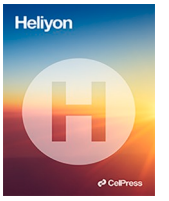
Heliyon 10 (2024) e25386

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Case report

Severe cough and hemoptysis induced reopening of patent foramen ovale leading to significant decrease in pulmonary artery pressure in a patient with idiopathic pulmonary arterial hypertension： A case report

Li-Li Wang [a], Bing Xu [b], Xiao-Qing Yu [a], Duan-Zhen Zhang [a,*]

[a] Department of Cardiology, the Second Hospital of Dalian Medical University, Dalian, 116023, Liaoning, People's Republic of China
[b] Department of Pharmacy, the Second Hospital of Dalian Medical University, Dalian, 116023, Liaoning, People's Republic of China

ARTICLE INFO

Keywords:
Pulmonary arterial hypertension
Patent foramen ovale
Hemoptysis

ABSTRACT

Pulmonary arterial hypertension (PAH) is a perilous disease that precipitates right ventricular hypertrophy, induces right heart failure, and exerts deleterious ramifications on prognostic outcomes. The establishment of atrial communication can create a right-to-left shunt, thereby ameliorating hemodynamic parameters. Previous reports suggested that opening of a patent foramen ovale (PFO) was common in patients with severe PAH, but exhibited no discernible impact on long-term survival. We reported the case of a 39-year-old man with severe idiopathic PAH, who underwent reopening of the PFO due to severe cough and hemoptysis, followed by a marked amelioration in symptoms and a substantial decrease in pulmonary arterial pressure. The patient has survived for more than 12 years, persisting in World Health Organization functional class II with mild PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) constitutes a life-threatening condition distinguished by pulmonary vascular endothelial dysfunction, smooth muscle proliferation, and progressive occlusion of the distal pulmonary arteries. Before the era of PAH-targeted drug therapy, the estimated median survival for patients with idiopathic PAH (IPAH) was 2.8 years [1]. Although pharmacological interventions, such as prostacyclin analogs and receptor agonists, phosphodiesterase 5 inhibitors, endothelin-receptor antagonists, and cGMP activators, have demonstrated enhancements in both quality of life and hemodynamic parameters for PAH patients, the malady remains devastating and exhibits rapid progression, with a mortality rate exceeding 50 % at seven years [2].

The establishment of atrial communication creates a right-to-left shunt , facilitating right ventricular decompression and consequential improvement in hemodynamic parameters [3]. A patent foramen ovale (PFO) may function as a "natural" septostomy, allowing right-to-left shunting when right atrial pressure (RAP) exceeds left atrial pressure. Although opening of a PFO is common in patients with severe PAH, previous studies indicated that its presence exerted no impact on long-term survival [4,5].

We reported the case of a 39-year-old man with severe IPAH, who experienced reopening of the PFO due to severe cough and hemoptysis, followed by a major improvement in symptoms and a substantial decrease in pulmonary artery pressure (PAP), and has

* Corresponding author.
E-mail address: zhdz69@163.com (D.-Z. Zhang).

https://doi.org/10.1016/j.heliyon.2024.e25386
Received 4 March 2023; Received in revised form 15 January 2024; Accepted 25 January 2024
Available online 30 January 2024

Abbreviations

IPAH	idiopathic pulmonary arterial hypertension
PAH	pulmonary arterial pressure
PAP	pulmonary artery pressure
PASP	pulmonary artery systolic pressure
PFO	patent foramen ovale
RAP	right atrial pressure
WHO-FC	World Health Organization functional class

survived for more than 12 years with mild PAH.

2. Case report

A 39-year-old male patient was admitted to hospital with recurrent post-activity chest pain and shortness of breath for more than 11 years and bilateral lower extremity edema for one week in March 2021. In 2010, he was admitted to hospital due to post-activity chest pain and shortness of breath for half a year. After comprehensive laboratory tests and imaging examination including echocardiography, chest CT scan and ventilation/perfusion lung scan excluding left heart disease, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary thromboembolism, congenital heart diseases and connective tissue disease during the hospitalization, he was diagnosed with IPAH with World Health Organization functional class (WHO-FC) II. Right heart catheterization was not performed due to the patient's refusal. The echocardiographically estimated pulmonary artery systolic pressure (PASP) was 80 mmHg. He received PAH-targeted therapy with sildenafil (25mg, PO, tid), yet experienced a gradual increase in PAP. The sequential echocardiographic follow-ups are documented in Table 1.

