ESC European Society of Cardiology

European Heart Journal - Case Reports (2020) **4**, 1–5
doi:10.1093/ehjcr/ytaa301

CASE REPORT
Cardiac imaging

Flow-driven right-to-left cardiac shunting in a patient with carcinoid heart disease and patent foramen ovale without elevated right atrial pressure: a case report and literature review

Parinita Dherange , Nelson Telles, and Kalgi Modi*

Department of Cardiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA, USA

Received 10 October 2018; first decision 21 November 2019; accepted 6 August 2020; online publish-ahead-of-print 22 November 2020

Background Carcinoid heart disease is present in approximately 20% of the patients with carcinoid syndrome and is associated with poor prognosis. It usually manifests with right-sided valvular involvement including tricuspid insufficiency and pulmonary stenosis. Patent foramen ovale (PFO) is present in approximately 50% of the patients with carcinoid heart disease which is twice higher than the general population. Right-to-left shunting through a PFO can occur either due to higher right atrial pressure than left (pressure-driven) or when the venous flow is directed towards the PFO (flow-driven) in the setting of normal intracardiac pressures. We report a rare case of flow-driven right-to-left atrial shunting via PFO in a patient with carcinoid heart disease.

Case summary A 54-year-old male with a metastatic neuroendocrine tumour to liver presented with progressive shortness of breath for 5 months. Patient was found to be hypoxic with oxygen saturation of 78% and examination revealed a holosystolic murmur. Arterial blood gas showed oxygen tension of 43 mmHg. A transthoracic and transoesophageal echocardiogram showed aneurysmal inter-atrial septum with a PFO, severe tricuspid regurgitation directed anteriorly towards the inter-atrial septum leading to a marked right-to-left shunt. Right heart catheterization showed right atrial pressure of 8 mmHg, mean pulmonary artery pressure of 12 mmHg, and normal oxygen saturations in the right atrium, right ventricle, and pulmonary arteries. The patient then underwent closure of the PFO along with tricuspid valve and pulmonary valve replacement at an experienced cardiovascular surgical centre and has been asymptomatic since.

Conclusion Right-to-left shunting through a PFO in patients with normal right atrial pressure can be successfully treated with closure of the PFO. Thus, understanding the mechanism of intracardiac shunts is important to accurately diagnose and treat this rare and fatal condition.

Keywords Case report • Carcinoid heart disease • Intracardiac shunts • Patent foramen ovale • Hypoxia

Learning points

- Patients with carcinoid heart disease presenting with hypoxia should have a high suspicion of patent foramen ovale (PFO) and right to left intracardiac shunt.
- Patients with carcinoid heart disease have a higher prevalence of PFO of 59% compared to the general population in which it is 20–25%.
- In presence of right to left intracardiac shunting through a PFO in patients with normal right atrial pressure, one should have a high suspicion of flow-driven shunting mechanism.

* Corresponding author. Email: kmodi@lsuhsc.edu
Handling Editor: Parham Eshtehardi
Peer-reviewers: Richard Alexander Brown; Subhi Akleh; Lilit Baghdasaryan
Compliance Editor: Stefan Simovic
Supplementary Material Editor: Peysh A. Patel

Introduction

Carcinoid heart disease is present in approximately half of the patients with carcinoid syndrome and is associated with poor prognosis. It usually manifests with right-sided valvular involvement including tricuspid insufficiency and pulmonary stenosis.[1] Patent foramen ovale (PFO) is present in approximately 50% of the patients with carcinoid heart disease which is twice higher than the general population.[2]Right-to-left (R-L) atrial shunting through a PFO occurs because of higher right atrial pressure than left atrial pressure (pressure-driven shunting)[3] or when venous flow is directed towards the PFO (flow-driven shunting) in normal intracardiac pressures.[4] We report a rare case of flow-driven R-L atrial shunt via PFO as a result of tricuspid regurgitation and normal right atrial pressure in a patient with carcinoid heart disease.

