Vasoreactive phenotype in children with pulmonary arterial hypertension and syncope

Alexandra N. Linder [1], Jill Hsia [2], Sheila V. Krishnan [1,3], Erika B. Rosenzweig [1,4] and Usha S. Krishnan [1,4]

[1]Division of Pediatric Cardiology, Dept of Pediatrics, Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, NY, USA. [2]Division of Pediatric Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA. [3]Stonybrook University School of Medicine, New York, NY, USA. [4]Co-senior authors.

Corresponding author: Usha S. Krishnan (usk1@cumc.columbia.edu)

Shareable abstract (@ERSpublications)
Syncope in children with PAH may not portend adverse outcomes or classify them as high risk, especially if associated with vasoresponsiveness on haemodynamic testing. Vasoresponsiveness is associated with excellent survival even in the presence of syncope. https://bit.ly/3RsppkS

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Abstract

Background Syncope in Group 1 pulmonary arterial hypertension (PAH) is an independent predictor of poor prognosis in adults, but this is not well studied in children. We hypothesise that syncope in children with PAH often occurs in association with a reactive pulmonary vascular bed with sudden vasoconstriction in response to adverse stimuli. In the current study, we sought to determine the association of syncope with acute vasoresponsiveness and outcomes in children with Group 1 PAH.

Methods A retrospective chart review of children with PAH at a single pulmonary hypertension centre from 1 January 2005 to 31 October 2018 was performed. Data included demographics, symptoms, imaging, haemodynamics, and outcomes at baseline and follow-up.

Results 169 children had Group 1 PAH; 47 (28%) had syncope at presentation or follow-up. Children with significant shunts were excluded from the analysis. Children with syncope were older at diagnosis (7.5 *versus* 5.0 years; p=0.002) and had a higher incidence of chest pain (p=0.022) and fatigue (p=0.003). They had higher pulmonary vascular resistance at baseline (14.9 *versus* 9.1 WU·m^2; p=0.01). More children with syncope were vasoresponders to inhaled nitric oxide (33% *versus* 22%; p=0.08–NS). Children with syncope and acute vasoresponsiveness had the highest survival, and non-responders with syncope on medications had the worst long-term survival.

Conclusions Children with syncope had higher rates of vasoreactivity compared to those without. This suggests that in some children with PAH, syncope may simply reflect acute pulmonary vasoconstriction to an adverse stimulus. Larger prospective studies are warranted to further assess syncope as a marker for a vasoreactive phenotype with implications for treatment and long-term outcomes.

Introduction

Pulmonary arterial hypertension (PAH) is a serious, potentially lethal condition that is challenging to manage due to nonspecific presentation and limited therapeutic options. Risk assessment and treatments for children are often adapted from research on adults with PAH. However, there are inherent differences in the aetiology, natural history and treatment response for children [1, 2].

Syncope is among the most common symptoms of PAH and is associated with poor survival in adults due to advanced pulmonary vascular disease and right ventricular (RV) failure [3–5]. Syncope is thought to occur due to RV dysfunction and inability to augment cardiac output particularly during exertion. Based on these findings, studies of children with PAH list syncope as a high-risk factor, with significant implications for functional classification and treatment selection [6, 7]. Recent guidelines suggest that adults with high-risk features should be started on more aggressive therapy [4], and it is unclear if syncope alone should place children in this higher risk group [8]. The aims of the current study are to determine

whether syncope is associated with acute vasoresponsiveness and to analyse outcomes in children with Group 1 PAH and syncope. We hypothesised that children with syncope are more likely to have acute vasoreactivity during vasodilator testing than those without syncope and may represent a vasoreactive phenotype with more favourable outcomes than adults.

