ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**, 1–6
https://doi.org/10.1093/ehjcr/ytac214

CASE REPORT
Other

Paroxysmal supine hypoxaemia with hyperthyroidism and atrial fibrillation: a case report of a diagnostic challenge

Liang Yen Liu [1]*, Yogesh N. V. Reddy [2], Alexander S. Niven [3], Tiffany Y. Hu[2], Kathryn F. Larson[2], Siva K. Mulpuru[2], and Michael W. Cullen[2]

[1]Mayo Clinic Alix School of Medicine, Rochester, MN, USA; [2]Mayo Clinic Rochester, Department of Cardiovascular Medicine, USA; and [3]Mayo Clinic Rochester, Department of Pulmonary and Critical Care Medicine, USA

Received 3 November 2021; first decision 31 December 2021; accepted 19 May 2022; online publish-ahead-of-print 24 May 2022

Background A patent foramen ovale (PFO) is a persistent embryonic defect in the interatrial septum. Platypnoea-orthodeoxia syndrome is characterized by positional hypoxaemia that is most commonly due to right-to-left shunting through a PFO. Dynamic right-to-left shunting through a PFO can also exacerbate positional hypoxaemia without platypnea-orthodeoxia syndrome.

Case summary A 78-year-old woman with hyperthyroidism and paroxysmal atrial fibrillation (AF) presented with positional hypoxaemia exacerbated by supine positioning. Diagnostic testing revealed intermittent right-to-left shunting through a PFO triggered by worsening atrial functional tricuspid regurgitation and elevated right atrial pressures. Diuresis, rate control, and thyroidectomy initially led to resolution of positional hypoxaemia, but recurrent AF episodes triggered right-to-left shunting with recurrent desaturation. Left atrial and cavo-tricuspid isthmus ablation led to restoration of normal sinus rhythm and resolution of positional hypoxaemia without PFO closure.

Discussion The clinical presentation of intermittent intracardiac right-to-left shunting can mimic decompensated heart failure with pulmonary oedema. Persistent hypoxaemia out of proportion to the degree of pulmonary oedema and minimally responsive to supplemental O_2 should raise suspicion for right-to-left shunt aetiology. Positional arterial blood gases can facilitate the diagnostic evaluation of refractory hypoxaemia in cases of suspected shunting. Diagnostic imaging for PFO detection includes both transthoracic and transesophageal echocardiography with Valsalva manoeuver and agitated saline injection. Closure of a PFO for management of arterial deoxygenation syndromes should not be performed before treating other causes of arterial deoxygenation and optimizing factors that may exacerbate shunting across the PFO.

Keywords Patent foramen ovale • Positional hypoxaemia • Intracardiac shunt • Hyperthyroidism • Atrial fibrillation • Case Report

ESC Curriculum 2.2 Echocardiography • 2.1 Imaging modalities • 4.5 Tricuspid regurgitation • 5.3 Atrial fibrillation • 6.1 Symptoms and signs of heart failure

* Corresponding author. Tel: (510) 565-2768, Email: liu.liangyen@mayo.edu
Handling Editor: Zaid Iskander
Peer-reviewers: Satish Ramkumar; Rami Riziq Yousef Abumuaileq; Maria Concetta Pastore
Compliance Editor: Polyvios Demetriades
Supplementary Material Editor: Tinka Julia van Trier

Learning points

- Persistent and profound hypoxaemia out of proportion to pulmonary oedema with little improvement in O_2 saturation with O_2 supplementation should raise suspicion for right-to-left shunt.
- The first-line imaging modality for patent foramen ovale detection is saline-contrast transthoracic echocardiogram. If undetected but still suspected, second-line imaging is with saline-contrast transesophageal echocardiogram.
- Patent foramen ovale closure for arterial deoxygenation syndromes should not be routinely performed before evaluation and treatment for other aetiologies exacerbating hypoxaemia.

