Two women with unexplained dyspnoea: removing the blame game from the lungs

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Shareable abstract (@ERSpublications)
Hypoxaemia due to right-to-left atrial shunt with normal pressures in the right heart cavities represents an underdiagnosed condition. A systematic approach to hypoxaemic respiratory failure based on pathophysiology can lead to an accurate diagnosis. https://bit.ly/4bTP8fJ

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Case report: patient 1

A 78-year-old woman was admitted to the hospital with fever up to 38°C, accompanied by progressively worsening shortness of breath and a mild productive cough. She reported fatigue and exercise intolerance over the past 3 months. She also complained of severe diffuse musculoskeletal pain. Her medical history included rheumatoid arthritis, treated with adalimumab (anti-tumour necrosis factor-α), low-dose prednisolone and leflunomide, diabetes mellitus, well-controlled arterial hypertension, and thyroidectomy under replacement treatment. She was a nonsmoker and obese, with a body mass index (BMI) of 37 $kg \cdot m^{-2}$.

On admission, the patient had high blood pressure (180/90 mmHg), tachycardia (105 beats per min), increased body temperature (38°C) and a respiratory rate of 20 breaths per min. The oxygen saturation was 88% on room air. Chest auscultation revealed mild crackles in both lung bases, more prominent on the right side. Heart sounds were rhythmic with no additional sounds. Neither jugular venous distention, nor peripheral oedema were noted. The rest of the clinical examination showed no abnormal findings. ECG revealed sinus tachycardia without apparent signs of ischaemia. Chest radiography was without any specific abnormal finding. Arterial blood gases (ABGs) revealed respiratory failure and respiratory alkalosis (inspiratory oxygen fraction (F_{IO_2}) 21%, oxygen tension (P_{O_2}) 49 mmHg, carbon dioxide tension (P_{CO_2}) 29 mmHg, pH 7.47, bicarbonate 24 $mEq \cdot L^{-1}$). Laboratory tests revealed mild leukocytosis (white blood cell count 11 900 per µL) and elevated C-reactive protein (CRP) (13.2 $mg \cdot dL^{-1}$ with upper limit of normal 0.8 $mg \cdot dL^{-1}$). D-dimer levels were also elevated, while the biochemistry results were within normal ranges (table 1).

Task 1

What kind of examination would you perform next?

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CTPA was conducted which demonstrated neither pulmonary embolism, nor major parenchymal pathology. The patient had a history of arterial hypertension but was lacking any known history or clear clinical/radiological evidence of heart failure. Transthoracic heart ultrasound showed the size of the heart cavities was within normal limits, there was normal systolic function of the left ventricle and no severe valvular abnormalities, apart from a mild degree of mitral valve regurgitation.

TABLE 1 Laboratory findings for patient 1

Arterial blood gases (F_{IO2} 21%)	
P_{O_2}	49 mmHg
P_{CO_2}	29 mmHg
pH	7.47
Bicarbonate	22 mEq·L^{-1}
Laboratory tests	
CRP	13.20 mg·dL^{-1}
D-dimer	1382 ng·mL^{-1}
White blood cell count	11 900 per µL
Haematocrit	38
Platelets	254×10^{9} per L
Urea	33 mg·dL^{-1}
Creatinine	0.7 mg·dL^{-1}
SGOT	27 U·L^{-1}
SGPT	22 U·L^{-1}
γ-GT	19 IU·L^{-1}
ALP	64 IU·L^{-1}
hs-cTnT	7.6 pg·mL^{-1}

F_{IO_2}: inspiratory oxygen fraction; P_{O_2}: oxygen tension; P_{CO_2}: carbon dioxide tension; CRP: C-reactive protein; SGOT: serum glutamic-oxaloacetic transaminase test; SGPT: serum glutamic pyruvic transaminase; γ-GT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; hs-cTnT: high-sensitivity cardiac troponin test.

