Management of systemic to pulmonary shunts and elevated pulmonary vascular resistance

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In selected CHD patients with moderately elevated PVR, partial or complete shunt closure and use of targeted PAH therapy was associated with improved haemodynamics and WHO functional class
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Abstract

Background Repair of systemic to pulmonary shunts is timed to prevent the development of irreversible pulmonary vascular disease, including in patients with other factors contributing to pulmonary hypertension. This study assessed outcomes of an individualised strategy for managing patients with mild–moderately elevated pulmonary vascular resistance (PVR) deemed borderline eligible for repair.

Methods A retrospective chart review was conducted of patients with systemic to pulmonary shunts and baseline indexed PVR (PVRi) $\geqslant 3$ WU·m^2 treated at a single centre from 1 January 2005 to 30 September 2019. Data included demographics, World Health Organization functional class (WHO FC), medications and haemodynamic data at baseline and serial follow-up.

Results 30 patients (18 females) met criteria for inclusion. Median age at diagnosis of pulmonary arterial hypertension was 1.3 years (range 0.03–54 years) and at surgery was 4.1 years (range 0.73–56 years). Median follow-up time was 5.8 years (range 0.2–14.6 years) after repair. Most patients received at least one targeted pulmonary arterial therapy prior to repair and the majority (80%) underwent fenestrated shunt closure. There was a significant decrease in mean pulmonary arterial pressure (mPAP) ($p<0.01$), PVRi ($p=0.0001$) and PVR/systemic vascular resistance ($p<0.01$) between baseline and preoperative catheterisation and a decrease in PVRi ($p<0.005$), mPAP ($p=0.0001$) and pulmonary to systemic flow ratio ($p<0.03$) from baseline to most recent catheterisation. WHO FC improved from FC II–III at baseline to FC I post repair in most patients ($p<0.003$).

Conclusions In carefully selected patients with systemic to pulmonary shunts and elevated PVR considered borderline for operability, the use of preoperative targeted therapy in conjunction with fenestrated or partial closure of intracardiac shunts is associated with improvement in WHO FC and clinical outcomes.

Introduction

Group 1 pulmonary arterial hypertension (PAH) is a progressive disease with a generally poor prognosis, culminating in right ventricular failure if left untreated. PAH associated with congenital heart disease (APAH-CHD) can be subclassified into four categories: patients with bidirectional shunts and Eisenmenger physiology, patients with large left-to-right shunts (typically operable), inappropriate PAH with small defects (coincidental congenital heart disease) and postoperative PAH [1]. The prognosis for patients with APAH-CHD is variable depending on the subtype and underling physiology, wherein patients with postoperative PAH and inappropriate PAH with small defects have outcomes comparable to idiopathic

pulmonary arterial hypertension (IPAH) [2, 3]. The prognosis of patients who ultimately develop Eisenmenger physiology in comparison with other subgroups of APAH-CHD is not clear, with some studies demonstrating similar survival rates, possibly due to inclusion of complex shunts, and others demonstrating improved survival compared to IPAH [4, 5]. However, the treatment approach for patients with shunts and moderately elevated pulmonary vascular resistance (PVR) remains an ongoing dilemma. In the era of novel drug therapy for PAH, the ability to "pretreat" and optimise PVR is an area of great interest and controversy.

In patients with PAH and systemic to pulmonary shunts, timing of surgical repair is aimed at preventing irreversible damage to the pulmonary vascular bed and subsequent development of worsening of PAH. Unfortunately, the repair may not be carried out in an appropriate timeline owing to late diagnosis of congenital heart disease (CHD), poor follow-up or lack of access to medical care. Identifying a window of operability before irreversible pulmonary vascular changes occur is crucial. Patients with CHD who present with pulmonary vascular disease need a timely and comprehensive evaluation to determine their candidacy for surgery or transcatheter intervention [6].

In these patients, a "treat and repair" strategy has been adopted in some institutions for the management of patients with PAH and CHD with mixed support [7–13]. These patients may have other factors contributing to the development of pulmonary hypertension as well, including genetic syndromes, prematurity and lung disease [7]. In the current therapeutic era, patients with elevated PVR are sometimes treated with PAH-targeted therapy in an attempt to improve haemodynamics prior to undergoing repair of their cardiac defect, and therapy is continued with close monitoring following intervention.