Introduction

A patent foramen ovale (PFO) is a persistent embryonic defect in the interatrial septum present in ~25% of the adult population; most are clinically silent. A PFO is associated with paradoxical embolism in cryptogenic stroke, migraines, and arterial deoxygenation syndromes.[1,2] We present a case of paroxysmal and positional hypoxaemia due to intermittent right-to-left shunting through a previously undetected PFO mimicking acute decompensated heart failure with pulmonary oedema.

Timeline

February 12, 2020	Initial diagnosis of atrial fibrillation.
May 19, 2020	Initial diagnosis of hyperthyroidism.
June 11, 2020	Patient presented to the emergency room.
June 12, 2020	Transthoracic echocardiogram performed.
June 15, 2020	Right-heart catheterization performed. Patient was discharged from the hospital.
June 23, 2020	Total thyroidectomy performed.
June 25, 2020	Transesophageal echocardiogram performed.
June 26, 2020	Patient discharged from hospital.
October 22, 2020	Patient presented for four-month post-hospitalization outpatient cardiology evaluation.
April 14, 2021	Patient presented for ten-month post-hospitalization outpatient cardiology evaluation. Transthoracic echocardiogram performed.
June 18, 2021	Patient presented for outpatient pulmonary vein isolation and cavo-tricuspid isthmus ablation.

Case presentation

A 78-year-old woman with hypertension, paroxysmal atrial fibrillation (AF) on apixaban (CHA_2DS_2-VASc = 4), and Graves' disease presented with progressive dyspnoea over 4 days. Heart rate (HR) was 110 beats/min, blood pressure (BP) was 155/122 mmHg, respiratory rate was 23 breaths/min, and oxygen saturation (SpO_2) was 85% on room air while supine. Physical examination revealed no gallops, rubs, or murmurs, scattered rales in the left posterior lung, and trace presacral and pitting oedema. Electrocardiogram showed AF with rapid ventricular response (RVR). Thyroid-stimulating hormone (TSH) was undetectable (normal 0.3–4.2), free thyroxine was 1.9 (normal 0.9–1.7), NT-proB-type natriuretic peptide was 6920 (normal ≤239). Chest X-ray showed mild pulmonary oedema. Despite adequate rate control to HR 85 beats/minute with metoprolol and diltiazem, 1 L diuresis with furosemide, BP controlled to 139/78 mmHg, and supplemental O_2 at 4 L/min, she saturated in the high 70%'s while both supine and ambulating. Chest computed tomography angiography (CTA) showed no pulmonary embolism or pulmonary arteriovenous malformations.

The following day she developed sudden-onset dyspnoea, saturating in the mid-70%'s while supine that persisted despite 15 L/min supplemental O_2. She received bilateral positive airway pressure and additional diuresis. SpO_2 improved into the high-80%'s but desaturations into the low-80%'s continued while supine. Transthoracic echocardiogram (TTE) showed moderately enlarged right ventricle (RV) with normal systolic function, severe tricuspid regurgitation (TR), biatrial enlargement, elevated central venous pressure, left ventricular ejection fraction of 60–65% with no regional wall motion abnormalities, and atrial-level right-to-left shunting (*Figure 1A–D*). After further diuresis, the patient underwent right-heart catheterization (*Figure 2A–C*). Pulmonary capillary wedge (PCW) pressure was 16 mmHg, mean pulmonary artery pressure was 21 mmHg and cardiac index was 2.1 L/min/m^2. SpO_2 was obtained at the following locations: superior vena cava 55%, right atrium (RA) 54%, pulmonary artery 54%, aorta 92%, PCW 99%, and inferior vena cava (IVC) to be 46%. Pulmonary/systemic flow ratio was 0.9. Despite evidence of atrial-level right-to-left shunt on TTE, transesophageal echocardiogram (TEE) was not pursued because her hypoxaemia, which resolved with diuresis, was attributed to her mild pulmonary oedema. She discharged from the hospital.

The patient underwent thyroidectomy 1 week later due to significant goitre mass effect and continued thyrotoxicosis despite medical therapy. Intraoperatively, SpO_2 declined into the high-70%'s despite escalating O_2 supplementation. Positional arterial blood gases (ABGs) suggested dynamic right-to-left shunting (*Table 1*) contributing to the hypoxaemia. Transesophageal echocardiogram confirmed a bidirectional shunt at rest through a PFO (*Figure 3A-B*) and severe functional TR. She was diuresed to euvolemia, rate controlled with full resolution of her O_2 requirement, and discharged on metoprolol for rate control without supplemental O_2.

