

# Carcinoid heart disease of gonadal primary presenting with hypoxia: a case report

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## Background

Carcinoid heart disease is a potential sequela of metastatic neuroendocrine tumour that has characteristic valve appearances. Patients can present with symptoms of carcinoid syndrome or be relatively asymptomatic until symptoms of progressive heart failure manifest.

## Case summary

We present a case of a 54-year-old male who was admitted to the hospital for investigation of hypoxia. Transthoracic echocardiogram was suggestive of carcinoid heart disease which subsequently led to a diagnosis of metastatic neuroendocrine (carcinoid) tumour of the testicular primary. Work-up revealed a patent foramen ovale with evidence of the right to left interatrial shunt from severe tricuspid regurgitation as the cause of his hypoxia. Prior to surgical excision of the primary tumour, percutaneous patent foramen ovale closure was performed resulting in improved arterial oxygen saturation and symptomatic improvement.

## Discussion

Carcinoid heart disease typically affects the right-sided cardiac valves and the tricuspid valve appearances were critical in leading to a diagnosis of a metastatic neuroendocrine tumour in our patient. This case demonstrates that percutaneous patent foramen ovale closure can be an effective intervention for hypoxia in those not managed surgically. A high index of suspicion should be maintained for gonadal primary carcinoid tumour when there is carcinoid heart disease in the absence of liver metastases.

## Keywords

Valvular disease • Echocardiography • Shunt • Patent foramen ovale • Neuroendocrine tumour • Case report

## Learning points

- Characteristic echocardiographic appearances of carcinoid heart disease can aid diagnosis in those not manifesting usual symptoms of carcinoid syndrome
- A high index of suspicion should be maintained for gonadal primary carcinoid tumour when there is carcinoid heart disease in the absence of liver metastases.
- Percutaneous patent foramen closure for hypoxia in carcinoid heart disease can be an effective intervention, including in those patients who are not surgically managed.

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## Introduction

Carcinoid heart disease is a rare condition associated with neuroendocrine (carcinoid) tumours. These tumours typically arise from the gastrointestinal and bronchopulmonary system, although very rarely they have been reported to arise from other sites.<sup>1</sup> Tumour release of circulating vasoactive substances including serotonin metabolites contribute to valvular fibrous plaque formation.<sup>2</sup> This subsequently leads to thickened, shortened, and retracted valve leaflets with associated concurrent valvular stenosis and regurgitation.<sup>3</sup> Patients may be diagnosed after presenting with symptoms of carcinoid syndrome; however, diagnosis is often delayed given the insidious onset of carcinoid heart disease symptoms.<sup>4</sup> We present a unique case of carcinoid heart disease from metastatic neuroendocrine tumour of testicular primary with a coexistent patent foramen ovale (PFO), diagnosed after investigation for hypoxia and successfully managed with percutaneous PFO closure.

## Timeline

Day 1	Pre-admission clinic for elective endoscopy, subsequently referred to emergency department after anaesthetist notes hypoxia. Computed tomography pulmonary angiogram shows left basal pulmonary embolism.
Day 5	Transthoracic echocardiogram (TTE) with valve appearances suspicious for carcinoid heart disease
Day 8	Seen by medical oncology team
Day 9	Discharge from hospital against medical advice
Day 29	68-Gallium DOTATATE positron emission tomography (PET) showing avid para-aortic lymph node and right testes
Day 42	Para-aortic lymph node computed tomography-guided biopsy confirms carcinoid tumour
Day 50	TTE bubble study strongly positive within three cardiac cycles
Day 53	Admitted to hospital with dyspnoea
Day 58	Digital subtraction pulmonary angiography confirms atrial level shunt
Day 62	Declined further investigation, discharged from hospital
Day 71	Agreed to transoesophageal echocardiogram with bubble study, confirms patent foramen ovale (PFO)
Day 93	Reluctant for surgery, multidisciplinary decision to proceed with percutaneous PFO closure, directly admitted to hospital
Day 96	PFO closure performed
Day 97	No residual interatrial flow on repeat TTE
Day 99	Right orchidectomy performed
Day 103	Discharged from hospital
Day 170	Stable symptoms at follow-up

## Case presentation

A 54-year-old male was admitted from pre-admission clinic for investigation of new-onset hypoxia. He was planned to have an endoscopy for investigation of weight loss, abdominal pain, and diarrhoea. He had additionally reported a history of intermittent palpitations and exertional dyspnoea.