While haemodynamic data cannot be used in isolation to determine operability, there have been various consensus guidelines for adults and children suggesting indexed PVR (PVRi) cut offs ranging from 3 to 8 WU·m^2 depending on the lesion, with significant variability in the recommendations for operability in the "grey zone" for patients with elevated PVR [1, 6, 7, 14, 15]. In some consensus guidelines, acute vasoreactivity testing (AVT) is mentioned as a tool used by some practitioners to determine operability, particularly in patients with borderline PVR. However, haemodynamic parameters for AVT in these patients have not been established and criteria do not exist for determining reversibility of PAH in this population using AVT [16].

To date, recommendations to determine operability are largely based on expert consensus opinion, because there are limited studies in adults and children that have looked at long-term outcomes in patients with elevated PVR who have been medically treated and subsequently undergo partial or complete repair of a congenital systemic to pulmonary shunt [8–11, 17–20]. Given the limited evidence describing outcomes in this subset of patients, we aimed to examine the outcomes after surgical and transcatheter shunt closure in patients with pulmonary vascular disease and CHD who were treated at a large single centre. We hypothesised that partial or total closure of shunts and use of targeted therapy in carefully selected patients with mild–moderately elevated PVRi halts progression of PAH and improves short-term and medium-term clinical outcomes.

Methods

Study subjects

The study cohort included patients with large intracardiac left-to-right shunts and elevated PVRi treated at Columbia University Irving Medical Center/New York Presbyterian Hospital from 1 January 2005 and 30 September 2019 with follow-up to 1 September 2022. Inclusion criteria included PVRi $\geqslant$3 WU·m^2 at baseline or PVR $\geqslant$2.3 WU on cardiac catheterisation prior to surgical and/or transcatheter correction of CHD [1]. Patients with univentricular hearts and complex CHD were excluded. Patients were also excluded if they had desaturations in room air suggesting established Eisenmenger physiology. As an institutional management protocol, patients who continued to have baseline desaturations at rest or exercise and evidence of right to left shunt despite targeted therapy or a PVR/systemic vascular resistance (SVR) ratio of >0.4 on repeat haemodynamic measurements following treatment were considered to have more advanced pulmonary vascular disease and Eisenmenger physiology and were not offered shunt closure. The study was approved by the Institutional Review Board of Columbia University Irving Medical Center (IRB-AAAK2059).

Study design and methods

A retrospective chart review was conducted of patients treated at Columbia University Irving Medical Center/New York Presbyterian Hospital from January 2005 to September 2019 with follow-up up to September 2022. The objective of this study was to examine the outcomes after surgical and transcatheter

shunt closure in patients with CHD-related pulmonary vascular disease treated at a large single centre. Data included baseline demographics, type of CHD, comorbid conditions, age at diagnosis of PAH, age at repair, postoperative follow-up time, biomarkers, echocardiography data, haemodynamic data, PAH medications and World Health Organization functional class (WHO FC) at baseline, prior to surgery and at most recent follow-up. These data are summarised in supplementary table S1, including detailed listing of the medications used before and after surgery. Patients were typically started on a single targeted PAH therapy, with the decision to start additional medications based on clinical expertise after assessing their response to monotherapy. Intravenous prostaglandins were used if insufficient response to oral therapy was noted based on repeat catheterisations or echocardiographic assessment at follow-up visits.

Haemodynamic measurements included right atrial pressure, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure, systemic arterial pressure and oxygen saturations in the superior vena cava, pulmonary artery and aorta. Acute vasodilator testing was performed for the majority of patients using inhaled nitric oxide (iNO) 80 ppm at the time of diagnosis or prior to repair. The decision to perform AVT was at the discretion of the treating physician and interventional cardiologist performing the catheterisation. Balloon occlusion of the patent ductus arteriosus (PDA) was performed in four out of eight patients prior to transcatheter closure based on provider preference for accurate estimation of PVR.

