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RESEARCH ARTICLE

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Long-term prognostic value of cardiac catheterization and acute vasodilator testing with inhaled iloprost in pediatric idiopathic pulmonary arterial hypertension

Chen Zhang[1] | **Konstantinos Dimopoulos**[2] | **Qiangqiang Li**[1] | **Hong Gu**[1]

[1]Department of Pediatric Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

[2]Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK

Correspondence
Hong Gu, Department of Pediatric Cardiology, Beijing Anzhen Hospital, Capital Medical University, 2 anzhen Rd, Chaoyang District, Beijing, China.
Email: koko_gu@hotmail.com

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Abstract

To assess the long-term prognostic value of cardiac catheterization and acute vasodilator testing (AVT) with inhaled iloprost in children with idiopathic pulmonary arterial hypertension (IPAH). Data on 81 consecutive children with IPAH referred to our center who underwent cardiac catheterization and AVT between June 2008 and August 2019 were collected. The correlation between the invasive hemodynamic data and transplant-free survival was analyzed. Twenty-four patients died and 1 underwent lung transplantation during a median follow-up of 3.8 years, with a 5-year transplant-free survival rate of 64.9%. Univariate analysis showed that predictors associated with improved survival included a lower pulmonary vascular resistance index (PVRI), PVRI/systemic vascular resistance index (SVRI), mean pulmonary arterial pressure (mPAP)/mean systemic arterial pressure, mean right atrial pressure, and a higher cardiac index (CI), mixed systemic venous oxygen saturations (SvO_2), and acute vasodilator response (AVR) according to the Barst criteria (decrease in mPAP and PVRI/SVRI ratio of >20% without a decrease in CI). In multivariate Cox regression analysis, Barst AVR and SvO_2 were independently related to transplant-free survival. Multiple hemodynamic variables from cardiac catheterization and AVT with inhaled iloprost have important prognostic value for long-term survival in children with IPAH, of which pulmonary vasoreactivity defined by the Barst criteria and SvO_2 are independent prognostic factors.

KEYWORDS
acute vasodilator testing, heart catheterization, iloprost, prognosis, pulmonary arterial hypertension

BACKGROUND

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive disease characterized by increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) due to pulmonary artery remodeling and obstructive lesions of the small pulmonary vessels without an identifiable primary cause, eventually resulting in right ventricular failure and death.[1] The natural history of IPAH is associated with a poor prognosis. Before pulmonary arterial hypertension (PAH)-targeted drugs became available, the median survival was 2.8 years in all patients with IPAH,[2] and <1 year in children.[3] Although the prognosis of IPAH has improved significantly in the modern medical era, a cure is still lacking. At present, improving long-term outcomes is our main focus, hence accurately predicting long-term prognosis is a cornerstone of the management of IPAH.

According to current guidelines, cardiac catheterization and acute vasodilator testing (AVT) are important components of the algorithm for the diagnosis and treatment of IPAH.[4,5] Cardiac catheterization can provide comprehensive hemodynamic information for the diagnosis of PAH, while AVT can identify the small subset of IPAH patients who may respond favorably to calcium channel blocker (CCBs) therapy.[3,6] Furthermore, hemodynamic parameters derived from cardiac catheterization and AVT may be associated with long-term outcomes, and can act as prognostic predictors.[7,8]

Although similar to adult IPAH in clinical manifestations, pediatric IPAH differs not only in terms of the younger age of onset, but also the lack of gender differences in incidence rate, and the greater severity and more adverse prognosis without treatment. These differences should be taken into account when children undergo hemodynamic assessment.[9,10] However, due to the rare nature of this disease, limited data are available on the invasive hemodynamics of pediatric IPAH, especially in Asians, and their relation to long-term outcomes. In this study, we analyzed cardiac catheterization and AVT data on pediatric IPAH patients assessed over 11 years in a large specialist center in China, focusing on their relation to long-term prognosis.

METHODS

Patients

We retrospectively reviewed consecutive pediatric patients (aged less than 18 years at diagnosis) with IPAH, who underwent cardiac catheterization at the Department of Pediatric Cardiology, Beijing Anzhen Hospital, one of the largest pediatric PH centers in China, between June 2008 and August 2019. Diagnosis of PAH was defined as baseline mean pulmonary arterial pressure (mPAP) >25 mmHg, with a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and PVR index (PVRI) ≥3 Wood units (WU)·m^2. PH related to congenital heart disease, connective tissue disease, chronic thrombo-embolic disease, portal hypertension, HIV infection, or hyperthyroidism was excluded by further diagnostic work-up, including echocardiography, serological testing (autoantibodies, liver function, thyroid function, HIV antibodies), high-resolution computed tomography, and pulmonary angiography. Two PH experts reviewed the information and agreed on the IPAH diagnosis. Only patients with complete invasive hemodynamic data, including AVT, that could be analyzed were included. In patients who had undergone more than one catheterization, the first available investigation was selected.

