



EDUCATIONAL OBJECTIVE: Readers will consider platypnea-orthodeoxia syndrome in the differential diagnosis of hypoxemia in appropriate settings

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An 85-year-old woman with respiratory failure and positional hypoxemia

AN 85-YEAR-OLD WOMAN WAS BROUGHT TO our intensive care unit because of worsening hypoxemia over the past day. About 3 weeks earlier she had been diagnosed with acute bilateral pulmonary emboli in the distal branches of the left and right lower lobes and right middle lobe, for which she was receiving anticoagulation therapy.

At presentation she had generalized fatigue and dyspnea at rest that was worse with exertion, but she denied having fever, chest pain, or cough. Her medical history included hypertension, hyperlipidemia, hypothyroidism, stage 1 breast cancer in remission, thromboembolic stroke, and myasthenia gravis. Before her hospital admission, she had been taking rosuvastatin, metoprolol tartrate, pyridostigmine, prednisone, furosemide, levothyroxine, and rivaroxaban. She did not smoke, she was retired, and she had not traveled recently.

Her blood pressure was 135/66 mm Hg, pulse 73 beats per minute, respiratory rate 16, temperature 35.4°C (95.7°F), and oxygen saturation 88% while receiving oxygen at 6 L/min via nasal cannula. Physical examination revealed mild edema in the lower extremities and basilar decreased breath sounds. She had no finger clubbing or cyanosis and was not using accessory muscles to breathe. Of note, her oxygen saturation remained more than 93% when she was recumbent but sharply dropped to less than 85% when she was upright.

Laboratory values

Results of initial laboratory testing were as follows:

- Sodium 138 mmol/L (reference range 132–148)
- Potassium 4.2 mmol/L (3.5–5.0)
- Chloride 99 mmol/L (98–111)
- Bicarbonate 29 mmol/L (23–32)
- Creatinine 0.52 mg/dL (0.7–1.4).
- White blood cell count $11.06 \times 10^9/L$ (3.7–11.0)
- Hemoglobin 12.6 g/dL (12–16)
- Platelet count $211 \times 10^9/L$ (150–400).
- International normalized ratio 1.4.

Electrocardiography and imaging studies

Standard 12-lead electrocardiography showed normal sinus rhythm with left axis deviation and left ventricular hypertrophy.

Chest radiography showed bilateral interstitial opacities and small pleural effusions.

Computed tomography (CT) of the chest with contrast, compared with a CT scan done 20 days earlier, showed that the pulmonary emboli had resolved.

Arterial blood gases

In view of her positional hypoxemia, blood for arterial blood gas measurements was drawn in the supine and upright positions.

Supine, with a fraction of inspired oxygen (F_{iO_2}) via high-flow nasal cannula of 45%, her values were:

- pH 7.45 (reference range 7.35–7.45)
- P_{CO_2} 34 mm Hg (36–46)
- P_{O_2} 81 mm Hg (85–95)
- Bicarbonate 23 mmol/L (22–26).

Her oxygen saturation:
> 93% supine
< 85% upright

Upright, her hypoxemia was significantly worse:

- pH 7.46
- P_{CO_2} 33 mm Hg
- P_{O_2} 57 mm Hg
- Bicarbonate 23 mmol/L.

The methemoglobin level was normal on both measurements.

During her stay in the intensive care unit, she required up to 100% F_{IO_2} because of persistent hypoxemia.

CAUSES OF HYPOXEMIA

1 So far, the patient's laboratory tests and imaging studies point to which of the following as the most likely cause of her severe hypoxemia?

- ☐ Ventilation-perfusion (V/Q) mismatch
- ☐ Diffusion abnormality
- ☐ Hypoventilation
- ☐ Shunting
- ☐ None of the above

The arterial blood gas measurements suggested the possibility of shunting as the cause, although further imaging would be needed to confirm that.

V/Q mismatch can occur in respiratory failure due to pulmonary embolism, pulmonary edema, or shunting. If ventilation is preserved but perfusion is impaired, the V/Q ratio approaches infinity (dead-space ventilation), a situation that can be seen in pulmonary embolism. If perfusion is preserved and ventilation is impaired, the V/Q ratio approaches zero, which is consistent with a physiologic shunt.

Hypoxemia may improve in less severe forms of V/Q mismatch. In our patient, the repeat CT with contrast showed that her pulmonary embolism had resolved, so this is probably not the cause of her severe hypoxemia.

Diffusion abnormalities are due to defects in the lung parenchyma, such as in chronic obstructive pulmonary disease, interstitial lung disease, and lung fibrosis.