The patient initially received antibiotics and mild diuresis. The inflammatory profile gradually improved with remission of cough and fever, and a decline of CRP levels; however, her respiratory failure was progressively getting worse. She barely maintained an acceptable oxygen saturation of 88–90% on a Venturi mask with 50% oxygen. From the first days of her hospitalisation, she preferred to stay in a supine position, claiming that the shortness of breath was more severe in the upright posture. A fall in oxygen saturation also accompanied the transition from a supine to a sitting position (platypnoea–orthodeoxia). The respiratory function of the patient worsened enough to require support with noninvasive mechanical ventilation. Transfer to the intensive care unit (ICU) was arranged for further investigation and treatment.

During her stay in the ICU, further investigation of the possible causes of persistent hypoxaemia was performed. Although ventilation/perfusion mismatch (atelectatic regions due to a prolonged bed-stay combined with obesity) might have partially explained her hypoxaemia, the presence of hypoxaemia refractory to oxygen supply pointed towards shunt as the main cause of the respiratory failure, while the rest of the causes were actually not considered to account for the severe respiratory failure (low inspired oxygen concentration, hypoventilation, diffusion abnormalities). Right heart catheterisation was performed and haemodynamic measurements were obtained. Pressures in the right heart chambers were all within the normal ranges. Shunt was calculated by taking a sample of mixed venous blood from the pulmonary artery which approximated 16%. During the procedure, the patient was being given a mixture of 100% oxygen concentration to eliminate the shunt-like effect. So, the calculated value of 16% represented the absolute shunt (normal range 3–5%). Saturation of the mixed venous blood (S_{VO_2}) was normal (76%), which excluded the last possible reason for hypoxaemia (low S_{VO_2}).

Task 2

What was the differential diagnosis?

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Shunt pathophysiology may be cardiac, intrapulmonary or systemic in nature. Cardiac causes include atrial or ventricular septal defects (*e.g.* patent foramen ovale (PFO) mainly in the context of elevated right heart pressures). A severe cause of intrapulmonary shunt had already been excluded by the CTPA, which ruled out not only pulmonary embolism, but also significant parenchymal abnormalities (figure 1). A computed tomography scan of the liver was performed and demonstrated no intrahepatic arteriovenous malformation, excluding systemic shunt as well.

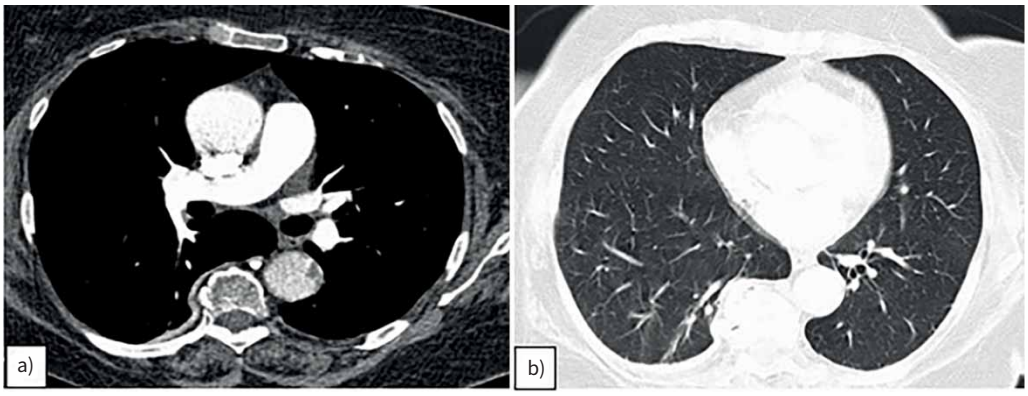

FIGURE 1 Computed tomography pulmonary angiography for patient 1. Axial images (1 mm slice thickness) showing a) no evidence of pulmonary embolism in a mediastinal window and b) no parenchymal abnormalities in a lung window.

In the context of investiging the possible existence of intracardiac shunting, transthoracic heart ultrasound was repeated, while agitated saline solution was injected through a peripheral vein (bubble test). Profuse passage of bubbles was noted from the right to the left atrium indicating interatrial communication (figure 2). To attain a more detailed assessment of the interatrial septum, a transoesophageal echocardiogram followed. The aortic root and ascending aorta were found to be mildly dilated (40 mm and 41 mm, respectively). Regarding the interatrial septum, a septal defect (PFO) and septal aneurysm were discovered, along with a prominent eustachian valve. A bubble test reconfirmed the interatrial communication. Therefore, the final diagnosis was hypoxaemia due to intracardiac shunt (PFO, along with septal aneurysm and prominent eustachian valve) in a patient without pulmonary hypertension.