In July 2016, the patient progressed from WHO-FC IIto IV and the PASP increased from 80 to 120 mm Hg (Fig. 1). A week later, the patient encountered severe cough and hemoptysis, approximately 50 ml in volume, attributable to a severe cold leading to pneumonia. Following the cessation of hemoptysis, he continued the treatment with sildenafil at the same dose as before.

The patient was acyanotic from 2010 to 2016, with a femoral artery oxygen saturation of 93.4 % observed during the 2016 hospitalization. However, subsequent to hemoptysis, he gradually became cyanotic, with a concomitant improvement in symptoms. At the same time, the PAP decreased and the left ventricle enlarged spontaneously.

The patient was re-admitted in March 2021 due to mild bilateral lower extremity edema for approximately one week. The CT scan of the chest revealed an enlarged hilar shadow and widened pulmonary arteries, but no parenchymal lesions were discerned. The echocardiographically estimated PASP was just 55 mm Hg (Fig. 2), much lower than that in 2016 and 2018. To elucidate the unanticipated alterations in PAP, right heart catheterization was performed subsequent to the patient's provision of informed consent. The results are delineated in Table 2. The PAP was 60/39 mmHg, notably lower than the aortic pressure. Nevertheless, the oxygen saturation of femoral artery was only 88.5 %, significantly lower than that in 2016. Pulmonary angiography revealed no evidence of pulmonary embolism or pulmonary arteriovenous fistulae.

As the catheter repeatedly crossed interatrial communication to the left atrium from the right atrium during the procedure, transesophageal echocardiography was conducted with the informed consent of the patient. The two-dimensional echocardiogram, coupled with continuous flow Doppler, revealed a PFO measuring 7.34 mm in width with a continuous, pure right-to-left shunt on colour flow mapping (Fig. 3). The patient received combination therapy with ambrisentan (10mg, PO, qd) and tadalafil (20mg, PO, qd), complemented with anticoagulant rivaroxaban (20mg, PO, qd) after discharge. The plasma N-terminal pro-brain natriuretic peptide was 94.2 pg/ml in August 2021, indicative of normal cardiac function, and the PASP estimated by echocardiography in June 2022 and February 2023 was 47 and 45 mmHg, respectively.

Table 1
Changes in cardiac chamber size and pulmonary artery pressures

	Dec-2010	Apr-2012	Dec-2014	Jul-2016	Dec-2016	Nov-2018	Mar-2021	Aug-2021	Jun-2022	Feb-2023
RA (mm)	66	70.6	63.7	72.6	70.3	68	69.8	74	76	74.9
RV (mm)	36	36.6	36.9	38.2	37	41	53.8	47.8	37.2	44
TAPSE (mm)	20	17.3	12	11.4	12	14.6	21.8	18	16.5	16.7
LA (mm)	32	31	31.5	29.3	32.6	35.3	36.8	35.1	37.9	36.4
LVEDD (mm)	43	36.5	34.2	35.6	36	40.6	42.8	42.7	38	38.1
TRV (m/s)	4.2	4.3	4.6	5.1	4.7	4.2	3.2	3.4	3.0	3.0
PASP(mmHg)	80	89	100	120	105	86	55	61	47	45

LA-left atrium; LVEDD-left ventricular end-diastolic diameter; RA-right atrium; RV-right ventricle; PASP-pulmonary artery systolic pressure; TAPSE-tricuspid annular plane systolic excursion; TRV- velocity of tricuspid regurgitation.