Background medical history included hypertension, obesity, type 2 diabetes mellitus, gastro-oesophageal reflux disease, and previous traumatic splenectomy. He was a lifelong non-smoker.

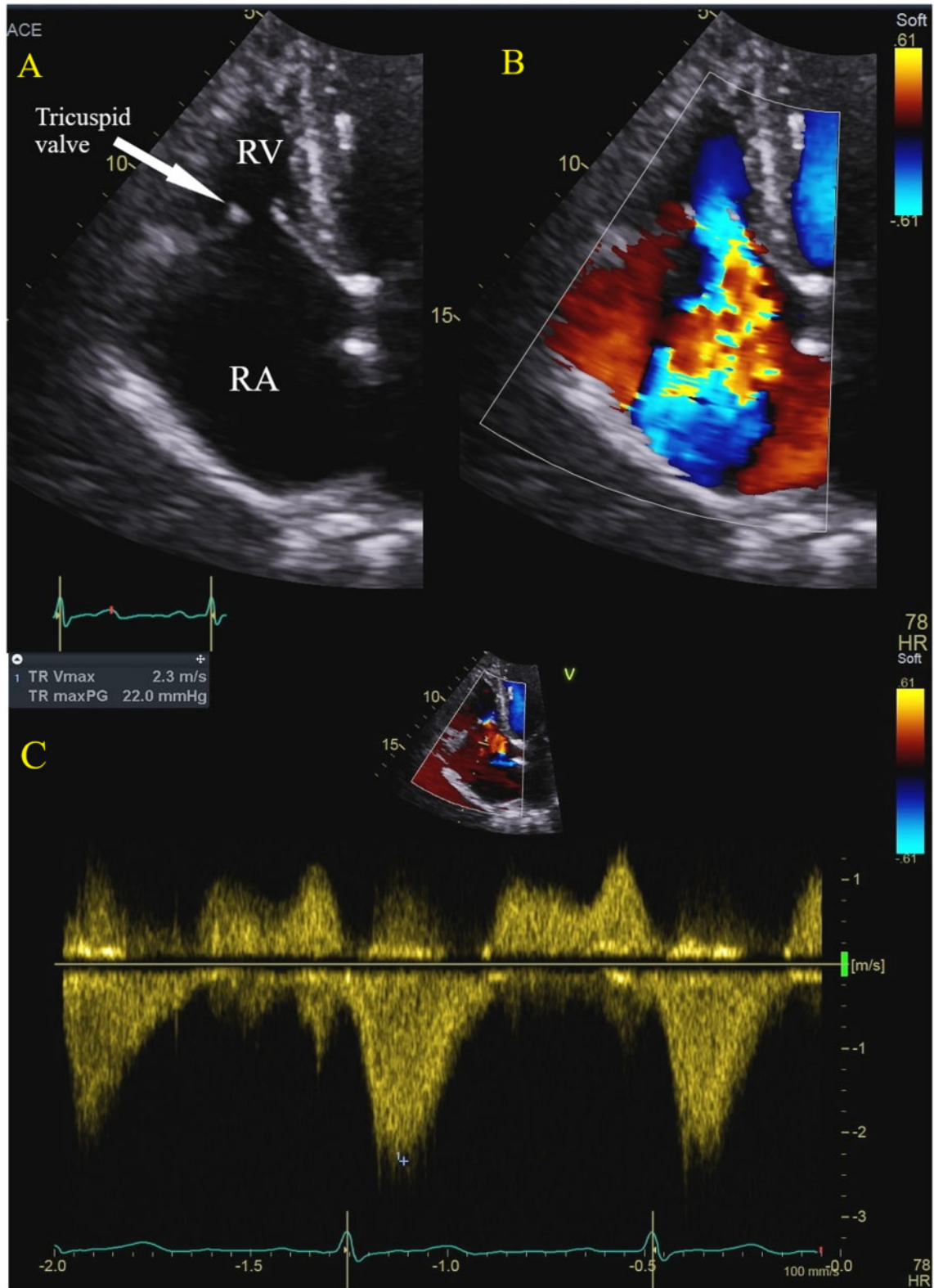
Physical examination revealed oxygen saturation of 81% on room air improving to 87% on 4 L via nasal cannula. There was no orthodeoxia. Lung auscultation was unremarkable. There was a Grade 3/6 pansystolic murmur at the left sternal edge associated with jugular venous pressure elevated to the angle of the jaw, with prominent 'v' waves and no peripheral oedema.