Case report: patient 2

A 76-year-old female with a past medical history of thyroid disorder and dyslipidaemia, under appropriate treatment (levothyroxine and statin), presented to our department with progressive dyspnoea on exertion for the past 3 years, and a nonproductive cough of 3 months duration. She was an ex-smoker (smoking history of 20 pack-years), having quit 7 years ago. She was not obese (BMI 22.3 $kg \cdot m^{-2}$), she had thoracic kyphoscoliosis, and she also reported being allergic to penicillin.

On admission, her vital signs were normal except for her oxygen saturation, which was 91% on room air. Her blood pressure was 144/75 mmHg, body temperature 36.5 °C and she had a respiratory rate of 16 breaths per min. ABGs revealed hypoxaemia (F_{IO_2} 21%, P_{O_2} 64 mmHg, P_{CO_2} 35 mmHg, pH 7.42,

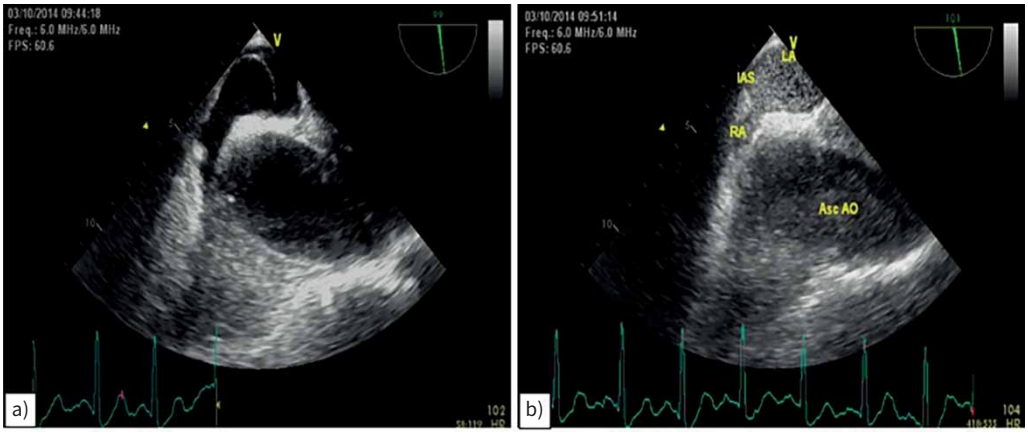

FIGURE 2 Transoesophageal echocardiogram in patient 1. a) Before and b) after injection of agitated saline solution (bubble test), showing interatrial communication. LA: left atrium; IAS: interatrial septum; RA: right atrium; Asc AO: ascending aorta.

TABLE 2 Laboratory findings for patient 2

Arterial blood gases (F_{IO2} 21%)	
P_{O_2}	64 mmHg
P_{CO_2}	35 mmHg
pH	7.42
Bicarbonate	22 mEq·L^{-1}
Laboratory tests	
CRP	1.70 mg·dL^{-1}
D-dimer	710 ng·mL^{-1}
White blood cell count	7 700 per µL
Haematocrit	40
Platelets	285×10^9 per L
Urea	54 mg·dL^{-1}
Creatinine	0.93 mg·dL^{-1}
SGOT	27 U·L^{-1}
SGPT	22 U·L^{-1}
γ-GT	19 IU·L^{-1}
ALP	64 IU·L^{-1}
hs-cTnT	2.8 pg·mL^{-1}

F_{IO_2}: inspiratory oxygen fraction; P_{O_2}: oxygen tension; P_{CO_2}: carbon dioxide tension; CRP: C-reactive protein; SGOT: serum glutamic-oxaloacetic transaminase test; SGPT: serum glutamic pyruvic transaminase; γ-GT: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; hs-cTnT: high-sensitivity cardiac troponin test.

bicarbonate 22 mEq·L^{-1}). The patient reported feeling less dyspnoeic in a supine position. A decrease in oxygen saturation more than 5% was confirmed from supine (97%) to an upright position (91%) (platypnoea–orthodeoxia). Physical examination did not reveal any other abnormalities. Chest radiography did not show any specific abnormal finding. ECG revealed sinus rhythm, 70 beats per min, without apparent signs of ischaemia.