Hypoxemia from diffusion defects is usually aggravated by a precipitating factor that increases oxygen demand, and it usually im-

proves with oxygen supplementation. This is unlikely in our patient, as she did not have a history of chronic interstitial lung disease and CT showed no evidence of severe lung parenchymal disease.

Hypoventilation is usually due to drugs that cause respiratory depression, to stroke, or to neuromuscular diseases such as myasthenia gravis that can cause respiratory muscle weakness. It results in elevation of P_{CO_2} and, if not corrected, respiratory acidosis.

Our patient had a diagnosis of myasthenia gravis, though hypoventilation is unlikely in her case because she had a normal respiratory rate and low P_{CO_2} values.

Shunting can be physiologic or anatomic and can occur in the heart or the lungs. In physiologic shunting, severe V/Q mismatch can occur when ventilation is affected, as in severe pulmonary edema and pneumonia. In anatomic shunting, a defect such as an atrial septal defect or a pulmonary arteriovenous malformation allows blood to bypass areas of ventilation from the venous to the arterial circulation, preventing it from being oxygenated. In true anatomic shunting, supplemental oxygen with 100% F_{IO_2} has little effect, whereas in V/Q mismatch it can raise the arterial oxygen saturation.

Our patient's radiograph did not suggest severe pneumonia or pulmonary edema, which makes these unlikely causes of her hypoxemia. At this point, because of her positional hypoxemia, further evaluation with contrast-enhanced echocardiography was needed to evaluate for anatomic shunting in the heart or lungs.

FURTHER TESTING

Transthoracic echocardiography (TTE) with agitated saline with a Valsalva maneuver was performed. Normally, no bubbles are seen in the left-sided chambers after intravenous injection of agitated saline contrast, whereas bubbles on the left side suggest an intracardiac or intrapulmonary shunt. In our patient, this test was negative, and her right ventricular systolic pressure was normal.

2 What further testing should be considered to evaluate our patient's hypoxemia?

In pulmonary embolism, the V/Q ratio increases; in pulmonary edema it decreases

- ☐ High-resolution chest CT
- ☐ Transesophageal echocardiography (TEE)
- ☐ Pulmonary function testing
- ☐ Repeated arterial blood gas measurement
- ☐ Edrophonium testing

Repeat imaging with **high-resolution CT** would likely not provide additional information and would expose the patient to additional radiation without adding much clinical benefit.

TEE could help further evaluate the intracardiac anatomy and look for shunting, which may be missed on TTE because of suboptimal positioning or image quality.

Pulmonary function testing is useful in establishing the baseline function and impairment in respiratory volumes. If an acute myasthenic crisis is suspected, measuring the negative inspiratory force and the forced vital capacity can be useful in monitoring worsening respiratory muscle weakness and assessing the need for mechanical ventilation.

In our patient, it is unlikely that pulmonary function testing would help, since her acute respiratory failure was probably not caused by neuromuscular weakness.

Repeated arterial blood gas measurement would likely only confirm that the patient still has positional hypoxemia but would not help sort through the differential diagnosis.

Edrophonium testing is useful in diagnosing myasthenia gravis and differentiating it from other neuromuscular diseases, such as Lambert-Eaton syndrome. Edrophonium, a reversible acetylcholinesterase inhibitor, prevents degradation of acetylcholine and prolongs its effect at the synaptic cleft, thus improving muscle weakness.

Our patient has already been diagnosed with myasthenia gravis, so this test is not likely to uncover the cause of her hypoxemia.

Because we still strongly suspected a shunt, TEE was performed with intravenous injection of agitated saline. TEE with the patient upright revealed intracardiac right-to-left shunting through a patent foramen ovale. The midesophageal view after saline injection showed a large interatrial septal aneurysm with total excursion of 2 cm, and right-to-left shunting within the first beat, consistent with an intracardiac shunt (**Figure 1**). Color Doppler im-

