypertension, we presumed that the most likely cause of the condition was long-standing hypoxemia due to right-to-left shunting through the PFO with malformed interatrial septum in the form of ASA.

The hospital team decided to deal with active malignant neoplasm (planocellular larynx cancer), and after achieving a stable stage, to introduce pulmonary hypertension therapy. As anesthesiologists suggested that general anesthesia for surgery was too risky, the oncology team indicated radiotherapy, but laryngeal stoma was necessary for this. The same day, a few hours after the procedure, the patient entered into respiratory arrest and was shortly reanimated and placed on mechanical ventilation, on which he spent the following 77 hours before he passed away.

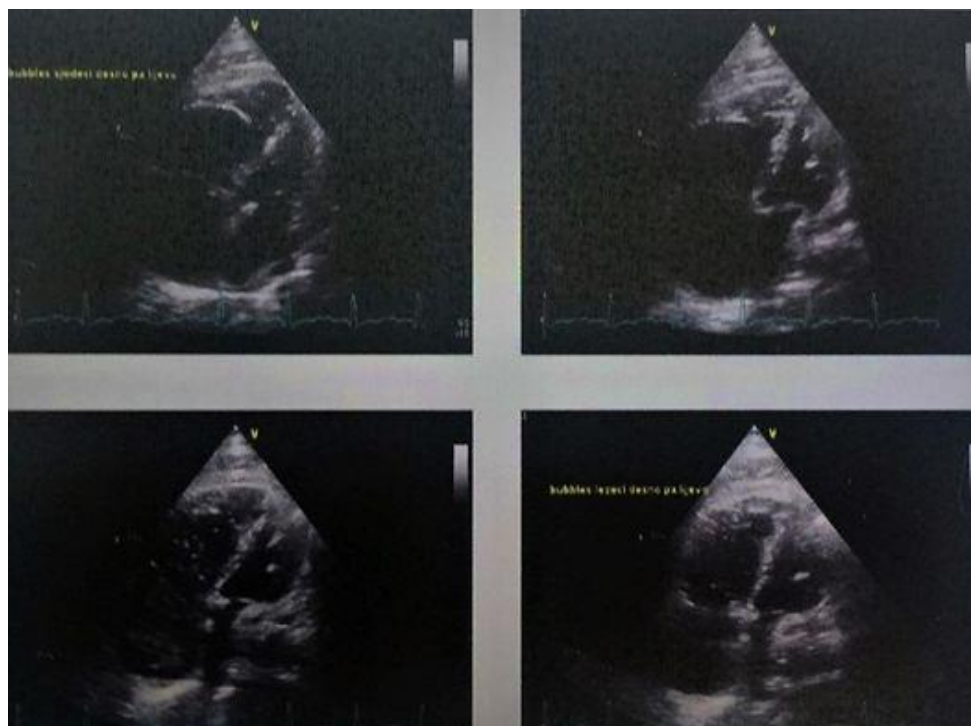


Figure 2 Transthoracic echocardiography showing markedly dilated right heart chambers and a bubble study
Slika 2. Transtorakalni ultrazvuk srca uz prikaz uvećanih desnostranih srčanih šupljina i kontrastna ehokardiografija

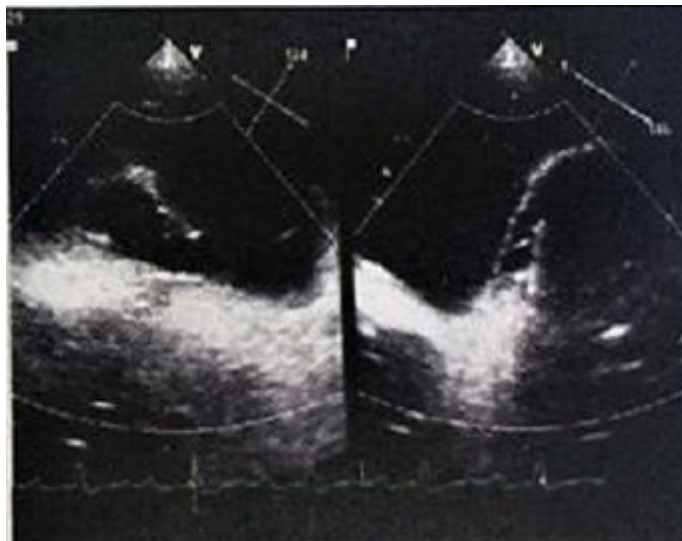


Figure 3 Transoesophageal ultrasound in an elevated position demonstrating patent foramen ovale
Slika 3. Transezofagijski ultrazvuk srca u povišenom položaju na kojem je prikazan otvoreni foramen ovale

Discussion

POS is an uncommon entity that can occur in a variety of clinical settings primarily caused by cardiac, pulmonary or hepatic diseases. It can be difficult to recognize without closely assessment of the patient's pattern of dyspnea.^{5,6} Various theories have been proposed to explain this condition, and they are discussed in the following text.

