DOI: 10.1002/pul2.12264

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Factors leading to supranormal cardiac index in pediatric pulmonary hypertension patients treated with parenteral prostanoid therapy

Kimberley G. Miles[1] | **Paul J. Critser**[1,2] | **Patrick D. Evers**[3] | **Michelle Cash**[1] | **Melissa Magness**[1] | **Elizabeth Geers**[1] | **Meredith O'Neil**[1] | **Zhiqian Gao**[1] | **Nicholas J. Ollberding**[2,4] | **Russel Hirsch**[1,2]

[1]The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

[2]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

[3]Division of Pediatric Cardiology, Oregon Health and Sciences University, Portland, Oregon, USA

[4]Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

Correspondence
Kimberley G. Miles, Cincinnati Children's Hospital Medical Center, 3333 Burnett Ave., MLC 2003, Cincinnati, OH 45229, USA.
Email: kimberley.miles@cchmc.org

Abstract

Parenteral prostanoid therapy (PPT) can result in supranormal cardiac index (SCI; >4 L/min/m^2) in pediatric pulmonary hypertension (PPH) patients. We evaluated the incidence, hemodynamic factors, and outcomes associated with SCI in PPH. This retrospective cohort study included 22 PPH patients on PPT from 2005 to 2020. Hemodynamic profiles were compared between the baseline and 3–6 month follow-up catheterization in the SCI and non-SCI cohorts. Cox regression analysis examined time to composite adverse outcome (CAO; Potts shunt, lung transplant, or death) controlling for initial disease severity. SCI developed in 17 (77%) patients, of whom 11 (65%) developed SCI within 6 months. The SCI cohort was characterized by significant augmentation of cardiac index (CI) and stroke volume (SV) as well as reductions in systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR). Conversely, the non-SCI cohort had unchanged SV despite a modest rise in CI as well as persistent vasoconstriction. After median follow-up of 4.3 years (range 0.2–13 years), non-SCI patients were at significantly increased risk for the CAO (5/5: three deaths, two Potts shunts) compared with SCI patients (5/17: two deaths, three lung transplants; adjusted hazard ratio 14.0 [95% confidence interval: 2.1–91.3], $p < 0.001$). A majority of PPH patients developed SCI within 6–12 months of starting PPT and demonstrated lower risk of adverse outcomes compared with non-SCI patients. These data suggest that change in SVR and SV after 3–6 months of PPT may be early markers of therapeutic response and prognosis.

KEYWORDS
cardiac index, outcomes, pediatric pulmonary hypertension, prostacyclin, systemic vascular resistance

INTRODUCTION

Pulmonary hypertension (PH) develops in the setting of diverse clinical pathologies and can lead to right ventricular failure and death.[1–5] With recent therapeutic advances, median survival for children with PH has significantly improved from approximately 10 months to over 5 years.[2,6,7] Right heart catheterization remains the gold standard for diagnosis of PH and risk stratification to determine medical management.[4,8,9] In patients with either high-risk profiles or low-risk profiles with inadequate response to first-line therapies, initiation of parenteral prostanoid therapy (PPT) is recommended.[4,8,9] PPT has revolutionized the management of PH since approval in the mid-1990s and has led to substantial improvements in long-term survival of adult[3,10–12] and pediatric[1,13,14] patients with severe PH.

Long-term outcome studies have demonstrated that increased cardiac output after starting PPT is associated with improved clinical outcomes and survival.[12,15] However, a proportion of patients treated with PPT can develop a supranormal cardiac index (SCI) of >4 L/min/m^2.[3,14,16–18] This was first described in a cohort of 12 adults treated with epoprostenol who developed an average cardiac index (CI) of 5.5 L/min/m^2, but were notably symptomatic with flushing, fatigue, and bloating.[17] As a result, their group incorporated goal-directed therapy with a targeted CI of 2.5–4 L/min/m^2 for titration of PPT with excellent outcomes in a cohort of 162 adults after 3 years of follow-up.[3]

Treatment goals for PPT remain poorly defined in pediatric PH (PPH) guidelines.[4,8] However, several recent publications have begun to identify dosing strategies associated with improved outcomes in this cohort. Tella et al. reported that initial clinical response of a reduction in mean pulmonary artery pressure (mPAP) >25% was found with treprostinil >80 ng/kg/min on average, though doses >100 ng/kg/min were not associated with further hemodynamic benefit.[18] Conversely, in a multi-center study evaluating PPT from 2000 to 2010, there was no upper limit of PPT dosage to predict long-term transplant-free survival.[19] Further, this study found that combination therapy with rapid titration of therapy and initiation early after PPH diagnosis was associated with better outcomes. In these and prior studies, SCI has been frequently noted in PPH patients on PPT.[3,14–16,18,19] However, the incidence and associations with outcomes have not been investigated in the pediatric population. In this single-center retrospective cohort study, we aimed to determine the incidence of, hemodynamic profiles associated with, and outcomes of SCI in a cohort of PPH patients managed with PPT.

METHODS

All children and young adults (<21 years of age) managed for PH at our institution and treated with PPT from July 2005 through July 2020 were identified. All patients with World Symposium on Pulmonary Hypertension (WSPH) group I (pulmonary arterial hypertension) or III (PH due to lung diseases and/or hypoxia) PH treated with intravenous (IV) or subcutaneous (SQ) PPT were included if patients underwent a complete baseline hemodynamic catheterization and at least one follow-up catheterization after initiation of PPT. No subjects were excluded from this study. In alignment with current definitions, PH was defined as patients >3 months of age with mPAP > 20 mmHg, indexed pulmonary vascular resistance (PVR) ≥ 3 WU·m^2, and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg.[4] Initiation of prostanoid therapy at our institution has followed the guideline recommendations for risk stratification and typically includes initiation of IV or SQ treprostinil in the cardiac intensive care unit after baseline hemodynamic evaluation in the catheterization laboratory.[4,20] Our current practice during the initial hospitalization is to aim for 10–25 ng/kg/min before discharge, followed by ~2 ng/kg/min increases weekly, as tolerated, to a goal of 35–50 ng/kg/min within the first 3–6 months. Follow-up catheterizations were obtained at 3–6 months to assess response to therapy and annually, or as clinically indicated, thereafter.[21] All patients were maintained on weight-appropriate phosphodiesterase 5 inhibitor (PDE5i) and endothelin receptor antagonist (ERA) therapy during the study period. This retrospective analysis was approved by the institutional review board of Cincinnati Children's Hospital Medical Center. Informed consent was waived.

Data collection

Demographic, medical history, and outcome data were collected through chart review. All catheterizations for hemodynamic assessment during prostanoid therapy were included. The baseline catheterization in this study was defined as the catheterization performed immediately before initiation of PPT. Acute vasoreactivity testing (AVT) was performed at the baseline catheterization, with positive testing based on the Sitbon criteria.[22] While these criteria have demonstrated survival benefit in only Group I PH, AVT is performed for all patients at our institution.