The patient returned 4 months later in normal sinus rhythm (NSR). Thyroid-stimulating hormone was 4.6 and free thyroxine was 1.4 on levothyroxine. Transthoracic echocardiogram demonstrated decreased RV size, decreased TR, and absence of right-to-left shunting across the PFO, suggesting resolution of her volume

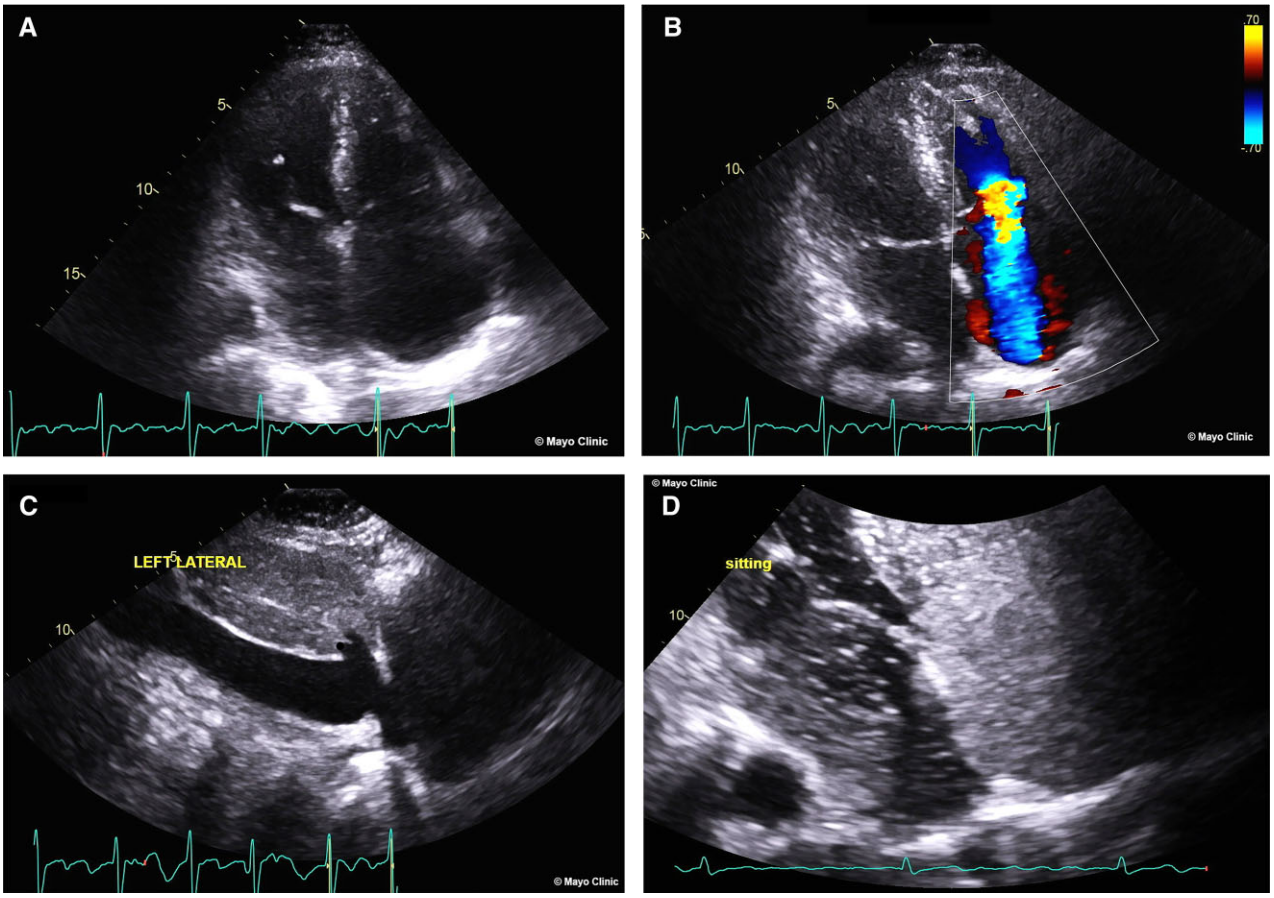

Figure 1 Transthoracic echocardiogram performed during first hospitalization, showing apical window four-chamber view (*A*) with colour-flow imaging (*B*), inferior vena cava view (*C*), and saline-contrast study (*D*).

