

# The importance of correct management in a 15-year-old boy with severe pulmonary arterial hypertension associated with patent ductus arteriosus

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## ABSTRACT

**Background:** Pulmonary arterial hypertension (PAH) is a condition in which pulmonary vascular pressure increases and is associated with diverse diseases or aetiologies. In children, 50% of PAH cases are caused by congenital heart disease (CHD), especially due to large left-to-right shunts. Large systemic to pulmonary shunts may develop in PAH if left untreated or repaired late. PAH, when present, markedly increases morbidity and mortality in patients with CHD.

**Case presentation:** We present a 15-year-old boy with a large patent ductus arteriosus (PDA) and severe pulmonary arterial hypertension. Catheterization under general anaesthesia was performed at the age of 16 years. We performed an acute vasoreactivity test (AVT), with the AVT result showing pulmonary arterial hypertension with high flow and low resistance. Transcatheter closure (TCC) of PDA was performed, resulting in no residual PDA. Meanwhile, the echocardiographic finding showed that there was still class II pulmonary arterial hypertension. We then gave heart failure medication and selective pulmonary vasodilator for 6 months. Post-treatment, pulmonary artery systolic pressure was significantly lower (TR Vmax 2.31 m/s, TR Max PG 21 mmHg, estimated PAP 24 mmHg). In this case, clinical evaluation, CXR, ECG, echocardiography, and cardiac catheterization data were presented with a review of the current guidelines regarding the management of paediatric patients with PAH associated with PDA.

**Summary:** TCC of PDA is an option to treat pulmonary hypertension in PDA patients. Combined use of drugs and TCC PDA proves beneficially synergistic effect with better outcomes and may reduce mortality.

**Keywords:** pulmonary arterial hypertension, congenital heart disease, patent ductus arteriosus, AVT, selective pulmonary vasodilator.

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## INTRODUCTION

The patent ductus arteriosus (PDA) is a vascular structure connecting the descending aorta proximal to the roof of the main pulmonary artery near the origin of the left pulmonary artery branch. These essential fetal structures usually close spontaneously after birth. Persistent ductal patency is considered abnormal if it persists after the first few weeks of life. Patent ductus arteriosus (PDA) has physiological implications and clinical significance depending on the patient's size and underlying cardiovascular status. The PDA may be "silent" (not evident clinically but diagnosed incidentally by echocardiography done for a different

reason), which can be small (1–1.5 mm), moderate (1.5–3 mm), or large (> 3 mm).<sup>1–6</sup> Some of the hemodynamic effects of PDA are pulmonary hypertension, systemic hypoperfusion, and volume overload in the left ventricle. The PDA initially produces an L-to-R shunt and excess LV LA volume. PAP will be found to be increased in moderate and large PDAs. In adult patients with moderate PDA, LV or PAH volume excess is predominant. It is estimated that around 10% of adults with CHD experience PAH, which impacts their quality of life. Most patients do not survive beyond 40 years, with right-sided heart failure being the leading cause of death.<sup>6</sup> In older children and adults, there are many cases of PDA with an atypical

clinical picture. Most of these cases have been instances of isolated patency of the ductus arteriosus in which some or even all of the usual diagnostic features have been missing, the most common feature usually being the absence of a continuous murmur. Studies made in some of these cases have demonstrated either marked elevation of pulmonary artery pressure or post-mortem evidence of its presence in the form of marked right ventricular hypertrophy.<sup>5,6</sup>

Patients with increased pulmonary artery pressure have a higher chance of developing pulmonary hypertension (PH). The remodeling of pulmonary artery resistance will lead to a primary abnormality in PH in the form of

increased afterload in the RV due to increased pulmonary vascular resistance. Patients with PH have higher morbidity and mortality compared to other CHD patients. In children, 50% of cases of PAH are caused by CHD, mainly due to a large left-to-right shunt. Patients with uncorrected left-to-right shunt lesions including simple lesions, such as atrial septal defects (ASD), ventricular septal defects (VSD), and PDAs are at high risk of developing PH if left uncorrected.<sup>1-6</sup>