Catheterization data collection included: general data (sex, age, body surface area [BSA], sedation vs. general anesthesia, hemoglobin, heart rate [HR], pulmonary

vasodilators, presence of an atrial septal defect [ASD]), oxygen saturation data (mixed venous and systemic saturations), and hemodynamic data. The presence of an ASD was determined for each catheterization by assessing for shunting on the most recent echocardiogram (within 3 months). To allow for longitudinal analysis of and comparison between prostanoid therapies, oral treprostinil, and IV epoprostenol dosage were converted to IV treprostinil dosage. Oral treprostinil was converted as per manufacturer recommendations: parenteral treprostinil dose (ng/kg/min) = oral treprostinil total daily dose/(0.0072 × weight in kg).[23] Parenteral epoprostenol conversion was converted to parenteral treprostinil dose using the midpoint from typical clinical practice conversion rates of ~1.5–2x epoprostenol dose: parenteral treprostinil dose (ng/kg/min) = parenteral epoprostenol dose (ng/kg/min) × 1.75.[19,24,25] Hemodynamic data included: mean right atrial pressure (mRAP), RV systolic pressure (RVSP), RV end-diastolic pressure (RVEDP), systolic pulmonary artery pressure (SPAP), mPAP, PCWP a-wave, mean PCWP, systolic blood pressure (SBP), mean arterial pressure (MAP), systemic and pulmonary cardiac indices (Qs and Qp, respectively); systemic and pulmonary vascular resistances (SVR and PVR, respectively). CI was determined by thermodilution in the absence of a significant intracardiac shunt or by Fick if an intracardiac shunt was present. Stroke work, an estimate of ventricular performance representing the contractile capacity in the setting of afterload, was calculated.[26–28] Right ventricular stroke work (RVSW, $L \times mmHg/m^2$) was calculated as the product of RVSP and RV stroke volume (SV; Qp/HR) and left ventricular stroke work (LVSW, $L \times mmHg/m^2$) as the product of SBP and LV SV (Qs/HR).[26]

The presence of SCI, defined as $>4\ L/min/m^2$, was determined in each subject via evaluation of the CI reported from all catheterizations performed while treated with PPT.[3,17] Data on the composite adverse outcome (CAO), defined as death, lung transplantation, or Potts shunt surgery, and last clinic follow-up were collected through June 2021.

Statistical analysis

Patient demographic and clinical characteristics were described as median (interquartile range [IQR]) and *n* (%). The incidence proportion of SCI was calculated as the number of new cases within the follow-up period divided by the total number of patients at risk. A cumulative frequency curve graphed time to SCI in the SCI cohort. Differences in clinical history and baseline hemodynamic variables between children who developed SCI (SCI cohort) and children who did not develop SCI on PPT (non-SCI cohort) were tested using Fisher's exact tests and Mann–Whitney *U* tests, as appropriate.

To determine the hemodynamic profiles associated with SCI, we utilized[1] time-dependent analyses comparing hemodynamic data at the baseline and 3–6 month follow-up catheterization after initiation of PPT and[2] generalized least squares (GLS) regression models to identify clinical covariates associated with CI.

Change in hemodynamic data between the baseline and 3–6 month follow-up catheterization on PPT were compared within the SCI and non-SCI cohorts using the Wilcoxon signed rank test. Given the variability in timing of subsequent catheterizations due to differences in clinical progression, delays due to viral illnesses, and logistical challenges, time-dependent analyses were not possible at later follow-up time points with adequate sample sizes. The non-SCI cohort was defined by absence of SCI at any follow-up catheterization and thus affected by timing of CAOs which, in turn, impacted time on PPT in this cohort. Thus, to account for the confounding effect of shorter PPT duration on hemodynamics and outcomes in the non-SCI cohort, a sensitivity analysis was pursued to evaluate for hemodynamic changes associated with early development of SCI after regrouping of subjects by presence or absence of SCI specifically at the 3–6 month follow-up catheterization.

A GLS regression model fit to the repeated measures data was used to examine associations between selected clinical factors and CI during the first 3 years of follow-up. An initial model was fit utilizing covariates of interest chosen based on their clinical association with CI and included sedation level, hemoglobin, presence of an ASD, time on PPT, and absolute PPT dosage. Subsequently, hemodynamic variables of interest (SVR, PVR, mPAP, and mRAP) were added and respectively fit in separate models. Time on PPT and SVR were modeled using restricted cubic spline terms with five and three knots, respectively using the default knot placements in rms (version 6.2.0). A compound symmetry correlation structure of the form 1 + time | id was used to model the within-subject correlation for the repeated measures. Results for time-averaged models are presented and Wald χ^2 tests used for formal testing of model coefficients.

Lastly, Kaplan–Meier survival analysis evaluated overall survival, transplant-free survival, and freedom from CAO in our cohort. Differences in the freedom from CAO were compared between the non-SCI and SCI cohorts using the log-rank test. Cox proportional hazards regression was used to compare the risk of the CAO between the cohorts controlling for baseline disease severity (RVSP/SBP and CI, respectively).

All statistical analyses were performed with R (version 4.1.1) and IBM SPSS statistics 27.0.[29,30] p Values < 0.05 were deemed statistically significant.

RESULTS

The study cohort comprised 22 pediatric PH patients treated with PPT (median age at PH diagnosis 8.6 years [IQR 4.5, 12.5]; 14 females [64%]). Demographic and clinical characteristics are provided in Table 1. Subjects with history of congenital heart disease ($n = 7$, 32%) underwent complete repair by 6 months of age, except for residual atrial level shunting. Two (9%) subjects had genetic syndromes (Trisomy 21 and a deletion of 12q22q23.2) and 2 (9%) additional subjects had PH-specific genetic mutations (ACVRL1 and BMPR2). The majority of patients ($n = 16$, 72.7%) were classified as WSPH Group I PH. Of the six (27.3%) WSPH Group III patients included in this study, the majority ($n = 4$) had no significant residual lung disease at the time of their PH diagnosis but were classified as Group III based on their history of developmental lung disease.

Including baseline and follow-up catheterizations, PPH patients underwent a median 6 catheterizations (range 3–16) over a median period of 4.3 years (0.6, 7). PPT therapy was begun following the initial diagnostic catheterization in 14 (64%) patients and after median 6.0 months (IQR 2.9–16.0) in 8 (36%) patients due to inadequate hemodynamic improvement on dual therapy. There were no differences in outcomes (SCI and CAO) between patients who began PPT at PH diagnosis versus after inadequate improvement on dual therapy. Initiation of PPT promptly followed the baseline catheterization, the catheterization preceding initiation of PPT, in all patients (median 0 days [IQR 0, 0]). Balloon atrial septostomy (BAS) was performed in 14 (64%) patients: 8 at the initial diagnostic catheterization and the remainder at subsequent cardiac catheterizations (median 3.5 years from initial diagnostic catheterization, range 9 days to 16.9 years).

Development of SCI

The incidence proportion of subjects who developed SCI on PPT was 17/22 (77%). Of the subjects who developed SCI, 11 (65%) developed SCI within 6 months of PPT (Figure 1). In patients who developed SCI on PPT, the median dosage of PPT was 44 ng/kg/min (IQR 33–61.5) at the time of the first catheterization associated with SCI (median 4.4 months after initiation of PPT [IQR 3.3–12.9]). There were no statistically significant differences in baseline demographics or medical history between the SCI and non-SCI cohorts (Table 1). Baseline functional class and hemodynamic data for the cohorts are provided in Table 2. The non-SCI cohort had worse hemodynamics at baseline including higher PVR and trends towards lower CI and higher RV filling pressures. All patients met high-risk criteria at their baseline catheterization before initiation of PPT (Table 2).