Material and methods

Study subjects

The study cohort included children (⩽18 years at presentation) treated for PAH at Columbia University Medical Center between 1 January 2005 and 31 October 2018 and included both incident and prevalent patients. Children with 5th World Symposium on Pulmonary Hypertension (WSPH) Group 1 PAH were included in the analysis [9]. The data collection was performed prior to 2019, and hence definitions and classifications were per the 5th WSPH. Group 1 PAH was defined as mean pulmonary artery pressure (mPAP) ⩾25 mmHg, pulmonary capillary wedge pressure (PCWP) ⩽15 mmHg and pulmonary vascular resistance (PVR) ⩾3 WU. Patients with Group 2–5 PAH were excluded. Patients with Group 1 PAH associated with congenital heart disease (APAH-CHD) with unrepaired or residual post-tricuspid shunts were excluded from statistical analysis of haemodynamics. The study was approved by the Institutional Review Board of Columbia University Irving Medical Center (IRB-AAAK2059).

Study design and methods

This study was a retrospective chart review of patients with PAH seen at a single large pulmonary hypertension (PH) centre. The objective of this study was to determine the association of syncope with acute vasoresponsiveness and outcomes in children with Group 1 PAH. Data included demographics, PAH subtype, symptoms, comorbidities, World Health Organization (WHO) functional class, brain natriuretic peptide (BNP) (2006–2014) and/or N-terminal pro-BNP (2014–2018), imaging, haemodynamics, treatment, and date of diagnosis and last follow-up as of September 2021. Symptoms including exertional dyspnoea, chest pain, palpitations, failure to thrive, fatigue, dizziness or syncope were documented. Echocardiographic findings included structural diagnosis, estimated RV systolic pressure and qualitative RV systolic ventricular function. Haemodynamic measurements included right atrial pressure, pulmonary artery pressure (PAP), PCWP, systemic arterial pressure, and oxygen saturations in superior vena cava, pulmonary artery and aorta. Haemodynamic data including acute vasodilator testing (AVT) with inhaled nitric oxide (iNO) 80 parts per million at the initial catheterisation and testing closest to the time of syncope were analysed. AVT responsiveness was determined according to Barst and Sitbon criteria. Barst *et al*. defined AVT response as a decrease in mPAP of >20% with a preserved cardiac index and an unchanged or decreased pulmonary to systemic vascular resistance ratio [10]. Sitbon *et al*. defined AVT response as a reduction of mPAP >10 mmHg to a value <40 mmHg with an increased or unchanged cardiac output [11, 12]. Risk scores were calculated using data from the time of diagnosis using the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk assessment guidelines [5] with grading as per the Swedish PAH registry studies [13].

Analysis

Data were expressed as mean±SD or median (interquartile range (IQR)) depending on distribution. Chi square tests for independence were used to compare categorical variables in patients with and without syncope and Fisher's exact tests were used for variables with low incidence. Mann–Whitney or Kruskal–Wallis tests were performed as appropriate to compare catheterisation data between groups, and Wilcoxon signed rank tests were used to compare data at baseline and AVT. The main outcome measure was time to death or lung transplant due to worsening disease. Kaplan–Meier survival analysis and log-rank tests were used to assess differences in transplant-free survival in patients with and without syncope. Statistical analysis was done using Excel 2016 with Data Analysis Toolpak add-in and R Studio Statistical Software version 1.0.153.

Results

Patient characteristics (table 1)

169 patients ⩽18 years were diagnosed with Group 1 PAH. 47 patients (28%) had syncope with 38 (81%) as their presenting symptom before initiation of PAH therapy. Patients with syncope were older at PAH diagnosis with median age of 7.9 years (0.4–19) *versus* 3 years (0–18.4) without syncope (p=0.002). Idiopathic pulmonary arterial hypertension (IPAH) was the most frequent subtype in the syncope group. Three of five heritable pulmonary arterial hypertension (HPAH) patients, all with hereditary haemorrhagic telangiectasia (HHT), had syncope and none of the five patients were vasoresponsive. One patient without syncope had a BMPR2 mutation and one had familial PAH with no genetic diagnosis. 60 patients with large shunts were excluded from further analysis (supplementary figure S1).