Our Institutional Medical Ethics committee waived the need for patient consent in this study, because of its retrospective nature and because individual patients were not identified.

Baseline hemodynamic measurements

Baseline evaluation included medical history, World Health Organization functional class (WHO-FC), and the first complete cardiac catheterization.

PH-specific therapy was withdrawn 12 h before catheterization for patients who had already received it. In young children, cardiac catheterization was performed under general anesthesia, and in older ones who could cooperate with the procedure, only local anesthesia was used. If possible, the children breathed room air during baseline catheterization, without tracheal intubation and oxygen inhalation. But if their oxygen saturation declined by more than 5% from baseline while under anesthesia, supplemental low oxygen was provided to maintain the baseline level. Catheterization was performed through the femoral vein and artery with a 5 or 6 F catheter. For comprehensive hemodynamic measurements, both right and left heart catheterization was performed. All procedures were performed by the first author.

Baseline hemodynamic measurements included mean right atrial pressure (mRAP), mean, systolic, and diastolic PAP (mPAP, sPAP, and dPAP), mean PAWP, mean, systolic, and diastolic systemic arterial pressure (mSAP, sSAP, and dSAP), left ventricular end diastolic pressure, and pulmonary arterial, systemic arterial, and mixed systemic venous oxygen saturations (SvO_2), and oxygen pressures. Cardiac index (CI) was

determined using Fick's method. PVRI and systemic vascular resistance index (SVRI) were calculated by the above related parameters.

Acute vasodilator testing

After baseline hemodynamic measurements, inhaled iloprost (Bayer Schering Pharma, Germany) was delivered at a dose of 20 μg (2 ml, mixed with 2 ml of saline), with the exception of children aged <3 years of age or those weighing <15 kg who received 10 μg. Iloprost was delivered via a mask connected to PARI TurboBOY-N air compressor nebulizer (PARI GmbH), which produced aerosolized particles with a mass median aerodynamic diameter of 2.2 μm, with 89% of the mass fraction <5 μm.[11] If patients were on supplemental oxygen during baseline hemodynamics, they also received oxygen at the same concentration. The inhalation lasted for 15–20 min, during which PAP, systemic arterial pressure (SAP), transcutaneous oxygen saturation and heart rate were continuously measured. Another complete set of hemodynamic measurements was obtained at the end of iloprost inhalation.

The presence of acute vasodilator response (AVR) in this study was evaluated according to two criteria:

(1) Sitbon criteria: decrease in mPAP of ≥10 mmHg to reach an absolute mPAP value of ≤40 mmHg without a decrease in CI.
(2) Barst criteria (modified)[12]: decrease in mPAP and PVRI/SVRI ratio of >20% without a decrease in CI.

Follow-up

Chronic drug therapies for PAH were initiated at the discretion of the responsible physician. The follow-up period ended in December 2020. The endpoint for survival analyses was all-cause death, or lung transplantation. Patients who underwent lung transplantation were censored at the time of operation. Date of death or lung transplantation was determined from the medical records and telephone follow-up. Patients lost to follow-up were censored at the date of last clinic visit or clinical communication.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median [range]. The Kolmogorov–Smirnov test was used to determine whether the data were normally distributed. Categorical variables were shown as number and percent.

Hemodynamic changes following iloprost administration were assessed with the paired Student's *t*-test or Wilcoxon signed-rank test. McNemar's χ^2 test was used to compare the proportion of acute responders to iloprost according to the Sitbon and Barst criteria. Comparisons of demographic and clinical characteristics between responders and nonresponders were performed using either the unpaired Student's *t*-test, Mann–Whitney U-test, or χ^2 test, as appropriate. Transplant-free survival was depicted through the construction of Kaplan–Meier curves for all patients, and subgroups of responders and nonresponders to AVT. Survival differences between the subgroups were compared with the Log-Rank test. Univariate Cox proportional hazards regression analysis was used to test the prognostic value of hemodynamic parameters and important clinical indicators, determining the hazard ratio and 95% confidence intervals. Variables significantly associated with survival in the univariate analysis were included in sequential multivariate Cox regression analysis (stepwise and forward).

Statistical analysis was performed using SPSS statistics 20 software (IBM Corporation). All tests were two-sided and $p < 0.05$ were considered statistically significant.