Change in hemodynamics

Of the 22 patients included in this study, 18 (82%) patients had follow-up catheterizations at 3–6 months. These catheterizations were performed per protocol, except for one patient who did not demonstrate adequate clinical improvement on PPT and thus underwent early hemodynamic re-evaluation after 2 months of PPT initiation and ultimately a Potts shunt after 2.3 months. Of the four excluded subjects, three subjects represented the first experience of PPT management at our institution before standardization of hemodynamic re-evaluation and the fourth subject had a delay in catheterization due to a viral illness.

Compared with the baseline catheterization, CI significantly increased at 3–6 months after initiation of PPT in the SCI cohort (median 3.5 L/min/m^2 [IQR 2.9, 4.1] to 5.0 L/min/m^2 [IQR 4.0, 6.7], $p = 0.03$), but not in the non-SCI cohort at this sample size (median 2.2 L/min/m^2 [IQR 1.2, 4.3] to 3.2 L/min/m^2 [IQR 2.4, 3.3], $p = 0.72$), despite similar duration and dose of PPT (Table 3 and Figure 2).

Ventricular SV and stroke work increased in the SCI cohort, but not in the non-SCI cohort (Table 3 and Figure 2). In the SCI cohort, LVSV and LVSW significantly increased compared to baseline within the first 3–6 months ($p = 0.003$ and $p = 0.006$, respectively); however, SBP were similar at 3–6 months ($p = 0.46$). Similarly, while RVSW trended up ($p = 0.13$) and RVSV significantly increased within the first 3–6 months ($p = 0.003$), RVSP decreased ($p = 0.003$). In contrast, in the non-SCI cohort, biventricular stroke work, SV, and RVSP did not significantly change within the first 3–6 months. The SBP increased after PPT, but this did not reach statistical significance at this sample size (Table 3).

In the SCI cohort, PVR and SVR proportionally decreased at 3–6 months (Table 3 and Figure 2). Compared to the baseline catheterization, PVR and SVR decreased by ~50% within the first 3–6 months after PPT (median PVR 13.7 WU·m^2 [IQR 13.4, 20.1] vs. 6.7 WU·m^2 [IQR 4.8, 8.6], $p = 0.003$; median SVR 15.5 WU·m^2 [IQR 13.4, 20.1] vs. 9.5 [IQR 7.5, 14.2], $p = 0.036$) compared with baseline. Conversely, in the

TABLE 1 Patient characteristics.

	Overall $N = 22$	Non-SCI $N = 5$	SCI $N = 17$	p Value
Age (years)	8.6 [4.5, 12.5]	12.5 [10.3, 13.7]	5.4 [3.8, 11.7]	–
Sex (F)	14 (63.6%)	4 (80.0%)	10 (58.8%)	–
Race				–
Black	2 (9.1%)	–	2 (11.8%)	
White	20 (90.9%)	5 (100.0%)	15 (88.2%)	
WSPH classification of PH				–
WSPH Group I	16 (72.7%)	4 (80.0%)	12 (70.6%)	
WSPH Group III	6 (27.3%)	1 (20.0%)	5 (29.4%)	
Medical history[a]				
Prematurity (≤32 weeks)	4 (18.1%)	–	4 (28.6%)	–
Congenital diaphragmatic hernia	2 (9.1%)	1 (20.0%)	1 (5.9%)	
Bronchopulmonary dysplasia	5 (22.7%)	–	5 (29.4%)	–
Congenital heart disease	7 (31.8%)	–	7 (41.2%)	–
VSD	3 (13.6%)	–	3 (17.6%)	–
PDA	3 (13.6%)	–	3 (17.6%)	–
TOF	1 (4.5%)	–	1 (5.9%)	–
D-TGA	1 (4.5%)	–	1 (5.9%)	–
Porto-pulmonary hypertension	2 (9.1%)	–	2 (11.8%)	–
Trisomy 21	1 (4.5%)	–	1 (5.9%)	–
PAH genetic testing				–
ACVRL1 (HHT)	1 (4.5%)	–	1 (5.9%)	
AP3B1 (VUS)	1 (4.5%)	–	1 (5.9%)	
BMPR2	1 (4.5%)	1 (20.0%)	–	
Negative	8 (36.4%)	2 (40.0%)	6 (35.3%)	
Not completed	11 (50.0%)	2 (40.0%)	9 (52.9%)	
Atrial septal defects				
Congenital ASD	6 (27.3%)	3 (60.0%)	3 (21.4%)	–
Underwent BAS	14 (72.7%)	3 (60.0%)	11 (64.7%)	–
PPT therapy and catheterizations				
Follow-up (years)	4.3 [0.6, 7.0]	0.4 [0.2, 0.9]	4.3 [1.8, 7.7]	**0.021**
Catheterizations per subject	6 (3–16)	3 (3–6)	8 (3–16)	**0.024**
Duration of PPT therapy				
(Excluding oral therapy; years)	3.1 [0.6, 6.6]	0.4 [0.2, 0.9]	3.6 [1.8, 7.2]	**0.026**
Peak dose of PPT (ng/kg/min)	102 [65, 140]	78 [50, 100]	106 [70, 141]	–
Time to peak dose PPT (years)	1.5 [0.5, 5.5]	0.4 [0.2, 0.9]	1.68 [0.5, 5.8]	–

Note: Cohort characteristics ($n = 22$). Data presented as N (%), median (range), and median [IQR]. Statistics include Fisher's Exact test and Mann–Whitney U test; p-values < 0.05 considered significant and are bolded; nonsignificant p values indicated with a dash.

Abbreviations: ASD, atrial septal defect; BAS, balloon atrial septostomy; d-TGA, d-transposition of the great arteries; HHT, hereditary hemorrhagic telangiectasia; PDA, patent ductus arteriosus; PH, pulmonary hypertension; PPT, parenteral prostanoid therapy; TOF, tetralogy of Fallot; VSD, ventricular septal defect; VUS, variant of unknown significance; WHO, world health organization.

[a]One patient had history of a VSD and a PDA; one patient had history of CDH and BPD, and four patients had history of prematurity and BPD.

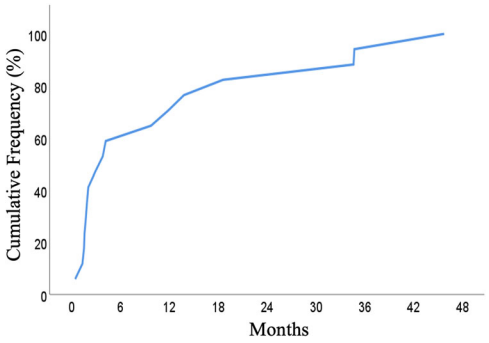

FIGURE 1 A cumulative frequency curve demonstrating that of the subjects who developed SCI, 11/17 (65%) developed this physiology by 6 months of receiving PPT and all by 4 years. PPT, parenteral prostanoid therapy; SCI, supranormal cardiac index.

non-SCI cohort, despite a 50% reduction in PVR, there was no change in SVR (Table 3).

After regrouping of subjects by presence ($n = 11$) or absence ($n = 7$) of SCI at the 3–6 month follow-up catheterization, a sensitivity analysis was performed comparing baseline and 3–6 month follow-up catheterization hemodynamics (Supporting Information: Table 1). Hemodynamics at the baseline catheterization were more comparable between these cohorts than the primary analysis. Patients who developed SCI by 3–6 months were characterized by significantly increased CI and SV as well as significantly decreased PVR and SVR. Patients who did not develop SCI at the 3–6 month follow-up catheterization were characterized by unchanged CI and SV. Further, SVR trended up in this

TABLE 2 Functional class, hemodynamics, and high-risk criteria met for PPT at baseline catheterization.

