Pulmonary hemodynamics before and after pediatric heart transplantation

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Abstract: BACKGROUND Pulmonary hypertension (PH) may limit the outcome of pediatric heart transplantation (pHTx). We evaluated pulmonary hemodynamics in children undergoing pHTx. METHODS Cross-sectional, single-center, observational study analyzing pulmonary hemodynamics in children undergoing pHTx. RESULTS Twenty-three children (female 15) underwent pHTx at median (IQR) age of 3.9 (.9-8.2) years with a time interval between first clinical signs and pHTx of 1.1 (.4-3.2) years. Indications for pHTx included cardiomyopathy (CMP) (n = 17, 74%), congenital heart disease (CHD) (n = 5, 22%), and intracardiac tumor (n = 1, 4%). Before pHTx, pulmonary hemodynamics included elevated pulmonary artery pressure (PAP) 26 (18.5-30) mmHg, pulmonary capillary wedge pressure (PCWP) 19 (14-21) mmHg, left ventricular enddiastolic pressure (LVEDP) 17 (13-22) mmHg. Transpulmonary pressure gradient (TPG) was 6.5 (3.5-10) mmHg and pulmonary vascular resistance (Rp) 2.65 WU*m^2 (1.87-3.19). After pHTx, at immediate evaluation 2 weeks after pHTx PAP decreased to 20.5 (17-24) mmHg, PCWP 14.5 (10.5-18) mmHg ($p < .05$), LVEDP 16 (12.5-18) mmHg, TPG 6.5 (4-12) mmHg, Rp 1.49 (1.08-2.74) WU*m^2 resp.at last invasive follow up 4.0 (1.4-6) years after pHTx, to PAP 19.5 (17-21) mmHg ($p < .05$), PCWP 13 (10.5-14.5) mmHg ($p < .05$), LVEDP 13 (10.5-14) mmHg, TPG 7 (5-9.5) mmHg, Rp 1.58 (1.38-2.19) WU*m^2 ($p < .05$). In CHD patients PAP increased ($p < .05$) after pHTx at immediate evaluation and decreased until last follow-up ($p < .05$), while in CMP patients there was a continuous decline of mean PAP values immediately after HTx ($p < .05$). CONCLUSIONS While PH before pHTx is frequent, after pHTx the normalization of PH starts immediately in CMP patients but is delayed in CHD patients.

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ORIGINAL ARTICLE

Pulmonary hemodynamics before and after pediatric heart transplantation

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Abstract

Background: Pulmonary hypertension (PH) may limit the outcome of pediatric heart transplantation (pHTx). We evaluated pulmonary hemodynamics in children undergoing pHTx.

Methods: Cross-sectional, single-center, observational study analyzing pulmonary hemodynamics in children undergoing pHTx.

Results: Twenty-three children (female 15) underwent pHTx at median (IQR) age of 3.9 (.9–8.2) years with a time interval between first clinical signs and pHTx of 1.1 (.4–3.2) years. Indications for pHTx included cardiomyopathy (CMP) ($n = 17$, 74%), congenital heart disease (CHD) ($n = 5$, 22%), and intracardiac tumor ($n = 1$, 4%). Before pHTx, pulmonary hemodynamics included elevated pulmonary artery pressure (PAP) 26 (18.5–30) mmHg, pulmonary capillary wedge pressure (PCWP) 19 (14–21) mmHg, left ventricular enddiastolic pressure (LVEDP) 17 (13–22) mmHg. Transpulmonary pressure gradient (TPG) was 6.5 (3.5–10) mmHg and pulmonary vascular resistance (Rp) 2.65 WU*m^2 (1.87–3.19). After pHTx, at immediate evaluation 2 weeks after pHTx PAP decreased to 20.5 (17–24) mmHg, PCWP 14.5 (10.5–18) mmHg ($p < .05$), LVEDP 16 (12.5–18) mmHg, TPG 6.5 (4–12) mmHg, Rp 1.49 (1.08–2.74) WU*m^2 resp.at last invasive follow up 4.0 (1.4–6) years after pHTx, to PAP 19.5 (17–21) mmHg ($p < .05$), PCWP 13 (10.5–14.5) mmHg ($p < .05$), LVEDP 13 (10.5–14) mmHg, TPG 7 (5–9.5) mmHg, Rp 1.58 (1.38–2.19) WU*m^2 ($p < .05$). In CHD patients PAP increased ($p < .05$) after pHTx at immediate evaluation and decreased until last follow-up ($p < .05$), while in CMP patients there was a continuous decline of mean PAP values immediately after HTx ($p < .05$).