RESULTS

Study group

A total of 81 children with confirmed IPAH who underwent complete catheterization and AVT were included in the analysis. Mean age was (8.3 ± 4.6) years and 46 (56.8%) were male. All patients were Han Chinese. Twenty patients (24.7%) had a WHO-FC III or IV assessment. Thirty-three patients (40.7%) were on one or more PAH-targeted medications at the time of catheterization. Among them, 29 cases had received this medication at the referring medical institutions before being seen in our center; the majority (72.4%) had received <4 weeks of treatment. In 4 cases, PAH-targeted therapy was initiated by our team before catheterization, because patients were critically ill. The demographic data and clinical characteristics of the patients studied are shown in Table 1.

Baseline heart catheterization and AVT

Cardiac catheterization was performed under general anesthesia in 56 cases (69%) of the children; in the remainder, sedation and local anesthesia was used. At baseline, mPAP was 67.9 ± 18.3 mmHg, PVRI was

TABLE 1 Demographic data and clinical characteristics of the study population at the time of catheterization

Variables	All patients ($n = 81$)	Sitbon criteria			Barst criteria		
		Responders ($n = 24$)	Nonresponders ($n = 57$)	p Value[a]	Responders ($n = 35$)	Nonresponders ($n = 46$)	p Value[a]
Age at catheterization (years)	8.3 ± 4.6 [0.83, 17.7]	8.1 ± 4.5	8.4 ± 4.7	0.827	7.9 ± 4.6	8.6 ± 4.7	0.471
Weight (Kg)	29.4 ± 17.4 [8, 86]	26.4 ± 13.9	30.7 ± 18.7	0.253	25.5 ± 14.2	32.4 ± 19.2	0.064
Body surface area (m^2)	1.01 ± 0.39 [0.38, 1.98]	0.97 ± 0.34	1.04 ± 0.41	0.477	0.95 ± 0.35	1.07 ± 0.42	0.158
Female sex	35 (43.2)	13 (54.2)	22 (38.6)	0.196	19 (54.3)	27 (58.7)	0.691
World Health Organization functional class							
I	8 (9.9)						
II	53 (65.4)						
III	18 (22.2)	3 (12.5)[b]	17 (29.8)[b]	0.099	5 (14.3)[b]	15 (32.6)[b]	0.058
IV	2 (2.5)						
Onset of symptoms (months)	12 [0, 85]	12.5 [0, 85]	9 [0, 48]	0.277	12 [0, 85]	7.5 [0, 48]	0.214
Symptom							
Fatigue	73 (90.1)	21 (87.5)	52 (91.2)	0.916	32 (91.4)	41 (89.1)	0.999
Angina	4 (4.9)	3 (12.5)	1 (1.8)	0.140	3 (8.6)	1 (2.2)	0.424
History of hemoptysis	2 (2.5)	0 (0)	2 (3.5)	0.999	0 (0)	2 (4.3)	0.503
History of syncope	27 (33.3)	11 (45.8)	16 (28.1)	0.121	14 (40.0)	13 (28.3)	0.267
History of edema	4 (4.9)	1 (4.2)	3 (5.3)	0.999	2 (5.7)	2 (4.3)	0.999
Transcutaneous oxygen saturation (%)	98 [86, 100]	98 [86, 100]	98 [86, 100]	0.912	98 [86, 100]	98 [88, 100]	0.849
Medication history							
PAH targeted therapy	33 (40.7)	8 (33.3)	25 (43.9)	0.379	12 (34.3)	21 (45.7)	0.302
Diuretics and digoxin only	6 (7.4)						
None	42 (51.9)						

Note: Values are in mean ± SD [range], median [range] or n (%).

Abbreviation: PAC, pulmonary arterial hypertension.

[a]Comparison between responders and nonresponders according to the Sitbon and Barst criteria, respectively, with either unpaired Student's t-test, Mann–Whitney U-test, or χ^2 test, as appropriate.

[b]WHO-FC III and IV.