Resting electrocardiogram showed sinus rhythm, rate of 71 beats per minute, normal axis, and no ischaemic changes. Chest X-ray showed clear lung fields. An arterial blood gas on room air showed hypoxia with a mild respiratory alkalosis and elevated alveolar-arterial (A-a) oxygen gradient (Table 1). Haemoglobin and renal function were normal. Computed tomography (CT) pulmonary angiogram on admission revealed normal lung parenchyma and a left posterior basal segmental pulmonary embolism without evidence of right heart strain, the size of which was thought to inadequately account for the hypoxia. Pulmonary function testing showed a mild restrictive pattern with FEV1 2.44 L (70% predicted), FVC 3.22 L (73% predicted), FEV1/FVC 75.90% (99% predicted), and carbon monoxide transfer coefficient 4.38 mL/(min\*mmHg\*L) (103% predicted), although there was variable performance in testing.

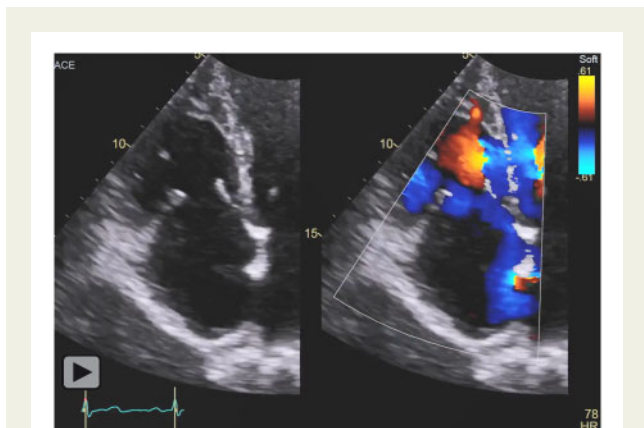
Transthoracic echocardiogram (TTE) showed the normal left ventricular size and systolic function. There was mild bi-atrial dilatation along with mild right ventricular dilatation (44 mm basal diameter) with hyperdynamic systolic function. Tricuspid annular plane systolic excursion was 30 mm. Tricuspid valve leaflets were noted to be thickened, immobile and retracted, not coapting in systole with free-flowing tricuspid regurgitation, which in the setting of a morphologically normal mitral valve was pathognomonic for carcinoid heart disease (Figures 1A and B, Video 1 and Supplementary material online, Video S1). The pulmonary valve had a normal appearance and mild regurgitation. Twenty-four hour urinary 5-hydroxyindoleacetic acid was elevated at 260 µmol/24 h (normal range 0–30), whilst chromogranin A was 156 ng/mL (normal range 0–104).

