Case Report

Pulmonary Circulation

Pushing the envelope: a treat and repair strategy for patients with advanced pulmonary hypertension associated with congenital heart disease

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Abstract

Pulmonary arterial hypertension (PAH) is a frequent complication of congenital heart disease as a consequence of altered pulmonary hemodynamics with increased pulmonary blood flow and pressure. The development of pulmonary vascular disease (PVD) in this patient population is an important concern in determining operative strategy. Early, definitive surgical repair, when possible, is the best therapy to prevent and treat PVD. However, this is not possible in some patients because they either presented late, after the development of PVD, or they have complex lesions not amenable to one-step surgical correction, including patients with single ventricle physiology, who have a continuing risk of developing PVD. These patients represent an important, high-risk subgroup and many have been considered inoperable. We present a case series of two patients with complex congenital heart disease and advanced PVD who successfully underwent a treat and repair strategy with aggressive PAH therapies before surgical correction. Both patients had normalization of pulmonary vascular resistance prior to surgical correction. Caution is warranted in applying this strategy broadly and long-term follow-up for these patients is crucial. However, this treat and repair strategy may allow for favorable outcomes among some patients who previously had no therapeutic options.

Keywords

pulmonary arterial hypertension, pulmonary circulation, heart defects, congenital, thoracic surgery

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Introduction

Despite recent advances in treating pulmonary vascular disease (PVD), patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) represent a challenging subpopulation. In fact, CHD remains one of the most common causes of PVD worldwide.[1] Overall, the best therapy for PVD associated with CHD is definitive early surgical correction.[2] Unfortunately in the developing world, many patients with CHD continue to be referred late for corrective surgery and up to 20% patients are considered "inoperable" at presentation, owing to advanced PVD.[3] PVD contributes significantly to perioperative morbidity and mortality as well as subsequent right heart failure and death years after late biventricular repair.[4,5] In fact, compared to other forms of PAH, survival is least favorable in the subset of patients that develop PVD following late repair of CHD.[6] This ongoing risk makes appropriate preoperative evaluation of the pulmonary vasculature critical in identifying those patients at risk.

The current American Heart Association (AHA) and American Thoracic Society (ATS) guidelines for pediatric pulmonary hypertension (PH) recommend that selected patient populations undergo cardiac catheterization before attempted surgical correction.[7] In patients with simple shunt

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Table 1. Cardiac catheterization data for Patient EJ.

Age	PAH-specific therapies	Condition	PAP (Sys/Dia/Mean, mmHg)	PVRi (WU/m^2)	CI (mL/min/m^2)	Qp:Qs	Systemic O2 Sat (%)	PVR:SVR
5 years 1 month	Sildenafil, oxygen	FiO_2 1.0, iNO 20 ppm	55/35/m45	7		0.76:1	60	0.92
5 years 8 months	Sildenafil, bosentan, treprostinil, oxygen	2L NC oxygen	38/13/m24	2.1-2.8	3.8	1.8:1	81	0.2
6 years 3 months (post-repair)	Sildenafil, bosentan, treprostinil	Room air	26/11/m17	2.2	3.3	1:1	96	0.16

lesions uncorrected beyond one year and those with more complex lesions not repaired in the neonatal period, cardiac catheterization should be considered. It is important to note that the assessment of preoperative pulmonary vascular resistance (PVR) and reactivity in patients with congenital heart disease is challenging.[8,9] The AHA/ATS guidelines[7] go on to suggest certain parameters for operability for patients with left to right shunts. If the indexed pulmonary vascular resistance (PVRi) is less than 6 WU*m^2 or the PVR:systemic vascular resistance (SVR) ratio is less than 0.3, repair is suggested. In patients with a PVRi ≥ 6 or PVR:SVR ≥ 0.3, no repair is recommended unless acute vasodilator testing leads to normalization of these values. The guidelines are necessarily less precise in the case of patients with single ventricle physiology.

In patients with initially unfavorable hemodynamics for surgical correction, it is possible to undertake a strategy of initiating advanced PH therapies with a plan for repeat preoperative catheterization. Some patients may have improvement in hemodynamics such that operative repair may be considered. In the current case series, we present two cases of patients with significant PVD and CHD. These patients underwent a ''treat and repair'' strategy, novel for patients with complex congenital lesions. Successful clinical outcomes in these cases highlight the possibility of decreasing PVR to allow for correction of cardiac defects in patients previously considered inoperable. However, this strategy must be applied judiciously and these patients must be followed long-term to evaluate outcomes and potential PVD progression. Still, this clinical strategy may help push the envelope of those patients considered good candidates for surgical repair.