The most common cause of POS is the intracardiac right-to-left shunt, present as PFO or, less commonly, as ASD and ASA.^{3,6-11} The condition becomes usually manifested after anatomic changes due to surgeries (pneumonectomy and lobectomy), or associated with kyphoscoliosis, aortic elongation and aneurysm.¹²⁻¹⁹ According to literature, there are also some other conditions related to POS in the presence of PFO: eosinophilic endomyocardial disease, hypovolemia, pericardial diseases, compression of the right heart by a hydatid cyst of the liver, hemidiaphragm paralysis, blunt chest wall trauma.^{6,20-26} In most cases, the pulmonary artery pressure remains normal.^{16,17} Cyanosis without pulmonary arterial hypertension should alert the possibility of an atrial right-to-left shunt, and considering the high frequency of PFO (according to autopsy studies the prevalence is 27%) as well as pulmonary surgeries performed nowadays, it could be possible that POS is underdiagnosed.²⁷ Why do the symptoms occur considering the absence of a pressure gradient between the right and left atrium (either in the sitting or supine position) and the interatrial septum normally being functionally closed even in the presence of PFO? The possible explanation

could be that orthodeoxia is generated from the stream of venous return being directed across the PFO, caused by mechanical deformation of the interatrial septum. Moreover, atrial emptying can be affected by changing the relationship of ventricular compliance in different pathologies (e.g. pneumonectomy or myocardial infarction) causing decrease in right ventricle compliance.^{6,8,11,27,28} It seems that an anatomic substrate like interatrial communication must coexist with a functional component that produces distortion in the interatrial septum thus resulting in preferential redirection of shunt flow in upright position through the interatrial defect even in the absence of a pressure gradient.²⁹ Nevertheless, why the right-to left shunt occurs only in raised positions is not completely understood.

On the other hand, the mechanism of intrapulmonary shunts in patients with chronic pulmonary disorders was explained by Altman and Robin on the basis of changes in the alveolar perfusion gradient.⁵ In the healthy lung, the blood flow is greater at the bases, while the alveolar pressure remains constant through the lung. The latter become substantially elevated as a result of alterations of ventilatory mechanics in different lung diseases. This is apparent in apical segments and intensified with upright positions. Finally, this can result in a decrease in pulmonary artery pressure and pulmonary capillary compression with respiratory dead space. The supine position virtually eliminates zone 1 (upper part of the lung) placing more of the lung in zone 3 (at the bases of the lung) so severe hypoxemia can occur when many gas exchange units are still perfused but not ventilated.

When the patient is in supine position, it is possible that the entire underperfused zone 1 converts into zone 3 leading to equal perfusion and ventilation, ultimately sufficient oxygenation and whenever the patient becomes erect, increased perfusion of poorly ventilated zone 3 causes ventilation perfusion mismatch leading to platypnoea-orthodeoxia.

In addition to intracardiac causes of POS, there are reports of POS occurring in various extracardiac disorders, mainly pulmonary. Hypoxic vascular pulmonary constriction may be inappropriate in COPD patients thus causing ventilation perfusion mismatch, and subsequently POS.³⁰ Platypnea occurred in one COPD patient during ileus and disappeared after ileus had been resolved. It was suggested that impaired abdominal muscle contraction when upright was responsible for the development of platypnea.³¹ In another COPD patient, the cause of POS was found to be multiple pulmonary emboli with condition being improved on anticoagulation therapy.⁶ Massive pulmonary embolism with significant ventilation perfusion mismatch was the cause of POS in the case presented by Khokhar et al.³² POS was described during adult respiratory distress syndrome, cryptogenic fibrosing alveolitis and in a patient with organophosphorus poisoning on mechanical ventilation.³³⁻³⁵ Continuous positive airway pressure treatment reduced orthodeoxia in the latter.³⁴ Tumors of the upper airways can produce platypnea because of positional compression of airways or vascular structures (not the case with our patient).³⁶ Platypnea has been described in a patient with postirradiation bronchitis which led to severe bronchial stenosis that was relieved by stent placement.³⁷ There are reports of the association of platypnea with autonomic dysfunction causing an orthostatic increase in ventilation perfusion mismatch and showing improvement with fluid challenge.^{6,38,39}

POS can happen in relationship to the hepatopulmonary syndrome (HPS). It is estimated that 15% to 45% of patients with liver cirrhosis are hypoxemic without manifest heart or lung disease.⁴⁰ HPS is a triad of hypoxemia, liver disease and intrapulmonary vascular dilatations.⁴¹ It may be transient as described in the case of an acute hepatitis A.⁴² Rodriguez-Roisin et al.⁴³ have proposed four diagnostic criteria for the HPS: absence of cardiopulmonary disease, presence of chronic hepatic disease, pulmonary gas exchange abnormalities and intrapulmonary shunts. There may be other features that are not always present: shortness of breath with or without orthodeoxia and platypnea, low diffusing capacity, reduced pulmonary vascular pressures and increased cardiac output. Hypoxemia in HPS has various causes: diaphragmatic dysfunction, pleural effusions, impaired hypoxic vasoconstriction,

precapillary and capillary intrapulmonary vascular dilatations resulting in shunts and impaired matching of ventilation to perfusion.⁴⁴ When the patient is raised, because of gravity, the blood is redirected to the dilated precapillary beds of the lower lung parts thus increasing the arteriovenous shunting and resulting in orthostatic hypoxemia.⁸

