Gac Méd Caracas 2024;132(2):508-516
DOI: 10.47307/GMC.2024.132.2.21

Cyanotic Severe Pulmonary Stenosis with an Intracardiac Shunt: A Case Report and Literature Review

Estenosis pulmonar cianótica grave con derivación intracardíaca: reporte de un caso y revisión de la literatura

Yulius Patimang[1,a,b], Andriany Qanitha[5,c*], Andi Alief Utama Armyn[2a], Idar Mappangara[3a,b], Muzakkir Amir[4a,b]

SUMMARY

Pulmonary stenosis is a congenital defect, with isolated severe cases rarely associated with cyanosis. We report a 10-year-old girl diagnosed with severe pulmonary stenosis (peak gradient 111 mmHg), presented with worsening cyanosis, chest discomfort, and exercise intolerance. We were perplexed by the presence of cyanosis in her current condition. The answer emerged during a right heart catheterization, revealing a previously undetected patent foramen ovale with eluded identification through a non-invasive trans-thoracic echocardiography. Correction of the primary causer was performed with percutaneous balloon pulmonary valvuloplasty (BPV), successfully reduced the PS gradient and improved the hypoxemia and patient's clinical outcomes. The recent literature review explained incidence and pathomechanism. Persistent cyanosis rarely manifests in cases of isolated pulmonary stenosis, necessitating a comprehensive assessment to ascertain the presence of an intracardiac shunt. BPV stands out as the preferred therapeutic option for individuals afflicted by severe pulmonary valve stenosis concurrent with an intracardiac shunt.

Keywords: *Balloon pulmonary valvuloplasty, cyanosis, hypoxemia, hyperviscosity syndrome, patent foramen ovale, pulmonary stenosis, a case report.*

RESUMEN

La estenosis pulmonar (EP) se presenta principalmente como una anomalía congénita, y los casos graves aislados rara vez se asocian con cianosis. Presentamos

DOI: https://doi.org/10.47307/GMC.2024.132.2.21

ORCID: 0000-0003-1543-1519[3]
ORCID: 0000-0002-4914-3542[4]
ORCID: 0000-0003-2420-0560[5]

[a]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia.
[b]Makassar Cardiac Center (Pusat Jantung Terpadu), Dr. Wahidin Sudirohusodo General Teaching Hospital, Makassar 90245, Indonesia.
[c]Department of Physiology, Faculty of Medicine, Universitas Hasanuddin, Makassar 90245, Indonesia.

Recibido: 1 de febrero 2024
Aceptado: 10 de marzo 2024

[1]MD, FIHA. E-mail: yulio_patimang@yahoo.co.id
[2]MD, FIHA. E-mail: andi.alief@med.unhas.ac.id
[3]MD, PhD, FIHA, FINASIM. E-mail: idar.mks@yahoo.com
[4]MD, PhD, FIHA. E-mail: dr.muzakkir@gmail.com
[5]MD, MSc, PhD. E-mail: qanitha@unhas.ac.id

*Corresponding author: Andriany Qanitha,
Dept. of Cardiology and Vascular Medicine,
Dept. Of Physiology, Faculty of Medicine, Hasanuddin University, Makassar 90245, Indonesia.
Jl. Perintis Kemerdekaan Km. 10, Makassar 90245, South Sulawesi, Indonesia.
E-mail: qanitha@unhas.ac.id
Tel.: +628114442501

el caso de una niña de 10 años diagnosticada con estenosis pulmonar grave (gradiente máximo 111 mmHg), que presentó empeoramiento de la cianosis, malestar torácico e intolerancia al ejercicio. Nos quedamos perplejos por la presencia de cianosis en su estado actual. La respuesta surgió durante un cateterismo cardíaco derecho, que reveló un foramen ovale permeable no detectado previamente y que no se pudo identificar mediante una ecocardiografía transtorácica no invasiva. La corrección del principal causante, se realizó con valvuloplastia valvuloplastia pulmonar percutánea con balón (VPP), fue exitosa para reducir el gradiente de EP, mejorar la hipoxemia y los resultados clínicos del paciente. La incidencia y el mecanismo patogénico fueron explicados por la reciente revisión de la literatura. La cianosis persistente rara vez se manifiesta en casos de estenosis pulmonar aislada, lo que requiere una evaluación integral para determinar la presencia de una derivación intracardíaca. La VPP se destaca como la opción terapéutica preferida para personas que padecen estenosis grave de la válvula pulmonar concurrente con una derivación intracardíaca.