**Table 1** Initial arterial blood gas

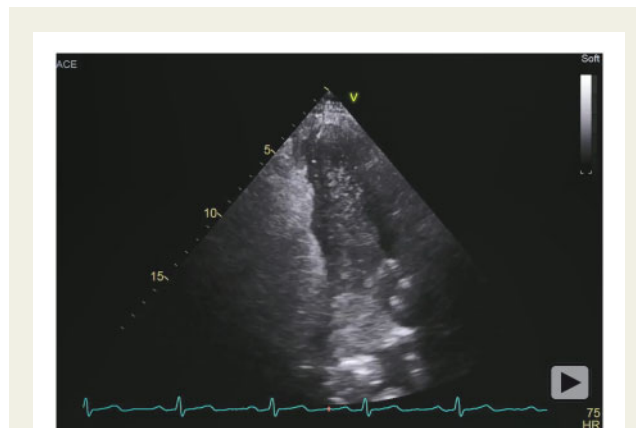
Measurement	Value	Normal values
pH	7.504	(7.35–7.45)
pO <sub>2</sub>	48.7 mmHg	(75–100 mmHg)
pCO <sub>2</sub>	28.1 mmHg	(35–45 mmHg)
HCO <sub>3</sub>	21.9 mmol/L	(22–26 mmol/L)
Base excess	-0.8 mmol/L	(±2 mmol/L)
Inspired oxygen (FiO <sub>2</sub> )	21%	
A-a gradient	66.0 mmHg	(17.5 mmHg)



**Figure 1** Transthoracic echocardiogram. Apical four-chamber zoomed tricuspid valve view, showing thickened and stenosed tricuspid valve leaflets in mid-systole (A), with colour Doppler showing free-flowing tricuspid regurgitation (B). Apical four-chamber tricuspid regurgitation spectral Doppler demonstrating typical 'dagger' shaped waveform (C). RA, right atrium; RV, right ventricle.



**Video 1** Transthoracic echocardiogram apical four-chamber zoomed tricuspid valve view with simultaneous colour Doppler showing severe tricuspid regurgitation.



**Video 2** Transthoracic echocardiogram Gelofusine bubble study showing early filling of the left atrium.

A TTE bubble study ([Video 2](#)) was performed due to radiographically normal lungs, the small size of the pulmonary embolism, and patient reluctance for a transoesophageal echocardiogram (TOE), which were strongly positive within three cardiac cycles suggesting shunt at the cardiac level. However, the passage of bubbles appeared to originate from the pulmonary veins which was suspicious for pulmonary shunting.

Dedicated digital subtraction pulmonary angiography ([Supplementary material online, Video S2](#)) was therefore performed which excluded pulmonary arteriovenous fistula and large pulmonary embolism but revealed early filling of the left atrium confirming an intracardiac shunt. The patient eventually agreed to a TOE ([Figure 2A and B, Supplementary material online, Video S3](#)) with bubble study ([Figure 2C, Video 3](#)) which confirmed a long tunnel patent foramen ovale with an aneurysmal interatrial septum. There was evidence of the significant right to left shunting on colour Doppler at rest in the supine position.

68-Gallium DOTATATE PET ([Figure 3](#)) and CT imaging identified a 27 mm × 36 mm × 57 mm avid retroperitoneal para-aortic lymph node and avid right testicular mass. Percutaneous biopsy of the retroperitoneal mass revealed a well-differentiated neuroendocrine (carcinoid) tumour WHO Grade 1.

Prior to excision biopsy of the right testicular tumour, consideration of surgical tricuspid valve replacement combined with PFO closure was declined by the patient. Given marked resting hypoxia, need for surgery and undetermined diagnosis and prognosis, percutaneous closure of the patent foramen ovale was considered appropriate.

Pre-procedural right heart catheterization demonstrated a right to a left atrial pressure gradient ([Table 2](#)). The PFO was successfully closed under fluoroscopic guidance with a 30mm Amplatzer PFO Occluder device ([Supplementary material online, Figure S1](#)). Pre-procedural arterial oxygen saturation of 82% improved to 88% immediately post-procedure. There were no procedural complications.

The patient underwent an inpatient orchidectomy with histopathology of the right testicle confirming a primary well-differentiated neuroendocrine (carcinoid) tumour. The patient was commenced on somatostatin analogue therapy. He was discharged a week following PFO closure with arterial oxygen saturation of 92% on room air. He has had durable relief of his symptoms. Repeat TTE showed no residual flow across the interatrial septum. The patient continues to decline consideration of tricuspid valve surgery.