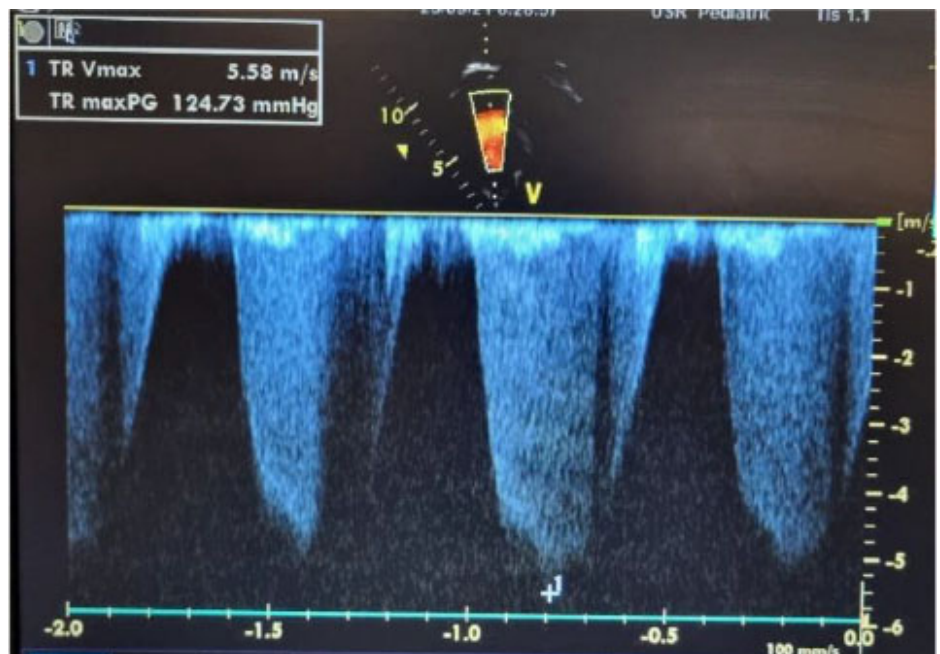
Treatment of severe PH in PDA poses a unique challenge. Like other large communications between the systemic and pulmonary circulations, a large PDA exposes the pulmonary arterial (PA) bed to high pressure and flow. Over time, the remodeling of the pulmonary vasculature occurs.<sup>4</sup> This condition will predispose to the development of pulmonary arterial hypertension. This case report highlights the importance of managing severe pulmonary arterial hypertension associated with a patent ductus arteriosus. In this report, we present a case of a 15-year-old boy with pulmonary arterial hypertension due to PDA and describe the management of PH in this population.

## CASE PRESENTATION

A 15-year-old boy presented to a paediatrician with a complaint of shortness of breath. He also experienced fatigue easily during mild to moderate activities. There was also difficulty in gaining weight. His medical history was a pronounced swelling on both of his legs. There was no known history of significant cardiac or pulmonary disorders.

The result of the physical examination performed on the patient indicated tachypnoea (RR 30 times per minute, with marked subcostal retraction, with oxygen saturation of 97%, and tachycardia with HR 110–120 bpm. On auscultation, there was an audible continuous murmur at the intercostal space II left parasternal line. Hepatomegaly was found 1/3 – 1/3. There was marked oedema at both of his lower extremities.

Echocardiography demonstrated a large PDA bidirectional shunt dominantly left to right with a PDA diameter of 12 mm, severe pulmonary hypertension with TR Vmax 5.58 m/s, Max PG 124.73 mmHg



**Figure 1.** Echocardiography shows severe pulmonary hypertension with TR Vmax 5.58 m/s and TR Max PG 124.73 mmHg.

(can be seen in Figure 1), right atrial and ventricular dilatation, moderate aortic regurgitation, mild tricuspid regurgitation, and severe pulmonary regurgitation. From ECG, this study found RAD (+) and RVH (+). From chest radiological examination, this study also identified cardiomegaly with increased pulmonary markings matching with congenital heart disease left-to-right shunt with pulmonary hypertension, emphysematous lung, and thickening of bilateral pleura. This radiology examination can be seen in Figure 2.