Timeline

15 months prior	• Diagnosed with neuroendocrine tumour with metastasis to liver and was started on monthly octreotide as well as chemoembolization for liver lesions.
5 months prior	• Right internal jugular catheter was inserted to initiate treatment with 5-fluorouracil and temozolomide after which patient started experiencing shortness of breath.
Day 1	• Presented with progressive shortness of breath and refractory hypoxia. • Arterial blood gas analysis showed marked hypoxaemia (oxygen tension of 43 mmHg). Other tests including chest radiography, electrocardiogram, and chest computed tomography angiography were normal.
Day 3	• 2D transthoracic echocardiogram showed moderate to severe dilation of the right ventricle, moderate tricuspid regurgitation, and a right-to-left (R-L) shunt with the injection of agitated saline.
Day 5	• A transoesophageal echocardiogram showed an aneurysmal inter-atrial septum (*Figure 1A*) with a patent foramen ovale (PFO) and a deformed tricuspid valve with severe tricuspid regurgitation anteriorly directed across the PFO causing an R-L shunt (*Figure 1B* and *C*) and (*Video 1*). Mild–moderate pulmonic stenosis on the Doppler analysis was also noted.
Day 8	• Left and right heart catheterization was performed which showed non-obstructive coronary artery disease, normal intracardiac pressures, and an R-L shunt with a Qp:Qs (ratio of pulmonary blood flow to systemic blood flow) of less than 1. (*Table 1*).
Day 13	• Transferred to an experienced cardiovascular surgical centre for PFO closure and tricuspid valve replacement.
Day 24	• Underwent bioprosthetic tricuspid valve and pulmonic valve replacement with patch augmentation of the right ventricular outflow tract. The PFO was surgically closed with several interrupted sutures.
Post-operative hospital course	• Prolonged hospitalization in an intensive care unit and developed a post-operative Klebsiella infection from the central line, which was appropriately treated.
Post-operative day 36	• Patient was discharged with an oxygen saturation of 95% on room air.
post-operative 2 months	• Echocardiogram showed normal functioning tricuspid (*Figure 2A*) and pulmonic bioprosthesis. Agitated saline study was negative for intracardiac shunt (*Figure 2B*). • Patient remained asymptomatic and no hypoxic events noted.
Post-operative 22 months	• Follow-up in oncology clinic. Patient remains asymptomatic.

Case presentation

A 54-year-old Caucasian male presented to our institution with progressive shortness of breath, fatigue, and refractory hypoxia on home oxygen. His medical history was significant for hypertension, hyperlipidaemia, and coronary artery disease requiring percutaneous coronary intervention to the left circumflex coronary artery. Fifteen months prior to admission, he was diagnosed with a jejunal low-grade neuroendocrine tumour with metastases to the liver. At that time, the patient received monthly treatment of octreotide and chemoembolization for the liver lesions. Five months prior to admission due to persistence of symptoms and liver lesions, he was treated with 5-fluorouracil and temozolomide via a right internal jugular catheter. The patient reported dyspnoea since that time.

On admission, the patient's oxygen saturation was 78% on room air in an upright position, which did not improve in a supine position. Oxygen saturation slightly improved to 86% with an inspired oxygen concentration of 100%. A physical exam revealed a Grade 3/6 holosystolic murmur best heard at the left lower sternal border. An arterial blood gas analysis was significant for marked hypoxaemia with oxygen tension of 43 mmHg. Chest radiography was within normal limits. Electrocardiogram showed normal sinus rhythm without any ischaemia changes. A chest computed tomography angiography was negative for pulmonary embolism or any

evidence of intrathoracic disease. A 2D transthoracic echocardiogram (TTE) had severe dilation of the right chambers, severe tricuspid valve regurgitation with an estimated right ventricular pressure of 35 mmHg. Right-to-left shunt was seen with injection of agitated saline. A transoesophageal echocardiogram was then performed that showed an aneurysmal inter-atrial septum (*Figure 1A*) with a PFO and marked R-L shunt evident by colour and with the injection of agitated saline (*Figure 1B*). In addition, the tricuspid valve was thickened and tethered with restricted motion of the anterior leaflet. There was colour Doppler evidence of severe tricuspid regurgitation with an anteriorly directed jet across the PFO leading to a marked R-L shunt (*Figure 1C*, *Video 1*). The mitral valve structure was normal with mild regurgitation. The pulmonic valve was not well visualized; however, there was mild–moderate pulmonic stenosis with Doppler analysis.

Right and left heart catheterization were performed on Day 8 of the presentation (in December 2016), to measure shunt fraction and left atrial oxygen saturation (*Table 1*). An R-L cardiac shunt was confirmed by a Qp:Qs (ratio of pulmonary blood flow to systemic blood flow) of <1 and absence of improvement in oxygenation despite increasing oxygen supplementation. Coronary angiography showed non-obstructive coronary artery disease and patent stent in the left circumflex coronary artery. Given these findings, the patient was referred for PFO closure and tricuspid valve replacement. Subsequently, he underwent tricuspid valve replacement with a 31 mm St Jude Epic ® bioprosthesis and pulmonic valve replacement with a 27 mm St Jude Epic® bioprosthesis (intra-operative assessment of the pulmonic valve showed a thickened and retracted valve) with patch augmentation of the right ventricular outflow tract. Bioprosthetic valves were placed for the ease of surgical planning and anticoagulation management for future treatment of the patient's underlying disease. The PFO was surgically closed with several interrupted sutures. The patient had a prolonged hospitalization in an intensive care unit and developed a post-operative Klebsiella infection from the central line. *Staphylococcus aureus* was also found in his sputum and this was appropriately treated. At the time of discharge, the patient had an oxygen saturation of 95% on room air.