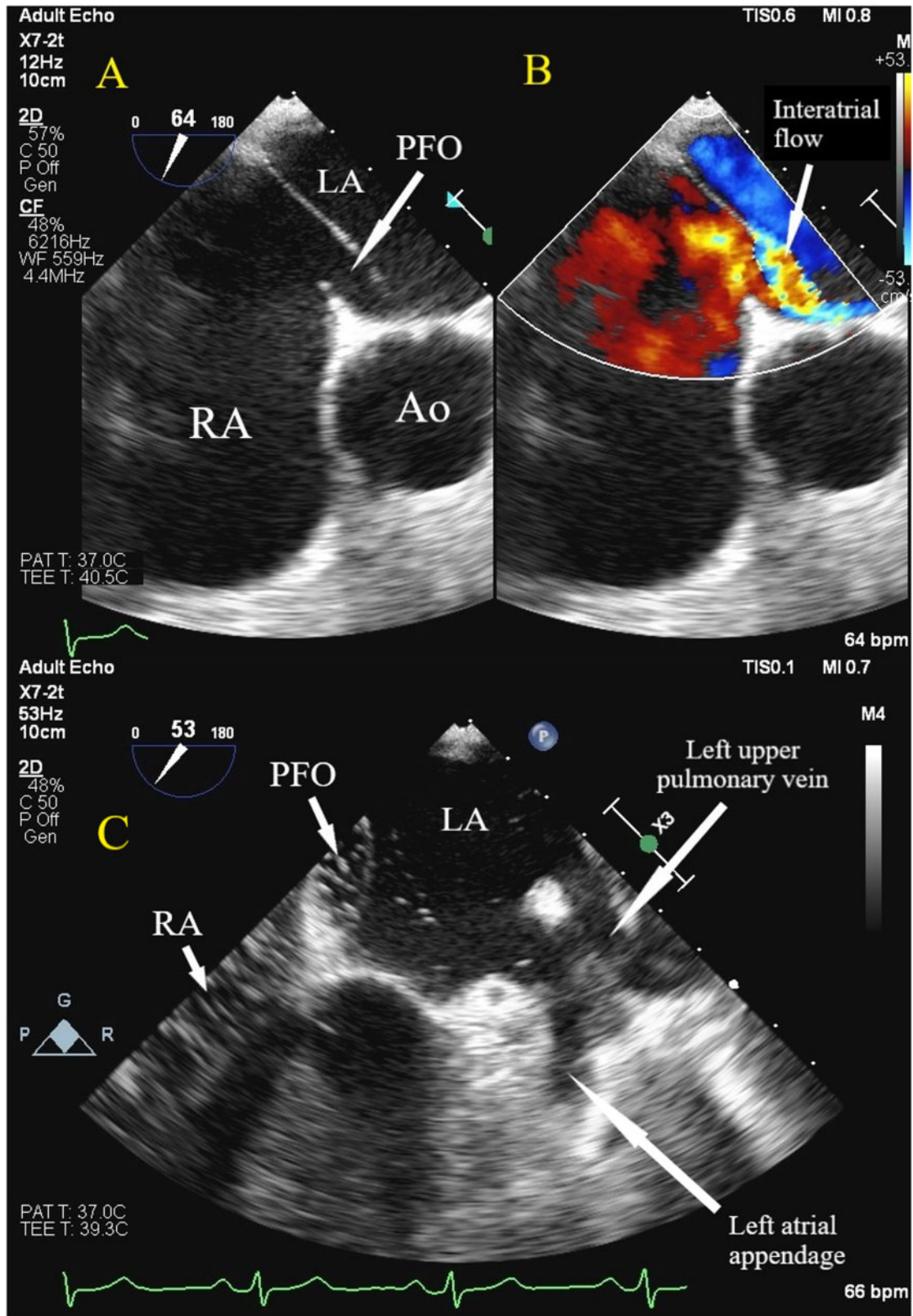
## Discussion

This educational and rare case describes a patient with newly diagnosed carcinoid valvular heart disease secondary to primary testicular neuroendocrine tumour (NET) discovered after investigation for hypoxia. The classic appearance of carcinoid heart disease on TTE was key to guiding further investigation to confirm the diagnosis in our patient. Right-sided valvular disease is the most common manifestation of carcinoid heart disease with the tricuspid valve most frequently involved,<sup>5</sup> while left heart valvular disease is rare in the absence of a PFO with right to left shunting or bronchopulmonary tumour.<sup>6</sup>

