Platypnea-orthodeoxia syndrome (POS) describes a clinical entity of arterial hypoxemia in the upright position associated with dyspnée, which is relieved by recumbency. The syndrome is caused by an intracardiac or intrapulmonary shunt, or ventilation-perfusion mismatching.[1] We describe here the first case of resolving/relapsing POS induced by intracardiac right-to-left shunting that was partly dependent on volume overload.

An 81-year-old man was admitted to hospital after an accidental fall without head injury or loss of consciousness. His past medical history was relevant for metastatic prostate cancer with bone metastasis (C2, C7, Th8, L1, L2, L4 and sacrum, without fracture), intestinal large B-cell lymphoma remitted after surgery and chemotherapy (CHOP-R) 6 years prior, idiopathic pulmonary embolism 4 years ago and mild cognitive impairment (mini mental state 22/30). On admission, the patient had mildly elevated blood pressure (140/62 mmHg), normal regular heart rate (60 beats/min), and no fever. Oxygen saturation was not documented. Bilateral pitting leg oedema with signs of chronic venous insufficiency was noted on physical examination, but otherwise normal pulmonary, cardiovascular, and neurological examinations. The patient had no stigmata of chronic liver disease.

On the third day of hospital stay, arterial oxygen saturation on room air was measured at 77% during routine nursing rounds. The patient expressed no breathlessness. There was no evidence of acute respiratory distress, nor new signs of heart failure (except persistent leg oedema). Blood gas analysis while the patient was receiving supplemental oxygen therapy showed isolated hypoxemia (\( \text{PaO}_2: 8.4 \text{ kPa} \); \( \text{PaCO}_2: 4.3 \text{ kPa} \); pH: 7.45). Brain natriuretic hormone (BNP) was slightly elevated (204 ng/L; normal < 100 ng/L). Complete blood count, liver and renal functions were all normal. Electrocardiogram was unchanged. Chest X-ray revealed increased heart size and mild vascular redistribution on both sides (considered to be discrete signs of heart failure). Computed tomography of the chest found no pulmonary embolism or lung abnormality.

Continuous positive pressure and oxygen therapy raised the saturation to 89%, with the patient in the seated position. Laying the patient down corrected the saturation to 94% on room air. A diagnosis of POS was made. Echocardiography enhanced with saline solution (microbubbles) confirmed an intracardiac shunt due to a patent foramen ovale (PFO) and an interatrial septal aneurism (Figure 1). The right-to-left shunt increased on Vasalva manoeuvre and sitting position (Figure 2).

Figure 1. Echocardiography. Note the defect in the interauricular septum (white arrow). IVC: inferior vena cava; LA: left auricle; PFO: patent foramen ovale; RA: right auricle.
Magnetic resonance imaging of the brain (done as part of the falls and cognition work-up) showed old ischemic lesions of the cerebellum. Carotid Doppler ultrasonography found a non-occlusive atheromatous plaque of the right carotid artery. No arrhythmia was found on 24 h of heart rhythm monitoring. The PFO was supposed to be a possible cause of these brain infarctions. Hypoxemia remitted shortly on diuretic therapy, but the patient was admitted several times thereafter for a relapsing profound hypoxemia. Patent foramen ovale was closed percutaneously with favorable results on arterial blood saturation.

POS is a rare clinical entity that was first identified half a century ago by Burchell, et al.[2] in a patient suffering from an arteriovenous shunt due to an atrial septal defect. Since then, although cases are increasingly reported in the medical literature (40 in 2002,[3] and 188 in 2012[4]) the condition is still probably often overlooked in practice because of lack of awareness.

Although miscellaneous causes have been associated with POS,[5] they can be roughly classified into three main categories: ventilation-perfusion mismatch, intracardiac shunts and pulmonary arteriovenous shunts.[1,4] Intracardiac right-to-left shunt, such in our case presentation, is the most common cause of POS, representing 84% of all reported cases.[4] PFO is found in nine out of ten of those intracardiac communications.[4,6] POS requires there to be sufficient right-to-left flow to allow signs and symptoms in the upright position, but to remain clinically silent in the recumbent position. Conversely, larger shunts generally have more dramatic clinical presentations causing persisting hypoxemia and are less likely to present as POS. Normal physiological cardiac pressure gradient would favour blood to flow from left to right, with left sided heart pressures overwhelming right-sided ones. Obvious contributing factors that favour right-to-left shunt can be found in roughly 60% of reported cases.[4] Two clinical circumstances can be distinguished,[4,7] circumstances where right-to-left shunt is caused by increased pulmonary artery pressure, either from a permanent or a transient pathology (e.g., pulmonary embolism) and those where the pulmonary pressure is normal. The latter situation represents almost 83% of reported cases of POS.[4] Several hypotheses, depending on the associated condition, have been postulated to explain the illogical right-to-left flow: anatomic changes that direct the flow through intracardiac communications (e.g., an interatrial septal aneurism); decreased right-sided heart compliance (e.g., ischemia, compression); or a transient increase in right sided pressure in the up-right position.[4,7] The positional hypoxemia observed clinically, may be the consequence of further anatomic pathological anomalies (such as pulmonary diseases, aortic deformation, or kyphoscoliosis) that induce stretching of the atrial septum in the upright position, which can increase opening of the foramen ovale opening, resulting in an exacerbation of the right-to-left shunt.[3] However, the clear underlying pathophysiological mechanism remains uncharacterized.