	Overall ***N* = 22**	**Non-SCI** ***N* = 5**	**SCI** ***N* = 17**	***p* Value**
Functional class				0.99
II	2 (9.1%)	–	2 (11.8%)	
III	15 (68.2%)	4 (80%)	11 (64.7%)	
IV	5 (22.7%)	1 (20%)	4 (23.5%)	
Hemodynamics				
Negative AVT	22 (100%)	5 (100%)	17 (100%)	0.99
mRAP (mmHg)	8 [6, 12]	12 [8, 13]	8 [6, 9]	0.19
mPAP (mmHg)	61 [53, 78]	76 [67, 78]	58 [52, 61]	0.066
mPCWP (mmHg)	12 [10, 14]	14 [13, 15]	11 [10, 13]	**0.048**
PVR (WU·m^2)	17.5 [9.3, 23.6]	33.9 [20.9, 66.1]	14.3 [7.8, 21.5]	**0.014**
SVR (WU·m^2)	17.2 [13.4, 23.7]	22.0 [17.6, 36.8]	16.2 [13.4, 20.1]	0.26
CI (L/min/m^2)	3.1 [2.1, 4.0]	1.9 [1.5, 3.0]	3.3 [2.6, 4.0]	0.13
RVSW (mmHg × mL/m^2)	2864 [2320, 3776]	2450 [1010, 2960]	2960 [2400, 4180]	0.16
LVSW (mmHg × mL/m^2)	2493 [1967, 4164]	1967 [1040, 3013]	3067 [2097, 4244]	0.09
High-risk indications for PPT				
CI < 2.5 L/min/m^2	6 (27.3%)	3 (60.0%)	3 (17.7%)	0.10
mRAP >10 mmHg	7 (31.8%)	3 (60.0%)	4 (23.5%)	0.23
mPAP/MAP $p > 0.75$	19 (86.4%)	5 (100%)	14 (82.4%)	0.54
PVR > 20 WU·m^2	9 (40.9%)	4 (80.0%)	5 (29.4%)	0.12
FC III/IV	20 (90.9%)	5 (100%)	15 (88.2%)	0.99

Note: Baseline functional class, hemodynamic characteristics, and high-risk criteria met for initiation of PPT, stratified by SCI during the follow-up period. Data presented as *N* (%) and median [IQR]. Statistics include Fisher's Exact test and Mann–Whitney *U* test; *p*-values < 0.05 considered significant and are bolded. High-risk indications for PPT as per Ivy et al.[20]

Abbreviations: AVT, acute vasoreactivity testing; CI, cardiac index; LVSW, left ventricular stroke work; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; RVSW, right ventricular stroke work; SVR, systemic vascular resistance.

TABLE 3 Hemodynamic change from baseline to 3–6 months after initiation of PPT.

	Non-SCI ($N = 4$)			SCI ($N = 14$)		
	Baseline	**3–6 months**	***p* Value**	**Baseline**	**3–6 months**	***p* Value**
Time (months)	–	2.9 [2.1, 4.4]	–	–	4.3 [3.3, 4.6][a]	–
Dose (ng/kg/min)	–	49 [43, 75]	–	–	41 [28, 57][a]	–
CI (L/min/m^2)	2.2 [1.2, 4.3]	3.2 [2.4, 3.3]	0.72	3.5 [2.9, 4.1]	5.0 [4.0, 6.7]	**0.027**
HR (bpm)	91 [88, 97]	103 [88, 125]	0.47	103 [73, 107]	99 [72, 120]	0.87
LVSW (mmHg × mL/m^2)	1801 [1040, 3014]	2705 [2187, 2885]	0.27	3687 [2120, 4327]	5001 [3892, 5976]	**0.003**
LVSV (mL/m^2)	28.9 [13.4, 44.4]	26.5 [21.3, 31.7]	0.72	39.9 [28.0, 55.8]	56.0 [38.2, 67.3]	**0.006**
SBP (mmHg)	73 [69, 79]	101 [85, 109]	0.07	79 [72, 90]	85 [77, 102]	0.46
RVSW (mmHg × mL/m^2)	1730 [933, 2705]	2152 [2013, 2772]	0.14	3343 [2321, 4379]	4168 [2067, 5582]	0.13
RVSV (mL/m^2)	26.4 [15.9, 33.9]	25.2 [19.3, 31.8]	0.67	39.9 [26.2, 55.9]	56.0 [38.2, 67.3]	**0.003**
RVSP (mmHg)	91 [89, 91]	92 [84, 110]	0.72	76 [71, 100]	64 [50, 94]	**0.008**
PVR (WU·m^2)	43.5 [19.5, 67.0]	22.3 [16.5, 32.5]	0.07	13.7 [7.8, 17.8]	6.7 [4.8, 8.6]	**0.003**
SVR (WU·m^2)	27.2 [12.6, 55.0]	22.1 [16.9, 28.6]	0.27	15.5 [13.4, 20.1]	9.5 [7.5, 14.2]	**0.036**
PVR/SVR	1.5 [1.0, 2.1]	1.1 [0.7, 1.6]	0.40	0.8 [0.7, 1.0]	0.7 [0.5, 0.9]	0.29
mRAP (mmHg)	10 [7, 13]	11 [7, 13]	0.71	8 [6, 9]	7 [5, 8]	0.06
mPAP (mmHg)	72 [67, 77]	64 [56, 87]	0.71	56 [50, 61]	49 [30, 66]	**0.002**
mPCWP (mmHg)	14 [12, 15]	12 [10, 13]	0.07	12 [12, 13]	12 [10, 14]	0.47
MAP (mmHg)	61 [58, 68]	69 [54, 86]	0.68	62 [56, 68]	56 [52, 73]	0.53

Note: Hemodynamic change from baseline to 3–6 months after initiation of PPT in the non-SCI and SCI cohorts who underwent repeat catheterization in this timeframe. Data presented as median [IQR]. Within group differences compared using the Wilcoxon signed rank test, p-values < 0.05 considered significant and are bolded.

Abbreviations: CI, cardiac index; HR, heart rate; LVSV, let ventricular stroke volume; LVSW, left ventricular stroke work; MAP, mean arterial pressure; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; RVSV, right ventricular stroke volume; RVSW, right ventricular stroke work; SBP, systolic blood pressure; SVR, systemic vascular resistance.

[a]Between group differences for time and dose compared using the Mann–Whitney U test ($p = 0.33$ and $p = 0.39$, respectively).

cohort with similar increased trend in MAP, while PVR and mPAP had only minimal decreases after initiation of PPT.

Factors associated with CI

To assess associations between CI and covariates, the GLS models demonstrated that sedation level, hemoglobin, presence of an ASD, and absolute PPT dosage were not associated with CI in either the initial or the four hemodynamic models (data not shown). CI was associated with PPH duration with a modest increase in CI up to 6 months post initiation of PPT which stabilized out to 3 years ($p = 0.05$; Figure 3a). In the hemodynamic models, mRAP was not significantly associated with CI ($p = 0.36$) at this sample size; however, plots of the predicted values suggested a possible inverse relationship between mRAP and CI (Figure 3b). There was no significant association between mPAP and CI ($p = 0.80$; data not shown). As expected, PVR ($p < 0.001$) and SVR ($p < 0.001$) were inversely associated with CI (Figure 3c,d).