Analysis

Descriptive statistics were performed, including mean±SD and median (IQR) depending on the distribution of the data. Chi-square tests for independence were used to compare categorical variables at the different time points and Fischer's exact tests were used for variables with low incidence. P-values for continuous variables were obtained using Wilcoxon signed-rank analysis for paired data. The main outcome measures were WHO FC and number of pulmonary hypertension medications at each follow-up visit. Statistical analysis was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) with Data Analysis Toolpak add-in and Stata version 16.1 (StataCorp, College Station, TX, USA).

TABLE 1 Patient characteristics

Total patients (N)	30
Gender	
Male	12 (40)
Female	18 (60)
Ethnicity	
African American	9 (30)
Asian	3 (10)
Hispanic	3 (10)
Middle Eastern	1 (3)
South Asian	7 (23)
White	7 (23)
Diagnosis	
ASD	9 (30)
VSD	2 (7)
PDA	5 (19)
Multiple shunts	14 (47)
Comorbid conditions	
Prematurity	19 (63)
Bronchopulmonary dysplasia	16 (53)
Trisomy 21	6 (20)
Repair type	
Complete closure	6 (20)
Partial (fenestrated) closure	24 (80)
Method of repair	
Percutaneous closure	8 (30)
Surgical closure	22 (70)
Age at diagnosis of PAH (years)	1.3 (5.1, 0.03–54)
Age at surgery (years)	4.1 (7.7, 0.73–56)
Follow-up (years)	5.8 (0.2–14.6)

Data are presented as n (%) or median (IQR, range), unless otherwise stated. ASD: atrial septal defect; VSD: ventricular septal defect; PDA: patent ductus arteriosus; PAH: pulmonary arterial hypertension.

Results

A total of 30 patients (60% female) met inclusion criteria (table 1). Nine patients were diagnosed with atrial septal defect (ASD), two with ventricular septal defect (VSD), five with PDA, and 14 with multiple shunts. The median age at diagnosis of PAH was 1.3 years (range 0.03–54 years, IQR 5.1 years). The median age at intervention was 4.1 years (range 0.73–56 years, IQR 7.9 years). Five patients (17%) had trisomy 21 and 19 patients (67%) were born preterm, of whom 16 (84%) had a prior history of bronchopulmonary dysplasia. Of the premature patients, nine (47%) were born at <30 weeks' gestation. Patients aged <4 years old with ASDs were more likely to have comorbidities, including prematurity, chronic lung disease and/or trisomy 21 (supplementary table S1). Seven patients (23%) underwent successful PDA closure *via* cardiac catheterisation (supplementary table S2). Seven patients (23%) underwent complete (non-fenestrated) repair: three ASD repairs, three PDA closures and one VSD and PDA closure.

At baseline prior to any treatment, the majority of patients had WHO FC II or III symptoms, which improved prior to surgery to FC I or II. Most patients had WHO FC I symptoms at the time of most recent follow-up. As shown in figure 1, there was a significant change in distribution between the baseline period and time of most recent follow-up (p=0.003). Median baseline oxygen saturation was 93% (range 77–100%) pretreatment and improved to a median of 97% (range 84–100%) preoperatively and 98% (range 95–100%) at most recent follow-up. Ten patients (33%) were on supplemental oxygen at the time of PAH diagnosis, of whom two were on oxygen only overnight. This included nine patients who were premature infants with lung disease and an adult patient with bronchiectasis. The majority of patients were treated with PAH-targeted medications preoperatively (figure 2): 20 out of 23 patients (87%) who underwent surgery and six out of seven patients (86%) who underwent transcatheter PDA closure. The patients who were not on medications prior to repair had closure of the shunt shortly after catheterisation, with one patient undergoing transcatheter PDA closure and three surgical closure, with one additional patient who was not on medications owing to intolerance. At the time of most recent follow-up, 15 patients (50%) were no longer on PAH medications. There was a significant reduction in the number of medications from the preoperative period to time of most recent follow-up (p=0.04). The details of medical treatment including the medications used for each patient pre and post shunt closure are listed in supplementary table S1.