Palabras clave: *Valvuloplastia pulmonar con balón, cianosis, hipoxemia, síndrome de hiperviscocidad, foramen oval permeable, estenosis pulmonar, reporte de caso.*

INTRODUCTION

Approximately 7 %-12 % of congenital heart diseases can be attributed to pulmonary stenosis (PS). It may manifest as an isolated condition or, more commonly (25 %-30 %), in combination with other congenital anomalies, particularly those affecting the pulmonary vasculature (1,2). Clinical presentations of PS exhibit a broad, ranging from the incidental detection of a murmur in asymptomatic individuals to symptoms such as dyspnea on exertion, fatigue, or chronic cyanosis. The hemodynamic severity of the obstruction determines the therapeutic approach. At the same time, planning the interventional treatment for PS requires a comprehensive strategy that includes echocardiography, cardiac computed tomography, and cardiac magnetic resonance.

In recent times, there has been an expansion in the range of transcatheter techniques accessible for addressing pulmonary stenosis. This expansion suggests that surgery could be a viable alternative in complex cases with anatomical conditions unsuitable for percutaneous interventions. The approach to intervention should not be limited solely to patients with severe pulmonary stenosis but should also encompass cases with non-severe stenosis in the presence of symptomatic manifestations. In this case, we emphasize the significance of conducting comprehensive examinations to establish a working diagnosis, elucidate the underlying pathomechanism of symptoms and signs, and outline the effective management of severe valvular pulmonary stenosis in young children through the application of percutaneous balloon pulmonary valvuloplasty (BPV).

Case Report

A 10-year-old girl was admitted to the hospital due to breathlessness upon exertion and chronic cyanosis. She also reported experiencing chest discomfort during physical activity. The cyanosis had been present since birth, and she had a documented history of congenital heart disease since the age of 4. The patient was undernourished, with a weight of 19 kg and a height of 132 cm, and had a history of failure to thrive.

Clinical examination revealed severe cyanosis, with oxygen saturation ranging from 41 % to 53 % in all four extremities. The patient exhibited clubbing of the fingers and reddened sclera. Hemodynamic parameters were within normal limits, with a blood pressure of 119/84 mmHg and a pulse rate of 110 beats per minute. A grade 3/6 ejection systolic murmur was detected at the upper left sternal border on auscultation.

Chest X-ray findings indicated slight cardiomegaly, right ventricular enlargement, and unspecified bilateral bronchopneumonia. Laboratory investigations revealed polycythemia vera, with a hemoglobin level of 23.2 g/dL and a hematocrit of 83 %. Thrombocytopenia was also observed, with a platelet count of 116 000/ μL, along with prolonged prothrombin time (PT) of 36.3 seconds, activated partial thromboplastin time (aPTT) of 58.2 seconds, and international normalized ratio (INR) of 3.57.

An echocardiogram demonstrated severe valvular pulmonary stenosis with a doming pulmonary valve and a gradient across the pulmonary valve measuring 111 mmHg. The

pulmonary annulus was 3.5 mm, and the mean pulmonary artery diameter measured 6.4 mm. Severe tricuspid regurgitation was also noted, with a maximum pressure gradient of 92 mmHg and a maximum velocity of 5.04 m/s (Figure 1). However, the left and right ventricular showed normal systolic functions.