Laboratory investigations were unremarkable with normal haemoglobin and haematocrit levels. The biochemistry results and inflammatory markers were within normal ranges (table 2). Pulmonary function tests showed normal spirometry, without restriction or obstruction and a total lung capacity of 110% of the predicted value, although there was a decrease in diffusing capacity of the lungs for carbon monoxide (D_{LCO}) to 44% of predicted and transfer coefficient of the lung for carbon monoxide (K_{CO}) to 53% of predicted. CTPA was then performed to exclude pulmonary embolism, arteriovenous malformation or other parenchymal abnormalities. The findings included only pleural thickening bilaterally and mild airway disease, which was already known and had been stable since 2020 (figure 3). A transthoracic echocardiogram did not demonstrate any significant pathology except for evidence of increased estimated

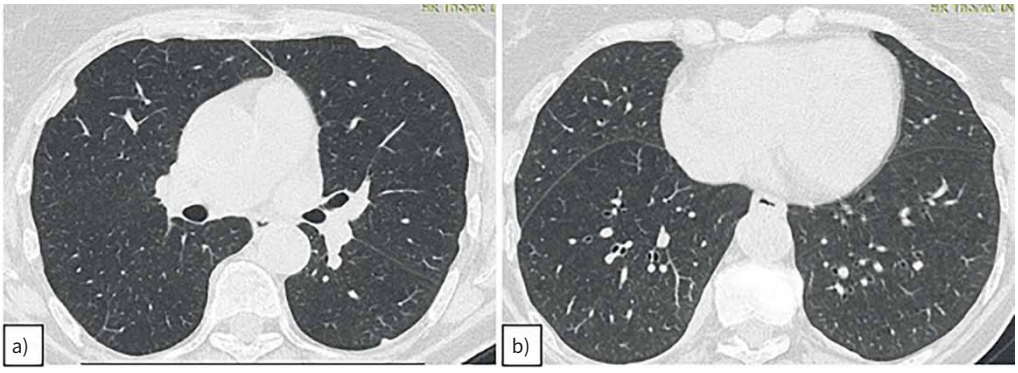

FIGURE 3 a, b) Axial images in a lung window of high-resolution computed tomography (0.625 mm slice thickness) of patient 2. No major parenchymal abnormalities were detected, apart from local pleural thickening (a stable finding over the past 5 years).

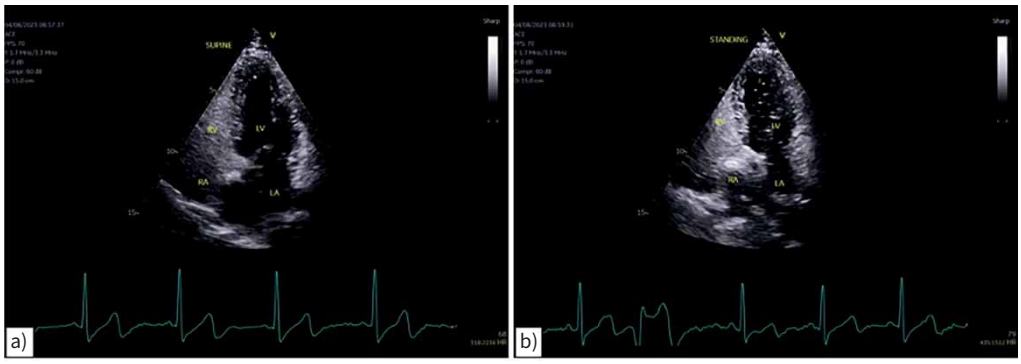

FIGURE 4 Transthoracic echocardiogram in patient 2, after injection of agitated saline solution (bubble test), in the a) supine and b) standing position. Profuse passage of bubbles was noted from the right to the left atrium indicating interatrial communication in the upright position. LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

mean pulmonary arterial systolic pressure. However, right heart catheterisation revealed normal pressures in the right heart chambers and normal cardiac output.