TABLE 1 Patient characteristics

	Syncope	Non-syncope	p-value
Subjects n	47	122	
Sex, female	29 (62)	66 (54)	0.40
Median age years	7.9 (0.4–19)	3.0 (0–18.4)	**0.002**
Symptoms			
Dyspnoea on exertion	43 (91)	118 (97)	0.08
Chest pain	20 (43)	30 (25)	**0.022**
Failure to thrive	9 (19)	40 (33)	0.075
Fatigue	34 (72)	57 (47)	**0.003**
PAH classification			
Idiopathic PAH	36 (76)	37 (30)	**<0.00001**
Heritable PAH	3 (6)	2 (2)	0.13
APAH-CHD	10 (21)	79 (65)	**<0.00001**
Repaired	5 (50)	53 (67)	0.29
Unrepaired	5 (50)	26 (33)	
APAH-CTD	1 (2)	4 (3)	1
APAH–portal hypertension	0	2 (1)	1

Data are expressed as median (range) or n (%) unless indicated otherwise. Bold p-values represent statistically significant differences. PAH: pulmonary arterial hypertension; APAH: associated pulmonary hypertension; APAH-CHD: PAH associated with congenital heart disease; APAH-CTD: PAH associated with connective tissue disease.

Haemodynamics studies

109 PAH patients without shunts had cardiac catheterisation at diagnosis (table 2). One patient with and two without syncope did not have baseline catheterisation due to critical status at diagnosis. One patient with and six patients without syncope did not have vasodilator testing done due to severity of illness requiring their catheterisation performed while on iNO.

Indexed pulmonary vascular resistance (PVRi) was higher in patients with syncope at diagnosis, with highest PVRi seen in patients with initial syncope on medications (p=0.04). There were no other significant haemodynamic differences at baseline. Patients with syncope on medications had higher PVRi

TABLE 2 Cardiac catheterisation data at presentation

	n	Syncope at diagnosis[#]	n	Syncope on medication[¶,+]	n	Non-syncope[§]	p-value
Baseline							
Mean RAP mmHg		7 (5–10)		7 (6–10)		7 (6–9)	0.86
Mean PAP mmHg		53 (37–65)		66.5 (51.8–72)		48.5 (36–64)	0.18
sPAP/sSAP		0.80 (0.50–0.99)		0.83 (0.76–1.10)	66	0.75 (0.50–0.95)	0.47
PVRi WU·m^2		13.7 (8.8–22.0)		20.1 (9.2–25.1)	66	9.05 (5.3–14.5)	**0.04**
Rp/Rs	30	0.7 (0.5–1)	5	0.7 (0.3–1.5)	59	0.6 (0.33–0.94)	0.42
CI L·min^{-1}·m^{-2}		3.0 (2.2–3.8)		2.8 (2.5–3.2)	66	3.5 (2.5–4.2)	0.19
AVT with iNO			5		64		
Mean RAP mmHg	25	6 (4–8.5)	3	7 (2–8)	44	7 (6–8.5)	
Mean PAP mmHg	35	38 (27–60)		63 (53–66.5)		37.5 (28–56.5)	0.15
sPAP/sSAP	34	0.60 (0.40–0.92)		0.77 (0.67–1.16)	59	0.65 (0.46–0.89)	0.30
PVRi WU·m^2	33	9.3 (5.1–17.3)		15.1 (11.9–19.5)	61	6.5 (3.7–11)	**0.02**
Rp/Rs	21	0.46 (0.29–0.72)		N/A	33	0.45 (0.21–0.83)	0.99
CI L·min^{-1}·m^{-2}	33	3.2 (2.4–3.8)		3.1 (2.7–3.8)	58	3.6 (2.6–4.6)	0.18
AVT responders (Barst)		14 (40)		0		15 (22)	**0.047**
AVT responders (Sitbon)		8 (23)		0		9 (13)	0.27

Data are expressed as median (interquartile range) or n (%). Bold p-values represent statistically significant differences. n: number of patients; RAP: right atrial pressure; PAP: pulmonary artery pressure; sPAP/sSAP: ratio of pulmonary artery/systemic arterial systolic pressure; PVRi: indexed pulmonary vascular resistance; Rp/Rs: ratio of pulmonary vascular resistance/systemic vascular resistance; CI: cardiac index; AVT: acute vasodilator testing; iNO: inhaled nitric oxide. [#]: n=36; [¶]: n=6; [+]: one patient with syncope on medication did not have a catheterisation available from the time of diagnosis; [§]: n=67.