CAO

The median follow-up time in the cohort was 4.3 years ([IQR 1.2, 9.1]; range 0.2–13 years). Ten (45.4%) subjects experienced a CAO while managed with PPT and weight-adjusted PDE5i and ERA.

The non-SCI subjects (5/5, 100%) were significantly more likely to develop CAOs compared with the SCI subjects (5/17, 30%; log-rank test $p < 0.001$; Figure 4). The non-SCI subjects continued to be at increased risk of developing the CAO compared with the SCI subjects

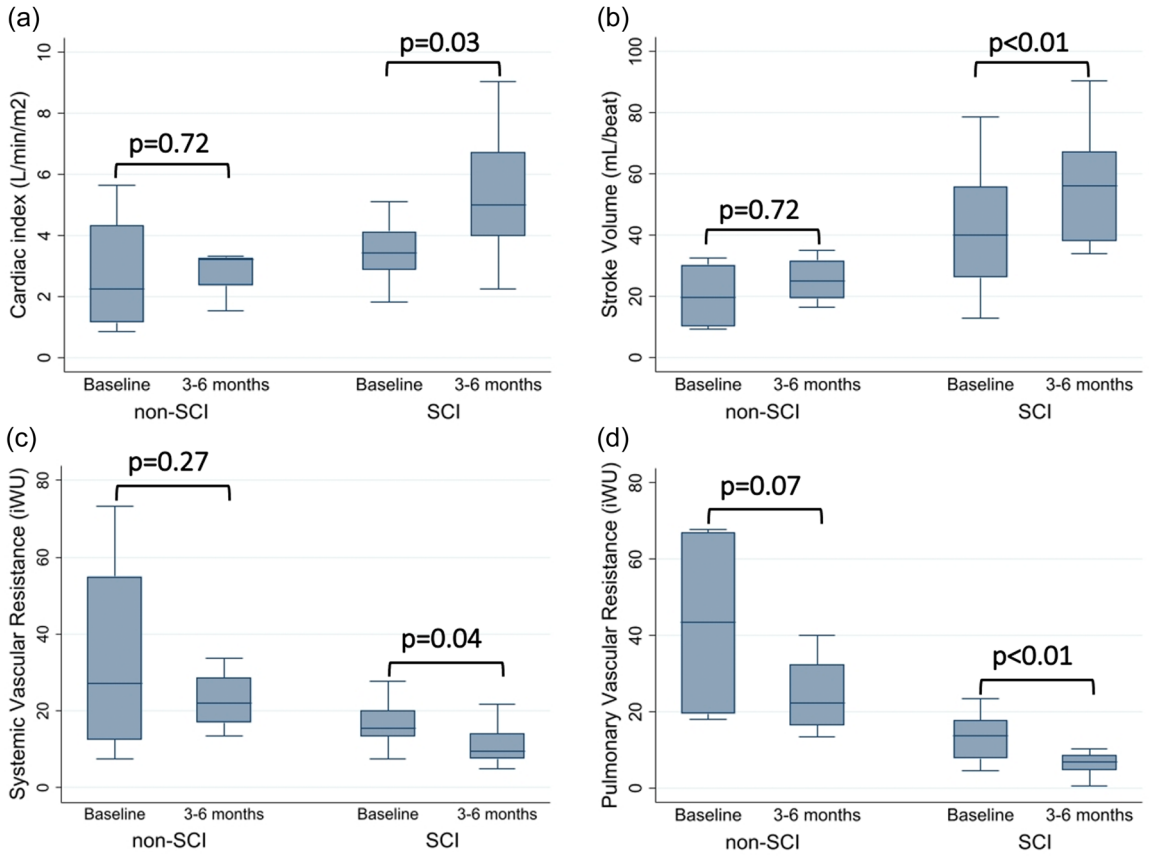

FIGURE 2 Box-and-Whisker plots demonstrating change in hemodynamics from baseline to 3–6 month follow-up catheterization after initiation of PPT (a–d). Patients who ultimately developed SCI demonstrated early differences in response to PPT, relative to the non-SCI cohort, including significant increases in cardiac index and stroke volume (a, b) and systemic vasodilation (c). PPT, parenteral prostanoid therapy; SCI, supranormal cardiac index.

when controlling for initial disease severity by either RVSP/SBP (adjusted hazard ratio [aHR] 14.0 [95% confidence interval (CI): 2.1–91.3]) or baseline CI (aHR 12.1 [95% CI: 2.5–57.2], $p = 0.002$). Further, to follow the sensitivity analysis, the non-SCI at 3–6 months cohort (5/7, 71.4%) remained significantly more likely to develop CAOs compared with the SCI at 3–6 months cohort (3/11, 27%; log-rank test $p = 0.04$; Supporting Information: Figure 1). Controlling for baseline RVSP/SBP and CI, respectively, the non-SCI at 3–6 months cohort similarly continued to be at increased risk of developing the CAO (aHR 4.9 [95% CI: 1.1–23.3], $p = 0.046$ and aHR 3.8 [95% CI: 0.9–16.2], $p = 0.057$, respectively).

The overall survival at 1, 3, and 5 years was 95.5%, 90.9%, and 81.3%, transplant-free survival was 86.4%, 76.2%, and 62.5%, and freedom from the CAO in this study were 77.0%, 63.2%, and 52.9%, respectively (Supporting Information: Figure 2).

In the SCI cohort, three (18%) subjects underwent a lung transplant and two (12%) subjects died. PPT was discontinued in the postoperative period in lung transplant patients. At the most recent clinic follow-up, the remaining 12 (70%) subjects were clinically stable on continued pulmonary vasodilator therapy. Of these, five remained on PPT while the remainder were transitioned to oral regimens given clinical improvement (triple therapy with selexipag, $n = 4$; dual therapy [PDE5i and ERA], $n = 2$; monotherapy [PDE5i], $n = 1$).

In the non-SCI cohort, all subjects had CAOs; two underwent a Potts shunt procedure due to inadequate clinical improvement and three died. The Potts shunt procedures were performed within ~2.5 and ~4 months of PH diagnosis and initiation of PPT. After the Potts shunt, PPT was weaned off within 6 months and both patients were alive at 3.5 and 4 years post-Potts shunt on dual therapy (PDE5i and ERA).