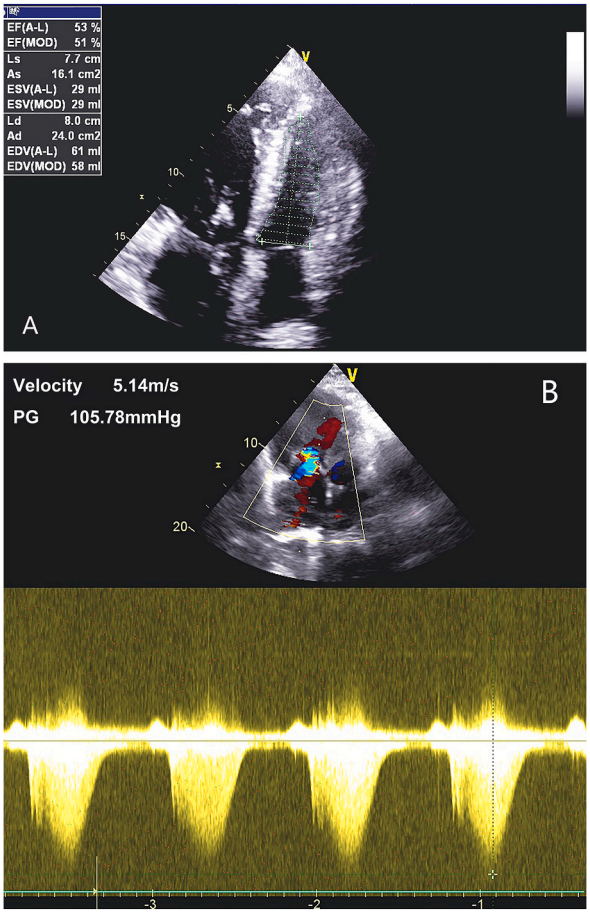


Fig. 1. Follow-up echocardiography in 2016. Transthoracic echocardiography demonstrated a markedly enlarged right atrium and right ventricle (A), along with tricuspid regurgitation, and an estimated pulmonary artery systolic pressure of 120 mm Hg (B).

3. Discussion

PAH represents a pathophysiological disorder that may involve multiple clinical conditions and complicate the majority of cardiovascular and respiratory diseases [6]. Despite the administration of sildenafil, the WHO-FC of the patient gradually progressed, accompanied by a persistent increase in PAP, suggesting a limited efficacy of sildenafil therapy on PAH in this case. Confusingly, patients with IPAH exhibit a notably low 10-year survival rate even under maximal combination therapy [7], but this patient survived 11 years without resorting to combination therapy or other interventions. The unexpected clinical improvements without additional intervention were also unexplainable in patients with IPAH. Hence, we performed right heart catheterization and *trans*-esophageal echocardiography which revealed a huge PFO. Based on the clinical observations and the laboratory findings, we hypothesize that the patient may have a PFO, which was very small or entirely closed, while repetitive sudden increase in RAP due to the patient's hemoptysis and severe cough in 2016 induced the reopening or enlargement of the PFO on the base of atrial septal stretch due to severe PAH. Sharan [4] and Gallo de Moraes [5] found that the incidence of a PFO in the PAH population increased with right-sided enlargement, suggesting that the PFO may be stretched open rather than congenital, which also supports our speculation. The reopening and enlargement of PFO resulted in a continuous pure right-to-left shunt through PFO, leading to cyanosis and gradual left ventricular enlargement. Contrary to previous reports [4,5] asserting that the presence of a PFO did not impact survival, this case suggests that a sizable PFO did contribute positively to survival in PAH. We presume that the size of PFO plays a key role in survival. Typically, the diameter of PFOs ranges from 1 to 3 mm [8,9]. Unlike a substantial PFO or an atrial septal defect, even with PAH-induced elevation in RAP, a PFO of such diminutive dimensions faces challenges in creating a right-to-left shunt sufficient to decompress the right-sided cardiac chambers and increase left ventricular preload and systemic cardiac output.

Balloon atrial septostomy has been proven to be an important palliative therapy for patients with refractory PAH unresponsive to maximal combination therapy. However, it was reported that nearly 30 % of patients experienced spontaneous closure of the septostomy, predominantly within the first year [10]. A PFO is reported in 27 % of patients with IPAH [5]. Considering the high incidence of spontaneous closure of the septostomy and the prevalence of PFO in IPAH, it is advisable to confirm the presence of PFO in PAH before undertaking septostomy. If a PFO is present, PFO balloon dilation seems to be an ideal alternative to septostomy. Notably, a PFO