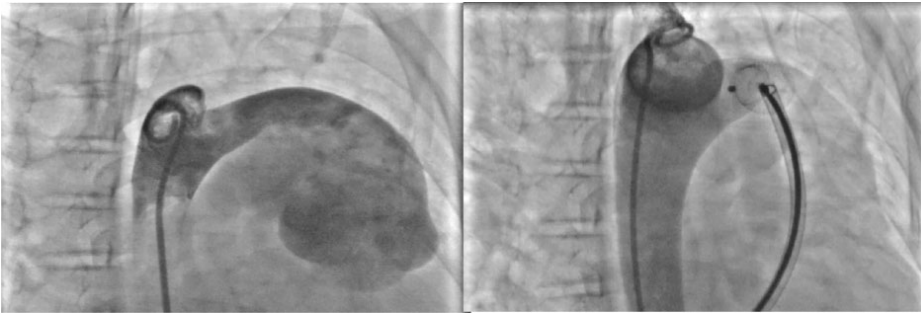
We identified that this patient suffers from large PDA, severe PH, heart failure NYHA Class III, and severe malnourishment. We planned for this patient to undergo heart catheterization. The result was a high flow ratio of 5.39 with m PAP 50 mmHg. We then gave the patient heart failure medication. After a year, the patient came to the outpatient installation, and the patient underwent a second catheterization, with the result after the AVT test: Flow Ratio 2.61, m PAP 44 mmHg, and PARI score 3.73 WU (High flow low resistance). Transcatheter closure (TCC) of PDA was performed, and the result was no residual PDA (Figure 3). One week post-closure, the patient still experienced pulmonary arterial hypertension.



**Figure 2.** Thoracic X-ray reveals cardiomegaly with increased pulmonary markings.

Moreover, there was an improvement in the heart failure symptoms, such as an improvement in dyspnoea, and the patient could carry out some moderate activities (Class II PAH). Post-PDA-closure, the patient received heart failure medication and selective pulmonary vasodilator. This medication (selective pulmonary vasodilator) was consumed for the next 6 months until age 16.

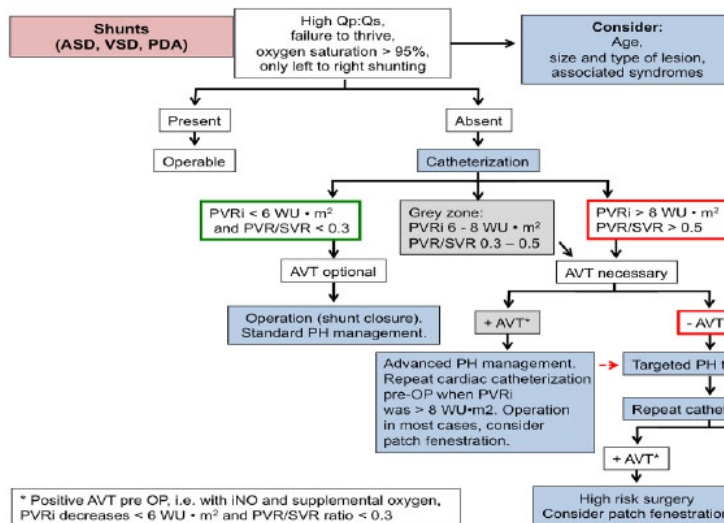
In January 2022, the patient underwent his last echocardiography. The result



**Figure 3.** Transcatheter Closure of PDA Before and After.

| Peak tricuspid regurgitation velocity (m/s) | Presence of other echo 'PH signs' <sup>a</sup> | Echocardiographic probability of pulmonary hypertension |
|---------------------------------------------|------------------------------------------------|---------------------------------------------------------|
| ≤2.8 or not measurable                      | No                                             | Low                                                     |
| ≤2.8 or not measurable                      | Yes                                            | Intermediate                                            |
| 2.9–3.4                                     | No                                             |                                                         |
| 2.9–3.4                                     | Yes                                            | High                                                    |
| >3.4                                        | Not required                                   |                                                         |

**Figure 4.** PH classification by echocardiography.<sup>9</sup>



**Figure 5.** The algorithm for the management of patients with CHD associated with PAH/PHVD and congenital shunt lesions.<sup>14</sup>

showed an improvement in his pulmonary hypertension with TR Vmax 2.31 m/s and TR Max PG 21 mmHg. Consequently, we discontinued the selective pulmonary vasodilator but maintained the heart failure medication.