Conclusions: While PH before pHTx is frequent, after pHTx the normalization of PH starts immediately in CMP patients but is delayed in CHD patients.

KEYWORDS
outcome, pediatric heart transplantation, pulmonary hypertension, pulmonary vascular resistance

1 | INTRODUCTION

Pediatric heart transplantation (pHTx) is an established ultima ratio therapy for end-stage heart failure in children. Being developed on the basis of experiences in adults undergoing heart transplantation, the outcome of children with pHTX continuously improved during the last decades.[1] Pediatric HTx represents around 14% of all heart transplantations, worldwide.[2] In Switzerland, between two and five pHTx are performed per year (*Annual Swisst transplant report 2013–2020*). In Europe, the most common indications for pHTx are cardiomyopathy (CMP) (most often dilated), and congenital heart disease (CHD).[3]

Chronic heart failure typically leads to pulmonary congestion resulting in elevated pulmonary arterial pressure (PAP) by modulating pulmonary vascular resistance (Rp). Initially, this change in pulmonary hemodynamics is reversible. But during long-term follow-up, pulmonary vascular remodeling can result in pulmonary hypertensive vascular disease (PHVD) and fixed pulmonary arterial hypertension (PH), which may limit the feasibility and outcome of pHTX.[4]

Following the 2018 World Symposium on Pulmonary Hypertension in Nice, the European Pediatric Pulmonary Vascular Disease Network, endorsed by the International Society for Heart and Lung Transplantation (ISHLT), defines pulmonary hypertension as a mean PAP higher than 20 mmHg in children older than 3 months of age.[5,6] A more precise specification of pulmonary hemodynamics for PH includes pulmonary capillary wedge pressure (PCWP), filling pressure, and calculation of Rp by the Fick principle as well as testing pulmonary vascular responsiveness by using oxygen and/or inhaled nitric oxide (iNO).[6] Although pHTx listing practices in respect of pulmonary hemodynamics may vary considerably within the international field, there seems to be a consensus that fixed pulmonary hypertensive vascular disease (PHVD) is considered an absolute contraindication for pHTx, beside differences in the definition of PH.[1,7,8] Therefore, avoiding fixed pulmonary hypertensive vascular disease (PHVD) as a contraindication for pHTx is mandatory. Unfortunately, some conditions culminating in end stage heart failure may cause pulmonary vascular remodeling and (at least transient) elevation of pulmonary artery pressure. In any case, PH and elevated Rp may be an additional burden for the right ventricle and might limit the right ventricular function of the donor heart transplant immediately after pHTx.[9] Still existing data on fixed PH is conflicting, as studies including patients with high pre-transplant Rp (>6 Wood units*m^2) did not show significantly worse survival, higher frequency of graft rejection or graft right ventricular failure after pHTx, but in some cases a temporary need of extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD).[10]

To improve risk stratification, it would be worthwhile to better understand hemodynamic differences between the two major groups of pediatric patients with *CMP* and *CHD* undergoing pHTx at end stage heart failure. This would include knowledge in regards to their natural pulmonary hemodynamic course before pHTx as well as afterward, where a decline of PH may be expected. Recently, a study demonstrated that *CHD* patients with single ventricle physiology tend to show delayed post pHTX normalization of pulmonary hemodynamics.[11] Therefore, knowledge of pulmonary hemodynamics in children undergoing pHTx is important for better predicting the acute perioperative course including the need for PH ventilation strategies and/or iNO, or ECMO. Additionally, long-term remodeling processes of pulmonary vascular structures with normalization of formerly elevated Rp will be of significance during long-term follow-up.

In this study, we aim to describe precisely pulmonary hemodynamics before and after pHTx in our heart transplantation population. Furthermore, we looked for factors before pHTx predicting the risk for adverse events after pHTx influencing the postoperative intensive care management.