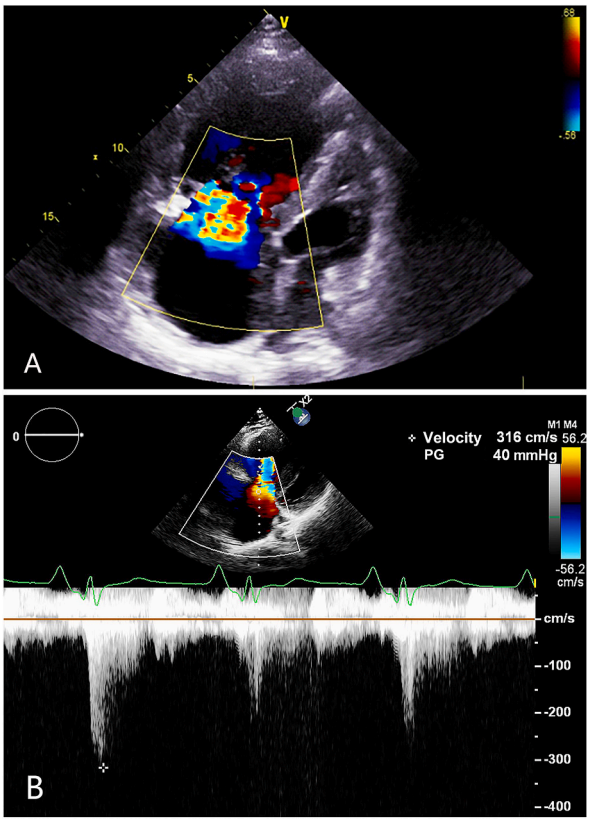


Fig. 2. Follow-up echocardiography in 2021. Despite the presence of severe tricuspid regurgitation (A), the estimated pulmonary artery systolic pressure was measured at 55 mm Hg (B).

Table 2
Results of right heart catheterization.

Hemodynamic parameters	Values
Oxygen saturations (%)	
Superior vena cava	62.6
Inferior vena cava	64.4
Right atrium (mean)	63.4
Right ventricle (mean)	63.5
Pulmonary artery	62.9
Femoral artery	88.5
Pressures (mm Hg)	
Right atrium	17/10
Right ventricle	60/4
Pulmonary artery	60/39
Aorta	136/87
Pulmonary capillary wedge pressure (mm Hg)	19/9
Pulmonary vascular resistance (Wood units)	11.1
Pulmonary-systemic shunt ratio	0.78
Cardiac index (L/min/m^2)	1.92

of 7 mm, as observed in this case, following balloon dilation appears to be an optimal size. This procedure is safer than septostomy because it circumvents transseptal puncture and may reduce the risk of spontaneous closure since it avoids the post-septostomy septal muscular retraction.

4. Conclusion

This report details a case of severe IPAH wherein substantial clinical improvements and significant decrease in PAP were observed following the reopening of PFO due to severe cough and hemoptysis. This suggests that a sufficiently large PFO has a positive impact on

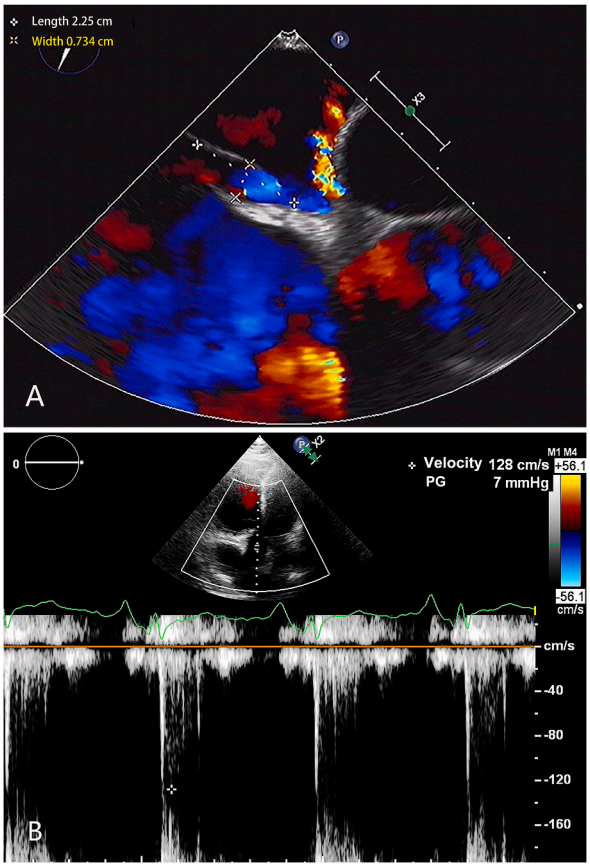


Fig. 3. Transesophageal echocardiography showing a patent foramen ovale (PFO) with a diameter of approximately 7.34 mm, displaying continuous right-to-left shunt through the PFO (A) at a velocity of 1.28 m/s (B).

survival of IPAH patients.