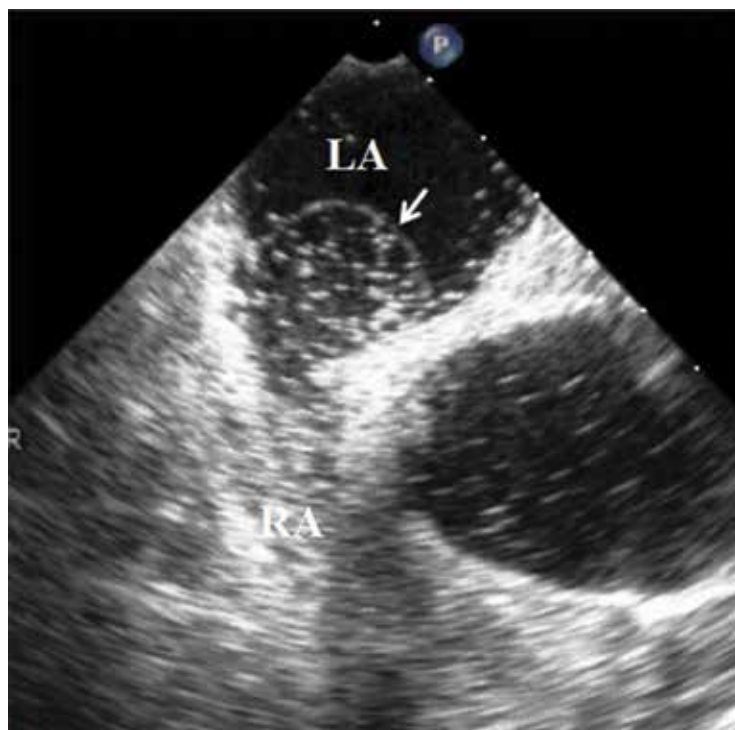


FIGURE 1. Transesophageal echocardiography with intravenous injection of agitated saline demonstrated shunting from the right atrium (RA) to the left atrium (LA) within the first beat, consistent with intracardiac shunting with a prominent atrial septal aneurysm (white arrow).

aging (**Figure 2**) demonstrated turbulent flow through the patent foramen ovale, consistent with right-to-left shunting, and also showed the patent foramen ovale in a closed position (**Figure 3**).

3 Which is now most likely the cause of our patient's hypoxemia?

- ☐ Chronic thromboembolic pulmonary hypertension
- ☐ Myasthenic crisis
- ☐ Platypnea-orthodeoxia syndrome due to the patent foramen ovale
- ☐ Methemoglobinemia

Chronic thromboembolic pulmonary hypertension is usually a long-term result of untreated or inadequately treated thromboembolic disease (eg, pulmonary emboli), which causes vascular remodeling and pulmonary arteriopathy, which in turn leads to increased pulmonary vascular resistance and pulmonary hypertension.

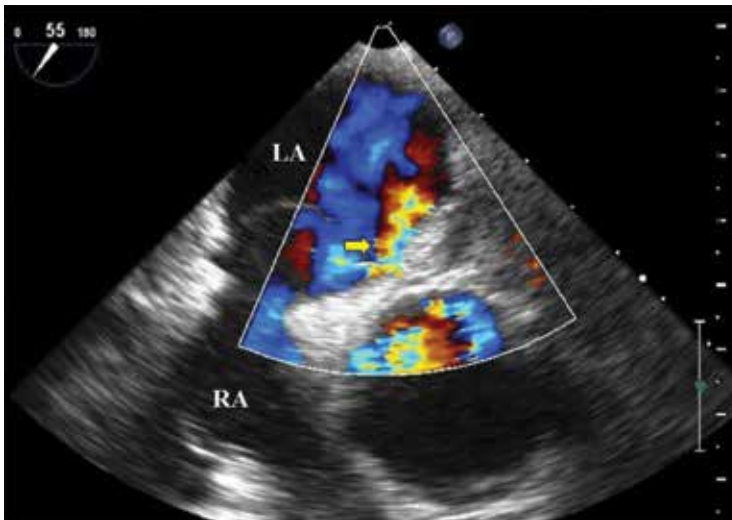


FIGURE 2. Transesophageal echocardiography with color Doppler imaging showed turbulent flow through a patent foramen ovale (yellow arrow) from the right atrium (RA) to the left atrium (LA).

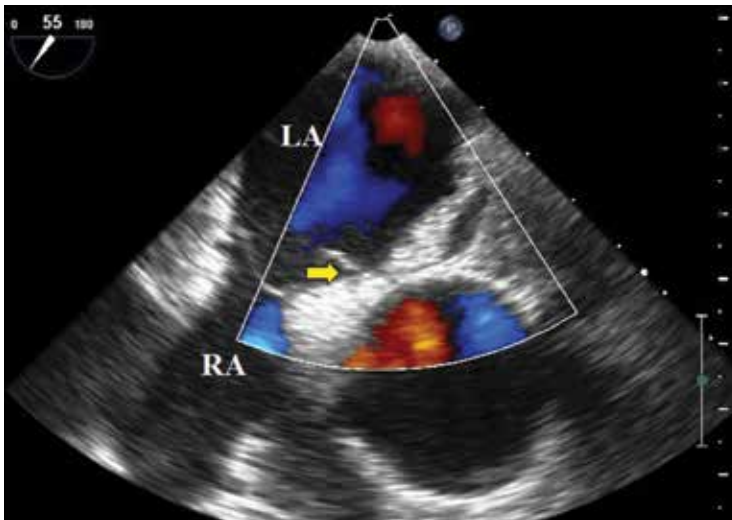


FIGURE 3. Transesophageal echocardiography with color Doppler also showed the patent foramen ovale in the closed position (yellow arrow). The patent foramen ovale can change positions due to changes in the intracardiac pressure.