DISCUSSION

In this single-center retrospective cohort study, we aimed to determine the incidence of SCI in PPH patients managed with PPT as well as the hemodynamic profiles and outcomes associated with SCI. In our cohort, the

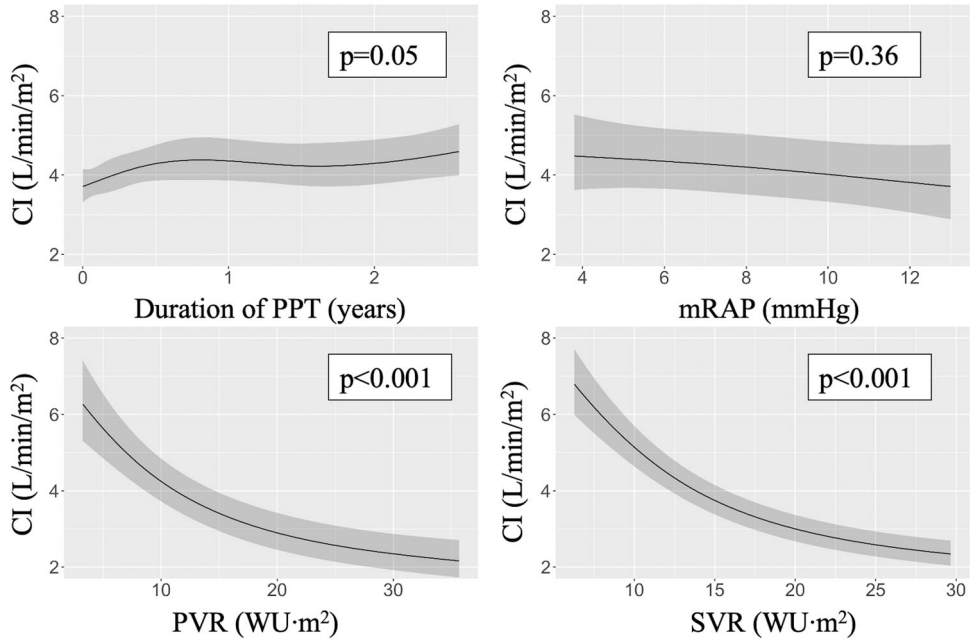

FIGURE 3 Time-averaged multivariate generalized regression plots. After adjustment for confounders, duration of PPT, and PPT dose, mRAP had a weakly inverse relationship with CI ($p = 0.34$). As expected, CI was strongly inversely associated with SVR and PVR ($p < 0.001$). Duration of PPT had a direct association with CI, particularly in the first 6 months of therapy ($p = 0.06$). Dose of PPT was not associated with CI (data not shown). CI, cardiac index; mRAP, mean right atrial pressure; PPT, parenteral prostanoid therapy; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; WU·m^2, indexed Wood units.

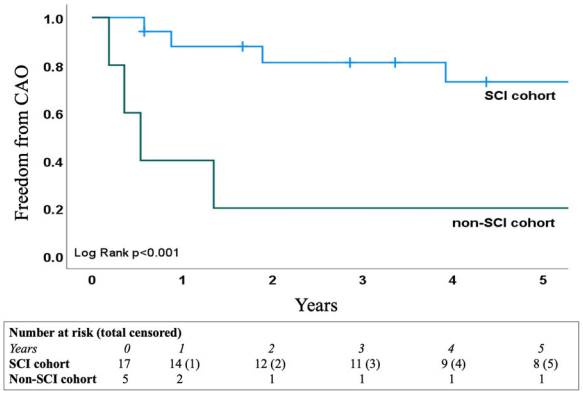

FIGURE 4 Comparison of freedom from CAOs, defined as Pott's shunt, lung transplant, or death, between the cohorts demonstrate that the non-SCI cohort had significantly worse outcomes (log rank test, $p < 0.001$). CAO, composite adverse outcome; SCI, supranormal cardiac index.

majority of PPH patients developed SCI within 6 months of PPT initiation. SCI was associated with SV augmentation and systemic vasodilation. Further, whether evaluated within the first 3–6 months after initiation of PPT or over the course of PPT therapy, our findings suggest that patients who do not augment their CI over 4 L/min/m^2 on PPT have increased risk of Potts shunt, lung transplantation, or death.

The development of a high cardiac output state (CI > 4 L/min/m^2) after starting PPT has been previously noted in adult and pediatric PH studies,[3,14–16] but this is the first study specifically describing the incidence and time course of SCI in the PPH population. In this cohort, SCI occurred in ~75% of patients by 12 months of therapy, consistent with prior reports observing maximal hemodynamic effects of PPT by 12–18 months of therapy.[3,13] In our study, neither PPT dose nor presence of an ASD were associated with CI. However, CI was associated with the duration of PPT. We postulate that a strategy of achieving the highest tolerated dose may be less important than the total time at the maximally tolerated dose to achieve a meaningful change in CI. Currently, PPT dose titration is based on side effect tolerance, but our data suggest that titration to attain SCI (>4 L/min/m^2) may be a reasonable treatment strategy.[16,19]

Survival in PH is strongly related to preservation of RV function.[2,12,31,32] In this cohort, increased SV after initiation of PPT may have been reflective of improved ventriculo-vascular coupling and ventricular performance, contributing to the improved survival in the SCI cohort.[33] Our findings are consistent with recent studies that change in SV after initiation of PPT, as opposed to CI, may be a better surrogate for ventricular performance.[4,34,35] In a study of 100 PPH patients, lowest tertile

cardiac MRI measurements of RV ejection fraction (<44%) and LVSV (<34 mL/m^2) were significantly associated with death and transplant-free survival.[31] In our cohort, this LVSV cut-off differentiated our non-SCI and SCI cohorts at 3–6 months: the median non-SCI subjects' SV was <34 mL/m^2 while the median SV were above this cut-off in the SCI subjects. More recently, Smith et al. demonstrated that RVSV at first follow-up catheterization (median 4.6 months [3.7, 7.8]) was the strongest hemodynamic prognostic variable for death and lung transplantation in 763 adult PH patients, whereas CI was not associated with prognosis.[35] In their study, an optimal cutoff of RVSV of 38 mL/m^2 was predictive for survival, a condition met by almost all of our SCI cohort subjects but none of their non-SCI counterparts.

Stroke work represents a ventricle's ability to generate a SV in the setting of afterload and thus can serve as an additional marker of RV performance. Increased RVSW after 3 months of PPT has been strongly correlated with change in CI and inversely associated with adverse outcomes.[15] However, RVSW must be interpreted with careful consideration of the patient's ventriculo-vascular coupling condition.[26] Increased RVSW in the setting of increased afterload is associated with increased pharmacotherapy requirements, deterioration in clinical status, and worse outcomes.[26,27] In our study, the highest left- and right-ventricular SW were found in the SCI cohort, predominantly due to changes in their SV over time. This supports our hypothesis that increased SV is an important and appropriate response to therapy.

The findings related to SVR trends after initiation of PPT in PPH patients are novel and have not, to our knowledge, been previously published.[3,14,36] After 3–6 months of PPT, the SCI cohort was characterized by significant systemic vasodilation after initiation of PPT. Conversely, the non-SCI cohort were differentiated by persistent systemic vasoconstriction with unchanged SVR and a rise in systemic blood pressure in the setting of a modest increase in CI in both the primary and sensitivity analyses. This physiology has been described elsewhere as sympathetic hyperactivity and upregulation of the renin-angiotensin-aldosterone system are associated with disease severity and mortality in PH.[37–40] In those studies, children with evidence of neurohormonal activation were noted to have increased SVR as extrapolated from reported mRAP, MAP, and CI. Akin to left heart failure, we hypothesize that right heart failure and impaired cardiac output in a subset of our cohort may be compensated for by neurohormonal activation and significant systemic vasoconstriction.[41,42] In the setting of afterload reduction from PPT, ventriculo-vascular coupling improves with resultant augmentation of RV efficiency and SV.[33] With increased cardiac output, neurohormonal upregulation may abate, contributing to the reduction in SVR. The systemic vasodilatory response to PPT may be a novel consideration in evaluating treatment response.