Sources of funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability statement

All data generated or analyzed in this study are included in this article.

CRediT authorship contribution statement

Li-Li Wang: Writing – original draft. **Bing Xu:** Writing – review & editing. **Xiao-Qing Yu:** Methodology. **Duan-Zhen Zhang:** Writing – review & editing, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] G.E. D'Alonzo, R.J. Barst, S.M. Ayres, E.H. Bergofsky, B.H. Brundage, K.M. Detre, A.P. Fishman, R.M. Goldring, B.M. Groves, J.T. Kernis, Survival in patients with primary pulmonary hypertension. Results from a national prospective registry, Ann. Intern. Med. 115 (1991) 343–349.
[2] H. Deshwal, T. Weinstein, R. Sulica, Advances in the management of pulmonary arterial hypertension, J. Invest. Med. 69 (2021) 1270–1280.
[3] M.S. Khan, M.M. Memon, E. Amin, N. Yamani, S.U. Khan, V.M. Figueredo, S. Deo, J.D. Rich, R.L. Benza, R.A. Krasuski, Use of balloon atrial septostomy in patients with advanced pulmonary arterial hypertension: a systematic review and meta-analysis, Chest 156 (2019) 53–63.

[4] L. Sharan, K. Stackhouse, J.D. Awerbach, T.M. Bashore, R.A. Krasuski, Effect of patent foramen ovale in patients with pulmonary hypertension, Am. J. Cardiol. 122 (2018) 505–510.
[5] A. Gallo de Moraes, A. Vakil, T. Moua, Patent foramen ovale in idiopathic pulmonary arterial hypertension: long-term risk and morbidity, Respir. Med. 118 (2016) 53–57.
[6] M. Humbert, G. Kovacs, M.M. Hoeper, R. Badagliacca, R.M.F. Berger, M. Brida, J. Carlsen, A.J.S. Coats, P. Escribano-Subias, P. Ferrari, D.S. Ferreira, H. A. Ghofrani, G. Giannakoulas, D.G. Kiely, E. Mayer, G. Meszaros, B. Nagavci, K.M. Olsson, J. Pepke-Zaba, J.K. Quint, G. Rådegran, G. Simonneau, O. Sitbon, T. Tonia, M. Toshner, J.L. Vachiery, A. Vonk Noordegraaf, M. Delcroix, S. Rosenkranz, ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, Aug 26:ehac237, Eur. Heart J. (2022), https://doi.org/10.1093/eurheartj/ehac237. Online ahead of print.
[7] H. Deshwal, T. Weinstein, R. Sulica, Advances in the management of pulmonary arterial hypertension, J. Invest. Med. 69 (2021) 1270–1280.
[8] H. Hara, R. Virmani, E. Ladich, S. Mackey-Bojack, J. Titus, M. Reisman, W. Gray, M. Nakamura, M. Mooney, A. Poulose, R.S. Schwartz, Patent foramen ovale: current pathology, pathophysiology, and clinical status, J. Am. Coll. Cardiol. 46 (2005) 1768–1776.
[9] G. Turc, J.Y. Lee, E. Brochet, J.S. Kim, J.K. Song, J.L. Mas, CLOSE and DEFENSE-PFO Trial Investigators. Atrial septal aneurysm, shunt size, and recurrent stroke risk in patients with patent foramen 0vale, J. Am. Coll. Cardiol. 75 (2020) 2312–2320.
[10] C. Yan, L. Wan, H. Li, C. Wang, T. Guo, H. Niu, S. Li, P. Yundan, L. Wang, W. Fang, First in-human modified atrial septostomy combining radiofrequency ablation and balloon dilation, Heart (2022 Jun 8), https://doi.org/10.1136/heartjnl-2022-321212 heartjnl-2022-321212.