## DISCUSSION

In general, the natural history of PDA is variable. Left ventricular volume overload and pulmonary hypertension are found when the shunt is large. The higher probability of pulmonary hypertension

means the larger the internal diameter of the narrowest part of the ductus arteriosus and the larger the left-to-right shunt.<sup>5,6</sup>

PH which is a clinical manifestation of congenital heart disease is a disease characterized by an average (mean) pulmonary arterial pressure (m PAP)  $\geq 25$  mmHg at rest.<sup>5,6</sup> Based on the new guidelines of the 6th World Symposium on the Pulmonary Hypertension (WSPH) Task Force, if an average pulmonary artery pressure (m PAP) is obtained  $> 20$  mmHg with pulmonary vascular pressure (PVR)  $\geq 3$  Wooden Units. The condition is classified as pre-capillary pulmonary hypertension (PH).<sup>7</sup> In the China study, 60.2% of pediatric patients with PDA have pulmonary hypertension, and the prevalence is higher with large duct sizes. This condition is caused by intimal proliferation, progressive hypertension, and prolonged hypoxemia.<sup>6</sup>

A study by Lammers et al. revealed that age at repairment and age at follow-up were the major risk factors for PH. The statement emphasized that correct diagnosis and closure of the shunt lesion before PH develops is essential. The increasing age causes the risk of developing PH may also increase so that CHD with closed defects requires lifelong follow-up and special supervision for PH. Patients will be significantly more symptomatic when PH develops compared to the other patients.<sup>3</sup>

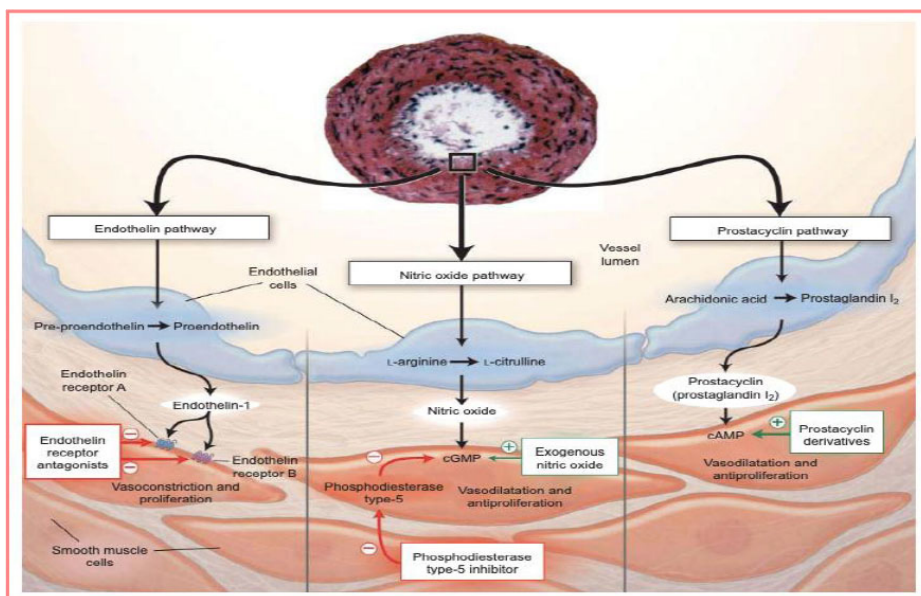
The initial symptoms are generally exercise-induced and associated with progressive right ventricular dysfunction. Besides that, there are also fatigue, shortness of breath, angina, and syncope. The onset of symptoms at rest may also occur in more advanced cases. In addition, the classical signs of hepatomegaly, abdominal distention, and ankle edema are more pronounced in cases of right heart failure.<sup>8</sup>