Since other causes of hypoxaemia had been excluded (low inspired oxygen concentration, hypoventilation, diffusion abnormalities due to parenchymal abnormalities, ventilation/perfusion mismatch, intrapulmonary shunt), an intracardiac shunt mechanism was suspected. The transthoracic echocardiogram with agitated saline (bubble test) showed evidence of a PFO with right-to-left shunting only in the standing position (figure 4b), while no bubbles appeared to cross in the supine position (figure 4a). The transoesophageal echocardiogram showed evidence of a "tunnel-like" PFO (figure 5), as well as aortic elongation. Intracardiac shunt can be seen in the case of aortic aneurysm, aortic root dilatation and aortic elongation, in patients with an atrial septal aneurysm or in patients with persistent eustachian valve or Chiari network. Nevertheless, a tricuspid regurgitant jet can also lead to blood projection directly to the left atrium *via* the intracardiac shunt as seen in the cardiac magnetic resonance imaging four-chamber view (supplementary video).

Task 3

What was the final diagnosis and how was the diagnosis confirmed?

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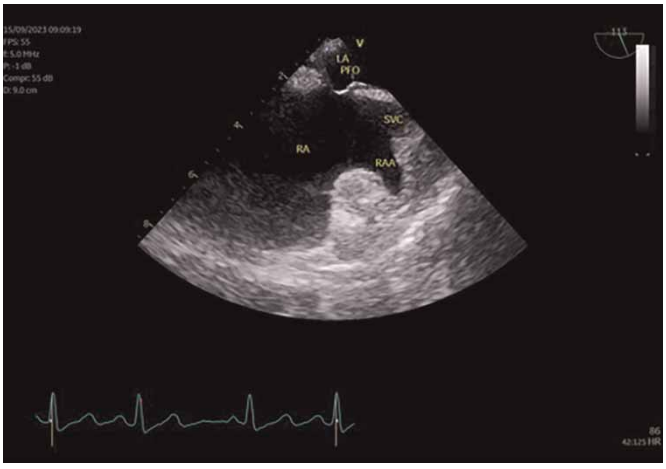

FIGURE 5 Transoesophageal echocardiogram in patient 2 showing a "tunnel-like" patent foramen ovale (PFO). LA: left atrium; RA: right atrium; RAA: right atrium appendix; SVC: superior vena cava.

Task 4

What was the clinical solution for these cases?

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Discussion

We have presented two cases of dyspnoea and hypoxaemia with a negative initial work-up in patients without an established respiratory disorder. The final diagnosis was hypoxaemia due to right-to-left intracardiac shunt through PFO, in the absence of elevated right-sided pressures. Both patients presented with platypnoea–orthodeoxia syndrome, which is a clinical entity associated with arterial desaturation in an upright posture and relieved in recumbence [2]. It can be caused by diversion of blood from the right to the left atrium through a PFO or an atrial septal defect [3]. Persistence of PFO is a common structural abnormality of the interatrial septum occurring in ∼30% of adults [4]. The defect is usually asymptomatic because it is flap-like mechanism and does not permit significant left-to-right shunting. However, under several pathological conditions, that produce elevation of pressures in the right cavities, the normal left to right atrial pressure gradient can be reversed resulting in right-to-left shunt, and finally in systemic hypoxaemia. Elevated pressures of the right heart cavities can be observed in right atrial myxomas, right ventricular infarction, severe tricuspid valve regurgitation or stenosis, pulmonary valve stenosis, Fallot tetralogy, pulmonary embolism, constrictive pericarditis, mechanical ventilation and other conditions [5–7].

However, development of systemic hypoxaemia in the setting of normal right cardiac pressures is rare [8, 9]. Several anatomical abnormalities need to be present and act in synergy to provoke right-to-left shunting without the presence of a pressure gradient. The predominant theory explaining shunt flow with normal pressures is that there is a constant flow rate with a preferential blood flow streaming from either the superior, or more commonly, the inferior vena cava to the left atrium. In patients with PFO and normal pulmonary pressure, blood flowing from the inferior vena cava might cross the interatrial septal defect by kinetic energy, in the absence of a pressure gradient between the right and left atrium, causing a right-to-left shunt [9–11]. Therefore, it represents flow related rather than a pressure related shunting.