A TTE performed at 2 months and 12 months post-operative showed normal functioning tricuspid (*Figure 2A*) and pulmonic valve bioprostheses. An agitated saline study was negative for intracardiac shunt (*Figure 2B*). The patient had no further hypoxic events and was asymptomatic 22 months after surgery.

Discussion

The incidence of carcinoid tumours is approximately 1 in 75 000[5] with a 29-year prevalence of 35 in 100 000 (estimated between 1973 and 2004)[6] and about 50% of patients develop carcinoid syndrome.[1] Carcinoid heart disease, also known as Hedinger syndrome is present in approximately 20% of patients with carcinoid syndrome.[7] Patients

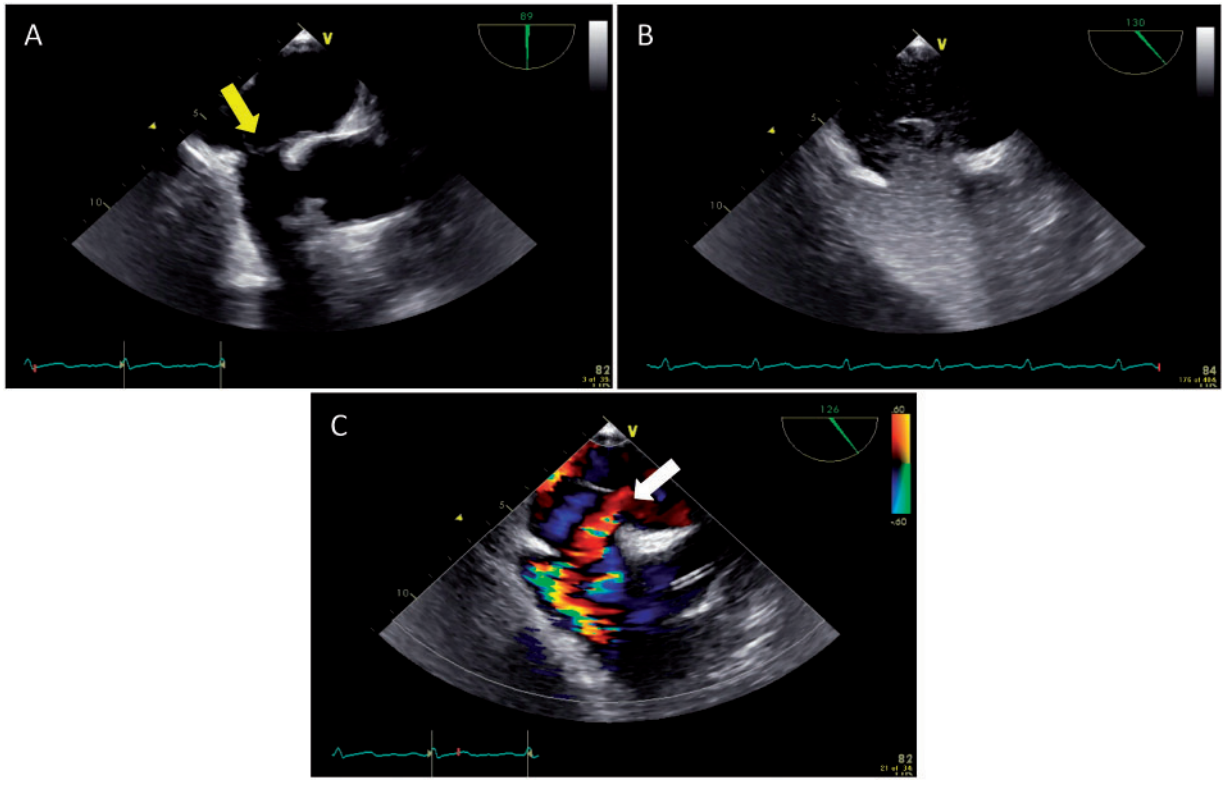

Figure 1 Transoesophageal echocardiogram bicaval view showing: (*A*) aneurysmal inter-atrial septum (yellow arrow), (*B*) positive bubble study through the patent foramen ovale, and (*C*) tricuspid regurgitation jet (white arrow) directed towards atrial septum causing an R-L shunt.