overload. However, 10 months post-thyroidectomy, she developed recurrent AF with RVR, dyspnoea, and pitting oedema. Thyroid-stimulating hormeleven

one was 12.3 and free thyroxine was 1.5 on levothyroxine. Transthoracic echocardiogram showed moderate right-to-left shunt through her PFO at rest, torrential TR, and severe IVC dilation with no inspiratory collapse. Because right-to-left shunting, RA enlargement-mediated severe TR and right-heart failure symptoms were triggered during AF, she underwent pulmonary vein isolation and cavo-tricuspid isthmus ablation with restoration of NSR. She had no recurrent AF or hypoxemic episodes and did not require PFO closure. She remained on apixaban with no complications.

Discussion

We present a case of positional hypoxaemia exacerbated by intermittent, intracardiac right-to-left shunting mimicking a common clinical presentation of decompensated heart failure with pulmonary oedema. Aetiologies for hypoxaemia are hypoventilation, reduced O_2 tension, ventilation-perfusion mismatch, diffusion impairment, and right-to-left shunt (*Table 2*). Right-to-left shunt is the only aetiology demonstrating minimal SpO2 improvement with supplemental O_2. Platypnea-orthodeoxia syndrome (POS) is a clinical syndrome characterized by dyspnoea and hypoxaemia when moving from supine to upright; the most common aetiology is right-to-left shunting across a PFO.[3] Our patient did not present with classic positional hypoxaemia associated with POS. Her hypoxaemia worsened while supine. However, her persistent hypoxaemia while upright was out of proportion to the degree of pulmonary oedema and minimally responsive to supplemental O_2, as the positional ABGs illustrate (*Table 1*), making ventilation-perfusion mismatch from pulmonary oedema a less likely aetiology. Despite its utility in directly measuring pulmonary and systemic flow, right-heart catheterization after diuresis failed to detect significant right-to-left shunting in the absence of volume overload with dynamic increases in atrial functional TR and RA pressure that worsened right-to-left shunting across the PFO. Increased preload in the supine position further increased TR and RA pressure, resulting in greater right-to-left shunting.

Hyperthyroidism is a well-known cause of AF. This patient had a compressive, toxic goitre that required semi-urgent removal. Restoration of NSR occurs in 47% of hyperthyroid patients with AF undergoing thyroidectomy.[4] Despite achieving restoration of NSR the patient reverted to AF with RVR 11 months after thyroidectomy. With her history of severe functional TR and positional right-to-left shunting, definitive treatment necessitated either catheter ablation for AF control or PFO closure for shunt source resolution.