Case 1: late diagnosis of transposition of the great arteries with ventricular septal defect

EJ was the full-term product of an uncomplicated pregnancy and delivery in Mexico. He was initially diagnosed with congenital heart disease when he presented at the age of four months with cyanosis; an echocardiogram performed at that time revealed a large, unrestrictive ventricular septal defect (VSD) and D-looped transposition of the great arteries (D-TGA). He was initially palliated in Mexico with pulmonary artery banding and was treated medically with digoxin, furosemide, sildenafil, spironolactone, captopril, and supplemental oxygen. His baseline oxygen saturations were 60–85%. He was significantly growth-restricted with a weight-for-age Z-score of –2.87 and was wheelchair bound secondary to extreme fatigue.

He subsequently presented for medical care in the United States aged five years with an intercurrent respiratory viral illness and oxygen saturations of 30–40%. He underwent cardiac catheterization and atrial septostomy at that time (Table 1). Given his critical condition, the only measurements were taken with both FiO_2 1.0 and inhaled nitric oxide (iNO) at 20 ppm; the study revealed significantly elevated mean pulmonary artery pressure (mPAP) of 45 mmHg, a PVRi of 7 WU/m^2, and a ratio of pulmonary to systemic blood flow (Qp:Qs) of 0.76:1. Systemic oxygen saturation increased after atrial septostomy from 40% to 60%.

The patient was transferred to our institution, where triple therapy was initiated with continued sildenafil 0.75 mg/kg TID, bosentan titrated to 2 mg/kg BID dosing, and treprostinil subcutaneously titrated to 90 ng/kg/min. Three months after triple therapy, repeated cardiac catheterization (Table 1) demonstrated improvement in PVRi to 2.1–2.8 WU/m^2, decrease in mPAP to 24 mmHg, and a Qp:Qs of 1.8:1.

He underwent operative repair five months after initiation of triple therapy (delayed slightly due to respiratory illness) with an arterial switch operation, VSD closure, atrial septal defect closure, and patch augmentation of the neopulmonary artery. In the perioperative period, his treprostinil therapy was transitioned from subcutaneous to IV, to obviate potential inconsistent subcutaneous absorption while on cardiopulmonary bypass. Six months following repair, he continued to have normal PVRi of 2.2 WU/m^2 and mPAP of 17 mmHg (Table 1). He has now been followed for ten months after corrective operation. The treprostinil has been discontinued and he remains on bosentan and sildenafil. The decision to discontinue treprostinil was made balancing his excellent clinical progress with the lack of availability of this drug in Mexico. Following his surgery, he has had remarkable catch-up growth for both weight and height, and now has a Z-score of –0.07 for weight and –0.87

for height. He has also had improvement in development, as he attends kindergarten and is now walking and active.

Case 2: hypoplastic left heart syndrome with pulmonary vascular disease

AT was born at 36 weeks' gestation with prenatally diagnosed high-risk hypoplastic left heart syndrome (HLHS) with mitral stenosis, aortic atresia, and a restrictive atrial septum. She initially underwent palliative surgery on her third day of life consisting of bilateral branch pulmonary artery bands and was continued on prostaglandin infusion to maintain ductal patency. At three weeks of age, cardiac catheterization revealed discrete left lower pulmonary vein stenosis as well as diffuse narrowing of the left upper and left lingular pulmonary veins with a 5-mmHg gradient without focal stenosis. Given these findings, she was not considered to be a good candidate for further surgical palliation. Prostaglandin infusion was discontinued and she was discharged home with palliative care on nasogastric feeds, enteral furosemide, and home oxygen therapy.

She presented to our institution aged seven months with worsening desaturation but otherwise adequate growth and development. Her ductus arteriosus remained widely patent. A cardiac catheterization was then performed at the age of eight months, which demonstrated a severely restrictive atrial septum with a left atrial pressure of 37 mmHg and compromised pulmonary blood flow with Qp:Qs 0.6:1. The right pulmonary artery was not entered and so total PVRi could not be calculated. There was no evidence of pulmonary vein stenosis at this catheterization. A 6-mm atrial stent was placed with a decrease in LA pressure to 15 mmHg and an increase in Qp:Qs to 1.6:1. Given the bilateral pulmonary bands, there were differential distal PAPs and differential pulmonary blood flow. At this time, both her transpulmonary gradient (17 mmHg pre, 54 mmHg post stent placement) and her total PVRi (8.94 WU/m^2 post stent) were significantly elevated (Table 2). Note that the total resistance was calculated using the relative flows to each lung determined by the flow scan performed later and described below.