TABLE 2 Hemodynamic parameters at baseline and after initiation of iloprost

	Baseline	After iloprost	*p* Value[a]
Systolic pulmonary artery pressure (mmHg)	92.4 ± 24.2	75.3 ± 26.8	**<0.001**
Diastolic pulmonary artery pressure (mmHg)	51.9 ± 16.4	37.1 ± 19.2	**<0.001**
Mean pulmonary artery pressure (mmHg)	67.9 ± 18.3	52.6 ± 21.1	**<0.001**
Systolic systemic arterial pressure (mmHg)	99.6 ± 13.3	98.1 ± 13.1	0.167
Diastolic systemic arterial pressure (mmHg)	64.8 ± 11.6	63.9 ± 10.7	0.296
Mean systemic arterial pressure (mmHg)	77.5 ± 12.4	79.0 ± 11.2	0.169
Mean right atrial pressure (mmHg)	8 [3, 19]	7 [3, 21]	**0.017**
mPAP/mSAP	0.90 ± 0.30	0.69 ± 0.30	**<0.001**
Cardiac index (L/min/m^2)	3.4 ± 1.1	3.7 ± 1.3	**<0.001**
Pulmonary vascular resistance index (WU·m^2)	18.4 ± 8.0	12.8 ± 8.1	**<0.001**
Systemic vascular resistance index (WU·m^2)	22.0 ± 7.3	21.0 ± 7.1	**0.019**
PVRI/SVRI	0.87 ± 0.36	0.63 ± 0.37	**<0.001**
Mixed venous oxygen saturation (%)	66.5 ± 7.5	69.3 ± 6.5	**<0.001**
Aortic oxygen saturation (%)	96 [81, 99]	96 [86, 100]	0.235

Note: Values are in mean ± SD or median [range]. Bold values are statistically significant *p* values.

Abbreviations: PVRI/SVRI, pulmonary to systemic vascular resistance index ratio; WU, woods units.

[a]Comparison between baseline and after initiation of iloprost, with paired Student's *t*-test or Wilcoxon signed-rank test as appropriate.

18.4 ± 8.0 WU·m^2, and the mPAP/mSAP was 0.90 ± 0.30. In 31 cases (38.3%) the mPAP was severely elevated and met or exceeded the mSAP. After initiation of iloprost inhalation, mPAP dropped to 52.6 ± 21.1 mmHg ($p < 0.001$), PVRI to 12.8 ± 8.1 WU·m^2 ($p < 0.001$), and mPAP/mSAP to 0.69 ± 0.30 ($p < 0.001$). There was also an increase in CI and SvO_2 compared to the baseline, while SAP and SaO_2 were not significantly affected. The hemodynamic parameters at baseline and after initiation of iloprost are summarized in Table 2.

According to the Sitbon and Barst criteria, there were 24 (29.6%) and 35 (43.2%) acute responders to inhaled iloprost, respectively. The number of acute vasodilator responders differed significantly when using the two different response criteria ($\chi^2 = 38.5$, $p < 0.001$). Almost all Sitbon responders were also Barst responders except one, who did not demonstrate a reduction of at least 20% in PVRI/SVRI during AVT (Table 3). There were no significant differences in demographic and clinical characteristics between responders and nonresponders according to either the Sitbon or Barst criteria (Table 1).

TABLE 3 Comparison of the number of acute responders according to Sitbon and Barst criteria

	Barst criteria		
Sitbon criteria	**Responders**	**Nonresponders**	**Total**
Responders	23	1	24
Nonresponders	12	45	57
Total	35	46	81

Note: $\chi^2 = 38.5$, $p < 0.001$, with McNemar's χ^2 test.

Overall survival

The follow-up period ranged from 4 months to 12.4 years, with a median follow-up time of 3.8 years. No patient was lost to follow-up, and 70% patients were followed for at least 3 years or until death or lung transplantation.

Ten acute responders to iloprost, as judged by the treating physician, received initial monotherapy with CCBs after catheterization, 2 of whom were switched to PAH-targeted drugs after 6 and 12 months because of clinical and hemodynamic aggravation. The remaining 71 patients were treated with one or more PAH-targeted drugs. Most responders to AVT did not receive CCBs because they refused repeat cardiac catheterization for confirming sustained response, or were not judged as responders by the treating physician.

During follow-up, 24 of 81 patients (30%) died: 17 from heart failure, 6 from sudden death after syncope, and 1 from severe hemoptysis. Of these, 7 (29%) died

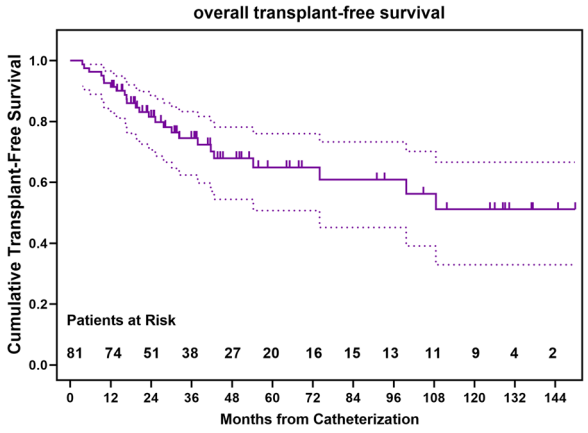

FIGURE 1 Kaplan–Meier survival curve (with 95% confidence intervals) of 81 children with idiopathic pulmonary arterial hypertension

during the first-year follow-up. One patient underwent lung transplantation at 42 months of follow-up, because of severe heart failure without response to medicine. Figure 1 shows overall transplant-free survival. Mean survival time from catheterization was 8.2 ± 0.7 years (95% confidence intervals, 6.9–9.5 years), with 1-, 2-, 3- and 5-year survival rates of 91.4, 81.5, 74.5% and 64.9%, respectively.