TABLE 3 Catheterisation data with acute vasodilator testing (AVT) for syncope patient responders *versus* non-responders using Barst criteria

	n	AVT responders[#]	n	AVT negative with syncope at diagnosis[¶]	n	AVT negative with syncope on medications[+]	p-value
Room air							
Mean RAP mmHg		6.5 (3–11)		7 (5–9)		9 (8–10)	0.36
Mean PAP mmHg		49 (32–66)		57 (43–70)		67 (61–81)	0.12
PVRi WU·m^2		11.1 (8.6–22)		16.3 (8.7–26)	6	20.0 (7.8–26.3)	0.80
Rp/Rs	11	0.7 (0.4–1)	20	0.9 (0.7–1)	6	1.3 (0.7–2.4)	0.14
CI L·min^{-1}·m^{-2}		2.8 (2.3–3.9)	20	2.98 (1.9–3.6)		3.8 (2.2–4.4)	0.45
AVT with iNO							
Mean RAP mmHg	9	6 (4–7)	15	8 (5–9)	6	9.5 (7.3–10.3)	0.07
Mean PAP mmHg		28 (20–31)[§]		58 (41–77)		64 (61–82)	**0.0003**
PVRi WU·m^2	12	5.1 (3.8–8.0)[§]		16.5 (9.3–22.7)	5	22.5 (7.5–26.9)	**0.002**
Rp/Rs	7	0.2 (0.2–0.4)[§]	13	0.7 (0.5–1.1)	5	1.1 (0.5–2.3)	**0.0015**
CI L·min^{-1}·m^{-2}		3.3 (2.6–3.9)	20	3.3 (2.2–3.8)		3.4 (2.4–4.2)	0.72

Data are expressed as median (interquartile range). Bold p-values represent statistically significant differences between AVT responders and AVT negative. One patient who responded to AVT on her initial catheterisation (included in that category in table 1) lost AVT response by time of syncope as reflected in her later catheterisation used here. RAP: right atrial pressure; PAP: pulmonary artery pressure; PVRi: indexed pulmonary vascular resistance; Rp/Rs: ratio of pulmonary vascular resistance/systemic vascular resistance; CI: cardiac index; iNO: inhaled nitric oxide. [#]: n=14; [¶]: n=21; [+]: n=7; [§]: represents statistically significant differences on room air compared to AVT.

with vasodilator testing, and none of these patients were vasoresponsive. More patients with syncope at diagnosis were AVT responsive compared to those without syncope. Using Barst criteria, 40% of children with syncope at diagnosis were vasoresponsive *versus* 22% without (p=0.047); using Sitbon criteria, 23% with syncope at diagnosis were responders *versus* 13% (p=NS).

Table 3 shows haemodynamic data at time of syncope using Barst criteria and table 4 using Sitbon criteria. There were no significant differences in haemodynamics at baseline. Those with positive response to AVT using Barst criteria had significant decreases in PVRi, mPAP and Rp/Rs ratio.

Treatments (table 5)

There were 29 total vasoresponders identified in this study. 10 out of 14 vasoresponsive patients with syncope were receiving calcium channel blockers (CCBs) at most recent follow-up; three received CCBs only. Four vasoresponders with syncope were not on CCBs at last follow-up. Two patients lost vasoresponsiveness and CCB was discontinued. The other two patients were not on CCBs due to age and poor function. Six out of 15 vasoresponsive patients without syncope received CCBs, of whom three were