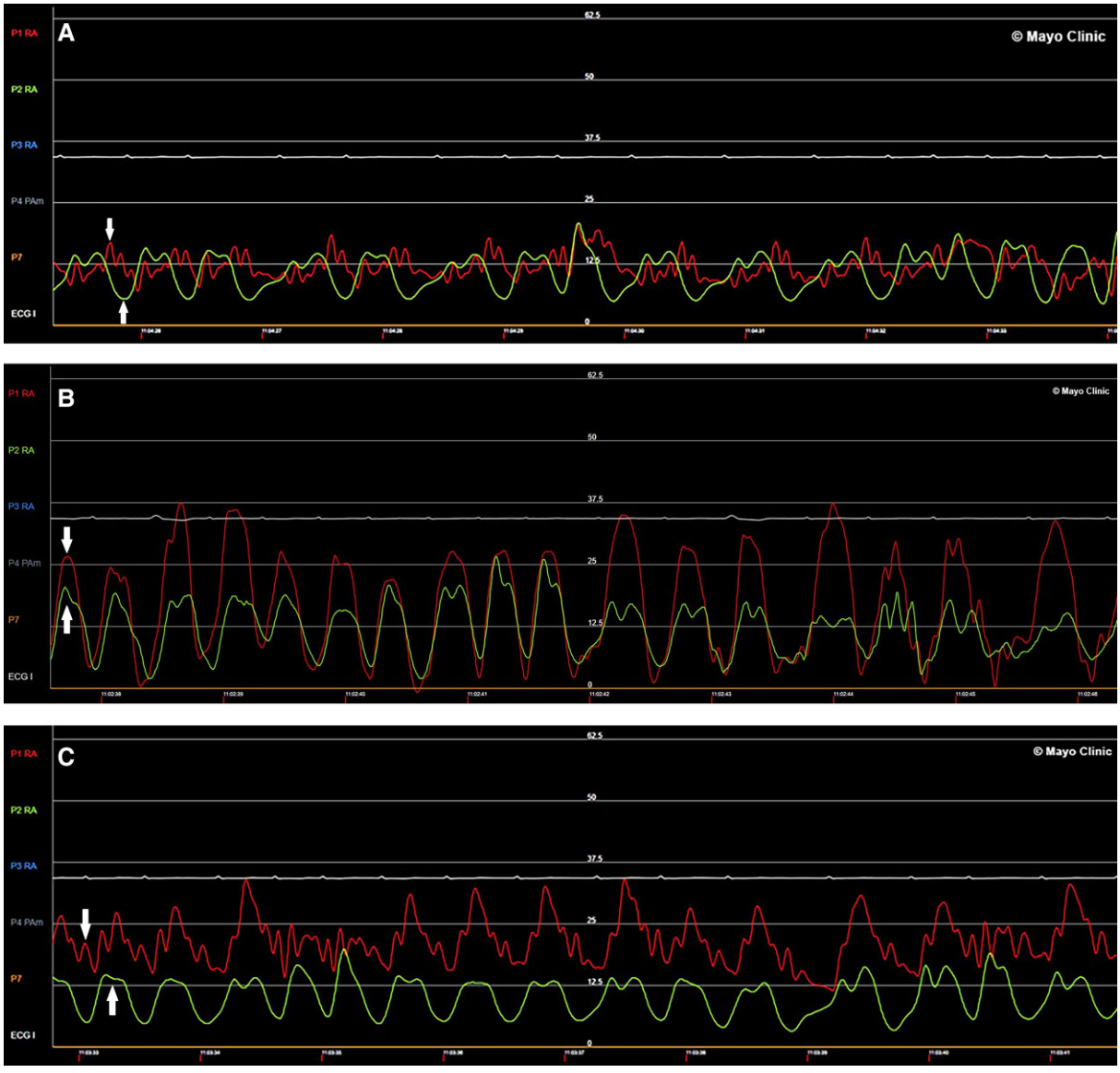

Figure 2 Right heart catheterization performed during first hospitalization, showing RA = up arrow and PA = down arrow pressures (*A*), RA = up arrow and RV = down arrow pressures (*B*), RA = up arrow and PCW = down arrow pressures (*C*).

Table 1 Post-thyroidectomy ABGs obtained in supine, sitting, sitting with 100% O_2, and standing positions.

	Supine	Sitting	Sitting with 100% O_2	Standing
pH	7.42	7.40	7.42	7.41
pCO_2 (mmHg)	30	31	22	30
pO_2 (mmHg)	73	75	92	239
FiO_2	0.65	0.65	1.00	0.65

The European Association of Cardiovascular Imaging recommends saline-contrast TTE with Valsalva manoeuver as the first-line imaging modality for PFO detection.[5] In the event of a negative saline-contrast TTE, patients can undergo saline-contrast TEE. However, saline-contrast TEE sensitivity for detecting PFO with right-to-left shunting can be reduced if patient sedation prohibits appropriate Valsalva manoeuver. Therefore, the best approach to PFO detection is likely a combination of saline-contrast TTE with Valsalva manoeuver without sedation and saline-contrast TEE with Valsalva manoeuver under sedation.[5] Patent foramen ovale closure should not be routinely performed in arterial deoxygenation syndromes but could be considered based on symptom severity and the pathogenic role of PFO in desaturation.[6] Atrial fibrillation is the most common post-procedural complication occurring in 4.6% of patients.[7] These data supported our decision to pursue AF ablation rather than PFO closure in this patient.