Hemodynamic and clinical factors related to survival

In univariate Cox regression analyses (Table 4), a series of variables were predictors of transplant-free survival including WHO-FC, and mSAP, mRAP, mPAP/mSAP, CI, PVRI, PVRI/SVRI, and SvO_2 at baseline, mPAP, sPAP, dPAP, mPAP/mSAP, CI, PVRI, PVRI/SVRI, and SvO_2 after iloprost challenge, and AVR according to the Barst criteria.

The Kaplan–Meier curves illustrated that survival tended to be better in responders than in nonresponders according to both the Sitbon and Barst criteria, but statistical significance was reached only for the Barst criteria, but not the Sitbon criteria (Figure 2). We conducted a further survival analysis in the 57 Sitbon nonresponders, and found Barst responders within this group still had a statistically significantly better survival than Barst nonresponders (Figure 3).

When multivariate Cox analysis was performed (Table 4), only baseline SvO_2 and Barst AVR remained in the Cox proportional hazard model, suggesting that these two factors were independent predictors of transplant-free survival in children with IPAH.

DISCUSSION

The present study demonstrates that invasive hemodynamics carry prognostic power in children with IPAH. Several hemodynamic parameters, at baseline assessment and/or on AVT were strongly related to transplant-free survival at long-term follow-up. We identified AVR fulfilling the Barst criteria and baseline SvO_2 as independent prognostic factors. Our study supports the role of cardiac catheterization and AVT in pediatric IPAH, not only in establishing the diagnosis and deciding on treatment, but also as a powerful tool for assessing long-term prognosis.

IPAH involves pathologic remodeling of the pulmonary vasculature and right ventricle.[13] Accordingly, hemodynamic parameters measured or calculated during cardiac catheterization can be classified into two categories: parameters related to pulmonary vasculature, including PAP, PVR, and AVR to vasodilator challenge, and parameters related to right ventricular function, including mRAP, CI, and SvO_2.

PAP and PVR are the most important hemodynamic variables that reflect changes in the pulmonary vasculature in IPAH. Variables derived from these include the ratio mPAP/mSAP and PVRI/SVRI. Our data demonstrated that baseline PAP, including sPAP, dPAP, and mPAP, had no significant correlation with transplant-free survival, while PAP on AVT, PVRI, mPAP/mSAP, and PVRI/SVRI, both at baseline and on AVT, were associated with long-term transplant-free survival. Similar to our results, a previous study on children with IPAH by Moledina et al.[14] showed that hemodynamic variables with predictive value at initial cardiac catheterization included the PVRI, both at baseline and on AVT, and mPAP on AVT, but not at baseline. PAP has the advantage of being measured directly and at a higher accuracy than PVR, which relies on an accurate assessment of CO. However, PAP is related, not only to the characteristics of the pulmonary vascular bed, but also to cardiac function. When right ventricular function is severely impaired, the relation between PAP and PVR changes. Therefore, PVR remains a more reliable measure of pulmonary vascular disease than PAP.[15] Integrating both pulmonary and systemic circulation into one metric, using the ratio of PVRI/SVRI or mPAP/mSAP has the advantage of being less susceptible to changes in CO, and makes up for some of the deficiencies of PAP and PVR.[15] None of these hemodynamic variables were included in the guidelines on the risk stratification of adults with PAH.[5,16] However, mPAP/mSAP and PVRI were included as risk stratification variables in the consensus statement on pediatric PH.[4,17] Our study supports the important prognostic value of PVR-related

TABLE 4 The results of univariate and multivariate Cox proportional hazards regression analysis for transplant-free survival in 81 children with IPAH