Seven patients (23%) received intravenous (*i.v.*) prostanoids as part of their therapy preoperatively, compared to only one on parenteral prostanoids, and three on oral prostacyclin agonists at most recent follow-up (p=0.05). The patients treated with prostanoids preoperatively had a significantly higher median PVRi before medication of 10 WU·m^2 (IQR 7.4–14 WU·m^2) compared to 6.2 WU·m^2 (IQR

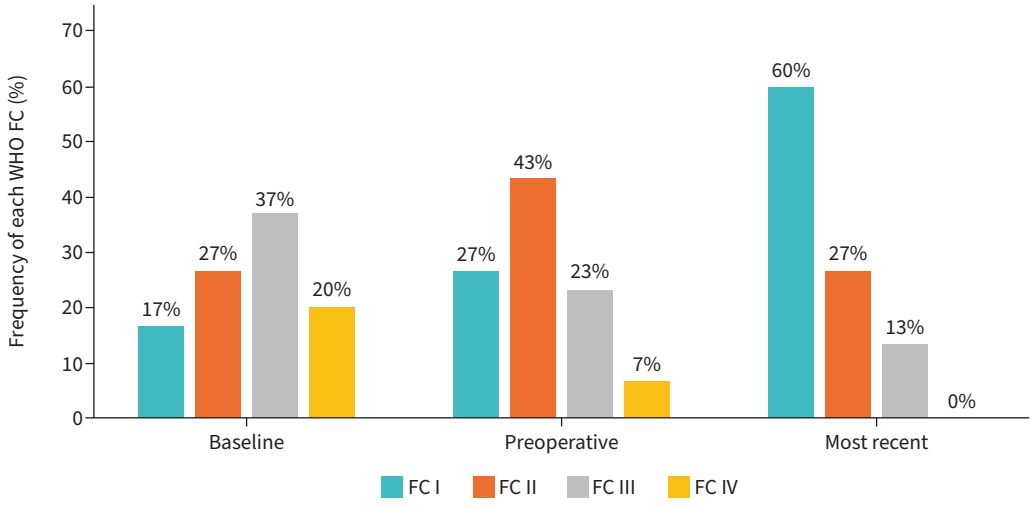

FIGURE 1 Prevalence of each World Health Organization functional class (WHO FC) at baseline (at time of diagnosis, prior to initiation of targeted pulmonary arterial hypertension medications), preoperatively and at most recent follow-up. At baseline, 19 of 30 patients (63%) had WHO FC II or III symptoms, which improved prior to surgery with 21 out of 30 patients (70%) having FC I or II symptoms. Most patients (18 out of 30, 60%) had WHO FC I symptoms at most recent follow-up. There was a significant change in distribution between baseline period and time of most recent follow-up (p=0.003).

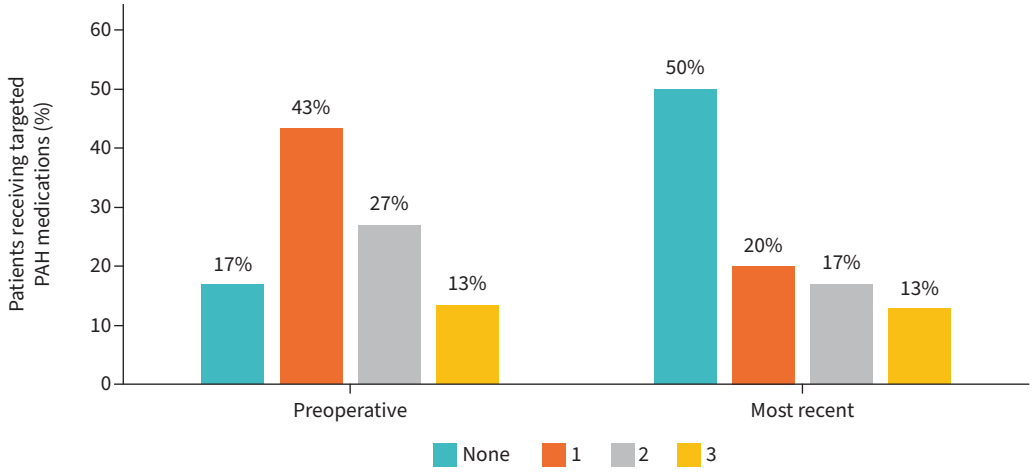

FIGURE 2 Percentage of the 30 patients receiving targeted pulmonary arterial hypertension (PAH) medications preoperatively (prior to surgical or transcatheter closure of systemic to pulmonary shunts) and at most recent follow-up. There was a significant change in the number of medications from the preoperative period to most recent follow-up (p=0.04). Half of patients (15 patients) were no longer on PAH-targeted medications at most recent follow-up.