Within the field of PPH, pharmacotherapy management remains highly variable across institutions as clinical guidelines remain unclear on optimal dosing regimens, therapeutic goals, and the definition of treatment failure.[4,8,16,21] Though this study was not designed to evaluate a dose-effect response, our study found that the median PPT dose at the first catheterization with SCI was 44 ng/kg/min (IQR 31–67). In recent literature, Tella et al. found a treprostinil dose of ~80 mg/kg/min was associated with hemodynamic benefit, defined as mPAP reduction of 25%, while Douwes et al. reported that the time-averaged treprostinil dose of ~40 ng/kg/min strongly predicted transplant-free survival in the first year after PPT initiation.[18,19] These studies suggest clinically effective doses can be less than 100 ng/kg/min, but future studies would be necessary to evaluate if hemodynamic outcomes, including SCI, could guide PPT dosage goal within the first year of therapy. While up-titration of therapy as tolerated is standard practice, the literature remains unclear regarding continued hemodynamic benefit.[18,19] For example, Tella et al. found that while SCI was common in their cohort, this was achieved in similar proportions in patients on 50–100 ng/kg/min versus >100 ng/kg/min of treprostinil. Lastly, while SCI has been poorly tolerated symptomatically in the adult population, children do not develop similar symptoms of bloating, excessive flushing, and significant fatigue in our experience.[3,17]

Currently, patients who fail to respond to maximal medical therapy are referred for palliative Potts shunt or lung transplantation.[4,8,21] Recently, the Potts shunt was demonstrated to have similar survival, improved morbidity, and improved perioperative outcomes relative to lung transplants, enabling it to potentially serve as a promising pretransplant surgical option.[43,44] Timing of referral, however, is challenging as patients with significant RV dysfunction have been shown to tolerate the Potts shunt poorly.[43,44] Our findings lend support to the concept that early hemodynamic changes (such as SV augmentation and SVR reduction) may be useful indicators of positive (or negative) responders to therapy.[12,15,35] This may help with the timing of surgical intervention or lung transplant evaluation.

This study has several important limitations. First, despite the use of an institutional clinical protocol for serial hemodynamic evaluations on PPT, there was significant variability in time to repeat catheterization in our cohort. Reasons for this include differences in clinical progression, delays due to viral illnesses,

logistical challenges for families, and family preferences. This represents the real-world experience of treating patients with complex disease and limited our analysis to evaluate changes in hemodynamic profiles at 3–6 months after initiation of PPT. While this limits our ability to determine the hemodynamic changes associated with SCI, this limitation did not impact our SCI incidence estimates nor CAO analyses. Second, the SCI and non-SCI cohorts are difficult to directly compare. The duration of therapy in the non-SCI cohort was shorter due to the early occurrences of a CAO. This limited the potential response these patients may have had to PPT and prevented a complete comparison of hemodynamics between the cohorts. The sensitivity analysis we performed to address this found similar early hemodynamic changes and demonstrated association between non-SCI subjects and poor outcomes. Lastly, due to the low prevalence of severe pediatric PH, our single-center cohort was small and was not powered to detect modest group differences, modest associations, and interactions with time.

In conclusion, a majority of PPH patients developed SCI. In this small cohort, the development of SCI was characterized by SV augmentation and systemic vasodilation, was evident within 3–6 months of initiating PPT in a majority of patients, and was associated with better outcomes. Based on these findings, we hypothesize that change in SVR and SV may serve as important early indicators of improved RV performance and response to PPT. However, future studies are necessary to validate these findings in large multicenter cohorts.

AUTHOR CONTRIBUTIONS

Conceptualization: Kimberley G. Miles, Paul J. Critser, Michelle Cash, Melissa Magness, Meredith O'Neil, and Russel Hirsch. *Patient inclusion*: Kimberley G. Miles, Paul J. Critser, Patrick D. Evers, Michelle Cash, Melissa Magness, Elizabeth Geers, Meredith O'Neil, and Russel Hirsch. *Data curation*: Kimberley G. Miles, Zhiqian Gao, and Nicholas J. Ollberding. *Data analysis*: Kimberley G. Miles, Zhiqian Gao, and Nicholas J. Ollberding. *Supervision*: Paul J. Critser, Patrick D. Evers, and Russel Hirsch. *Writing—review and editing*: all authors. All authors read and approved the manuscript.

ACKNOWLEDGMENTS

No additional acknowledgments other than financial support from HIRC. This study was supported by the Heart Institute Research Core (HIRC) at Cincinnati Children's Hospital Medical Center.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This retrospective analysis was approved by the institutional review board of Cincinnati Children's Hospital Medical Center. Informed consent was waived.

ORCID

Kimberley G. Miles http://orcid.org/0000-0003-3093-4384

Patrick D. Evers http://orcid.org/0000-0002-9299-1926

REFERENCES

1. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation. 1999;99(9):1197–208.
2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, Levy PS, Pietra GG, Reid LM, Reeves JT, Rich S, Vreim CE, Williams GW, Wu M. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343–9.
3. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002;106(12):1477–82.
4. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger RMF. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916.
5. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, Kawut SM, Langleben D, Lumens J, Naeije R. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J. 2019;53(1):1801900.
6. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation. 2012;125(1):113–22.
7. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension service for children 2001-2006. Heart. 2008;95(4):312–7.
8. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, Budts W, D'Alto M, Gatzoulis MA, Hasan BS, Kozlik-Feldmann R, Kumar RK, Lammers AE, Latus H, Michel-Behnke I, Miera O, Morrell NW, Pieles G, Quandt D, Sallmon H, Schranz D, Tran-Lundmark K, Tulloh RMR, Warnecke G, Wåhlander H, Weber SC, Zartner P. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019;38(9):879–901.
9. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. JACC. 2015;65(18):1976–97.
10. Barst RJ. Survival in primary pulmonary hypertension with Long-Term continuous intravenous prostacyclin. Ann Intern Med. 1994;121(6):409.