2 | PATIENTS AND METHODS

2.1 | Study design

This single-center, cross sectional, long-term observational study analyses the data of all consecutive patients undergoing pHTx at our institution from 2005 to 2019. Data were taken from patient's medical records, available on paper or on digital format. Hemodynamic data were retrieved from cardiac catheter protocols for further analysis.

The study obtained approval by the Cantonal Ethical Committee of Zurich (BASEC-No. 2020-00567).

2.2 | Patients

We included all consecutive patients undergoing orthotopic heart transplantation at our center under 18 years of age between January 2005 and December 2019 (15 years). Additionally, we included patients transplanted at an external institution, if medical care before and after pHTx took place in our center. Informed consent had to be available in all included patients.

We excluded all patients being listed for pHTx, but died before pHTx, or no informed consent was available. We did not exclude patients waiting for pHTx on ECMO or VAD.

Data acquisition comprises the time between being listed for pHTx (including relevant medical variables before pHTx) until the last invasive hemodynamic re-asssessment follow-up after pHTx. Patients' study endpoint was defined as a transition to adult cardiology, age of >18 years, death, or reaching follow-up study endpoint of July 1, 2020.

2.3 | Medical variables

After patients' study inclusion, we analyzed anthropometric, medical, echocardiographic, hemodynamic, and follow up data before and after

pHTx. In order to describe the patient's clinical signs, an experienced senior physician (WK) graded the reports of first symptoms and symptoms at admission referring to Ross Heart Failure Classification.[12] According to the ISHLT registry, the diagnoses leading to pHTx were categorized in four groups: *CHD*, cardiomyopathy, re-transplantations, and others.[3] The *CHD* group includes patients with single ventricle physiology after failing Glenn or failing Fontan procedure.[13–15]

Echocardiographic data at first admission were analyzed. Two-dimensional echocardiographic measurements included left ventricular end diastolic and end systolic diameter, including the associated Z-scores, shortening fraction, ejection fraction, mitral regurgitation, systolic left ventricular (LV) function, right ventricular (RV) function, and systolic Doppler pressure gradient assessment using tricuspid valve regurgitation for estimation of right ventricular systolic pressure. The impairment of systolic LV and RV function was categorized as normal, mild, moderate, or severe.

Invasive hemodynamic data were assessed before and during follow-up after pHTx according to clinical routine. Hemodynamic assessment was part of cardiac catheterization under general anesthesia including invasive pressure measurement, blood oxygen measurement, further shunt determination as well as systemic and pulmonary vascular resistance calculation according to the Fick principle. Concerning PH, we evaluated mean PAP, mean PCWP, and mean aortic pressure and calculated Rp. Complete hemodynamic assessment included mean right atrial pressure, right ventricular systolic, early diastolic and enddiastolic right ventricular pressure, as well left ventricular systolic, early diastolic and enddiastolic ventricular pressure, systolic, diastolic and mean PAP, and systolic, diastolic and mean aortic pressure.

Pulmonary arterial hypertension was defined according to the 2019 updated consensus statement of the European Pediatric Pulmonary Vascular Disease Network, endorsed by Association for European Paediatric and Congenital Cardiology, European Society of Paediatric Radiology, and ISHLT.[6]

Intraoperative data of heart transplantation included extracorporeal circulation time, aortic clamping time, and lowest body temperature.

Regarding the immediate post-transplant care on *pediatric intensive care unit* (PICU), we focused on the acute postoperative management of PH including ventilation strategies and/or iNO therapy, postoperative mechanical ventilation time, and PICU length of stay. The long-term anti-pulmonary hypertensive medication was given, by clinical practice.

We also analyzed the results of right ventricular *endmyocardial biopsies* (EMB) before pHTx in respect to etiology and after pHTx for transplant rejection detection. The biopsies were taken during repetitive follow-up cardiac catheterizations using the ISHLT grading system of 1990, classifying the rejection in grades 0, 1A, 1B, 2, 3A, 3B, 4. These histological reports can be adapted to the 2004 ISHLT grading system ranging from 0R to 3R according to: grade 0 defined as grade 0R, grade 1A, 1B, and 2 defined as grade 1R, grade 3A defined grade 2R; and grade 3B and 4 defined as grade 3R.[16] For this analysis, we used the ISHLT grading system of 1990 and defined ISHLT <2 as no histological rejection, and ISHLT ≥2 as histological rejection.