4.1–8.6 WU·m^2) in those who were on oral or no therapy (p=0.03). PVRi improved to 3.2 WU·m^2 (IQR 2.9–6.2 WU·m^2) in the patients on *i.v* medications compared to 4.6 WU·m^2 (IQR 2.9–6.4 WU·m^2) in those on all oral therapies, with no significant difference in PVRi between these patients preoperatively (p=0.97)

TABLE 2 Cardiac catheterisation data

	Baseline	Preoperative	Postoperative	Most recent
Total patients (N)	30	20	12	20
RA pressure (mmHg)	6 (5–7)	7 (4–9)	6 (5–7)	5 (3–7)
Patients (n)	29	19		
p-value		p=0.84	p=0.11	p=0.09
mPAP (mmHg)	48 (38–59)	35 (27–51)	29 (24–40)	26 (22–31)
Patients (n)		19		
p-value		**p=0.008**	**p=0.002**[#]	**p=0.0001**[¶]
PCWP (mmHg)	9 (7–10)	9 (6–11)	9 (7–10)	8 (7–10)
Patients (n)	29	19		
p-value		p=0.91	p=0.43	p=0.13
PVRi (WU·m^2)	7.1 (4.8–10.0)	3.8 (2.9–6.7)	5.9 (4.6–7.3)	4.2 (3.1–6.7)
Patients (n)				
p-value		**p=0.0001**	**p=0.012**	**p=0.004**
PVR/SVR	0.5 (0.3–0.9)	0.3 (0.2–0.4)	0.4 (0.3–0.6)	0.3 (0.2–0.5)
Patients (n)	25	16		18
p-value		**p=0.0016**	**p=0.04**	p=0.18
Qp/Qs	1.4 (1.0–2.0)	1.9 (1.5–2.2)	1.0 (1.0–1.2)	1.0 (1.0–1.1)
Patients (n)	29			
p-value		**p=0.028**	**p=0.019**[#]	**p=0.028**[¶]
Cardiac index (L·min^{-1}·m^{-2})	3.6 (2.8–4.6)	3.3 (2.9–3.9)	3.5 (3.0–4.0)	3.6 (3.2–4.4)
Patients (n)	28	18		
p-value		p=0.59	p=0.76	p=0.44

Data are presented as median (IQR). The number of patients for whom we had recorded data for each measure are indicated if there were missing data at any time point. p-values listed indicate comparison of paired data (when available) to baseline. Bold text indicates statistically significant data. RA: right atrial; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVRi: indexed pulmonary vascular resistance; PVR/SVR: pulmonary vascular resistance to systemic vascular resistance ratio; Qp/Qs: pulmonary to systemic flow ratio. [#]: p<0.05, comparing haemodynamic values to preoperative values; [¶]: p<0.01, comparing haemodynamic values to preoperative values.

or at most recent follow-up (p=0.71). Those who were treated with *i.v.* prostanoids preoperatively were more likely to be on triple therapy at most recent follow-up (p=0.03). The patients receiving *i.v.* prostanoids were not more likely to be premature or have trisomy 21 compared to those who did not.

Cardiac catheterisation data (where available) at baseline, prior to surgery, following surgery and at time of most recent catheterisation are listed in table 2. There was an improvement in the mean pulmonary arterial pressure (mPAP), PVRi, pulmonary to systemic flow ratio (Qp/Qs) and PVR/SVR ratio between the baseline and preoperative period. There was also a significant improvement in the mPAP, PVRi and Qp/Qs from the baseline period to the time of most recent catheterisation. The PVRi trends over time for each patient are depicted in figure 3. With regards AVT, 23 out of the 30 patients (77%) included in the study had AVT performed at the time of diagnosis and 15 out of 20 patients (75%) who had follow-up catheterisations preoperatively had AVT performed at that time. Three patients (15%) met vasoreactivity criteria on cardiac catheterisation prior to surgery. One patient met Barst criteria, one patient met Sitbon criteria, and one patient met both Barst and Sitbon criteria for vasoreactivity (supplementary table S3).