with carcinoid heart disease present with early symptoms of right-sided valvular heart disease, including fatigue and dyspnoea on exertion, secondary to tricuspid regurgitation and pulmonic valve stenosis. As the disease progresses, right-sided heart failure occurs in a majority of patients causing worsening dyspnoea, oedema, and ascites owing to severe dysfunction of the tricuspid and pulmonary valves.[1] Carcinoid heart disease causing severe valvular heart disease has become a major cause of morbidity and morbidity in patients with malignant carcinoid disease and has a 3-year survival rate of only 31%.[8] In patients with severe cardiac involvement, valvular surgery is the best modality of treatment in terms of relieving symptoms and improving outcomes.[9]

PFO is a remnant of foetal circulation through which unidirectional blood flows from right to left atrium. It has a prevalence of 59% in patients with carcinoid heart disease, which is higher than the overall prevalence of 20–25% in the adult population.[2] In normal circumstances, the left atrial pressure is higher than the right atrial pressure; thus, there is no blood flow from the right atrium to the left atrium through a PFO. However, haemodynamic or anatomic changes can cause shunting of blood from R-L via a pressure-driven shunting mechanism[10] or a flow-driven shunting mechanism,[4] respectively.

Traditionally, in a patient with carcinoid heart disease, haemodynamic changes occur due to right-sided valve involvement causing either tricuspid regurgitation or due to pulmonic stenosis. This causes right-sided volume or pressure overload, leading to right atrial and ventricular enlargement and eventually causes right ventricular systolic dysfunction. When the right atrial pressure exceeds the left atrial pressure, R-L shunting through PFO can be seen through a pressure-driven shunting mechanism.[3] This causes dyspnoea from symptomatic hypoxaemia. Many patients can present with platypnoea–orthodeoxia syndrome where deoxygenation and dyspnoea occurs in upright position (orthodeoxia) and is relieved in a supine position (platypnoea).[11]

In our case report of carcinoid heart disease, a flow-driven R-L cardiac shunting was seen through a PFO in the setting of normal intracardiac pressures. Such a shunting mechanism in a patient with carcinoid heart disease is a rare finding. To our knowledge, there have been three such cases reported in the literature (*Table 2*). Chaudhari *et al.*[12] reported a case of a patient with carcinoid heart disease causing R-L shunt via flow-driven mechanism due to external compression of the vena cava by tumour mass directing caval blood towards the PFO. The other two cases were reported by Yang *et al.*[13] and Wrona *et al.*[14] (*Table 2*), and like our patient showed flow-driven R-L shunting due to the tricuspid regurgitation jet directing deoxygenated blood towards the PFO, resulting in hypoxaemia and dyspnoea.

Table 1 **Right heart catheterization data**

	Pressure (mmHg)	Oxygen saturation (%)
Right heart catheterization data		
Inferior vena cava	—	54
Superior vena cava	—	48
Right atrium	6	51
Right ventricle	25/3	51
Pulmonary artery (mean)	15/2 (12)	51
Pulmonary artery wedge (mean)/ pulmonary vein	7	83
Arterial oxygen saturation	—	78.5
Calculated measurements		
Cardiac output		5.8 L/min
Cardiac index		2.4 L/min/m^2
Qp:Qs (ratio of pulmonary to systemic blood flow)		0.91

Conclusion

Right-to-left shunting through a PFO in patients with normal right atrial pressure due to flow-driven shunting mechanism can be successfully treated with closure of the patent foramen ovale. Thus, understanding the mechanism of intracardiac shunts in carcinoid heart disease is important to accurately diagnose and treat this rare and fatal cause of acquired cyanotic heart disease.