2.4 | Statistical analysis

Data are presented as absolute numbers or percentages, or using median, interquartile or absolute range, or mean ± standard deviation, as appropriate. Statistical analysis was performed using descriptive and comparing statistical tests depending on the data distribution with Student's *t*-test, Mann–Whitney-*U*-test, Pearson correlation coefficient or Spearman's rank correlation coefficient. *p*-values lower than .05 were considered significant. SPSS Statistics version 27 was used for statistical analysis.

3 | RESULTS

3.1 | Patients

Between January 2005 and December 2019, 23 pediatric patients undergoing orthotopic heart transplantation (15 female) were analyzed. Twenty-two of these 23 pHTx were performed in our institution, while one patient underwent pHTx abroad in another tertiary care center. The median age (IQR) at first cardiac symptoms was .4 (0–4.2) years, at hospital admission .4 (.1–6.8) years respectively. Pediatric HTx was performed at an age of 3.9 (.9–8.2) years, with a body weight at pHTx of 12.5 (8–23.3) kg, body height 94 (68–126) cm, and body surface area .57 (.36–.9) m^2. The time interval between first cardiac symptoms and pHTx was 1.1 (.4–3.2) years with a time interval being listed for pHTx of 102 (50–257) days. The waiting time listed for pHTx was shorter for infants (<1 year) compared to older children (>1 year) [26 (13–38) days vs. 216 (94–311) days; $p < .012$].

3.2 | Cardiac diagnosis

End-stage heart failure due to *CMP* ($n = 17$, 74%) was the most frequent cardiac indication for pHTx, followed by *CHD* ($n = 5$, 22%), and *other* ($n = 1$, 4%) (Table 1). The latter was a neonate with an intracardiac fibroma obstructing the left ventricle and the main left bronchus.[17] There was no need for re-transplantation in our cohort during follow up. Further details on cardiac diagnosis are shown in Table 1.

The majority of patients with *CMP* ($n = 17$) suffered from dilated *CMP* ($n = 16$), only one of these patients had restrictive *CMP* ($n = 1$).

3.3 | Preoperative care

At hospital admission, *clinical signs of heart failure* determined by the Ross Classification[18] were severe for the patients with *CMP* with grade 4 ($n = 10$), or grade 3 ($n = 6$), resp. for the patients with CHD with grade 4 ($n = 4$), and grade 3 ($n = 1$).

Systolic LV myocardial function was severely resp. ($n = 15$, 88.2%) moderately reduced ($n = 1$, 6.3%), or preserved ($n = 1$, 6.3%). Systolic

TABLE 1 Cardiac diagnosis leading to heart transplantation.

	Patients ($n = 23$)	Age at pHTx (years)
Congenital heart disease	5	1.5 (1.4–6.9)
HLHS (Failing Glenn)	2	
HLHS (Failing Fontan)	2	
Borderline left ventricle	1	
Cardiomyopathy*	17	4.5 (.6–10.5)
Dilated	16	
Restrictive	1	
Re-transplantation	0	–
Other	1	.1
Intra-cardiac fibroma	1	

Abbreviations: HLHS, hypoplastic left heart syndrome; pHTX, pediatric heart transplantation.
*Dilated CMP were idiopathic ($n = 11$), genetic ($n = 2$), infectious due to Parvovirus B 19 chronic lymphocytic myocarditis ($n = 2$), or toxic (anthracycline-induced CMP, $n = 1$) after chemotherapy ($n = 1$). The patient with restrictive CMP had a myofibrillar myopathy.
Data for age are given as median (IQR).

RV function was assessed as normal ($n = 2$), mildly reduced ($n = 6$), or moderately reduced ($n = 4$), or undetermined ($n = 5$).

Left ventricular internal diameter (LVID) in the *CMP* patients was 46.4 ± 16.5 mm in diastole (LVIDd) and 40.3 ± 15.7 mm in systole (LVIDs). With Z-scores of 4.2 ± 2.3 for LVIDd and 5.8 ± 2.2 for LVIDs, the values were significantly higher than the physiological range adapted to height and weight. Shortening fraction (SF) and ejection fraction (EF) were reduced. The mean SF was 14% ± 10.3%, the mean EF 21% ± 13.2% in all *CMP* patients.