There were six patients who did not have fenestrations at the time of repair. These patients had a median PVRi of 3.8 WU·m^2 (IQR 3.6–3.9 WU·m^2) at diagnosis. Half of these patients were on one targeted PAH medication preoperatively and the remainder were not started on medications but underwent shunt closure soon after catheterisation. None of these patients were on medications at most recent follow-up. The patients who had fenestrations at the time of closure had a significantly higher median PVRi of 7.8 WU·m^2 (IQR 6.4–10.5 WU·m^2) at diagnosis (p=0.00056) compared to those without fenestrations.

Discussion

This single institution retrospective study aimed to examine outcomes and management of patients with systemic to pulmonary shunts and elevated PVRi at time of presentation who had a combined medical-interventional/surgical approach to treatment. Patients were treated with PAH-targeted therapy prior to and/or following correction of systemic to pulmonary shunt. In this cohort of patients, the mean baseline PVRi at first cardiac catheterisation was 7.1 WU·m^2, with 10 of the 30 patients (33%) having a baseline PVRi >8 WU·m^2. PAH-targeted therapy led to an improvement in haemodynamics on cardiac catheterisation prior to surgery: no patients who underwent repeat catheterisation had a PVRi >8 WU·m^2. This improvement was sustained in the majority of patients until the time of most recent follow-up. Of note, prostanoids were used when the initial PVRi was very high but it dropped significantly on therapy to enable fenestrated repair and then continued to show improvement.

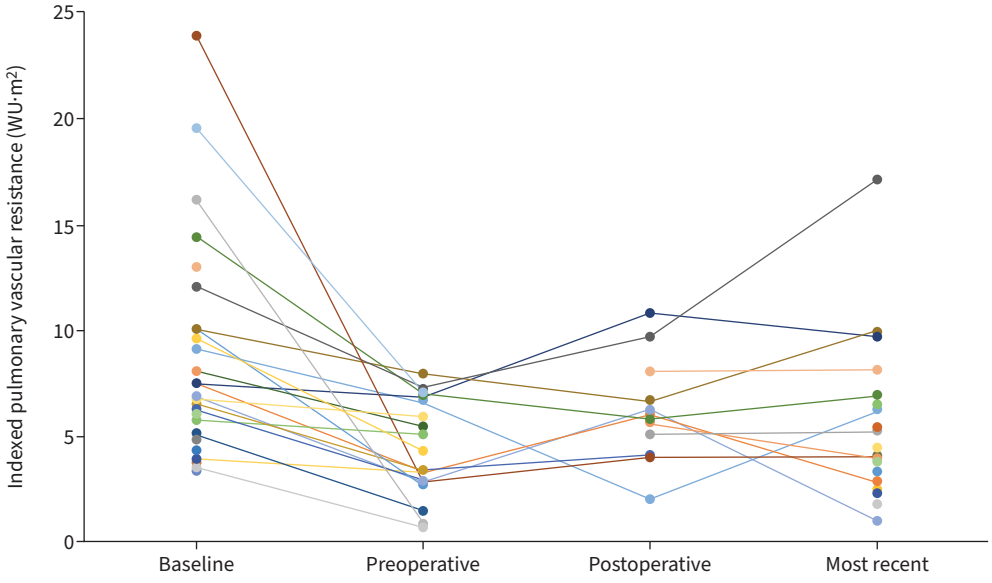

FIGURE 3 Indexed pulmonary vascular resistance (PVRi) calculated for each patient who underwent cardiac catheterisation, at the time of diagnosis, preoperatively, postoperatively and at the most recent catheterisation. There was a significant decrease in median PVRi from 7.1 WU·m^2 at diagnosis to 3.8 WU·m^2 preoperatively (p=0.0001) and 4.2 WU·m^2 at most recent follow-up (p=0.004).