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence intervals)	*p* Value	Hazard ratio (95% confidence intervals)	*p* Value
Age (months)	0.998 (0.991, 1.006)	0.686		
Weight (Kg)	0.999 (0.976, 1.023)	0.927		
Female sex	0.928 (0.416, 2.071)	0.855		
WHO-FC III and IV	3.560 (1.619, 7.827)	**0.002**		
Onset of symptoms (months)	0.990 (0.966, 1.016)	0.458		
History of syncope	1.546 (0.615, 3.889)	0.355		
Transcutaneous oxygen saturation (%)	0.988 (0.884, 1.104)	0.829		
Hemodynamic parameters at baseline				
sPAP (mmHg)	1.005 (0.990, 1.021)	0.510		
dPAP (mmHg)	1.022 (0.998, 1.047)	0.071		
mPAP (mmHg)	1.009 (0.988, 1.030)	0.393		
mSAP (mmHg)	0.957 (0.926, 0.989)	**0.009**		
mRAP (mmHg)	1.147 (1.009, 1.303)	**0.035**		
mPAP/mSAP	3.644 (1.040, 12.769)	**0.043**		
CI (L/min/m^2)	0.473 (0.274, 0.817)	**0.007**		
PVRI (WU·m^2)	1.065 (1.013, 1.120)	**0.014**		
PVRI/SVRI	3.005 (1.075, 8.401)	**0.036**		
SvO_2 (%)	0.920 (0.876, 0.967)	**0.001**	0.932 (0.887, 0.980)	**0.006**
SaO_2 (%)	0.948 (0.852, 1.054)	0.319		
Hemodynamic parameters after iloprost challenge				
sPAP (mmHg)	1.021 (1.004, 1.037)	**0.012**		
dPAP (mmHg)	1.043 (1.017, 1.069)	**0.001**		
mPAP (mmHg)	1.031 (1.009, 1.054)	**0.005**		
mSAP (mmHg)	0.974 (0.938, 1.012)	0.180		
mRAP (mmHg)	1.051 (0.936, 1.180)	0.402		
mPAP/mSAP	7.871 (1.931, 32.080)	**0.004**		
CI (L/min/m^2)	0.593 (0.377, 0.932)	**0.023**		
PVRI (WU·m^2)	1.074 (1.029, 1.121)	**0.001**		
PVRI/SVRI	4.868 (1.677, 14.135)	**0.004**		
SvO_2 (%)	0.944 (0.901, 0.990)	**0.018**		
SaO_2 (%)	1.001 (0.882, 1.135)	0.990		
Pulmonary vasoreactivity				
Sitbon response	0.668 (0.408, 1.092)	0.108		
Barst response	0.203 (0.075, 0.548)	**0.002**	0.237 (0.087, 0.643)	**0.005**

(Continues)

TABLE 4 (Continued)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence intervals)	*p* Value	Hazard ratio (95% confidence intervals)	*p* Value
mPAP change (mmHg)	0.936 (0.899, 0.975)	**0.001**		
mPAP change (%)	0.962 (0.937, 0.987)	**0.003**		
PVRI/SVRI change (%)	0.222 (0.052, 0.948)	**0.042**		

Note: Bold values are statistically significant *p* values.

Abbreviations: CI, cardiac index; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; mPAP/mSAP, pulmonary to systemic arterial pressure ratio; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; PVRI, pulmonary vascular resistance index; PVRI/SVRI, pulmonary to systemic vascular resistance index ratio; SaO_2, aorta saturation; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; WHO-FC, World Health Organization functional class.

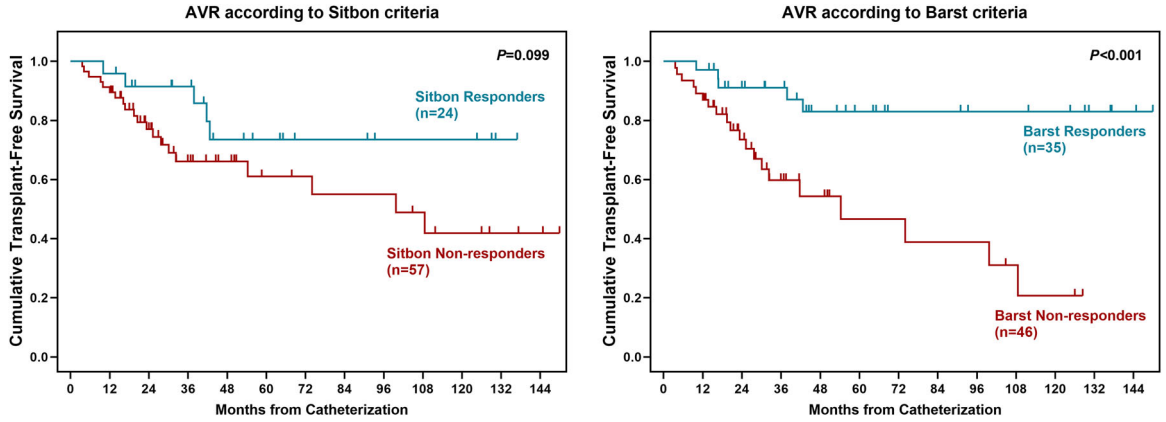

FIGURE 2 Kaplan–Meier survival curves comparing responders versus nonresponders according to the Sitbon and Barst criteria, respectively