Twelve out of 23 (52.2%) analyzed patients needed a ventricular assist device (VAD) as bridge-to-transplant treatment.[19] Before pHTX, eight patients were treated in PICU for a median time of 43 (23–73) days.

Besides one patient with the left ventricular tumor and a patient with a borderline left ventricle (each $n = 1$), the majority ($n = 10$) of VAD treated patients suffered from a cardiomyopathy. Left ventricular assist device (LVAD) was most frequent implanted in these patients ($n = 8$, 66.7%), followed by LVAD that was later switched to biventricular assist device (BiVAD) ($n = 3$, 25%). Initial BiVAD treatment was established in one patient ($n = 1$, 8.3%). The median time between VAD implantation and pHTx was 98 (65–165) days.

Among the 11 implanted LVAD, there were 8 Berlin Heart® devices, 2 Heartware® devices, and 1 Thoratec PediVAS® device, while all 4 BiVAD were Berlin Heart® devices. Accordingly, a pulsatile flow pattern was preferred at our center as a bridging regimen. Within the VAD patients, baseline cardiac catheterization before pHTx took place before VAD implantation in seven cases and after VAD implantation in four cases. The patient with the intracardiac fibroma recieved a Berlin Heart® LVAD but did not underwent cardiac catheterization before pHTx.

Before pHTx, half of the patients (48%) were treated with phosphodiesterase three inhibitor, milrinone, and/or endothelin receptor antagonist bosentan, as pulmonary vasodilatator.

3.4 | Heart transplantation and postoperative care

In all cases, orthotopic pHTx was performed using cardiopulmonary bypass under moderate hypothermia with a lowest body core temperature of 30°C (28°–32°), with an extracorporeal circulation time of 201 (153–303) min, and aortic clamping time of 177 (102–245) min.

After pHTX, patients have been treated in the PICU for 11 (9–19) days, including a postoperative mechanical ventilation time of 2 days (1.75–5). Our standardized intensive care management included a perioperative immunosuppressive treatment protocol starting with methyl-prednisolone during surgery, followed by anti-human-T-lymphocyte-immunoglobulines after surgery, and by a long-term patient-individual immunosuppressive treatment with cyclosporine A, tacrolimus, everolimus, mycophenolate, or azathioprine adapted to the patient individual clinical course, side effects and compliance.

Longer ventilation time was not associated with longer time being listed for pHTx ($p = .53$), but *CHD* patients were longer ventilated compared to *CMP* patients (12 vs. 2 days, $p = .002$) after pHTx.

Acute postoperative anti-pulmonary hypertensive management included iNO in 16 of 20 (3 patients missing data) patients (80%) after pHTx, comparable in *CHD* and *CMP* patients.

Chronic postoperative anti-pulmonary hypertensive medication included Bosentan, Sildenafil, calcium receptor antagonists (e.g., Amlodipin) and oxygen. The duration of medical treatment using chronic anti-pulmonary hypertensive medication was 356 (12– 665) days after pHTX. In details, after pHTx Sildenafil was administered short term in 22% of the patients (less than 7 days) after weaning from iNO, long-term in 22% of the patients (more than 7 days) with a median (range) time of 205 days (143–294).

3.5 | Pulmonary hemodynamics

Table 2 shows the invasively determined pulmonary hemodynamics for the patients analyzed (1) *before*, (2) at *first time after pHTx*, and (3) at *last follow up after pHTX*.

The patient-individual course of pulmonary hemodynamics undergoing pHTX is depicted in Figure 1. Complete hemodynamic data was available for 17 of 23 patients.

Overall, there was a decline of mean PAP, PCWP, LVEDP, and Rp immediately after pHTx and until last follow up in children undergoing pHTX (Table 2). TPG remained stable before and after pHTx.

In the *CHD* group, mean PAP increased after pHTX (mean PAP before 21.4 ± 6.6 mmHg vs. after pHTx 31.6 ± 8.7 mmHg, $p < .05$), and decreased again until last follow up (mean PAP after pHTx 31.6 ± 8.7 vs. at last follow up 22.6 ± 4.7 mmHg, $p < .05$).