Consequently, POS should be considered in the differential diagnosis of unexplained dyspnea and refractory hypoxemia. Demonstration of platypnea and blood gas analysis in supine and upright positions are the initial assessments to confirm orthostatic desaturation. Then, the next step is identification of the underlying mechanism of POS. A definitive diagnosis can be made in most cases by contrast-enhanced echocardiography (bubble study) with postural manoeuvres (bed tilt).⁴⁵ Contrast tilt-table transoesophageal echocardiography (TOE) is the most sensitive test for the noninvasive diagnosis of a right-to-left shunt and should be performed with the patient both supine and upright.⁴⁶ Intrapulmonary shunts should be considered if an intracardiac shunt is not detected. The presence of intrapulmonary vascular dilatations can be shown by: ^{99m}Tc-labeled macroaggregated albumin scanning, contrast-enhanced echocardiography, pulmonary arteriography. Once again, contrast-enhanced echocardiography is the method of choice but the passage of contrast through the dilated pulmonary vessels to the left atrium shows a delay of 3-6 heart beats. Angiography is reserved for patients with poor response to therapy and defines whether embolization could be performed.^{8,47,48}

The treatment of POS depends on the cause. Closure of the defect is the treatment of choice for intracardiac (usually interatrial) communication without pulmonary hypertension. It can be performed surgically or by transcatheter techniques with different devices.^{6,8,10,13,16,49-51} The treatment of the underlying pulmonary condition leads to a better ventilation perfusion matching.⁸ No definitive medical treatment has been effective in improving symptoms in HPS except in an anecdotal case with antimicrobial agents in cirrhosis since they can reduce endotoxemia and nitric oxid production which is a potent vasodilator.^{44,52,53} Approximately 80% of patients with HPS improved oxygenation after liver transplantation but hypoxemia carries a high perioperative mortality.⁴⁷ Intrahepatic portosystemic shunt can be also considered for patients with HPS.⁵⁴

Our patient's initial symptoms were connected to severe hypoxia without right heart remodeling and significant pulmonary hypertension. Hypoxia that does not improve on oxygen could not be only due to COPD (especially when only moderate obstructive ventilation

disorders are present and there is no CO₂ retention as in our patient), but it is often caused by a shunt, either intracardial or intrapulmonary, which in turn causes pulmonary hypertension. It was not possible to detect the shunt only performing standard TTE without position manoeuvres so the defect remained unrecognized. Desaturation in the upright position was primarily caused by anatomic opening of the foramen ovale and probably enhanced by ASA which resulted in the redirection of shunt flow across a malformed septum when upright. Desaturation later, increased by development of secondary pulmonary hypertension, led to a vicious circle. On the other hand, with simple primary or secondary pulmonary exactly the opposite hypertension would be expected to happen – the load of the right heart would be reduced by erection and thus the shunt. POS is a relatively rare cause of dyspnea and cyanosis and it is often not considered by physicians. It is essential to have a high index of suspicion to diagnose POS, and if suspected, contrast echocardiography should be done in supine as well as in upright position, ideally with TOE. Unfortunately, the condition in our patient was diagnosed too late and in an advanced stage in which the patient could not cope with the risks of general anesthesia.

Abbreviations

ASA – atrial septal aneurysm
 ASD – atrial septal defect
 BE – base excess
 COPD – chronic obstructive pulmonary disease
 DLCO – diffusing capacity
 FEV₁ – forced expiratory volume in first second
 FEV₁/FVC – Tiffeneau-Pinelli index
 FVC – forced vital capacity
 HPS – hepatopulmonary syndrome
 HRCT – high-resolution computed tomography
 K_{CO} – carbon monoxide transfer coefficient
 L – liter
 MSCT – multi-slice computed tomography
 pH – potential of hydrogen
 PaCO₂ – partial pressure of carbon dioxide
 PaO₂ – arterial partial pressure of oxygen
 PFO – patent foramen ovale
 POS – platypnea-orthodeoxia syndrome
 SaO₂ – oxygen saturation
 TOE – transoesophageal echocardiography
 TTE – transthoracic echocardiography
 VA – alveolar volume

Ethics approval and consent to participate

The case report was approved by the Zagreb University Hospital Ethics Committee and written according to the Declaration of Helsinki and other relevant international and national laws. Relatives of the patient were informed about the case and their written consent was given before starting any writing on the case.

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