Platypnoea-orthodeoxia syndrome, an underdiagnosed cause of hypoxaemia: four cases and the possible underlying mechanisms

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Abstract Cardiac platypnoea-orthodeoxia syndrome (POS) is a position-dependent condition of dyspnoea and hypoxaemia due to right-to-left shunting. It often remains unrecognised in clinical practice, possibly because of its complex underlying pathophysiology. We present four consecutive patients with POS and patent foramen ovale (PFO) who underwent a successful percutaneous PFO closure, describe the mechanism of their POS and provide a review of the literature.

Keywords Platypnoea-orthodeoxia · Dyspnoea · Foramen ovale, patent · Atrial septum · Mechanism

Introduction

 Platypnoea-orthodeoxia syndrome (POS) is an uncommon clinical condition, characterised by position-dependent dyspnoea and oxygen desaturation in an upright position which resolves by lying supine. In addition to cardiac defects, pulmonary and abdominal defects have also been reported in association with POS (Tables 1 and 2) [1]. POS was first described in a patient with an atrial septal defect (ASD); however, cardiac POS has subsequently been more often observed in patients with a patent foramen ovale (PFO) [2]. What seems essential for cardiac POS to exist are both an anatomical communication between the right and left atrium as well as a structural component that redirects shunt flow causing right-to-left shunting in the upright position [3]. Usually this structural component is a deformation of the right atrium or of the inter-atrial septum. POS is primarily characterised by normal right atrial and pulmonary artery pressures contrary to Eisenmenger’s syndrome [4]. The exact mechanism of position-dependent change in shunting, including the gravitational forces on the cardiac structures involved, remains elusive. The final common
pathway appears to be a position-dependent opening of the PFO with right-to-left shunting. We present four cases of POS treated at the Centre for Congenital Heart Disease Amsterdam Leiden (CAHAL), and discuss the pathophysiological mechanism of POS and its diagnostic and therapeutic pitfalls.

### Case 1

A 46-year-old woman was referred to our hospital for percutaneous PFO closure, after having experienced symptoms of dyspnoea in the upright and left supine position for several months. She had a history of chronic obstructive pulmonary disease GOLD II and had undergone left pneumonectomy 6 months earlier, to remove an adenocystic carcinoma. In the weeks, thereafter, she developed progressive and position-dependent shortness of breath. Physical examination revealed a blood pressure of 100/65 mmHg with a resting heart rate of 122 beats/min. She had central cyanosis, with a transtheoretical oxygen saturation of 91 %, while breathing 1.5 L oxygen as measured by pulse oximetry. Her heart sounds were shifted to the left on auscultation. Chest X-ray (Fig. 1a1) and computed tomography (CT) scan of the thorax showed a midline shift of the right lung with a consequent position of the heart to the left thoracic wall. No evidence was found of cancer recurrence or other pulmonary causes such as pleural effusion or atelectasis. Echocardiographic images revealed a PFO (Fig. 1a2) and a right-to-left shunt fraction measured 20 % when breathing 100 % oxygen in an upright position. At this point the patient was severely incapacitated; she could only lie on her right side, which

| Conditions associated with cardiac POS | Pulmonary | Abdominal | Other |
|---------------------------------------|-----------|-----------|-------|
| Congenital abnormality                | Acute respiratory distress syndrome | CMV pneumonia | Chest wall trauma |
| Absent superior vena cava             | Chronic obstructive pulmonary disease | Hepatopulmonary syndrome | Diabetic autonomic neuropathy |
| Ascending aortic aneurysm             | Pneumonectomy | Pneumonectomy | Organophosphate poisoning |
| Atrial septal aneurysm                | Pulmonary embolism | Autoimmune hepatitis | Paraesophageal hernia repair |
| Ebstein’s anomaly                     | Pulmonary hypertension | Hepatitis A | Parkinson’s disease |
| Partial anomalous venous return       | Cardiac | | |
| Persistent left superior vena cava    | Constrictive pericarditis | | |
| Prominent Eustachian valve            | Pericardial adipose deposition | | |
| Transposition of the great vessels   | Pericardial effusion | | |
| Unroofed coronary sinus               | | | |
| Post-surgical repair                  | Pneumocystis and CMV pneumonia | | |
| Aortic valve replacement              | Pneumonectomy | | |
| Ascending aorta repair                | Pulmonary arteriovenous malformations | | |
| Atrial switch procedure               | Pulmonary embolism | | |
| Fontan procedure                      | Radiation-induced bronchial stenosis | | |
| Tumours                               | Traumatic bronchial rupture | | |
| Cardiac cyst/mass                     | | | |
| Lipomatous hypertrophy of the inter-atrial septum | | | |
| Other                                 | Noninfective pulmonary hypertension | | |
| Eosinophilic endomyocardial disease   | Schistosomiasis | | |
| Hepatic cyst                          | | | |
| Tortuous ascending aorta              | Kyphoscoliosis | | |
| Tricuspid regurgitation or stenosis   | | | |