TABLE 2 Pulmonary hemodynamics in children undergoing pHTx.

Timepoint of evaluation	Before pHTx 138 (91–290) days	*p* value before vs. after	After pHTx 24 (15–28) days	*p* value after vs. last	Last follow-up 4.2 (1.8–6.1) years	*p* value before vs. last
Mean PAP [mmHg]	24.5 ± 7.0	.188	22.0 ± 7.7	**.036**	19.5 ± 3.9	**.010**
PCWP [mmHg]	16.9 ± 5.8	.024	14.1 ± 5.1	.132	12.8 ± 3.3	**.011**
LVEDP [mmHg]	17.1 ± 6.2	.240	15 ± 4.2	.066	12.5 ± 3.5	.139
Rp [WU*m2]	2.77 ± 1.61	.189	2.14 ± 1.73	.134	1.77 ± .68	**.031**
Mean TPG [mmHg]	6.6 ± 5.0	.340	8.9 ± 6.9	.371	7.1 ± 3.5	.203

Abbreviations: LVEDP, left ventricular enddiastolic pressure; PAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; Rp, pulmonary vascular resistance, TPG, traspulmonary gradient.
Data for age are given as median (IQR) resp. mean (±SD).

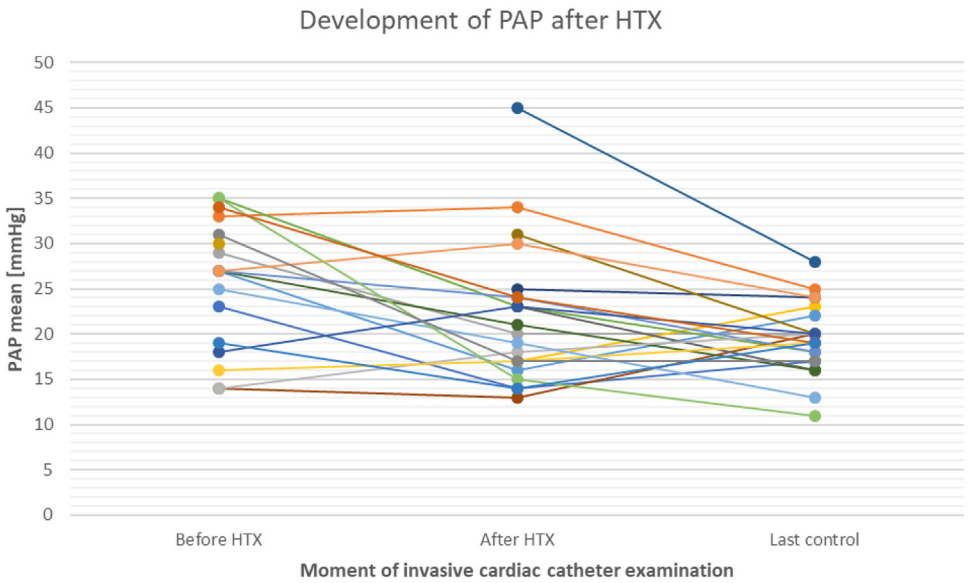

FIGURE 1 Patient-individual course of pulmonary hemodynamics in children undergoing pHTx.

In contrast, the *CMP* group showed a stepwise decline of mean PAP after pHTX and until last follow up (mean PAP before 25.1 ± 7.1 mmHg vs. at last follow up 18.3 ± 3.2 mmHg, $p < .01$).

Elevated mean PAP after pHTX correlated with prolonged hospitalization on PICU ($p < .01$). A significant correlation between time being listed for pHTx and elevated mean PAP after pHTX was not found ($p = .42$).

Patients with LVAD before pHTX had higher mean PAP before HTX (mean PAP with LVAD 27.4 ± 7.3 mmHg, $p < .05$), while after pHTX mean PAP, PCWP, LVEDP, and Rp normalized.

3.6 | Frequency of pulmonary hypertension undergoing pHTx

Table 3 provides an overview of the number of patients meeting the criteria for PH according to the 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension.[6]

3.7 | Long-term follow up

The median follow-up time lasted 4.0 (1.4–6) years. Three patients died, 21 days, 311 days, and 2860 days after pHTx. All of them were male and suffered from former dilated cardiomyopathy. One patient with autoimmune myocarditis died 3 weeks after acute failing pHTx due to multiorgan failure, the second patient during uneventful clinical follow up for unknown reason, and the third after transition to adult cardiology care. PH was not assessed as a cause for death.