An electrocardiogram (ECG) can support the diagnosis of PH, but a normal EKG does not rule out the diagnosis. Abnormal ECGs are generally more common in severe PH than in mild PH. ECG abnormalities may include P pulmonale, RV hypertrophy, right axis deviation, RV strain, QTc prolongation, and right bundle branch block. RV hypertrophy has a sensitivity of 55%



| Recommendations                                                                                                                                                                                                                  | Class <sup>a</sup> | Level <sup>b</sup> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|
| In patients with evidence of LV volume overload <sup>c</sup> and no PAH (no non-invasive signs of PAP elevation or invasive confirmation of PVR <3 WU in case of such signs), PDA closure is recommended regardless of symptoms. | I                  | C                  |
| Device closure is recommended as the method of choice when technically suitable.                                                                                                                                                 | I                  | C                  |
| In patients who have developed PAH with PVR 3–5 WU, PDA closure should be considered when there is still significant L–R shunt (Qp:Qs >1.5).                                                                                     | IIa                | C                  |
| In patients who have developed PAH with PVR ≥5 WU, PDA closure may be considered when there is still significant L–R shunt (Qp:Qs >1.5) but careful individual decision in expert centres is required.                           | IIb                | C                  |
| PDA closure is not recommended in patients with Eisenmenger physiology and patients with lower limb desaturation on exercise. <sup>d</sup>                                                                                       | III                | C                  |

**Figure 6.** Recommendation for intervention in PDA.<sup>17</sup>



**Figure 7.** A management algorithm of PH in CHD patients.<sup>21</sup>

while a specificity of 70% as a screening tool, RV strains are more sensitive. Severe disease is indicated by lengthening of the QRS and QTc complexes.<sup>9</sup> Transthoracic

echocardiography can be used to monitor the effect of PH on the heart and assess PAP by continuous wave Doppler measurement.

Echocardiographic assessment of pulmonary artery pressure in children with PDA has the advantages of being simple, safe, and accurate, with a very high cost-benefit ratio. Pulmonary hypertension can be calculated by adding the calculated pressure gradient across the tricuspid valve and the right atrial pressure (PASP =  $4V^2$  + right atrial pressure). Normal right atrial pressure is 3 mmHg and is generally added to the TR rate at a normal IVC.<sup>6</sup> Echocardiography is mandatory when PH is suspected and can be used to conclude the diagnosis of PH in patients whose multiple echocardiographic measurements are consistent with the diagnosis. In considering the drug given, echocardiography alone is insufficient to make a decision and the cardiac catheterization is needed. PH classification can be seen in Figure 4.<sup>9</sup>

The hallmark of PDA in physical finding is the “machinery” murmur, a continuous murmur located at the upper left sternal border. Murmurs are often found radiating to the left side of the sternum and back, and may be accompanied by a thrill. Every child with congenital heart disease, clinical examination should focus on assessing common signs of PH including: (1) left parasternal heave caused by right ventricular enlargement, assessed by placing the heel of the hand over the left parasternal region; (2) second heart sound to assess pulmonary component accentuation (P2); (3) paradoxical splitting of the second heart sound, and (4) pulmonary regurgitation with diastolic murmur; (5) the systolic murmur on the VSD sounds softer and the diastolic murmur/machinery murmur in PDA disappears.<sup>7</sup>

In this case report, the patient showed up to the paediatrician at 15. The patient presented with heart failure signs and symptoms. He experienced shortness of breath during mild-to-moderate activities without desaturation, susceptibility to fatigue, palpitations, and failure to gain weight. However, we found a splitting of S2 sound and continuous murmur at the intercostal space II parasternal line, hepatomegaly, and oedema at both lower

extremities. This is consistent with the physical examination found in PDA and PAH. The patient showed symptoms of heart failure. This follows a study by Schneider, who observed that children and adults with moderate to large patent ductus often experience symptoms of congestive heart failure. The presence of right pulmonary circulation and excess volume causes this.<sup>1</sup>