Non-cardiac associations with POS include pulmonary conditions which cause pulmonary vascular shunting (e.g. arteriovenous malformation), ventilation-perfusion mismatching (e.g. pleural effusion, pneumonia, bronchial stenosis) or an anatomic distortion of the right atrium or ventricle (e.g. hemidiaphragmatic dysfunction). Hepatopulmonary syndrome causes POS through a high alveolar-arterial gradient (e.g. in portal hypertension, hepatitis). Orthostatic hypotension as a symptom of autonomic dysfunction (e.g. Parkinson, diabetic autonomic neuropathy, organophosphate poisoning) causes POS through an increase in orostatic alveolar dead space and subsequent ventilation-perfusion mismatching. CMV Cytomegalovirus.

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**Table 1** Conditions associated with cardiac POS

**Table 2** Non-cardiac conditions associated with platypnoea-orthodeoxia syndrome
had resulted in severe muscular atrophy. POS was finally diagnosed 6 months after the onset of her symptoms. Cardiac catheterisation was performed, which showed a normal right atrial and pulmonary artery pressure, and pulse oximetric saturations of 90% and 83% in right and left supine positions, respectively. The PFO was successfully closed with a 25 mm Amplatzer PFO Occluder (St. Jude, Minneapolis, USA) after which the arterial saturation improved immediately to 97% in the upright position. Her dyspnoea was resolved but an extensive rehabilitation course followed. She was able to gradually resume her daily routine and her exercise capacity improved significantly. No complications have been reported in 3 years of clinical follow-up. On her last transthoracic echocardiogram (TTE), the estimated systolic pulmonary artery pressure was 28 mmHg and no residual shunt was seen over the closed PFO.

Case 2

A 36-year-old woman with a history of right mid and lower lobe resection due to a carcinoid in the right main bronchus 3 years earlier was referred to our hospital. She complained of progressive pain and dyspnoea since her operation, which was most prominent during exercise and when lying in the right supine position. Before the bilobectomy she had participated in competitive long distance running, but now the referring pulmonologist noted that she desaturated from 96 to 87% with severe dyspnoea after performing only 10 squats. Previously, a bronchoscopy revealed an open but narrow bronchus to the right upper lobe. This narrowing worsened in the right supine position and was therefore thought to be the cause of her dyspnoea in the right supine position. One year later, cardiac magnetic resonance (CMR) imaging and resting transoesophageal echocardiography (TEE) showed a PFO without a right-to-left shunt as measured in normal supine position so no POS was suspected (Fig. 1b1–2). None of the previous diagnostic tests could explain the coexistent position-dependent and exercise-induced dyspnoea. A cardiopulmonary exercise test showed an early arterial partial CO2 pressure (PaCO2) increase during exercise. Also, an increase of end-tidal O2 pressure and decreased end-tidal CO2 pressure were seen at an acute load of 150 W, with a desaturation from 96 to 93% seen on pulse oximetry. Both her pulmonologist and cardiologist agreed that her symptoms had to be attributed to a mechanism involving her PFO. Firstly, the exercise-induced right-to-left shunt itself, and secondly, the consequently triggered ventilatory impairment related to the loss of alveolar tissue after pulmonary resection preventing adequate compensatory hyperventilation to normalise the PaCO2. Subsequently, the PFO was closed successfully with a Premere 25 mm device (St. Jude, Minneapolis, USA). She underwent extensive cardiac rehabilitation and on her latest outpatient visit, after 4 years of follow-up, no complications were found. She reported having run a marathon again, despite her unchanged ventilatory impairment. Her final TTE showed a normal pulmonary artery pressure and no residual shunt.

Case 3

A 73-year-old woman presented to our emergency department with acute dyspnoea and a severe hypoxaemia with a saturation of 63% measured by pulse oximetry in the upright position. She had a history of frequent recurrent pulmonary embolism due to essential thrombocytosis; however, a CT scan of the thorax excluded recurrent pulmonary embolism as a cause of dyspnoea this time. A TTE was performed to exclude pulmonary hypertension. Surprisingly, the echocardiogram in the left supine position revealed a PFO and a mildly elevated systolic pulmonary artery pressure of 36 mmHg. A subsequent TEE confirmed the existence of POS; pulse oximetric saturations dropped from 100% and 82% within 60 s when the patient changed from supine to upright position. Coincidentally, she was known with a stable aortic root and ascending aorta dilatation (diameters of 42 mm and 49 mm respectively, Fig. 1c1). The PFO was successfully closed with an Amplatzer 18 mm PFO Occluder. Due to a residual shunt on the procedural TEE, an additional 6 mm ASD Septal Occluder device was also implanted (Fig. 1c2) and the PFO was successfully closed. At one year follow-up she had no residual shunt and she had physically recovered from her former incapacitated condition.