In this case, diagnostic testing for intracardiac right-to-left shunt source was pursued after evaluating for a pulmonary shunt with

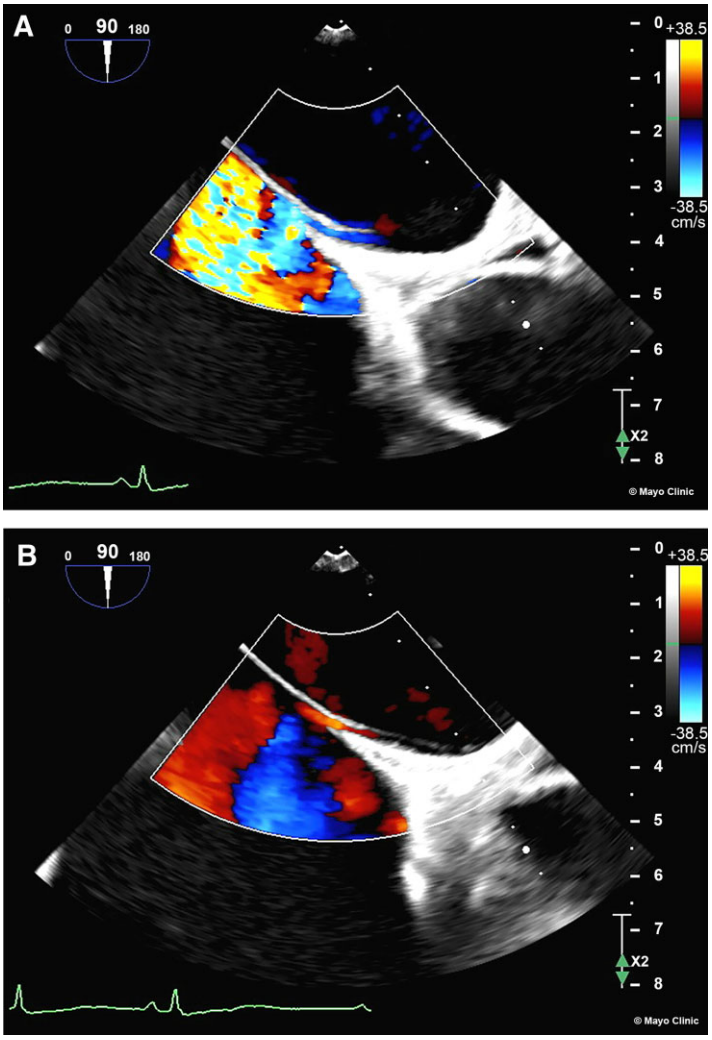

Figure 3 Transthoracic echocardiogram obtained during second hospitalization showing right-to-left shunt with bidirectional flow from left atrium to right atrium (*A*) and right atrium to left atrium (*B*) at rest through a PFO.

Table 2 Clinical presentation of different aetiologies of hypoxaemia

Aetiologies of hypoxaemia	Clinical examples	Alveolar–arterial gradient	Response to supplementary oxygen
Hypoventilation	• Opioid overdose• Pickwickian syndrome	Normal	Dramatic improvement
Reduced oxygen tension (low FiO2)	• High altitude	Normal	Dramatic improvement
Ventilation-perfusion mismatch	• Pulmonary embolism• Pulmonary oedema• Pneumonia	Elevated	Mild-to-moderate improvement
Diffusion impairment	• Interstitial lung disease	Elevated	Mild-to-moderate improvement
Right-to-left shunt	• Intracardiac (PFO, atrial septal defect)• Extracardiac (pulmonary arteriovenous malformation)	Elevated	Minimal to no improvement