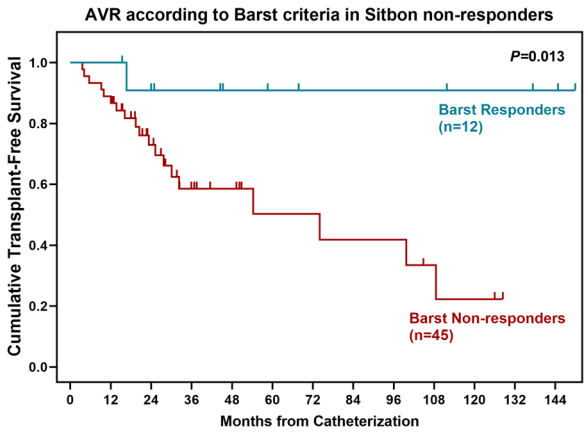

FIGURE 3 Kaplan–Meier survival curves comparing survival of responders versus nonresponders according to the Barst criteria in the 57 Sitbon-non-responders

hemodynamic variables in pediatric IPAH. Hemodynamic parameters assessed during AVT were related to survival even more significantly in our pediatric IPAH and may provide additional prognostic power to baseline assessment.

Inhaled nitric oxide and iloprost are recommended vasodilator agents for performing AVT,[5] but nitric oxide is not available in China, hence inhaled iloprost is commonly used for AVT in Chinese PH centers.[11] Data of AVT with iloprost in children with IPAH is very limited. This study provides AVT data using inhaled iloprost in a large cohort of children with IPAH and confirms that inhaled iloprost is a remarkably effective pulmonary vasodilator, with little effect on the systemic circulation, which is consistent with previous research in adults and other types of PAH.[18–20]

To determine AVR, we examined two sets of criteria. The Sitbon criteria were adopted by most guidelines on PH,[5,16] but are mainly based on adult data and remains controversial in children. The Barst criteria are more frequently used in children with IPAH to define AVR than the Sitbon criteria.[10,21] The proportion of responders with pediatric IPAH has been reported to be higher when using the Barst criteria (30%–35%) than the Sitbon criteria (15%–19%).[4,8,22] In our study, Barst responders were indeed significantly more than Sitbon responders (43.2% vs. 29.6%), and almost all Sitbon responders were

also Barst responders. However, the overall proportion of acute responders according to both sets of criteria were higher than previously reported, which may be partly attributed to the different agents used for AVT, or ethnic differences.

It is still debated whether there is a correlation between age and frequency of acute responders in IPAH. The proportion of responders with IPAH has been reported to be higher in children than in adults by some studies,[12,23] while no difference was identified in other studies.[7,8] Our data showed that the proportion of IPAH responders in Chinese children according to the Sitbon criteria is almost twice that reported in Chinese adults by Jing et al.[11] suggesting more pulmonary vasoreactivity in children compared with adults. This may be due to different pathological changes in the pulmonary vessels of children compared to adults[23]: children with IPAH have more pulmonary vascular medial hypertrophy, less intimal fibrosis and fewer plexiform lesions,[24,25] therefore have greater potential for pulmonary vascular disease reversal, and may influence prognosis.

Indeed, previous studies have indicated that patients with a predominant reversible vasoconstriction and less irreversible vascular remodeling are more likely to respond to AVT,[26] and may have a more favorable treatment response and clinical outcomes.[7,8,27] However, most previous studies on AVT focused on the outcome of CCBs treatment,[10,28] while few studies had shown that the decrease of mPAP and PVR during AVT can predict long-term survival, independent of CCBs treatment.[27] The Sitbon criteria are considered more efficient than the Barst criteria in predicting the outcome of CCBs treatment,[8] but may be less efficient in evaluating long-term prognosis after treatment with any PAH therapy. We found that both the absolute and percent mPAP decrease, and the percent PVRI/SVRI decrease after AVT, are significantly correlated with long-term survival. Yet, there was no significant correlation between AVR according to Sitbon and long-term survival, while Barst responders had a better long-term outcome. Even within Sitbon nonresponders, acute responders according to the Barst criteria had a better survival. Furthermore, AVR according to the Barst criteria emerged as an independent predictor of outcome on multivariate analysis, supporting the use of the Barst criteria in this population for the purpose of long-term prognosis evaluation. Our results were consistent with some previous studies in adults and other types of PAH. Leuchte et al.[29] studied 66 adult IPAH patients who did not meet Sitbon criteria during AVT with inhaled iloprost, and also found that patients with residual pulmonary vasodilative reserve, defined as a PVR reduction of ≥30% during AVT, had a better long-term survival. Malhotra et al.[27] reported that PAH patients with a ≥30% reduction in PVR and ≥12% reduction in mPAP during AVT had a 53% and 55% relative reduction in mortality, respectively. Among the 35 Barst responders in our study, PVRI decreased by 28%–90% during AVT, mostly by more than 30% except for two patients (in whom PVRI dropped by 28% and 29%, respectively), essentially matching the criteria of pulmonary vasodilative reserve proposed previously. Hence, the Barst criteria appear more efficient than the Sitbon criteria in predicting the long-term survival of children with IPAH receiving modern treatment, because it can identify patients with pulmonary vasodilative reserve (rather than having to reach a mPAP <40 mmHg in AVT). These patients may be very different from those with almost no pulmonary vasodilative reserve in pulmonary pathological changes, such as pulmonary vascular fibrosis and vascular stiffness,[30] which may be the basis of different treatment response and long-term prognosis. However, since there were still some other studies inconsistent with our results,[8,31] further research is necessary.