Case 4

A 61-year-old male patient was referred to our hospital’s congenital team for PFO closure due to POS. He had a history of pulmonary adenocarcinoma and had undergone a right pneumonectomy 6 months earlier. After the subsequent chemotherapy, he complained of progressive general deterioration and dyspnoea in the upright position. On presentation he was unable to walk more than five steps. Physical examination showed saturations of 97% versus 90% in the supine and upright position, respectively, measured by pulse oximetry with 3 L oxygen. Analysis by contrast echocardiography revealed a right-to-left shunt due to a PFO with a measured shunt fraction of 26%. The chest X-ray showed a complete shift of the heart to the right (Fig. 1d1). CMR showed pleural effusion in the right hemithorax (Fig. 1d2) and no evidence was found for shunting in the supine position. During diagnostic heart catheterisation, systolic and diastolic pulmonary artery pressures were 33 mmHg and
blood gas during catheterisation provided oxygen saturations of 96% and 85% in supine and upright position. Due to 16 mmHg, respectively, when lying supine, and 48 mmHg and 28 mmHg, respectively, in the upright position. Arterial Fig. 1 Different imaging modalities of case 1(a), 2(b), 3(c) and 4(d), respectively, for the purpose of diagnosing POS by PFO. a1 Chest X-ray showing the heart position against the left thoracic wall. a2 Four chamber view of a Doppler TEE with a right-to-left shunt by PFO. b1 CMR showing malposition of the right thoracic wall resulting in a heart shift to the right and presence of PFO (arrow). b2 Short axis basal view of a Bubble contrast TEE showing no resting right-to-left shunting over the PFO. c1 CT angiography showing the dilated ascending aorta (A) and aorta root (B). c2 Periprocedural angiographic image of both Amplatzer devices. d1 Chest X-ray showing a tracheal shift to the left after pneumonectomy. d2 CMR shows a right hemithorax filled with pleural effusion and a compressed right atrium (arrow). RA right atrium, LA left atrium, RV right ventricle, LV left ventricle, R right, AO aorta, PA pulmonary artery, SVC superior vena cava.
Right ventricular afterload is also increased by post-pneumonectomy fluid overload in the operated hemithorax [7, 8]. These haemodynamic changes cause a right-to-left shunt due to a transient pressure gradient since right atrial pressure increases. An upright position reduces right ventricular preload and cardiac output. Orthodeoxia might consequently develop due to an increase in the alveolar dead space known as ‘pulmonary zone I’ (Fig. 2), in which the pressure in alveoli exceeds the orthostatic decrease in pulmonary arteriolar pressures, causing an additional ventilation-perfusion mismatch [8]. Though not reported in our cases, a different cause of dyspnoea after lung surgery can be phrenic nerve injury, particularly after right-sided pneumonectomy [9, 10]. The elevated right hemidiaphragm causes right ventricular compression and subsequent outflow impairment, which in turn causes a transient pressure gradient resulting in the right-to-left shunt. In these particular cases, plication of the diaphragm is preferred over PFO closure to remove the underlying cause [9]. Figure 3 summarises the haemodynamic explanation in a schematic view.

The second explanation is the relocation of the atrial septum which facilitates preferential flow of caval venous blood into the opening of the atrial defect. Intrathoracic post-pneumonectomy changes also account for this positional change of the inter-atrial communication, along with the haemodynamic shift as described above. A spontaneous mediastinal relocation to the opposite side, which occurs approximately 3 weeks to 7 months after pneumonectomy, predisposes to stretching and distortion of the atrial septum as the inferior caval vein remains in place [11]. In the upright position additional stretching occurs due to gravity, which
right atrium to make the PFO more mobile and permeable for shunting [13–15].

Several important observations are worth mentioning. Firstly, in all presented cases POS was diagnosed several months after the onset of symptoms and clinical presentation. Beside the fact that clinicians are relatively unfamiliar with POS as compared with other causes of dyspnoea, its complicated underlying mechanism often requires different diagnostic imaging modalities which add to the delay in establishing a plausible diagnosis. Therefore clinicians must consider diagnosing POS when patients present with position-dependent dyspnoea, even before the common causes of dyspnoea have been excluded. Secondly, an immediate symptom relief is present as soon as the PFO is successfully closed, as confirmed in this case series. Clinical verification of the efficacy of PFO closure is indicated when symptom continuation implies a residual shunt.

In conclusion, diagnosing POS remains a challenge since clinicians must recognise the heterogeneous presentation in severely dyspnoeic patients. Position-dependent dyspnoea and desaturation should provide the clue. Initial assessment of POS can be made by observing the platypnea, pulse oximetry and positional echocardiography. In some cases, POS can only be confirmed after observing the immediate symptom relief after PFO closure. Physicians should be reminded that a PFO, in combination with a pulmonary condition, can become symptomatic at older age as shown in this case series. In such cases, the debilitating dyspnoea can be successfully relieved by closure of the inter-atrial communication. Most importantly, clinical awareness is essential to recognise POS and prevent unnecessary delays.

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