11. Richter MJ, Harutyunova S, Bollmann T, Classen S, Gall H, Gerhardt MD F, Grimminger F, Grimminger J, Grünig E, Guth S, Halank M, Heine A, Hoeper MM, Klose H, Lange TJ, Meyer K, Neurohr C, Nickolaus K, Olsson KM, Opitz CF, Rosenkranz S, Seyfarth HJ, Warnke C, Wiedenroth C, Ghofrani HA, Ewert R. Long-term safety and outcome of intravenous treprostinil via an implanted pump in pulmonary hypertension. J Heart Lung Transplant. 2018;37(10):1235–44.
12. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau GE. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. JACC. 2002;40(4):780–88.
13. Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. Heart. 2007;93(6):739–43.
14. Yung D, Widlitz AC, Rosenzweig EB, Kerstein D, Maislin G, Barst RJ. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation. 2004;110(6):660–5.
15. Evers PD, Critser PJ, Cash M, Magness M, Hirsch R. Prognostic value of change in cardiac index after prostacyclin initiation in pediatric pulmonary hypertension. Pediatr Cardiol. 2021;42(1):116–22.
16. Oudiz RJ, Farber HW. Dosing considerations in the use of intravenous prostanoids in pulmonary arterial hypertension: an experience-based review. Am Heart J. 2009;157(4):625–35.
17. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. JACC. 1999;34(4):1184–7.
18. Tella JB, Kulik TJ, McSweeney JE, Sleeper LA, Lu M, Mullen MP. Prostanoids in pediatric pulmonary hypertension: clinical response, time-to-effect, and dose-response. Pulm Circ. 2020;10(4):1–10.
19. Douwes JM, Zijlstra WMH, Rosenzweig EB, Ploegstra MJ, Krishnan US, Haarman MG, Roofthooft MTR, Postmus D, Hillege HL, Ivy DD, Berger RMF. Parenteral prostanoids in pediatric pulmonary arterial hypertension: start early, dose high, combine. Ann Am Thorac Soc. 2022;19(2):227–37.
20. Ivy DD, Abman SH, Barst RJ, Berger RMF, Bonnet D, Fleming TR, Haworth SG, Raj JU, Rosenzweig EB, Schulze Neick I, Steinhorn RH, Beghetti M. Pediatric pulmonary hypertension. JACC. 2013;62(25 Suppl):D117–26.
21. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015;132(21):2037–99.
22. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RMF, Weintraub RG, Geiger R, Marx M, Jing ZC, Sondergaard L, Apitz C, Hager A, Szatmari A, Milanesi O, Saji T, Pulido T, Moll J, Michalak KW, Kawalec W, Zuk M, Fasnacht Boillat M, Olguntürk R, Kula S, Alehan D, Schulze-Neick I, Atz AM, Mallory GB, Austin ED, Moore DJ, Feinstein JA, Day RW, Yung D, Berger JT. Acute vasodilator response in pediatric pulmonary arterial hypertension. JACC. 2016;67(11):1312–23.
23. United Therapeutics Corp. Orenitram (treprostinil) [package insert]. Research Triangle Park; 2020.
24. Gomberg-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitz AC, Barst RJ. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med. 2005;172(12):1586–9.
25. Rubenfire M, McLaughlin VV, Allen RP, Elliott G, Park MH, Wade M, Schilz R. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. Chest. 2007;132(3):757–63.
26. Di Maria MV, Campbell KR, Burkett DA, Younoszai AK, Landeck BF, Mertens L, Ivy DD, Hunter KS, Friedberg MK. Parameters of right ventricular function reveal ventricular-vascular mismatch as determined by right ventricular stroke work versus pulmonary vascular resistance in children with pulmonary hypertension. J Am Soc Echocardiogr. 2020;33(2):218–25.
27. Di Maria MV, Younoszai AK, Mertens L, Landeck BF, Ivy DD, Hunter KS, Friedberg MK. RV stroke work in children with pulmonary arterial hypertension: estimation based on invasive haemodynamic assessment and correlation with outcomes. Heart. 2014;100(17):1342–7.
28. Yang W, Marsden AL, Ogawa MT, Sakarovitch C, Hall KK, Rabinovitch M, Feinstein JA. Right ventricular stroke work correlates with outcomes in pediatric pulmonary arterial hypertension. Pulm Circ. 2018;8(3):1–9.
29. Jr FEH. 2021. Regression modeling strategies: R package version 6.2-0. Available from: https://cran.r-project.org/package=rms
30. R Foundation for Statistical Computing. 2016. R: a language and environment for statistical computing [Internet]. Available from: https://www.R-project.org/
31. Moledina S, Pandya B, Bartsota M, Mortensen KH, McMillan M, Quyam S, Taylor AM, Haworth SG, Schulze-Neick I, Muthurangu V. Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6(3):407–14.
32. van Loon RLE, Roofthooft MTR, Delhaas T, van Osch-Gevers M, ten Harkel ADJ, Strengers JLM, Backx A, Hillege HL, Berger RMF. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol. 2010;106(1):117–24.
33. Vanderpool RR, Desai AA, Knapp SM, Simon MA, Abidov A, Yuan JXJ, Garcia JGN, Hansen LM, Knoper SR, Naeije R, Rischard FP. How prostacyclin therapy improves right ventricular function in pulmonary arterial hypertension. Eur Respir J. 2017;50(2):1700764.
34. Douwes JM, Roofthooft MTR, Bartelds B, Talsma MD, Hillege HL, Berger RMF. Pulsatile haemodynamic parameters are predictors of survival in paediatric pulmonary arterial hypertension. Int J Cardiol. 2013;168(2):1370–7.
35. Weatherald J, Boucly A, Chemla D, Savale L, Peng M, Jevnikar M, Jaïs X, Taniguchi Y, O'Connell C, Parent F, Sattler C, Hervé P, Simonneau G, Montani D, Humbert M, Adir Y, Sitbon O. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. Circulation. 2018;137(7):693–704.

36. Siehr SL, Dunbar Ivy D, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: long-term hemodynamics. J Heart Lung Transplant. 2013;32(5):546–52.
37. Ciarka A, Doan V, Velez-Roa S, Naeije R, van de Borne P. Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2010;181(11):1269–75.
38. de Man FS, Tu L, Handoko ML, Rain S, Ruiter G, François C, Schalij I, Dorfmüller P, Simonneau G, Fadel E, Perros F, Boonstra A, Postmus PE, van der Velden J, Vonk-Noordegraaf A, Humbert M, Eddahibi S, Guignabert C. Dysregulated renin-angiotensin-aldosterone system contributes to pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012;186(8):780–9.
39. Mercurio V, Pellegrino T, Bosso G, Campi G, Parrella P, Piscopo V, Tocchetti CG, Hassoun PM, Petretta M, Cuocolo A, Bonaduce D. Cardiac sympathetic dysfunction in pulmonary arterial hypertension: lesson from left-sided heart failure. Pulm Circ. 2019;9(3):2045894019868620.
40. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation. 2000;102(8):865–70.
41. Peters EL, Bogaard HJ, Vonk Noordegraaf A, de Man FS. Neurohormonal modulation in pulmonary arterial hypertension. Eur Respir J. 2021;58(4):2004633.
42. Maron BA, Leopold JA. Emerging concepts in the molecular basis of pulmonary arterial hypertension: part II: neurohormonal signaling contributes to the pulmonary vascular and right ventricular pathophenotype of pulmonary arterial hypertension. Circulation. 2015;131(23):2079–91.
43. Grady RM, Canter MW, Wan F, Shmalts AA, Coleman RD, Beghetti M, Berger RMF, del Cerro Marin MJ, Fletcher SE, Hirsch R, Humpl T, Ivy DD, Kirkpatrick EC, Kulik TJ, Levy M, Moledina S, Yung D, Eghtesady P, Bonnet D, Magness SM, Anderson VR, Mullen MM, Gorbachevsky SV, Zaets SB, Haarman MG, Szezepanski I. Pulmonary-to-systemic arterial shunt to treat children with severe pulmonary hypertension. JACC. 2021;78(5):468–77.
44. Lancaster TS, Shahanavaz S, Balzer DT, Sweet SC, Grady RM, Eghtesady P. Midterm outcomes of the Potts shunt for pediatric pulmonary hypertension, with comparison to lung transplant. J Thorac Cardiovasc Surg. 2021;161(3):1139–48.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Miles KG, Critser PJ, Evers PD, Cash M, Magness M, Geers E, O'Neil M, Gao Z, Ollberding NJ, Hirsch R. Factors leading to supranormal cardiac index in pediatric pulmonary hypertension patients treated with parenteral prostanoid therapy. Pulm Circ. 2023;13:e12264. https://doi.org/10.1002/pul2.12264