This is unlikely the cause of our patient's acute hypoxemia, as her symptoms did not suggest it. Moreover, an elevated right ventricular systolic pressure on TTE would suggest pulmonary hypertension, but TTE did not show this, and repeat chest CT indicated that her pulmonary embolism had been adequately treated and had resolved. A V/Q scan and right heart catheterization would help

rule out chronic thromboembolic pulmonary hypertension, although these were not done in our patient.

Myasthenic crisis is the progressive fatiguing and paralysis of respiratory muscles ultimately requiring mechanical ventilation to sustain life. It is often brought on by infection or drug therapy.

Our patient did not require intubation and she had no signs or symptoms of myasthenic crisis such as ptosis, dysphagia, or dysarthria. She had a negative inspiratory force of -21 cm H₂O, and pulmonary function testing 4 days before her hospital admission had shown a forced vital capacity of 1.84 L, making myasthenic crisis an unlikely cause of her respiratory failure.

Platypnea-orthodeoxia syndrome is a syndrome of dyspnea (platypnea) and hypoxemia (orthodeoxia) that is induced by sitting upright or standing and resolves when lying down. It is a result of right-to-left intracardiac or intrapulmonary shunting in the presence of an anatomic defect and a functional element causing redirection of shunt flow through the anatomic defect in an upright position.¹ It is associated with specific cardiac, pulmonary, and hepatic diseases, such as atrial septal defect, pulmonary arteriovenous malformation, and hepatopulmonary syndrome.² It can occur even if right-sided chamber pressures are normal, and several mechanisms of the underlying pathophysiology have been described.³

Platypnea-orthodeoxia syndrome can be triggered by an event that causes a spontaneous transient elevation of right atrial pressure and pulmonary hypertension, such as our patient's acute pulmonary embolism. Increased right-to-left shunting occurs in an upright position, causing preferential redirection of flow from the inferior vena cava through the interatrial septum and the patent foramen ovale.⁴

Our patient was elderly and, like one in every four people in the world, she had had a patent foramen ovale since the day she was born. Never causing a problem, it had remained undiagnosed until complicated by platypnea-orthodeoxia syndrome after her recent pulmonary embolism.

Methemoglobinemia. Methemoglobin has a lower affinity for oxygen than normal hemoglobin. Elevations usually occur with medica-

tions such as anesthetics and nitrates and can be diagnosed through an elevated level on arterial blood gas testing.

Our patient did not have elevated methemoglobin on her blood gas measurements on admission; therefore, this is unlikely to be the diagnosis.

■ CASE CONCLUDED

Percutaneous closure of the patent foramen ovale with a 30-mm Amplatzer Cribriform Occluder brought significant improvement in our patient's functional status and arterial oxygenation saturation, and 2 weeks later at follow-up she no longer needed supplemental oxygen. TEE 6 months later showed an intact closure device and no interatrial shunting.

■ WHEN HYPOXEMIA DOES NOT RESPOND TO OXYGEN

In the intensive care unit, time is critical, and when hypoxia is refractory to high FiO_2 , shunting should be considered.

In the acute-care setting, platypnea-orthodeoxia syndrome can be identified quickly by pulse oximetry and serial blood gas measurements in the upright and supine positions. A drop in arterial oxygenation in the upright position vs the supine position helps confirm the diagnosis.

Other conditions in the differential diagnosis of this syndrome include recurrent pulmonary embolism, acute respiratory distress syndrome, interstitial pulmonary fibrosis, intrapulmonary shunting due to arteriovenous malformation, and diaphragm paralysis due to neuromuscular disease.

In our patient, positional blood gas measurements demonstrated a significant drop in arterial oxygen saturation from the supine to the upright position, raising our suspicion of shunting. It helped narrow the differential diagnosis and guided our selection of additional diagnostic tests.

The initial chest radiograph in our patient was normal. TTE did not reveal shunting and showed a normal right ventricular systolic pressure. TTE with agitated saline also failed to reveal shunting. Because of suboptimal positioning and image quality, TTE may miss

the shunting physiology, and that is why we proceeded to positional TEE, which can better evaluate the hemodynamic effects of positional changes on patent foramen ovale and shunting.