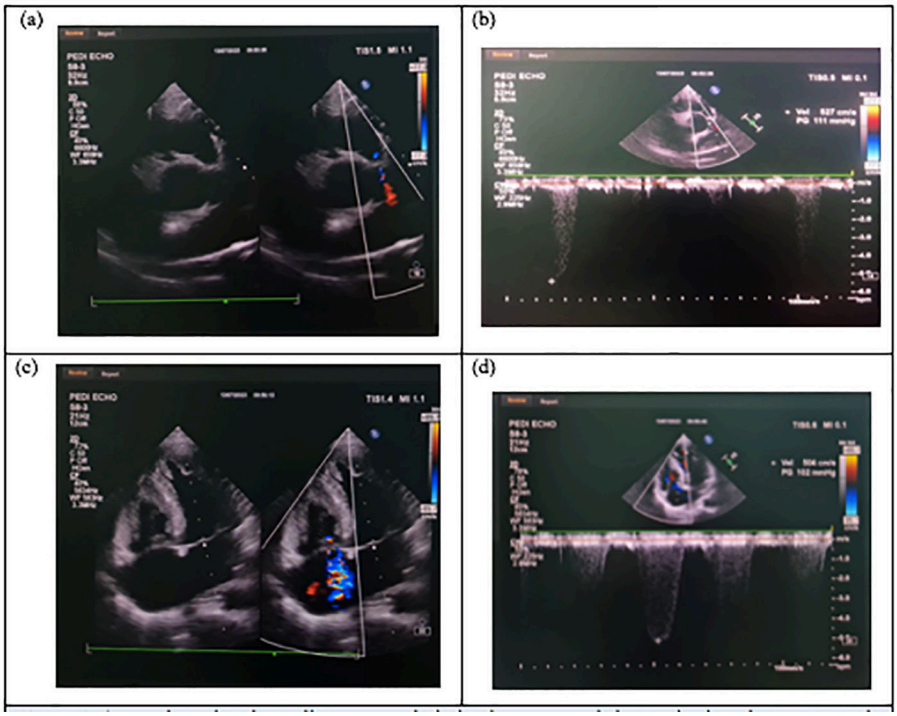

Figure 1. A transthoracic echocardiogram on admission in parasternal short-axis view shows a severely narrowed pulmonary valve (a) with a severe transvalvular gradient of 111 mmHg (b). An apical 4-chamber shows severe tricuspid regurgitation (c) with peak velocity (Vmax) of 5.04 m/s and maximum pressure gradient (maxPG) of 102 mmHg (d).

Due to abnormal hemostasis, the planned right heart catheterization (RHC) was deferred to improve the patient's general condition. On the 12th day of hospitalization, the patient underwent RHC, during which we incidentally discovered an intracardiac shunt that explained the progressive cyanosis observed in this patient (Figure 2). The patent foramen ovale (PFO) was tunnel-like, causing a right-to-left shunt.

Subsequently, the patient underwent transcatheter percutaneous BPV. The initial hemodynamic assessment revealed a gradient of 95 mmHg between the pulmonary valve and the right ventricle. *Right Ventricular Outflow Tract* (RVOT)-graphy indicated valvar pulmonary stenosis with post-stenotic dilatation. The pulmonary annulus measured 12.5 mm. We successfully dilated the pulmonary valve using a TYSHAK II balloon sized at 14 mm × 30 mm, resulting in favorable outcomes (Figure 3). Following BPV, a follow-up echocardiogram demonstrated a good opening of the pulmonary valve leaflet with a reduction in the PS peak gradient from 111 mmHg to 48 mmHg (Figure 4). Additionally, the patient's oxygen saturation improved from 41 % to 85 %. This desaturation was attributed to right-to-left shunting across the atrial-level shunt. The patient maintained beta-blocker therapy to alleviate infundibular stiffness. Notably, the right and left ventricular systolic function remained adequate, with an LV ejection fraction of 65.5 %.

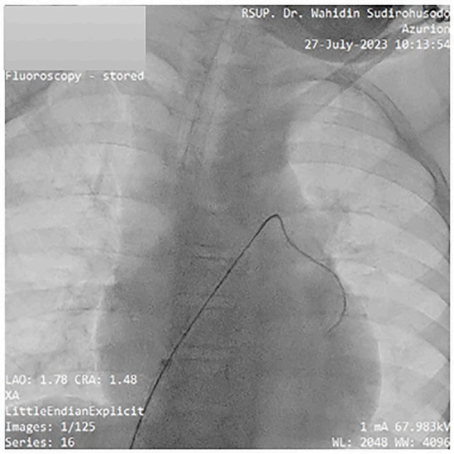

Figure 2. The wire inadvertently crossed the interatrial septum, revealing an incidental finding of a patent foramen ovale (PFO) in this patient.