PFO along with atrial septal aneurysm and prominent eustachian valve are congenital heart defects that in combination form the perfect anatomical set up for intracardiac shunting. Disorientation of atrial septal axis may also contribute to preferential blood flow. Interatrial septum displacement toward the horizontal position places the atrial defect directly in line with the blood flow from the inferior vena cava at its entrance to the right atrium. A streaming effect is generated making blood flow pass from inferior vena cava, *via* the prominent eustachian valve and through the atrial septal defect, directly to the left atrium despite a normal pressure gradient [9, 10, 12, 13]. Change in the axis of the atrial septum may be secondary to various conditions, like an enlarged or distorted aortic root and a dilated proximal ascending aorta [13]. Kyphosis may progressively make the ascending aorta and atrial septum more horizontal. The fact that the occurrence of the above conditions increases with age, probably answers the question of why patients with a congenital effect develop symptoms later in life. Displacement of the septal axis may also be observed after pneumonectomy, abdominal surgery or paralysis of the right hemidiaphragm, which alter the intrathoracic relationships [13].

In patients in whom this is suspected, diagnosis can be confirmed by careful assessment of the atrial septum by transthoracic or transoesophageal echocardiogram and a bubble test, which demonstrate the passage of bubbles from the right into the left atrium. The appearance of agitated saline contrast in left-sided heart structures is consistent with either an intracardiac or an intrapulmonary shunt. Direct visualisation (within three cardiac cycles) of bubbles crossing the interatrial septum increases the specificity of the bubble study to identify an intracardiac shunt, such as a PFO or atrial septal defect. Transoesophageal echocardiogram can detect the possible underlying congenital or acquired intrathoracic structural modifications more accurately. If right-to-left shunting is not evident in a supine position, the saline contrast study should be repeated in an upright posture for definitive exclusion of the diagnosis [3, 12].

Conclusion

- The differential diagnosis of dyspnoea associated with hypoxaemic respiratory failure may sometimes be challenging.
- We presented two cases of dyspnoea and hypoxaemia with a negative initial work-up in patients with a history free from respiratory disorders. A systematic approach to the hypoxaemia on the basis of pathophysiology led us to accurate diagnosis and proper treatment.
- Hypoxaemia due to right-to-left atrial shunt with normal pressures in the right heart cavities represents an underdiagnosed condition.

- Considering the prevalence of PFO (~30% in the adult population), as well as the fact that structural modifications promoting a streaming effect intensify with age, we aim to highlight that this kind of shunt should be included in the differential diagnosis of unexplained hypoxaemia when other more common aetiologies have been excluded.

Answer 1

The patient presented with respiratory failure, and the provisional diagnosis upon admission was lower respiratory tract infection, due to the fever and increased inflammatory markers, while the increased levels of D-dimer along with increased heart rate could also suggest pulmonary embolism. Computed tomography pulmonary angiography (CTPA) could help to rule out pulmonary embolism, and also provide further information about the lung parenchyma.

<< Go to Task 1

Answer 2

The causes of respiratory failure are the following: ventilation/perfusion mismatch, low inspired oxygen concentration, hypoventilation, diffusion abnormalities and shunt. Increased calculated value of shunt during right heart catheterisation, along with the exclusion of the rest of the causes, led to the differential diagnosis of a shunt pathophysiology, either cardiac, intrapulmonary or systemic.

<< Go to Task 2

Answer 3

The final diagnosis was hypoxaemia caused by intracardiac shunt, in particular PFO, in the absence of elevated right heart pressures, in a patient with thoracic kyphoscoliosis and elongation of the aortic root with concomitant direct tricuspid regurgitation jet into the interatrial septum. The appearance of agitated saline contrast in left-sided heart structures is consistent with either an intracardiac or an intrapulmonary shunt. Direct visualisation (within three cardiac cycles) of bubbles crossing the interatrial septum increases the specificity of the bubble study to identify an intracardiac shunt, such as a PFO.

<< Go to Task 3

Answer 4

Percutaneous closure of the interatrial septal defect was performed in both cases using a specific occluding device [1]. In the post-operative period, both patients showed clinical improvement with gradual restoration of arterial oxygen saturation.

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Consent was obtained from the patients included in this manuscript.

Conflicts of interest: The authors have nothing to disclose.

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