We did not determine the development of severe coronary artery vasculopathy, or need of re-transplantation during follow up.

3.8 | Endomyocardial biopsies during follow up

During follow up after pHTX, a total of 189 EMB were taken. Overall, 38 of 189 were pathological with histological signs of rejection (defined as ISHLT ≥2), leading to a pathological rate of 20.5%, whereas 147 of

TABLE 3 Pulmonary hypertension in children before and after pHTx using different cutoff levels.

Mean PAP	Before pHTx	After pHTx	At last follow-up
>20 mmHg (CHD patients/CMP patients)	13 (1/12)	11 (5/6)	6 (3/2)
<20 mmHg (CHD patients/CMP patients)	9 (4/5)	11 (0/10)	16 (2/14)
>25 mmHg (CHD patients/CMP patients)	11 (1/10)	4 (3/1)	1 (1/0)
<25 mmHg (CHD patients/CMP patients)	11 (4/7)	18 (2/15)	21 (4/16)

Abbreviations: CHD, congenital heart disease; CMP, cardiomyopathy; pHTx, pediatric heart transplantation.
Absolute number of patients are illustrated in the table.

189 biopsies were non-pathological (defined as ISHLT <2), leading to a non-pathological rate of 79.5%. There were four missing values noted.

Within the first 3 years after pHTx, 129 biopsies were taken, 27 of them turned out to be pathological, leading to a pathological rate of 20.9%. Three years after pHTx 11 out of 56 biopsies were pathological, leading to a pathological rate of 19.6%.

Except for the one patient with acute pHTX failure, all patients had at least two cardiac catheterizations including standardized right ventricular EMB taken. Nine of 23 patients (39%) had no histological rejection (ISHLT <1). The maximum rate of pathological biopsies were 9 cardiac catheterizations with ISHLT ≥2 in one patient.

There was no correlation between pulmonary hemodynamics and histological rejection episodes.

4 | DISCUSSION

In this single center cohort study, we evaluated the invasively measured pulmonary hemodynamics during cardiac catheterizations of children undergoing pHTx over a 15 year time period (Table 1). Our main findings were elevated mean PAP and Rp before pHTx, both start to normalize after pHTx and during long-term follow up (Table 2). The early and late mortality after pHTx was not associated with PH. Nevertheless, the PH recovery is limited for the acute phase after pHTx in *CHD* patients after failing Glenn or Fontan physiology, compared to the larger group of patients with *CMP* in our cohort. While *CHD* patients show an increase in mean PAP and Rp first before normalization of PH parameters develops, *CMP* patients show a stepwise decline immediately after pHTX. The *CHD* patients need longer time to adopt to normal pulsatile pulmonary perfusion after pHTx (Table 2).

The clinical characteristics of our pediatric heart transplantation cohort depict typical features of a European pediatric heart transplantation cohort (Table 1).[2,21–24]

This analysis focuses on the pulmonary hemodynamics in children undergoing pHTx (Table 2). We observed a significant decline in mean PAP (19.5 ± 3.9 mmHg, $p = .010$) and Rp (1.77 ± .68 WU*m^2, $p = .031$) until the last cardiac catheterization during follow-up. Studies on this postoperative normalization have been available for over 25 years.[27]

Nevertheless, the positive aspect of left VAD especially in CMP patients improving outcome after pHTx has been shown.[28,29]

The pulmonary hemodynamics after pHTx differ between *CHD* and *CMP* patients. In contrast to *CMP* patients, failing Glenn or Fontan patients show an acute increase of PH immediately after pHTx, which normalizes during long-term follow up. Therefore, our data confirm this delay in normalization of hemodynamics for the failing Fontan and Glenn *CHD* patients compared to *CMP* patients, which has been described by Stephens et al.[11] We also assume several contributing factors related to the underlying disease, such as pulmonary vessel alterations that have been described in HLHS as well as diastolic dysfunction in chronically affected systemic ventricle.[30]

The decrease of PH after pHTx was more pronounced in patients with VAD support, which may be explained by a more severe PH in the patients with need for VAD support resp. reflects the higher rate of CHD patients with no VAD support and more delayed normalization of pulmonary hemodynamics.