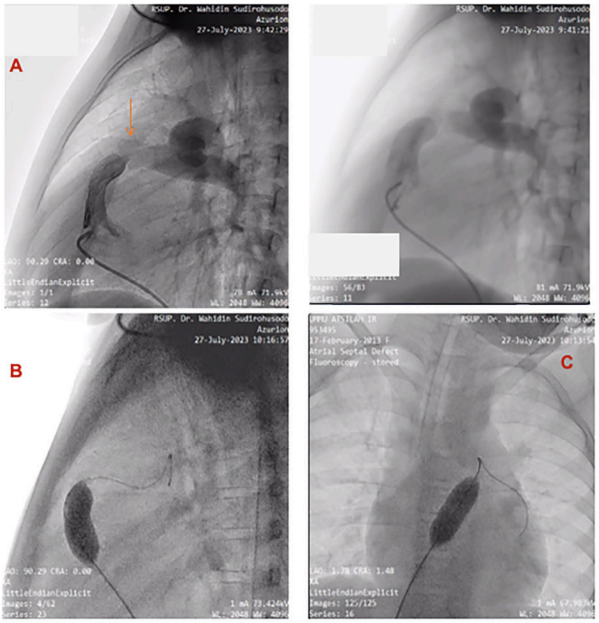

Figure 3. A: RVOT obstruction caused by severe valvar Pulmonary Stenosis. B and C: Dilatation of balloon on stenotic pulmonary valve (lateral and AP frontal view)

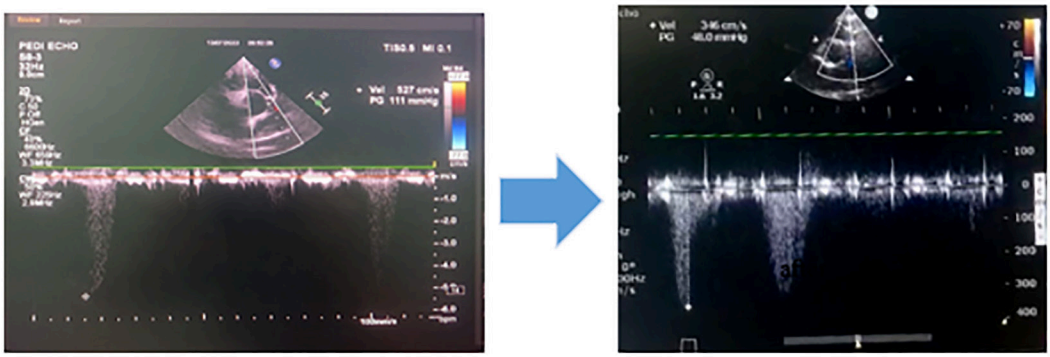

Figure 4. The peak gradient before and after BPV, the PS peak gradient was reduced from 111 mmHg to 48 mmHg.

DISCUSSION

Pulmonary valve stenosis (PS) is among the common congenital heart lesions. PS can occur at the subvalvar, valvar, or supravalvar level and is quite common at 8 % to 10 % of all congenital heart defects. Depending on the severity of the obstruction, the patient may be asymptomatic or may present with signs and symptoms of RV failure and cyanosis from R-L shunting through an atrial septal defect (ASD). This structural abnormality usually presents with a murmur and minor exercise intolerance and tends to progress

slowly. It is observed more frequently in females. PS is commonly found in conjunction with other congenital heart diseases, including tetralogy of Fallot (TOF), single ventricle defects, and others (3). Recent cases of cyanotic pulmonary stenosis are documented in Table 1.

This case underscores the challenges of diagnosing the underlying factors contributing to symptoms in a pediatric patient experiencing acute exacerbations of chronic hypoxemia. Initially, the patient exhibited clear evidence of PS on trans-thoracic echocardiography. The patient remained asymptomatic until seeking care at our facility. Despite the evident presence of PS and the absence of intracardiac shunting on the initial echocardiogram, there was still suspicion of shunting at that time. A PFO was not detected during the patient's initial presentation, and no bubble study was conducted during her hospitalization.