chest CTA. Visualization of right-to-left interatrial shunting was achieved with contrast TTE and further clarified by TEE. Arterial blood gases obtained in different positions and levels of supplemental oxygen established the dynamic nature of hypoxaemia and identified right-to-left shunting as a contributor to the hypoxaemia. Definitive treatment of hypoxaemia was achieved through AF ablation and durable restoration of NSR, which improved functional TR, lowered RA pressure, and decreased right-to-left shunting. Therefore, PFO

closure was not necessary. Our case illustrates the importance of comprehensive evaluation of shunt-associated arterial deoxygenation syndromes and careful patient selection for PFO closure.

Lead author biography

Liang Yen (Larry) Liu is a third-year medical student at the Mayo Clinic Alix School of Medicine Rochester campus.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Acknowledgements

None.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: All co-authors have no conflicts of interest to declare.

Funding: The authors did not receive any funding for this manuscript.

References

1. Teshome MK, Najib K, Nwagbara CC, Akinseye OA, Ibebuogu UN. Patent foramen ovale: a comprehensive review. *Curr Probl Cardiol* 2020;**45**:100392.
2. Mojadidi MK, Ruiz JC, Chertoff J, Zaman MO, Elgendy IY, Mahmoud AN, Al-Ani M, Elgendy AY, Patel NK, Shantha G, Tobis JM, Meier B. Patent foramen ovale and hypoxemia. *Cardiol Rev* 2019;**27**:34–40.
3. Cheng TO. Platypnea-orthodeoxia syndrome: etiology, differential diagnosis, and management. *Catheter Cardiovasc Interv* 1999;**47**:64–66.
4. Fierro N, Gonnella C, Pietropaolo L, Morelli A, Di Cola G, D'Ermo G, *et al.* Fibrillazione atriale ed irpertiroidismo: risultati dopo intervento di tiroidectomia [Atrial fibrillation and hyperthyroidism: results after thyroidectomy]. *G Chir* 2002; **23**:431–433.
5. Cohen A, Donal E, Delgado V, Pepi M, Tsang T, Gerber B, Soulat-Dufour L, Habib G, Lancellotti P, Evangelista A, Cujec B, Fine N, Andrade MJ, Sprynger M, Dweck M, Edvardsen T, Popescu BA, Bertrand P, Galderisi M, Haugaa KH, Sade LE, Stankovic I, Cosyns B. EACVI recommendations on cardiovascular imaging for the detection of embolic sources: endorsed by the Canadian Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2021;**22**:e24–e57.
6. Pristipino C, Germonpré P, Toni D, Sievert H, Meier B, D'Ascenzo F, Berti S, Onorato EM, Bedogni F, Mas J-L, Scacciatella P, Hildick-Smith D, Gaita F, Kyrle PA, Thomson J, Derumeaux G, Sibbing D, Chessa M, Hornung M, Zamorano J, Dudek D. European position paper on the management of patients with patent foramen ovale. Part II - Decompression sickness, migraine, arterial deoxygenation syndromes and select high-risk clinical conditions. *EuroIntervention* 2021;**17**:e367–e375.
7. Pristipino C, Sievert H, D'Ascenzo F, Mas JL, Meier B, Scacciatella P, Hildick-Smith D, Gaita F, Toni D, Kyrle P, Thomson J, Derumeaux G, Onorato E, Sibbing D, Germonpré P, Berti S, Chessa M, Bedogni F, Dudek D, Hornung M, Zamorano J, D'Ascenzo F, Omedè P, Ballocca F, Barbero U, Giordana F, Gili S, Iannaccone M, Capodanno D, Valgimigli M, Byrne R, Akagi T, Carroll J, Dalvi B, Ge J, Kasner S, Michel-Behnke I, Pedra C, Rhodes J, Søndergaard L, Thomassen L, Biondi-Zoccai GGL. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism [published correction appears in Eur Heart J. 2021 May 7; 42(18):1807]. *Eur Heart J* 2019; **40**:3182–3195.