TABLE 4 Catheterisation data with acute vasodilator testing (AVT) for syncope patient responders *versus* non-responders using Sitbon criteria

	n	AVT responders[#]	n	AVT negative with syncope at diagnosis[¶]	n	AVT negative with syncope on medications[+]	p-value
Room air							
Mean RAP mmHg		8 (1–16)		7 (5–9)		9 (8–10)	0.33
Mean PAP mmHg		52 (41–66)		54.5 (32–69.8)		67 (61–81)	0.15
PVRi WU·m^2		19.5 (11.8–23.7)		14.2 (8.2–24.5)	6	20.0 (7.8–26.3)	0.67
Rp/Rs	6	0.7 (0.6–0.8)	25	0.9 (0.5–1)	6	1.3 (0.7–2.4)	0.22
CI L·min^{-1}·m^{-2}		2.3 (1.8–3.2)	27	3.1 (2.3–3.8)		3.8 (2.2–4.4)	0.15
AVT with iNO							
Mean RAP mmHg	4	6 (3–9)	20	6.5 (5–8.8)	6	9.5 (7.3–10.3)	0.13
Mean PAP mmHg		29 (28–31)		52.5 (26.3–74.8)		64 (61–82)	**0.01**
PVRi WU·m^2	5	7.9 (6–8)		13.2 (4.7–20.9)	5	22.5 (7.5–26.9)	0.22
Rp/Rs	3	0.4 (0.2–0.4)	17	0.7 (0.3–1)	5	1.1 (0.5–2.3)	
CI L·min^{-1}·m^{-2}		3.1 (2.6–4.4)	27	3.4 (2.3–3.8)		3.4 (2.4–4.2)	0.73

Data are expressed as median (interquartile range). Bold p-value represents statistically significant difference between AVT responders and AVT negative by Sitbon criteria. RAP: right atrial pressure; PAP: pulmonary artery pressure; PVRi: indexed pulmonary vascular resistance; Rp/Rs: ratio of pulmonary vascular resistance/systemic vascular resistance; CI: cardiac index; iNO: inhaled nitric oxide. [#]: n=7; [¶]: n=28; [+]: n=7.

TABLE 5 Treatment at last follow-up

	Syncope	AVT$^+$	AVT$^-$	Non-syncope	AVT$^+$	AVT$^-$	p-value (syncope *versus* non-syncope)
Subjects n	42	14	28	67	14	53	
CCB for vasoresponsiveness	10 (24)	10$^{\#}$	0	6 (6)	6$^{\#}$	0	**0.03**
CCB monotherapy	3 (6)	3¶	0	3 (3)	3¶	0	0.67
Single PAH therapy	6 (14)	4	2	18 (27)	5	13	0.12
Dual PAH therapy	13 (31)	3	10	11 (16)	1	10	0.07
Triple PAH therapy	18 (43)	3¶	15	23(34)	3	21	0.37
No medication	2 (4)	1	1	12 (18)	2	10	**0.046**
IV/SQ prostanoid	20 (48)	1 (7)	19$^+$ (68)	15 (22)	1 (7)	14 (26)	**0.006**

Data are expressed as n or n (%). Bold p-values represent statistically significant differences between patients with and without syncope. AVT: acute vasodilator testing; CCB: calcium channel blocker; PAH: pulmonary arterial hypertension; IV: intravenous; SQ: subcutaneous. $^{\#}$: p for AVT$^+$ *versus* AVT$^-$ <0.00001; ¶: p for AVT$^+$ *versus* AVT$^-$ <0.05 (for syncope CCB only, p=0.03; for syncope triple PAH therapy, p=0.047; for non-syncope CCB only, p=0.007); $^+$: p for AVT$^+$ *versus* AVT$^-$ =0.0002.

on CCB alone and three were on triple therapy including prostanoids. The remaining vasoreactive patients without syncope had APAH-CHD and were not started on CCBs. Significantly more patients with syncope were on CCBs (p=0.03).