Nonetheless, the persistence of erythrocytosis, hyperviscosity syndrome, and consistently low oxygen saturations necessitated a more in-depth investigation. Our inquiry was ultimately resolved through the unexpected discovery of a concomitant PFO during the RHC procedure. After the intervention, the patient's overall condition showed significant improvement, as confirmed during cardiac follow-up. The peak gradient of pulmonary stenosis and arterial oxygen saturation levels demonstrated satisfactory outcomes. Although Eisenmenger syndrome was initially considered a possible cause of the right-to-left shunt, it seemed less likely due to the significant improvement observed following the BPV (4).

Cyanotic severe PS, when coexisting with a PFO, can lead to persistent cyanosis, polycythemia, and clubbing. Rectifying the primary culprit with BPV can potentially allow for the safe correction of the PFO and alleviating hypoxemia. Achieving optimal management for cyanotic severe PS in the presence of a PFO necessitates a careful balance between pulmonary blood flow and systemic oxygenation. In specific situations, a PFO may be beneficial in reducing proper heart pressure and promoting increased left-sided cardiac output, albeit at the expense of inducing hypoxia. Further research is needed to establish the effectiveness of concurrent percutaneous interventions for PFO closure in conjunction with percutaneous BPV. However, prior cases and research have shown favorable outcomes when employing simultaneous percutaneous interventions to address secundum-type atrial septal defect and pulmonary stenosis (5,6).

Severe PS accompanied by an intracardiac shunt represents a complex congenital heart anomaly. In this particular condition, structural abnormalities obstruct the flow of deoxygenated blood to the lungs, leading to reduced oxygenation and decreased oxygen partial pressure in the arterial bloodstream. Consequently, peripheral tissues receive inadequate oxygen supply, resulting in typically cyanosis. Symptoms in affected individuals typically include exertional dyspnea or fatigue, which varies depending on the extent of the obstruction and the cardiac compensatory reserve. In cases of severe stenosis, patients may also experience exertional chest pain or fainting, as reported in our patient (7).

Our patient has been diagnosed with severe valvar PS and hyperviscosity syndrome. Hyperviscosity syndrome is a medical condition characterized by abnormally thick blood, resulting in reduced blood flow. The increased viscosity can be attributed to various factors, including alterations in the shape of red blood cells (RBCs), leading to RBC aggregation and impaired blood circulation. Additionally, elevated levels of blood components such as increased RBCs, white blood cells, platelets, or serum proteins in certain pathological conditions can contribute to heightened blood viscosity (8). In the context of cyanotic congenital heart disease, mechanisms responsible for thrombocytopenia include reduced platelet production, decreased megakaryocyte production, increased platelet destruction, and heightened platelet activation (8). Figure 5 describes a detailed explanation of the underlying pathomechanisms responsible for the patient's signs and symptoms.

Transcatheter BPV has emerged as the universally acknowledged, secure, and efficacious intervention for valvular PS in individuals of all age groups (9). Nevertheless, the BPV procedure may lead to various unwanted complications. The abrupt alleviation of valvular obstruction can lead to severe distress in the right ventricle

Table 1. Recent literature reported a cyanotic pulmonary stenosis with concomitant intracardiac shunt