Following this procedure, she was started on bosentan titrated to 2 mg/kg BID and treprostinil subcutaneously titrated to 79 ng/kg/min. Given her history of gastroesophageal reflux, sildenafil therapy was not initiated. A follow-up cardiac catheterization two months later demonstrated continued restriction of the atrial septum, which was balloon dilated. PVRi remained elevated at 4.03 WU/m^2 (Table 2). One month later, a pulmonary flow scan was performed, which demonstrated 61% pulmonary blood flow to the left, 39% to the right. Repeat catheterization at this time showed minimal residual gradient at the atrial septum and a total PVRi of 4.62 WU/m^2 on room air, which improved to 1.76 WU/m^2 with iNO at 40 ppm and FiO_2 1.0 (Table 2). With vasodilators, the transpulmonary gradient was 16 mmHg in the left lung and 3 mmHg in the right lung. Pressures in the individual pulmonary veins were measured and no stenosis was found. Pulmonary vein angiography also confirmed the absence of pulmonary vein stenosis.

She then underwent comprehensive stage 2 HLHS palliative repair with pulmonary artery reconstruction, atrial septostomy, PDA ligation, bidirectional Glenn, and Norwood reconstruction of the neoaorta and aortic arch with Damus-Kaye-Stansel anastomosis. Similar to the first case, her subcutaneous treprostinil therapy was transitioned to IV in the perioperative period. Sildenafil therapy was also added to her regimen at this time. Her postoperative course was complicated by a thrombus in her native ascending aorta, which resolved on heparin therapy. She was discharged on sildenafil, bosentan, treprostinil, and supplemental oxygen.

Table 2. Cardiac catheterization data for Patient AT.

Age	PAH-specific Tx	Condition	LAP mmHg	Qp L/min/m^2	Qp left lung	LPAP mmHg	PVRi left lung (WU/m^2)	Qp right lung	RPAP mmHg	PVRi right lung (WU/m^2)	PVRi total (WU/m^2)
8 months –after atrial stent	None	Intubated FiO_2 0.50	15	3.58	2.18	54	17.86	1.40	40	17.91	8.94
10 months	Bosentan, treprostinil oxygen	Intubated FiO_2 0.21	12	4.00	2.44	35	9.43	1.56	23	7.05	4.03
11 months	Bosentan, treprostinil oxygen	Intubated FiO_2 0.21	12	2.51	1.53	32	13.06	0.98	19	7.15	4.62
		FiO_2 1.0, iNO 40 ppm	12	3.38	2.06	28	7.76	1.32	15	2.28	1.76
15 months – post Glenn	Sildenafil, bosentan, treprostinil oxygen	FiO_2 0.21	14	1.54		19			19		3.25
		Post-coil collaterals, FiO_2 0.21	14	1.68		19			19		2.98

Left and right pulmonary blood flow are calculated based on a lung perfusion scan, which demonstrated 61% flow to left lung, 39% flow to right lung. PVRi (in WU/m^2) for each lung was then calculated using branch PAP distal to pulmonary band and relative flow. Total resistance was calculated using the formula: $1/R_{TOTAL} = 1/R_{Right} + 1/R_{Left}$. Using this calculation, the highest normal resistance of each lung (assuming normal blood flow distribution 45% left, 55% right) would be $R_{Right} = 5.45$ WU/m^2, $R_{Left} = 6.67$ WU/m^2, and $PVRi_{TOTAL} = 3$ WU/ m^2. Given that the left lung was relatively less protected by the pulmonary band (as evinced by differential blood flow on perfusion scan), the differential elevation in resistance in the left lung is not surprising. The comprehensive stage 2 repair included bilateral branch PA arterioplasty; thus, there was no residual pressure or flow differential in the branch pulmonary arteries.
LAP, mean left atrial pressure; LPAP, mean left pulmonary pressure; RPAP, mean right pulmonary pressure.

She presented five months later following her comprehensive stage 2 palliation with increasing head circumference and lower systemic saturations. Cardiac catheterization at that time demonstrated an elevated Glenn pressure (19 mmHg) with elevated atrial pressures (14 mmHg) and significant tricuspid valve regurgitation. In additional, one venovenous collateral was identified and coiled, and multiple aortopulmonary collaterals were embolized. Her PVRi was calculated as 3.25 WU/m^2 at the beginning of the catheterization and 2.98 WU/m^2 following intervention (Table 2), both within normal limits for a patient with Glenn physiology. She then underwent repair of her tricuspid valve with mild improvement in valve regurgitation. She was also started on carvedilol in the setting of moderate right ventricular systolic dysfunction. Her most recent echocardiogram demonstrated mildly diminished right ventricular systolic function.