■ MORE ABOUT PATENT FORAMEN OVALE

The prevalence of patent foramen ovale is estimated at 27% in the general population, but it is usually not symptomatic. It can be associated with atrial septal aneurysm and Chiari network malformations. When associated with atrial septal aneurysm, it carries a higher risk of stroke.⁵

Our patient had a large atrial septal aneurysm with a septal excursion of 2 cm as well as a history of thromboembolic stroke, which was likely associated with the patent foramen ovale and the atrial septal aneurysm.

Atrial septal aneurysm is rare, with a prevalence of 1% at autopsy and 1.9% by TTE. It is defined by a septal excursion of at least 10 mm and a base diameter of at least 15 mm and is more frequently detected on TEE than on TTE.⁶

Studies have shown that contrast and color Doppler TEE are superior to TTE for detecting patent foramen ovale.⁷ Tilt-table TEE with contrast enhancement has also been used to better demonstrate the morphology of the interatrial septum and the degree of shunting due to the separation between the septum primum and septum secundum causing the patent foramen ovale.⁸ Contrast-enhanced transcranial Doppler has also been shown comparable to contrast TEE to detect interatrial shunting. However, TEE provides additional anatomic information.⁹

In our patient, atrial septal aneurysm and patent foramen ovale were exaggerated by upright positioning, which opened the aneurysm and increased the shunting through the patent foramen ovale.

The treatment of choice in symptomatic patients with platypnea-orthodeoxia syndrome is directed at the underlying cause, in this case closure of the foramen ovale. This treatment has been shown to be safe and effective in these patients,¹⁰ but caution should be used when considering foramen ovale closure in patients with pulmonary hypertension.¹¹

Transthoracic echo with agitated saline contrast was negative for patent foramen ovale, but suspicions remained

In patients with irreversible or severe pulmonary hypertension, closure of the patent foramen ovale can exacerbate right heart dysfunction and lead to right heart failure. There are situations when closure of a patent foramen ovale can be considered in pulmonary hypertension; however, each decision is individualized, and caution must be used. A

detailed discussion is beyond the scope of this paper.

A thorough history and physical examination are important in differentiating the various causes of hypoxemia. Appropriate diagnostic testing is needed along with prompt treatment of the underlying cause of platypnea-orthodeoxia syndrome. ■

REFERENCES

1. **Cheng TO.** Mechanisms of platypnea-orthodeoxia: what causes water to flow uphill? *Circulation* 2002; 105:e47.
2. **Natalie AA, Nichols L, Bump GM.** Platypnea-orthodeoxia, an uncommon presentation of patent foramen ovale. *Am J Med Sci* 2010; 339:78–80.
3. **Acharya SS, Kartan R.** A case of orthodeoxia caused by an atrial septal aneurysm. *Chest* 2000; 118:871–874.
4. **Irwin B, Ray S.** Patent foramen ovale—assessment and treatment. *Cardiovasc Ther* 2012; 30:e128–e135.
5. **Mas JL, Zuber M.** Recurrent cerebrovascular events in patients with patent foramen ovale, atrial septal aneurysm, or both and cryptogenic stroke or transient ischemic attack. French Study Group on Patent Foramen Ovale and Atrial Septal Aneurysm. *Am Heart J* 1995; 130:1083–1088.
6. **Kerut EK, Norfleet WT, Plotnick GD, Giles TD.** Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol* 2001; 38:613–623.
7. **Hausmann D, Mügge A, Becht I, Daniel WG.** Diagnosis of patent foramen ovale by transesophageal echocardiography and association with cerebral and peripheral embolic events. *Am J Cardiol* 1992; 70:668–672.
8. **Roxas-Timonera M, Larracas C, Gersony D, Di Tullio M, Keller A, Homma S.** Patent foramen ovale presenting as platypnea-orthodeoxia: diagnosis by transesophageal echocardiography. *J Am Soc Echocardiogr* 2001; 14:1039–1041.
9. **Sloan MA, Alexandrov AV, Tegeler CH, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.** Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2004; 62:1468–1481.
10. **Blanche C, Noble S, Roffi M, et al.** Platypnea-orthodeoxia syndrome in the elderly treated by percutaneous patent foramen ovale closure: a case series and literature review. *Eur J Intern Med* 2013; 24:813–817.
11. **Tobis J, Shenoda M.** Percutaneous treatment of patent foramen ovale and atrial septal defects. *J Am Coll Cardiol* 2012; 60:1722–1732.

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