The majority of patients with syncope unresponsive to vasodilator testing were on two or three PAH medications. Fourteen patients (26%) with syncope and 19 (68%) without syncope received parenteral prostanoids (p<0.00001). There were three patients without syncope who received CCBs prior to current treatment era due to limited available medications. Additionally, 10 patients with syncope (all with IPAH) underwent at least one balloon atrial septostomy (BAS). Three patients had BAS at time of syncope, and the remainder had septostomy after recurrent syncope or otherwise progressive disease.

Treatment with parenteral prostanoids

Of the seven patients who were on PAH medications at the time of first syncope, one was on intravenous (*i.v.*) prostanoids with syncope secondary to pump malfunction. 17 (40%) patients had recurrent syncope after starting targeted oral PAH medication, triggering a start of prostanoid therapy in nine patients. Eight patients (19% of all with syncope) had recurrent syncope while on *i.v.* prostanoids, only one of whom had positive AVT response and was lost to follow-up. In this group, two patients died and one received lung transplant. Another underwent atrial septostomy and was referred for lung transplant. One patient underwent reversed Potts shunt.

Risk assessment (2015 ESC/ERS guidelines)

The median number of variables used for risk scoring was 6 (IQR 5–7). Patients with syncope had a higher risk score of 1.8 (IQR 1.57–2.00), as syncope was included as a component of the score (p<0.0001). Patients without syncope had a median risk score of 1.47 (IQR 1.28–1.67), which is low risk. There was no difference between risk scores in syncope patients with and without AVT response (p=0.88).

Syncope and outcomes

Nine patients with syncope died during the entire study period and four underwent lung transplant (28% for both outcomes combined). Seven deaths were PAH related, one patient with HHT died due to a massive gastrointestinal bleed, and one due to treatment noncompliance. 14 patients (11%) without syncope died or underwent lung transplant – one lung transplantation, eight PAH, three infection (sepsis, meningitis), and two from unknown causes. Figure 1 shows the transplant-free survival curves for the entire cohort. There was no difference in event-free survival at 10 years (p=0.31). However, the event-free survival probability was higher in patients without syncope for the entire follow-up period (p=0.02). Supplementary table S1 shows the causes of death or transplant status, RV function and syncope status for the whole cohort.

Vasoresponsiveness and outcomes

Death or transplant-free survival was also examined stratified by syncope and AVT response (figure 2). Figure 2 shows survival probability of 100% for all patients with syncope and positive AVT response at initial catheterisation with no significant difference in survival between groups at 10 years (p=0.12) but

significantly better survival in those with positive AVT response over the entire follow-up period (p=0.0006). Non-vasoresponsive patients with syncope had significantly worse long-term survival, with the worst survival seen in patients with syncope on medications compared to responders with syncope (p=0.0005) and responders without syncope (p=0.001). Patients with syncope at diagnosis had significantly better survival with positive AVT response (p=0.017).