Discussion

These cases demonstrate good short-term outcomes in patients with complex CHD treated aggressively with pulmonary vasodilators preoperatively, who had previously not been considered operative candidates owing to advanced PVD at initial presentation. While these results are encouraging, caution is warranted in applying this "treat and repair" strategy more broadly. Lung biopsies were not obtained in these patients at the time of operation; thus, the histologic status of their pulmonary vascular pathology is unknown. The long-term outcomes for these patients are not known, and there is possibly a risk of progression of underlying PVD. In particular, patients with elevated pulmonary venous/left atrial pressures associated with CHD often have mixed PAH with added post-capillary vascular disease, as was the case for both of our patients. The natural history of PVD associated with these complex lesions following surgical repair or palliation is unknown.

One case series from China is intriguing in assessing the long-term viability of a treat and repair strategy in patients with PH associated with CHD.[10] This group treated 49 patients with Eisenmenger physiology with advanced PH therapies—both those with simple shunt lesions (atrial and ventricular septal defects, PDA) and with transposition of the great arteries. They did not present cardiac catheterization data, but rather relied on an increase in systemic oxygen saturation (reflective of increased Qp:Qs) as a response to therapy before undertaking surgical correction. They report excellent outcomes with no reported deaths, even among the two patients in the series with advanced pulmonary vasculopathy (plexiform lesions) from lung biopsies taken at the time of surgical correction. Apart from this large case series, the treat and repair strategy for patients with PVD and CHD is reported in the literature as case reports.[11–16] Additionally, the treat and repair concept was comprehensively presented by Dimopoulos et al., who recently reviewed a series of case reports and outlined the principles of this strategy, suggesting it may be applied in select cases.[17] Importantly, these cases were patients with simple shunt lesions, while the cases presented here represent more complex congenital disease.

In implementing this treatment strategy, it is critical that these high-risk patients be cared for in a center with advanced pediatric PH services, including coordinated congenital cardiac surgery, cardiology, critical care, and ancillary services. Myriad factors will put these patients at particular risk for progression of PVD, including the size and type of defect, the degree of obstruction to pulmonary venous flow or left atrial hypertension, delayed referral, or the presence of associated syndromes (particularly Down syndrome).[18] Given the heterogeneity of complex cardiac lesions and associated defects, it is unlikely that a single set of guidelines will ever be comprehensive enough to include all clinical scenarios. However, successful treatment of these patients involves several critical aspects including normalization of PVR prior to surgical correction and aggressive surgical or procedural intervention on residual lesions. Importantly, the timing between aggressive medical therapy and surgical intervention was as brief as possible, once the patient's hemodynamics were favorable. Notably, we feel that these cases highlight the additive value of repeated cardiac catheterization in addition to other non-invasive modalities. Finally, for patients with uncorrected CHD lesions, it is evident that lowering PVR in the absence of a fixed anatomic obstruction to pulmonary blood flow will lead to elevation of Qp:Qs, which not only increases acute metabolic demand but also exposes the pulmonary vasculature to the injurious effects of increased flow.[19] Here, the PH and congenital cardiac surgical teams must be nimble in their management to optimize outcomes.

In addition to appropriate patient selection for this treat and repair strategy, another vexing clinical question is the ongoing management of specific PH therapies postoperatively. In our first case, practical considerations – the family's impending move to Mexico – necessarily impacted clinical decision-making in the timing of discontinuing therapies. Even in this setting, therapies were stepped down with great caution and repeated catheterization evaluations; additionally, the patient will remain on some pulmonary vasodilator therapy (sildenafil and bosentan) indefinitely. The timing of removing therapies, or the necessity of removing them at all, remains an important unanswered clinical question.

In conclusion, patients with advanced PVD associated with CHD represent a challenging clinical cohort. The application of a novel treat and repair strategy for patients whose presenting hemodynamics initially preclude surgical correction or palliation is an appealing strategy for patients who otherwise would have no viable therapeutic options. Care for these patients must be undertaken with multidisciplinary input and great caution, including tempering patient and family expectations for long-term outcomes in the absence of established data. Despite these

cautionary statements, the strategy of aggressive medical therapy with multiple drug classes followed by prompt surgical repair once hemodynamics are normalized represents an exciting frontier in advancing care for patients with PVD and PH.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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