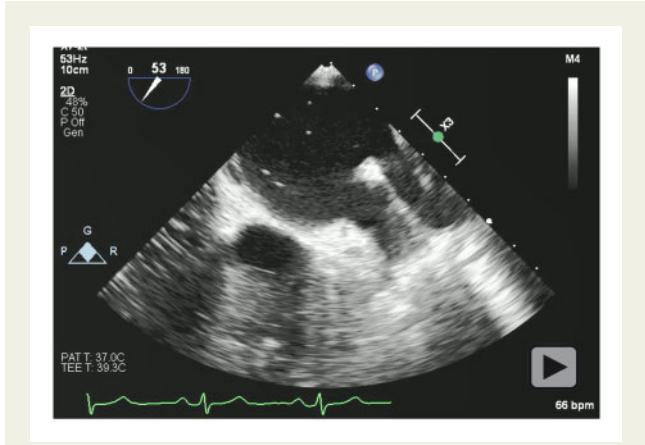
The patient's hypoxia was explained by right to left intracardiac shunting through a PFO, secondary to severe regurgitation from the carcinoid-affected tricuspid valve, with potential mechanisms including both right atrial pressure elevation and preferentially directed venous blood flow across the interatrial septum from the regurgitant jet. Our case demonstrates the importance of assessment for PFO in those diagnosed with carcinoid heart disease and unexplained hypoxia.

International consensus guidelines for the diagnosis and management of carcinoid heart disease published in 2017,<sup>7</sup> recommend that patients be referred for consideration of valve surgery when there is severe regurgitation and development of symptoms or evidence of early right ventricular dysfunction, as was the case with our patient. These guidelines also recommend PFO closure at the time of valve surgery. Our case highlights that even in





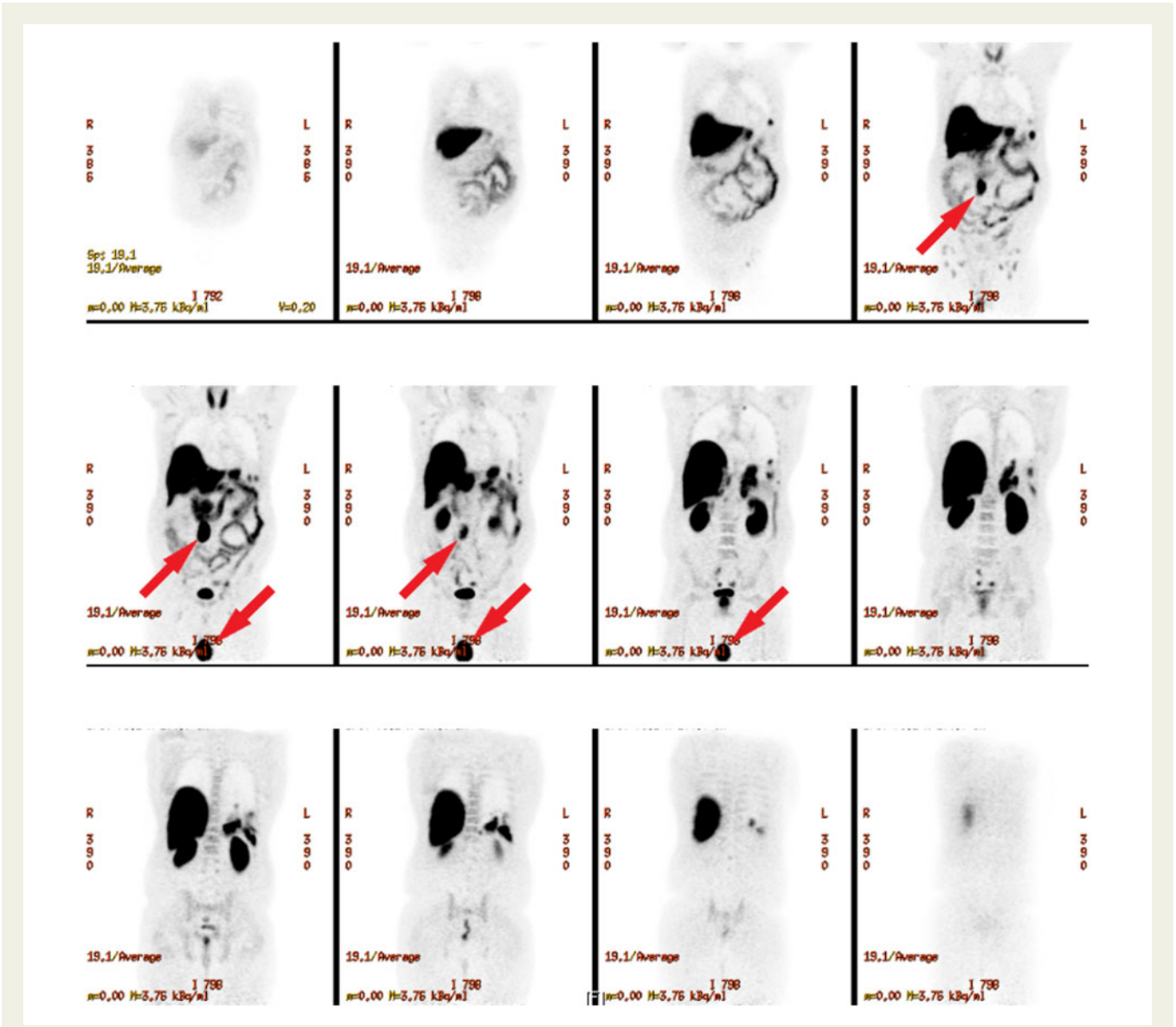
**Figure 2** Transoesophageal echocardiogram. Mid-oesophageal interatrial septum view showing patent foramen ovale (A) and colour Doppler with right to left shunt (B). Transoesophageal echocardiogram bubble study demonstrating origin of bubbles from patent foramen ovale, without involvement of left upper pulmonary vein (C). Ao, aorta; LA, left atrium; PFO, patent foramen ovale; RA, right atrium.