It is generally accepted that right ventricular dysfunction is the strongest predictor of mortality in PAH.[32,33] In patients with IPAH, clinical severity mainly depends on right ventricular morphologic and functional features,[13] and right ventricular failure is the leading cause of death,[2,33] which was also the case in our population. Despite the causal relationship between changes in the pulmonary vasculature and right ventricular function, there is no fixed corresponding relationship in severity due to heterogeneity,[13] hence the parameters related to right ventricular function are independent of those related to pulmonary vasculature.

mRAP is an important marker of right ventricular function, and has been used for risk stratification in most PAH guidelines.[4,16,17,34] Some studies indicated that mRAP was lower in children than that in adults, and only correlates to survival in adult patients, not in children.[7] In our study, mRAP at baseline, but not during AVT, was modestly correlated to transplant-free survival. Further studies are needed to determine whether mRAP is a valid predictor of survival in children with IPAH.

CI and SvO_2 are important cardiac function indicators reflecting blood supply provided by systemic circulation, and were both included in the risk stratification model for adults with PAH,[16,34] but only a low CI was deemed a risk factor in the pediatric guidelines.[4,17,35,36] It may be partly due to the sparse pediatric data. Our data suggests that SvO_2, as well as CI, is an important predictor of outcome in pediatric IPAH. In univariate analysis, baseline CI and SvO_2 were highly predictive of transplant-free survival, while their predictive power was modest after AVT. On multivariate

analysis, only baseline SvO_2 was an independent predictor of outcome. Previous studies in adult IPAH patients have also shown that SvO_2 is a more effective prognosticator than CI.[37] As a parameter measured directly rather than calculated, SvO_2 has a high accuracy, while CI may be prone to error depending on the method used.[38] CI quantifies blood supply by the heart, while SvO_2 reflects whether the cardiac output is sufficient to meet the tissue oxygen demands,[37] which may be related to the reserve of cardiac function and long-term outcome more closely.

Study limitations

Because of its retrospective nature, no standardized treatment protocol was followed in this study. Although catheterization should generally be performed at diagnosis, before the initiation of PH-specific treatment, about 40% of patients in this cohort had received PAH-targeted medications before catheterization, which did not meet the real baseline status. Furthermore, not all acute responders identified by AVT were treated with CCBs, and the choice of PAH-targeted drugs after catheterization was influenced by other factors besides risk state, including financial/insurance issues. However, this was a single-center study from one of the largest pediatric PH centers in China, with a large sample size for a rare disease. Our data reflect real-life clinical practice and are of clinical relevance, strengthened by the standardized diagnostic and treatment strategies applied in our clinical practice and the complete long-term follow-up.

CONCLUSIONS

In conclusion, cardiac catheterization and AVT with inhaled iloprost, which can provide multiple hemodynamic parameters related to pulmonary vasculature and right ventricular function, has important prognostic value in terms of long-term transplant-free survival in children with IPAH. AVR defined by the Barst criteria and SvO_2 are independent prognostic factors and should be integrated in the risk stratification of pediatric IPAH.

AUTHOR CONTRIBUTIONS

Chen Zhang designed the study, performed the procedures and data analyses, and drafted the manuscript. Konstantinos Dimopoulos and Hong Gu contributed to data interpretation and manuscript writing. Qiangqiang Li assisted at the procedures. Hong Gu takes responsibility for the content of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

It is hereby certified that our study have passed the review of our hospital ethics committee. The review number is 2022143X.

ORCID

Chen Zhang http://orcid.org/0000-0002-8573-8236
Qiangqiang Li http://orcid.org/0000-0002-2649-6775

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