Given the proposed physiopathology of POS, late diagnosis is not uncommon. In fact, all cases identified in a recent review were older than 50 years, with a mean age in the 70s.[4] Right-to-left flow through the atrial septum is normal during foetal life. PFO results from a failure of fusion of the two embryonic septums (primum and secondum) after birth, a mechanism normally favoured by the drastic increase in left side heart pressures following closure of the ductus arteriosus. The defect is thus present in the very early years, but clinically silent most of the time. Anatomical and physiological changes, with the increased number of comorbidity conditions at older ages explain a part of late diagnosis of a congenital defect. Most notably, age-related stiffness of the right ventricle,[8] anatomical changes such the...
shape and position of the aorta,[9] volume and compliance of the thorax due to vertebral fracture/osteoporosis amongst other disease processes[10] may influence the magnitude and direction of the flow through a PFO. The loss of abdominal musculature and malnutrition seen in older individuals can result in less diaphragmatic support in the prone position.[1,11,12] Moreover, over the years, interatrial septal defect size may increase,[4,13] favouring the shunt flow and the manifestation of POS.[4]

Intravascular volume is a well-established contributing factor for the manifestation of POS. Volume-dependent POS usually worsens in the dehydrated state.[6,8,12,14] Cases reports have described a transient improvement of dyspnea after isotonic fluid infusion.[8] We report the first case of POS that worsens in a state of volume overload with a relapsing-resolving presentation depending on diuretic treatment. We suspect that the pathophysiology underpinning this phenomenon has two components: first, intra-thoracic fluid causes an elevation in pulmonary arterial pressure, favouring right-to-left shunt flow, and consequently limiting right sided heart output. Second, pulmonary extravasation of fluid increases pulmonary ventilation-perfusion mismatching exacerbating hypoxaemia. With reestablishment of a normovolemic state and normal right atrial pressure, the abnormal shunt decreases, resulting in improvement in oxygen saturation.

Since asymptomatic intracardiac communication, notably a patent foramen ovale, is frequent (more than 20% in the general population),[15] workup of POS should first exclude other etiologies of shunt. An intracardiac cause of POS is most often appreciated with echocardiographic examinations, often detected by an agitated saline contrast injection (to reveal an associated PFO) during a Valsalva manoeuvre and/or postural provocation. The passage of microbubbles to the left atrium in the first three beats after right-cavity opacification confirms the diagnosis (microbubbles appearing later, are more commonly observed in intrapulmonary shunts). Transoesophageal echocardiography is more sensitive than transthoracic echocardiography and is considered the gold standard for the diagnosis of PFO.[16,17] Shunt evaluation can be further performed by more invasive serial blood oxygen saturations measurement in the left atrium and the pulmonary veins in upright and prone positions by cardiac catheterization.[6] This procedure has the advantage of also reliably assessing the pulmonary pressure, since closure of a PFO can further increase the PAP.[6]

The patient described in this case report suffered a possible embolic ischemic stroke, in the context of active malignancy, and with a PFO allowing passage of a peripheral clot to bypass the lung and enter the cerebral circulation. The association between PFO, POS and cryptogenic embolism has been found in up to 11% of reported cases.[4]

Although there is controversy surrounding the utility of PFO closure to reduce stroke recurrence, it remains the only treatment to alleviate or correct platypnea and orthodeoxia for the vast majority of intracardiac shunts not related to a transient mechanism. There is also fair evidence to propose percutaneous closure as first line therapy, with failures in 4% of cases and complications in 1%–2%.[4] Long term consequences of closure of the PFO, however, are not known.[6]

In conclusion, platypnea orthodeoxia is a clinical condition often associated with a patent foramen ovale. However, due to the high frequency of clinically silent PFO in the population, diagnostic work-ups should first exclude other causes of POS. Contributing factors should be corrected first, despite most conditions favouring a POS not being transient. If the patient is symptomatic, percutaneous closure can be considered first line treatment.

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