Left-to-right shunt through the ductus arteriosus results in excess pulmonary circulation and left volume overload. An increase in pulmonary flow from the shunting duct causes the increase in pulmonary fluid volume. In patients with a moderate or large shunt, it can cause a decrease in lung compliance, causing an increase in the work of breathing.<sup>10</sup>

ECG examination, chest x-ray, and echocardiography are the first investigations used to assess CHD patients. Echocardiogram is more often recommended to manage the therapy given and assess clinical conditions. Echocardiography is also performed to assess PAH's severity and provide a predictive outcome. Based on guidelines developed by Chemla et al., pulmonary hypertension is defined when the mean pulmonary artery pressure exceeds 20 mmHg. The pulmonary artery systolic pressure of about 30 mm Hg corresponds to a mean pulmonary artery pressure of 20 mm Hg. Classification of pulmonary hypertension includes mild if it is 30-50 mmHg, moderate if it is 51-65 mmHg, and severe if it is  $\geq 65$  mmHg.<sup>11</sup> Characteristics of the lesion, overall clinical status, and time of appearance are considered for cardiac catheterization (to measure the PVR index (PVRI) and to determine operability) in children with significant structural heart defects that have not been repaired.<sup>7</sup>

Nevertheless, the patient in this study underwent serial echocardiography. The first echocardiography revealed pulmonary hypertension (TR Max PG 124.73 mmHg) with a large PDA (12 mm). ECG examination may show enlargement of the right atrium and ventricle while chest X-ray shows cardiomegaly with increased pulmonary signs

Children with congenital heart disease generally experience decreased

energy, cardiac acidosis, tissue hypoxia, intestinal malabsorption, peripheral acidosis, infection, and increased energy requirements due to increased metabolic rate which leads to abnormal growth. Very poor growth is more common in children with congenital heart defects than in healthy children.<sup>12</sup> Factors that cause failure to thrive in children with CHD are heart failure, hypermetabolism, impaired function of the gastrointestinal tract, comorbidities or diseases, like Down's Syndrome and Turner's Syndrome, associated infections, and decreased energy intake. The ability of children with CHD to receive food intake is usually only 76% compared with normal children. In addition, there is a high risk of developing neurodevelopmental disorders (NDD) and psychiatric conditions in children with CHD. This includes behavior, speech, adaptive, motor, cognitive, executive functions, psychiatric conditions, and autism spectrum disorders.<sup>12,13</sup> This study included patients with malnutrition. The results of this study follow research conducted in India which showed that most of the malnutrition experienced by CHD sufferers. In the cyanotic group, weight and height were more influential.

Based on the cardiac catheterization in this patient, the AVT test results indicate a flow ratio of 2.61, m PAP of 44 mmHg, and PARI score of 3.73 WU. This statement is in accordance with a study by Hansmann et al., in patients who experienced PAH with a PVR of 3-5 WU, PD. If there is still a significant L-to-R shunt then closure will be considered ( $Q_p:Q_s > 1.5$ ) (Figure 5,6).<sup>14</sup>

The main goals of cardiac catheterization in children with PAH are (1) assessing the severity of the disease and establishing the diagnosis; (2) assess response to pulmonary vasodilator (AVT) before therapy is given; (3) to assess response or need for changes in therapy; (4) exclude potentially treatable diseases; (5) assessing operability with systemic to pulmonary artery shunts as part of patient assessment; and (6) determine eligibility for heart or lung transplantation. Critically ill patients requiring immediate initiation of further therapy will be excluded.<sup>15</sup>

Patients can be treated as early as possible with interventions appropriate to their diagnosis. It is very important to

determine with certainty the specific cause of PAH and establish a timely and accurate diagnosis of PAH.<sup>16</sup>

Making the wrong diagnosis of the cause of PH in patients can cause patients to fail to get the right treatment according to their specific type of PAH.