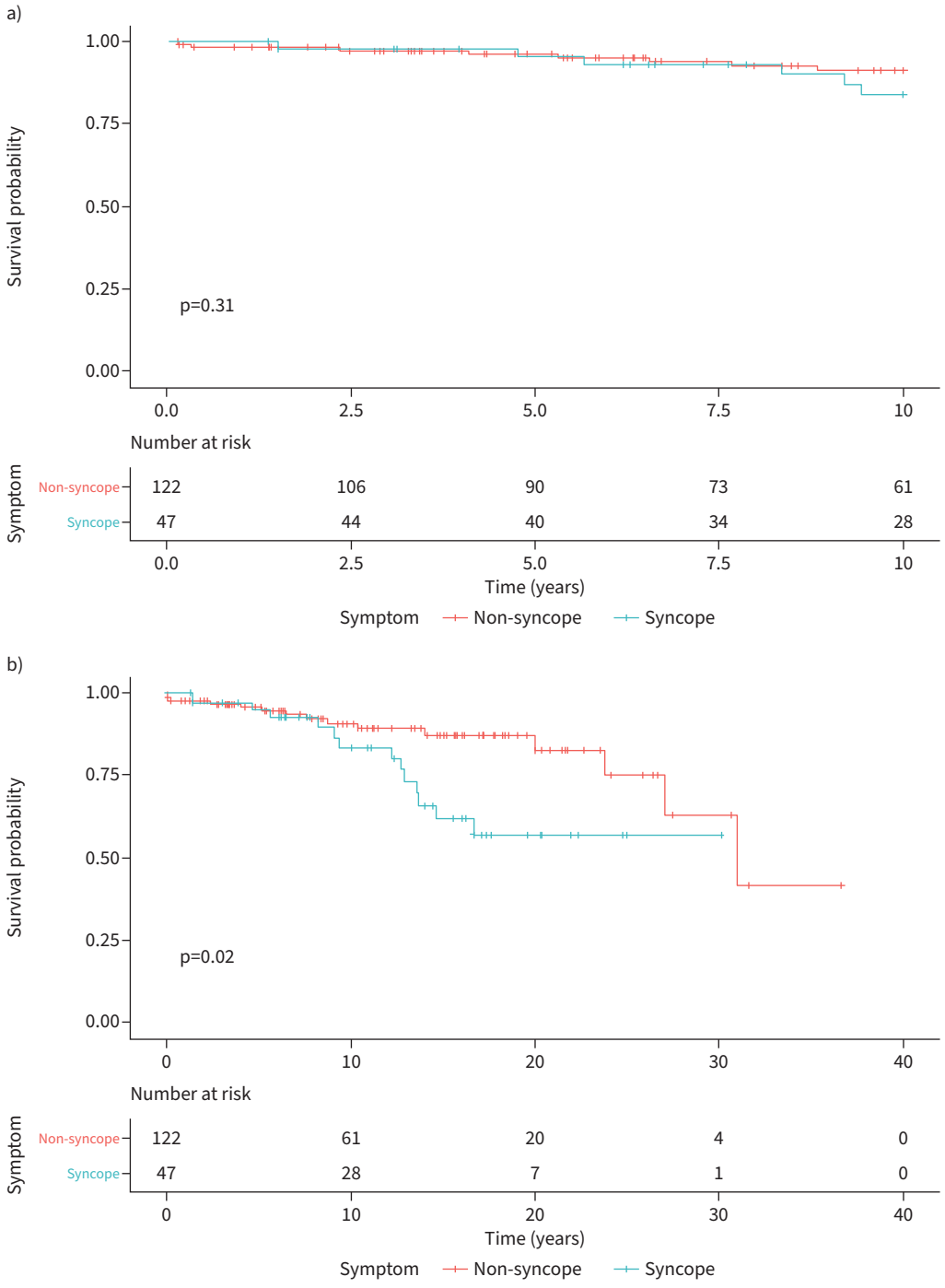

FIGURE 1 Survival in pulmonary arterial hypertension patients with and without syncope. a) Survival probability over time (in years) showed no difference in survival at 10 years between those with syncope during their clinical course compared to those without. b) Patients with syncope had significantly worse survival over the entire follow-up period.

IPAH/HPAH sub-analysis

As seen in table 6, among patients with IPAH with and without syncope, there were no significant differences in haemodynamics at baseline or with vasodilator testing. Figure 3 shows long-term survival was significantly worse in non-vasoresponsive IPAH patients with syncope (p=0.012). Those with an initial syncopal episode on medications had the worst outcomes. All the patients followed long term died, and none were vasoresponsive. Patients with syncope at diagnosis and negative AVT response had 50% survival at 15 years. Survival was 100% in vasoresponders, both in patients with syncope at diagnosis and those without syncope. Survival trends were similar when using Sitbon criteria for AVT response.