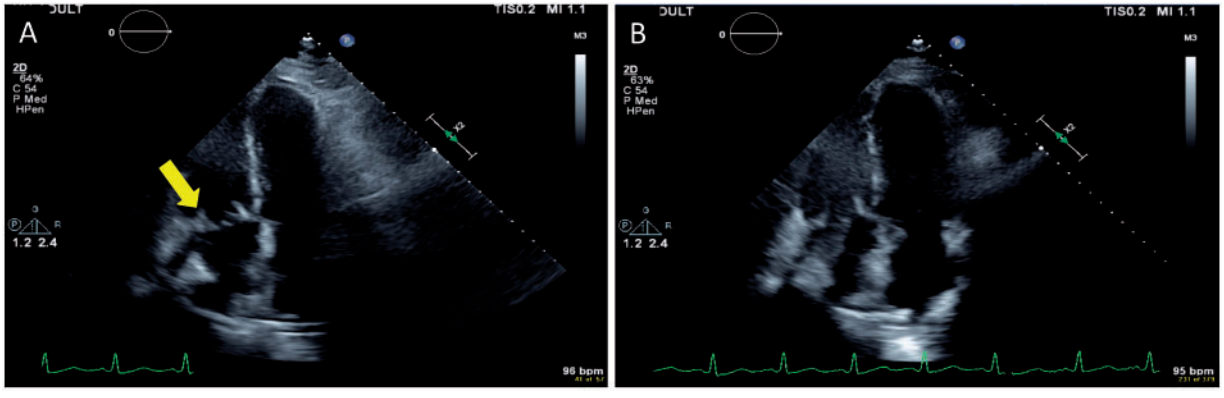

Figure 2 Postoperative transthoracic echocardiogram apical 4 chamber view showing: (*A*) bioprosthetic tricuspid valve (yellow arrow), (*B*) negative bubble study post-surgical closure of patent foramen ovale.

Table 2 Reported cases of carcinoid heart disease with right to left intracardiac shunting due to flow-driven mechanism

Study (year)	Mechanism of hypoxaemia causing R-L shunt	Treatment	Outcome
Chaudhari *et al.* (2007)[11]	External compression of the vena cava by tumour mass directing caval blood towards the PFO	Surgical closure of PFO	Died post-operative 3 months
Yang *et al.* (2018)[12]	Tricuspid jet streaming directly across the PFO	Percutaneous closure of the PFO	Alive post-operative 4 months
Wrona *et al.* (2018)[13]	Tricuspid regurgitation jet directed towards the PFO	Percutaneous closure of PFO	Unknown

PFO, patent foramen ovale.

Lead author biography

Parinita Dherange has completed her cardiology fellowship and is currently pursuing cardiac electrophysiology fellowship.

Supplementary material

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

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

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References

1. Fox DJ, Khattar RS. Carcinoid heart disease: presentation, diagnosis, and management. *Heart* 2004;**90**:1224–1228.
2. Bancal C, Arnoult F, Krapf L, Bonay M. [Patent foramen ovale and hypoxaemia with or without elevated right heart pressures]. *Rev Mal Respir* 2011;**28**:967–977.
3. Bhattacharyya S, Davar J, Dreyfus G, Caplin ME. Carcinoid heart disease. *Circulation* 2007;**116**:2860–2865.
4. Zanchetta M, Rigatelli G, Ho SY. A mystery featuring right-to-left shunting despite normal intracardiac pressure. *Chest* 2005;**128**:998–1002.
5. Basson MD, Ahlman H, Wangberg B, Modlin IM. Biology and management of the midgut carcinoid. *Am J Surg* 1993;**165**:288–297.
6. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;**26**:3063–3072.
7. Yuan S-M. Valvular disorders in carcinoid heart disease. *Braz J Cardiovasc Surg* 2016;**31**:400–405.
8. Connolly HM, Nishimura RA, Smith HC, Pellikka PA, Mullany CJ, Kvols LK. Outcome of cardiac surgery for carcinoid heart disease. *J Am Coll Cardiol* 1995;**25**:410–416.
9. Mokhles P, van Herwerden LA, de Jong PL, de Herder WW, Siregar S, Constantinescu AA et al. Carcinoid heart disease: outcomes after surgical valve replacement. *Eur J Cardiothorac Surg* 2012;**41**:1278–1283.
10. Ghamande S, Ramsey R, Rhodes JF, Stoller JK. Right hemidiaphragmatic elevation with a right-to-left interatrial shunt through a patent foramen ovale: a case report and literature review. *Chest* 2001;**120**:2094–2096.
11. Seward JB, Hayes DL, Smith HC, Williams DE, Rosenow EC 3rd, Reeder GS et al. Platypnea-orthodeoxia: clinical profile, diagnostic workup, management, and report of seven cases. *Mayo Clin Proc* 1984;**59**:221–231.
12. Chaudhari PR, Abergel J, Warner RR, Zacks J, Love BA, Halperin JL et al. Percutaneous closure of a patent foramen ovale in left-sided carcinoid heart disease. *Nat Rev Cardiol* 2007;**4**:455–459.
13. Yang C, Sharma A. Hypoxemia from patent foramen ovale in a 65-year-old woman with carcinoid heart disease. *CMAJ* 2018;**190**:E933–E936.
14. Wrona K, Grabka M, Lelek M, Mizia-Stec K. Patent foramen ovale with an enormous right-to-left shunt: unusual reversible cause of hypoxia in carcinoid syndrome. *Eur Heart J* 2019;**40**:2096.