While we also did not found a correlation between the pulmonary hemodynamics with the long-term outcome, we noted that *CHD* patients had a longer ventilation time than *CMP* patients ($p < .01$) as well as a prolonged hospitalization on PICU ($p < .01$) resembling a more complicative PICU course after pHTx. While the *CHD* patients showed more cases of PH at the last follow-up, all deaths occurred in the *CMP* group. This does not suggest a higher mortality in patients with PH and also does not support the already well described worse mortality in *CHD* patients.[31–35] Reference should be made to a recent work of Riggs et al. showing that *CHD* as a non-modifiable risk factor especially leads to a worse outcome, if associated with a modifiable risk factor such as renal or hepatic dysfunction.[36] In a recent systematic review and meta-analysis, Horacio Márquez-González et al. investigated the risk of death following heart transplantation in failing Fontan patients, reporting an immediate survival of 88%.[37] They described an association between mortality and chronic kidney disease as well, while they did not find association between mortality and other Fontan related pathologies such as protein-losing enteropathy, plastic bronchitis, or heart failure.[37]

The overall amelioration of PH after pHTx may be explained by the normal intracardiac enddiastolic ventricular pressures and filling pressure in a normal functioning heart transplant in combination with no preexisting fixed alterations of the Rp. This advantage may even allow to accept children for pHTx even at a higher defined cut off value for Rp or higher mean PAP pressure than recommended in the literature. Therefore, Daftari et al. were able to show successful pHTx in patients with Rp above 6 WU*m^2.[10] Facing such single center reports and the dynamic surgical evolution in pediatric heart transplantation, the sparse international guidelines remain vague.[38–41] According to our

experience, we also support an individual interdisciplinary approach to evaluate the indication for pHTx as well as we try to anticipate the temporary use of ECMO for supporting the right ventricular function and optimizing pulmonary hemodynamics by a detailed planning before pHTx.

Shaddy et al. showed a correlation between elevated mean PAP and complications in the postoperative course more than two decades ago.[42] This corresponds with our current findings concerning the association between PH and a prolonged ventilation time. Azeka et al. described further risk factors leading to a prolonged intubation time after pHTx including underlying diagnosis, renal dysfunction, inotropic support and mechanical ventilation, but did not find a correlation with death. Pietra et al. described nonwhite race, smaller left ventricular dimension, and myocarditis as early predictors for higher post transplantation mortality. Buddhe et al. showed increased mortality at one and three months after pHTx in children with higher TBG (>12 mmHG).[43] Further research in this regard would be desirable.

Histological rejection after pHTx is beside infections or secondary neoplastic immunosuppressive associated complications the most feared complication after pHTx. Therefore, in our center cardiac catheterization is performed on a clinical routine basis including pulmonary hemodynamics as well as right ventricular endomyocardial biopsy. The pulmonary hemodynamics were not correlated with histological rejection. This corresponds with the findings of Stephens at al.[11]

Even though more subtle techniques including echocardiography, emerging biomarkers, and cardiac magnetic resonance imaging gain importance, routine surveillance biopsies remain the gold standard in detecting rejection.[49] Nevertheless, routine surveillance biopsies after more than 2–3 years are controversial, as studies show a significant decrease in the positivity rate of biopsies.[50] We cannot confirm these findings as the positivity rate of surveillance biopsies before or after 3 years stayed stable in our cohort.

4.1 | Limitations

The retrospective study design and the limited number of patients result in a small clinical study group. Nevertheless, the time period of 15 years offered the possibility to document the amelioration of PH in most cases, although the use of iNO was within the follow up period, while chronic use of sildefanil was not standard of care in the first years of the study period. Hemodynamic assessment of PH may be limited in children during VAD and in case of veno-venous collaterals or fenestrated Fontan patients. Furthermore, the findings of a standardized study protocol is used for the treatment of patients after pHTx, but the number of confounders and covariates in regards to a small study group limited further statistical subgroup analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Request for data availability please contact the corresponding author.

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