Author, year, country	Patient sex and age	Diagnosis	Cardinal symptoms, onset	O_2 saturation on room air	Intervention, balloon	PS gradient pre-BPV	PS gradient pos-BPV	RV Pressure
This case, 2023, Indonesia	Girl, Ten years	• Severe valvar pulmonary stenosis • Hyperviscoucity syndrome • Patent foramen ovale (PFO)	• Chronic cyanosis • Chest pain	• Right hand: 53 % • Left hand: 41 % • Right foot: 53 % • Left foot: 53 %	BPV with Tyshak® balloon catheter 14 × 30 mm	111 mmHg	48 mmHg	53 mmHg
Siagian, 2021, Indonesia	Boy, 13 years	• Severe valvar pulmonary stenosis • Atrial Septal Defect • Biventricular heart failure	• Severe breathlessness • Severe cyanotic	40 %-50 %	BPV with Tyshak® balloon catheter 12 × 30 mm	88 mmHg	67 mmHg	23 -12 mmHg (6 months after intervention)
Wardhani, 2022, Indonesia	Female, 26 years	• Severe valvar pulmonary stenosis • Secundum atrial septal defect (ASD)	• Cyanosis • Shortness of breath	91 %	BPV was performed using a 12 mm Tyshak II Balloon. Balloon inflation was carried out five times.	99.2 mmHg	33.8 mmHg	160 - 44 mmHg (after BPV)
Singhi, 2022, India	• Case 1: Boy, 12 years	• Severe pulmonary valvular stenosis • Heart failure (FC III) • Patent foramen ofale (PFO) • Mild pericardial effusion	-Exertional palpitation -Cyanosis and clubbing	72 % C 97 %	BPV was initially done with a Tyshak II balloon 14 X 40 mm, followed by a Tyshak II balloon 18 X 40 mm.	200 mmHg	50 mmHg	217 mmHg
	• Case 2: Boy, 6.5 years	• Severe valvular pulmonary stenosis • Patent foramen ovale (PFO)	• Breathlessness on exertion • Progressive cyanosis	79 % -90 %	Thysak II balloon 14 mm × 40 mm, followed by a 16 mm × 40 mm balloon.	113 mmHg	14 mmHg	N/A
Kuntartiwi, Indonesia, 2021		• Severe valvar pulmonary setenosis • Atrial Septal defect (ASD) • Patent Ductus Arteriosus (PDA)	-Cyanosis on lips and fingertips since born	60 %-70 % - 96 %	Percutaneous transluminal balloon valvuloplasty (PTBV)	125.9 mmHg	22 mmHg	129 - 70 mmHg

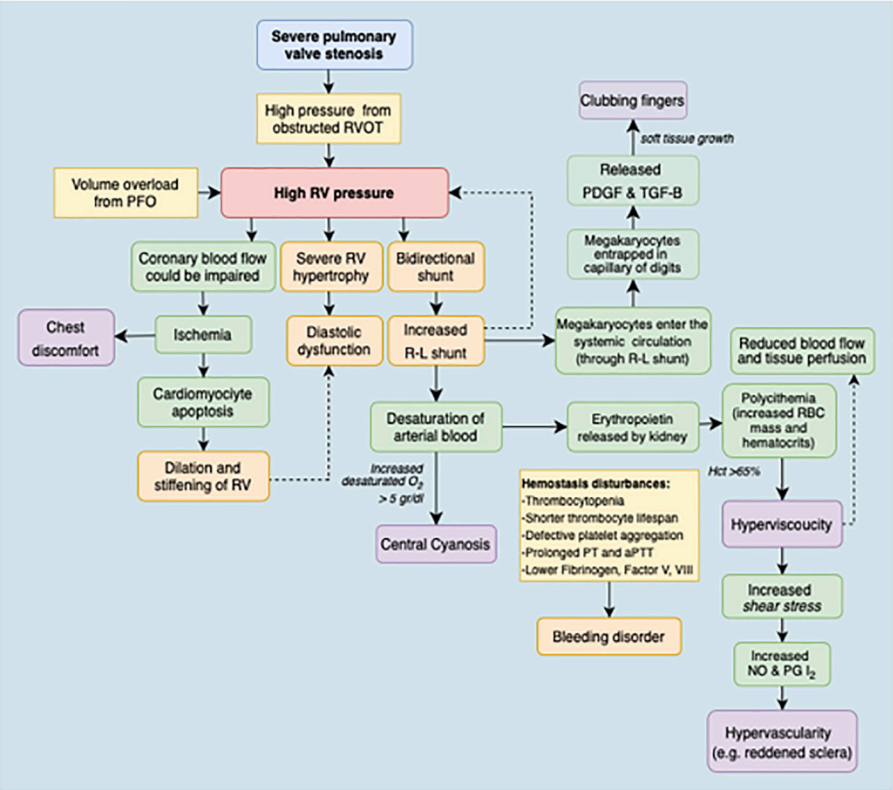

Figure 5. Pathomechanism and clinical manifestations of this patient PFO: patent foramen ovale; RVOT: right ventricle outflow tract; RV: right ventricle; R-L shunt: right to left shunt; PDGF: platelet-derived growth factor; TGF: transforming growth factor; RBCs: red blood cells; Hct: hematocrit; NO: nitric oxide; PG I2: prostacyclin.