Given that outcomes for patients with shunts that remain unrepaired and who develop Eisenmenger physiology are generally more favourable than outcomes in those who develop postoperative PAH, the decision to undergo shunt closure should not be taken lightly. However, the superior survival of patients with Eisenmenger physiology has been less clear in paediatrics, with some studies showing improved survival in children with Eisenmenger syndrome and others showing no difference [3, 21]. Although there have been PVR cut-off ranges suggested between 4–6 WU to proceed with repair, no general consensus has been established [1, 6, 7]. The 2015 American Heart Association (AHA) and American Thoracic Society (ATS) as well as the European Pediatric Pulmonary Vascular Disease Network guidelines suggest a PVRi of 6–8 WU·m^2 as an area of individualised consideration for operability [6, 7]. The AHA/ATS guidelines also include a cut-off of a PVR/SVR ratio <1/3 to be considered for operability [7]. The 6th World Symposium on Pulmonary Hypertension suggests a PVRi of 4 WU·m^2 (PVR 2.3 WU) as a cut-off for operability, with individualised consideration for patients with a PVRi between 4 and 8 WU·m^2 (PVR 2.3–4.6 WU) [1]. Patients with a PVRi >8 WU·m^2 (PVR >4.6 WU) are considered inoperable [1]. The 2022 European Society of Cardiology/European Respiratory Society guidelines now recommend considering shunt closure at a PVR of 3–5 WU, with a lower class of recommendation for closure (Ib) if PVR is >5 WU. They emphasise individualised decision-making for all borderline patients. The level of evidence for all these recommendations is C (based on expert opinion and/or small studies, retrospective studies or registries) [14].

There have been multiple case series and studies in the adult literature examining the feasibility of delayed closure of ASDs with elevated PVRi, with most patients doing well following surgery [8, 9, 12, 22–24]. The paediatric literature includes a broad spectrum of CHD in addition to the ASDs that are often the focus in adult studies [10, 11, 17–20]. Given these limited data, there remains debate about management in terms of interventions due to the risk of closure in the setting of elevated PVR potentially leading to worsening right heart failure, and there is a lack of studies exploring this in paediatric patients.

Our study suggests that selected patients with PAH and CHD with an elevated PVRi at time of presentation could be treated with targeted PAH therapy and re-evaluated for surgical candidacy. Some patients may require multiple medications to sufficiently decrease PVRi to allow for consideration of shunt closure. Such patients clinically and haemodynamically may improve with fenestrated or partial shunt closure, possibly because of reduced shear stress from shunt flow in the pulmonary arteries; however, they may require continued targeted therapy on follow-up. Our cohort had a high rate of shunt closure with creation of a fenestration to allow a small pop-off in the postoperative period in case of pulmonary hypertensive crises. Given the preoperative haemodynamic profiles of our patients, we had a very low threshold to leave or create a fenestration. If patients had a PVRi <5 WU·m^2 at the time of diagnosis and no other concerning features, we did not typically leave a fenestration. There were two patients with PVRi <5 WU·m^2 at diagnosis who did have residual fenestrations, one with a residual tiny defect that was not closed and the other with multiple shunts and lung disease who was felt to be at high risk of ongoing PAH at the time. The residual defects were small, as seen by the Qp/Qs on postoperative and most recent catheterisations, and likely not substantial contributors to any ongoing pulmonary hypertension. In addition, if a larger atrial septal fenestration were created, it would be possible to later close these defects *via* transcatheter methods if needed. Our institutional practice considerations for leaving a fenestration are listed in table 3.

Of importance, a subgroup of patients in our study were born preterm and may have had some degree of PVR attributable to chronic lung disease, which is known to improve over time. There may have been some component of the improvement of pulmonary hypertension in these patients that was due to the natural history of their comorbidities in addition to the effects of pulmonary vasodilator therapy and repair of CHD, and the contribution of each of these is sometimes not clear [25]. For example, when we looked at patients aged <4 years old with ASDs only, they all had associated comorbidities that could affect the development of PAH, *e.g.* prematurity, chronic lung disease or trisomy 21. We observed that this was less likely in older patients or those with other lesions. However, the same overall approach to treatment was taken in these patients in terms of medications used and careful consideration of time of closure regardless of age or shunt type.