**Video 3** Transoesophageal echocardiogram bubble study showing early filling of the left atrium through a long-tunneled patent foramen ovale.

those not managed with surgical valve replacement initially, percutaneous catheter-based closure of patent foramen ovale is a reasonable, minimally invasive option for a significant right to left interatrial shunt causing hypoxia.

Neuroendocrine tumour of testicular primary remains exceedingly rare.<sup>1</sup> While our patient only had metastasis to a retroperitoneal lymph node, other metastatic sites including liver, lung, vertebrae, heart, and contralateral testicle have been reported in those with testicular carcinoid.<sup>8</sup> It is interesting that our case has presented with carcinoid heart disease in the absence of significant metastatic burden, given it is typically associated with liver metastases.<sup>9</sup> It has been reported that because venous drainage from the ovaries bypass the portal circulation, this may explain why primary ovarian carcinoid can present with carcinoid heart disease without liver metastases.<sup>10</sup> Theoretically this should also be true for primary testicular carcinoid tumours, although it is ultimately unknown.



**Figure 3** 68-Gallium DOTATATE PET scan. 68-Gallium DOTATATE PET scan demonstrating avid uptake in retroperitoneal lymph node and right testicle (red arrows). Left upper quadrant uptake secondary to previous splenectomy.

**Table 2** Pre-procedural right heart catheterization pressures

Site	Pressure (mean) (mmHg)	Normal values for mean pressure (mmHg)	Heart rate (beats per minute)
Left atrium	14/14 (11)	(4–12)	73
Right atrium	20/21 (16)	(0–7)	72
Inferior vena cava	22/24 (21)	(1–10)	71

## Lead author biography



Ronan O'Driscoll is a Basic Physician Trainee at St George Hospital in Sydney, Australia. He will soon commence as a Cardiology Registrar at The Canberra Hospital. He also has an ongoing interest in global health.

## Supplementary material

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

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**Slide sets:** A fully edited slide set detailing these cases 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 guidelines.

**Conflict of interest:** None declared

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