and constriction of the infundibulum, resulting in a notable reduction in pulmonary blood flow. This subsequent increase in cyanosis and deterioration of proper ventricular function poses a challenge in the intensive care unit (ICU), often requiring the administration of inotropic support, mechanical ventilation, and beta-blocker therapy, as documented in prior cases (10,11). Continuous monitoring of cardiac function and heart imaging remains imperative for precise therapeutic adjustments.

Conversely, infundibular stenosis that might have been concealed can become evident following balloon dilatation of the pulmonary valve, potentially leading to persistent pressure gradients. The coexistence of right ventricular stiffness and residual infundibular stenosis can result in right-to-left shunting at the atrial level, further contributing to persistent cyanosis. In our case, there was a significant reduction of more than 50 % in the initial pressure gradient. Significantly, it is worth noting that infundibular hypertrophy, a well-documented occurrence in longstanding cases of PS, tends to diminish progressively over several weeks to months, often with the use of beta-blocker therapy (12). In the present case, a beta-blocker was administered on the first day of the patient's hospitalization.

In cases of long-standing severe PS, BPV can sometimes lead to the development of pulmonary edema, a condition influenced by several contributing factors. The sudden influx of blood into the pulmonary circulation resulting from the opening of valve leaflets, combined with a small, underfilled, and noncompliant left ventricle, can precipitate pulmonary edema. Furthermore, reperfusion injuries can occur in long-standing cases, with reported incidence

rates of up to 71 % (13). Fortunately, we did not encounter such complications in our case.

BPV remains the preferred approach for addressing severe pulmonary stenosis in symptomatic children and adolescents, particularly when they present with challenges associated with long-standing uncorrected heart disease. In these cases, comprehensive imaging assumes a pivotal role in both diagnosis and the on-site management of patients in the ICU. To reduce the risk of post-BPV pulmonary edema, some medical facilities employ a cautious approach by opting for elective ventilation and a graded strategy for valvuloplasty. Many patients tend to continue experiencing persistent ventricular dysfunction due to the longstanding nature of their condition. In specific healthcare institutions, preprocedural medications such as milrinone or dobutamine enhance systolic and diastolic ventricular functions, decreasing the likelihood of periprocedural complications. The administration of beta-receptor antagonists, diuretics, and afterload-reducing agents can also improve ventricular function (2,13).

Re-stenosis remains a significant concern following pulmonary valvuloplasty, with a reported frequency ranging from 8 % to 14 %. A subsequent balloon valvuloplasty has been identified as an effective and preferred treatment for patients experiencing restenosis after the initial procedure. Predictors of poorer outcomes following balloon pulmonary valvuloplasty include the presence of a dysplastic valve, a small annular size, a higher gradient immediately after the procedure, and neonatal age (< 1 year) (14).

Given the severity of the stenosis and the onset of cyanosis, there should be a heightened suspicion regarding the potential existence of an intracardiac shunt (4). Our present case also highlights the critical importance of using a bubble study in assessing patients diagnosed with severe pulmonary stenosis, mainly when they manifest symptoms of erythrocytosis. It is imperative to emphasize the necessity for extended and comprehensive examinations to ascertain the precise etiology and to facilitate the implementation of tailored and effective management strategies.

CONCLUSIONS

This case suggests that patients with cyanotic severe PS should be investigated thoroughly for the presence of intracardiac communication and shunting. Transcatheter BPV stands out as the preferred therapeutic option for patients suffering from severe PS alongside an intracardiac shunt.

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors certify that the patient and family have obtained all appropriate patient consent forms. In the form, the patient's parents have consented for images and other clinical information to be reported in the journal. The patient's parents understand that names and initials will not be published, and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Availability of data and material

Not applicable

Competing interests

The authors declare no competing interests.