CHD related to PAH (CHD-APAH) should be assessed at specialist centers that can assess CHD and PAH patients regularly. Standards used for CHD-PAH centers have not been established yet. During their disease, patients may experience clinical deterioration at any time. These conditions include lung infections or dehydration at high altitudes and during noncardiac operations requiring general anesthesia.<sup>8</sup>

Procedures to repair the defect by surgery or catheterization are the treatment options for reversible PAH. After correction, the morbidity and mortality rates due to PAH are still high. Pharmacological treatment of PAH includes CCB, PDE5i, ERA, and prostacyclin agonists. Depending on the clinical functional class, they can be chosen as medications for PH. The patient in this study received sildenafil as a phosphodiesterase-5 inhibitor and captopril as an ACE inhibitor. Sildenafil is a type 5 phosphodiesterase inhibitor (PDE5i) widely used because of its low cost and ease of use in increasing levels of cyclic guanosine monophosphate (cGMP) in the body. A series of cellular changes can occur due to the accumulation of cGMP, leading to increased right ventricular function, decreased intracellular calcium levels, and decreased vascular smooth muscle contraction (Figure 7). As a selective vasodilator, sildenafil has been used broadly and proven effective for the adult population.<sup>18,19</sup> Reviewed from the study by Genet, more patients treated with sildenafil showed an improved response to therapy compared to placebo administration, at least one NYHA functional class after 12 weeks of treatment. Initially most of the patients were at NYHA level 2 or 3.

Taking captopril in patients with pulmonary hypertension can significantly reduce systemic blood pressure and vascular resistance; this effect persists at submaximal levels. Captopril does not



change pulmonary artery pressure or resistance, stroke volume, and cardiac output at rest or during exercise.<sup>16,18</sup>

However, TCC of PDA in patients remains a challenging clinical problem especially in patients with severe PH. PHT is often reversible in neonates and infants; however, in older patients, PHT improvement depends on the reversibility of pulmonary vascular resistance (PVR). associated with this subset of patients are complications and long travel distances.<sup>20</sup> In a study undertaken by Bhalgat that examines the outcome of TCC in PDA with PH in 76 patients, the author found that 6 months of follow-up is required for all patients with complete closure of the PDA.

Studies show that TTC in large PDAs and left-to-right shunts were found to be effective and safe in the short and immediate term improved significantly.<sup>20</sup>

However, in our patient, we provided a combination of oral medication and TCC of PDA. The result was promising and the patient's follow-up data was remarkable. There was, however, still a lack of data about the patient's long-term nutrition status. As a result, it would only be appropriate to perform longer follow-ups in patients with PDA and PH after intervention(s).

Lifelong tertiary care is mandatory for all patients with PAH. Patients require close follow-up after cardiac intervention either by cardiac catheterization or rehabilitation because PAH is persistent and must undergo at least one full assessment every six months. In a recent report with 1103 shunt patients, the cumulative incidence of PAH ranged from 2.1% immediately after closure to more than 15% 50 years later. Lifestyle monitoring is essential including signs and symptoms of heart failure (NYHA), family planning and exercise, nutritional status, growth, and development.<sup>5,7</sup>

## CONCLUSION

One of the most common acyanotic heart diseases is Patent ductus arteriosus (with various clinical manifestations). Some hemodynamic changes that can occur in a PDA are pulmonary hypertension, systemic hypoperfusion, and volume overload in the left ventricle. This case

report explains that an accurate diagnosis of The causes of PH are associated with several challenges. Clinical assessment and basic examinations are required including CXR, EKG, and echocardiography to estimate the degree of PH and PA pressure. The combination of drugs and TCC PDA is proven to have a synergistic effect with better results, while reducing morbidity and mortality.

## DISCLOSURE

### Consent for Publication

Written informed consent was obtained from the patient to publish this case report.

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### Conflicts of interest

The author declared that there is no conflict of interest.

### Author contribution

All authors contributed equally in preparing and writing this manuscript.

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