TABLE 3 Institutional practice considerations for fenestration at time of shunt closure

Need for dual or triple pulmonary arterial hypertension therapy preoperatively
Intravenous prostanoids preoperatively
Right ventricular dysfunction
Indexed pulmonary vascular resistance >5 WU·m^2 at time of diagnosis

Overall, this cohort of patients did well following surgery and there was only one death noted at most recent follow-up, which was due to a non-cardiac cause. Although PVRi remained elevated in our cohort, it was improved from baseline and patients were on less medication compared to preoperatively. In addition, patients demonstrated improvement in WHO FC when comparing their most recent follow-up to baseline. This is in concordance with the findings of Liu *et al.* [11] of improved effort tolerance following surgery in patients with a mPAP of >50 mmHg with a VSD. Liu *et al.* [11] also found improvements in 6-min walk test (6MWT) distances. The majority of our patients were too young to perform a 6MWT prior to surgery or during the perioperative period. However, it is important to note that for patients who can complete a 6MWT, it is an objective and validated measure of cardiopulmonary function in adult patients with pulmonary hypertension and may be used to monitor patients over time [6, 26]. WHO FC is also not as accurate in younger patients in assessing functional status and there is ongoing study to create better tools for assessing children with PAH [27].

Only three of our patients who underwent cardiac catheterisation had documented robust acute vasoreactivity by the Barst or Sitbon criteria prior to undergoing surgery. This is not surprising, because patients with PAH and CHD tend to be less vasoreactive in comparison to patients with IPAH [4, 28]. Thomaz *et al.* [20] also found that non-responders still demonstrated improvement in haemodynamic parameters following surgery and targeted therapy. Thus, acute vasoreactivity may not be a prognostic indicator of a patient's candidacy for surgery, but rather potentially an indicator of long-term response to therapy. Further study is warranted to determine the role of AVT in this population.

Very careful patient selection incorporating clinical, echocardiographic and haemodynamic parameters is important in patients who have elevated PVR considered borderline operable by current PAH treatment guidelines. Patients with evidence of baseline right to left shunts and desaturation at rest or on exercise should continue targeted therapy and be treated as with Eisenmenger syndrome. Only those patients who show improved clinical and haemodynamic status after at least 6–12 months of targeted therapy should be considered for complete or fenestrated shunt closure. As seen in the current study, patients who underwent shunt closure showed improved WHO FC as well as demonstrated a decrease in the number of medications required to treat their PAH. We propose several criteria that should be considered in determining the need for fenestration at the time of shunt closure (table 3).

Our study had several limitations including its retrospective nature, small sample size, limited follow-up period for some patients, and lack of cardiopulmonary exercise testing and 6MWT data due to patient ages. One patient had died at the time of last follow-up due to a non-cardiac cause, and no patients required heart or lung transplant listing. While this is a reassuring initial finding, the follow-up period varied greatly between patients. In addition, more than half of the patients included in this study had a history of prematurity, some with chronic lung disease, which may have contributed to their pulmonary hypertension presentation. However, owing to the overall small sample size, we were unable to examine these patients separately in this study. Larger multicentric studies with longer periods of follow-up are needed to evaluate the long-term risks that closing systemic to pulmonary shunts may confer in patients with elevated PVRi.

In conclusion, in carefully selected patients with CHD and moderately elevated PVRi, the use of targeted PAH therapy in combination with partial or complete closure of shunts was associated with improvement in haemodynamic parameters and WHO FC. Prospective studies with a larger number of patients followed long term are needed to identify exactly which patients are best suited to a treat and repair strategy and to determine appropriate haemodynamic values as optimal for operability. Longer-term follow-up will help further the understanding of shunt closure in borderline PVR on later-term cardiopulmonary health. Given the relative paucity of patients seen at individual centres who develop PAH secondary to unrepaired CHD and the heterogeneity of the clinical features, multicentre collaboration will be crucial to adequately study outcomes and to establish evidence-based treatment guidelines.

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