Funding

The authors have not declared a specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

YP, AQ, and AAU contributed to the initial conceptions and ideas. AQ performed literature searching and prepared the initial manuscript. YP, AAU, IM, and MZ reviewed and advised for critical revisions. All contributing authors approved the final draft.

Acknowledgments

The authors gratefully acknowledge the patient and family members for their cooperation and willingness to provide written informed consent.

List of abbreviations

ASD:	atrial septal defect
aPTT:	activated partial thromboplastin time
BPV:	balloon pulmonary valvuloplasty
Hct:	hematocrit
ICU:	intensive care unit
INR:	international normalized ratio
NO:	nitric oxide
PDGF:	platelet-derived growth factor
PG I_2:	prostacyclin
PFO:	patent foramen ovale
PS:	pulmonary stenosis
PT:	prothrombin time
RBCs:	red blood cells
RHC:	right heart catheterization
R-L shunt:	right to left shunt
RVOT:	right ventricle outflow track
TGF:	transforming growth factor

REFERENCES

1. Marchini F, Meossi S, Passarini G, Campo G, Pavasini R. Pulmonary Valve Stenosis: From Diagnosis to Current Management Techniques and Future Prospects. Vasc Health Risk Manag. 2023;19:379-390.
2. Cuypers JAAE, Witsenburg M, van der Linde D, Roos-Hesselink J. W. Pulmonary stenosis: update on diagnosis and therapeutic options. Heart. 2013;99:339-347.
3. Heaton J, Kyriakopoulos C. Pulmonic Stenosis. 2023. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. PMID: 32809585.
4. Arvanitaki A, Giannakoulas G, Baumgartner H, Lammers AE. Eisenmenger syndrome: Diagnosis, prognosis and clinical management. Heart. 2020;106:1638-1645.
5. Xu X-D, Ding X-Y, Liu S-X, Bai Y, Zhao X-X, Qin Y-W. Immediate- and medium-term effects of simultaneous percutaneous corrections of secundum type atrial septal defect combined with pulmonary valve stenosis in local anesthesia and without transesophageal echocardiography guidance. J Cardiol. 2015;65:32-36.
6. Medina A, de Lezo JS, Delgado A, Caballero E, Segura J, Romero M. Combined percutaneous atrial septal defect occlusion and pulmonary balloon valvuloplasty in adult patients. Tex Heart Inst J. 2000;27(2):216-217.
7. Park MK. Pediatric Cardiology for Practitioners. Mosby/Elsevier, 2008.
8. Puspitasari F, Harimurti G. Hyperviscoucity in Cyanotic Congenital Heart Disease Febtusia. J Kardiol Indones. 2010;31:41-47.
9. Stanger P, Cassidy SC, Girod DA, Kan JS, Lababidi Z, Shapiro SR. Balloon pulmonary valvuloplasty: Results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. Am J Cardiol. 1990;65(11):775-783.
10. Singhi A, Mohapatra S, Dey S, Chatterjee D, De A. Challenges in balloon pulmonary valvotomy for severe pulmonary stenosis presenting with cyanosis and ventricular dysfunction. J Indian Coll Cardiol. 2022;12:139.
11. Al Kasab S, Ribeiro P, Al Zaibag M. Use of a double-balloon technique for percutaneous balloon pulmonary valvotomy in adults. Br Heart J. 1987;58:136-141.
12. Fontes VF, Esteves CA, Sousa JE, Silva MV, Bembom MC. Regression of infundibular hypertrophy after pulmonary valvuloplasty for pulmonic stenosis. Am J Cardiol. 1988;62:977-979.
13. Tefera E, Qureshi SA, Bermudez-Cañete R, Rubio L. Percutaneous balloon dilation of severe pulmonary valve stenosis in patients with cyanosis and congestive heart failure. Catheter Cardiovasc Interv. 2014;84: E7-15.
14. Aldoss O, Gruenstein D. Percutaneous Balloon Pulmonary Valvuloplasty. Pediat Therapeut. 2012;S5:003.