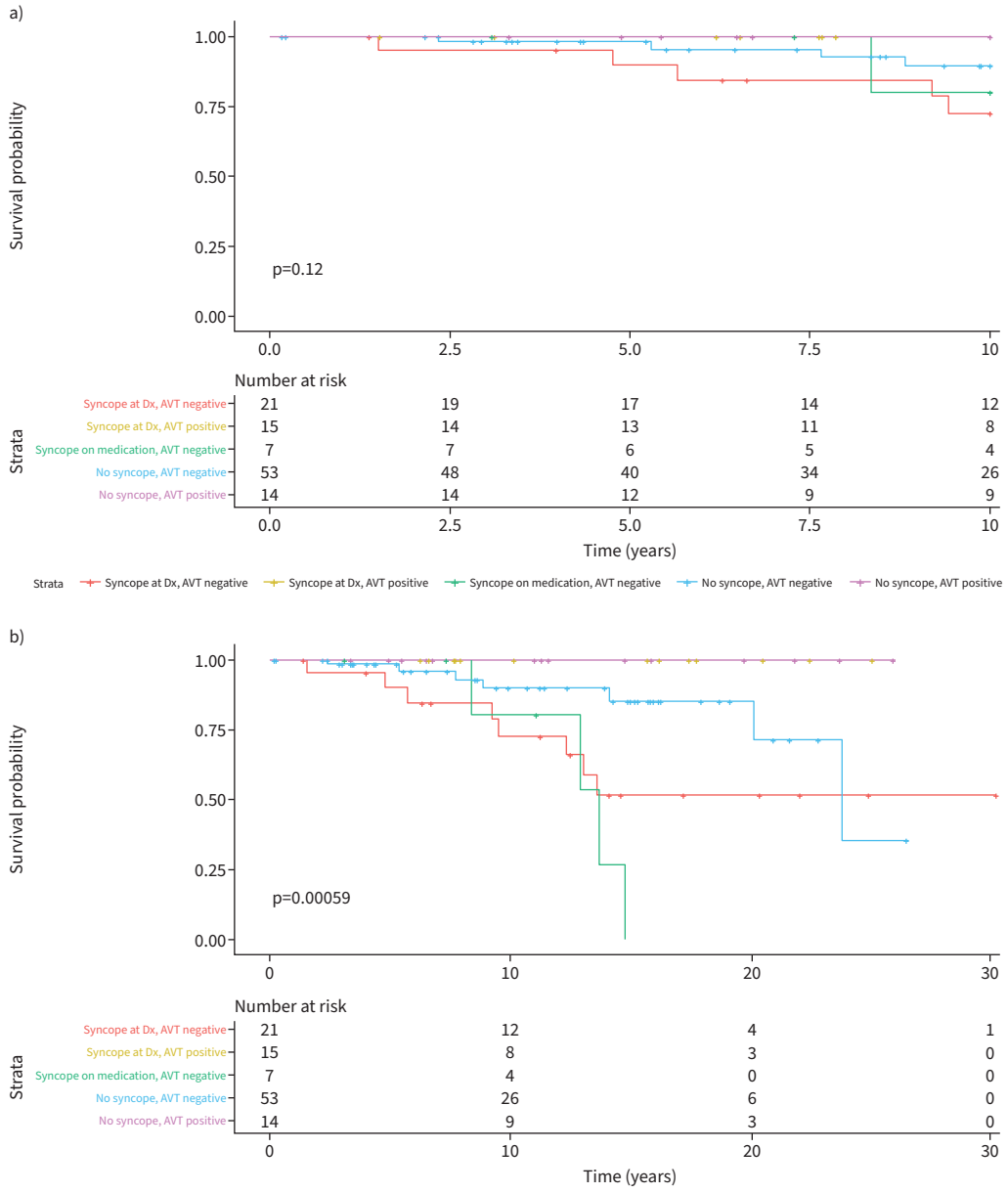

FIGURE 2 Survival in patients with Group 1 pulmonary arterial hypertension stratified by syncope and acute vasodilator testing (AVT) response. a) There was no significant difference in survival at 10 years regardless of syncope or AVT response. b) Over the entire follow-up period (range 0.17–30.2 years), those with and without syncope and positive response to AVT had 100% survival. Those with syncope and without response to acute vasodilator testing had the worst survival, with the poorest survival in patients with syncope on medications. Dx: diagnosis.

TABLE 6 Cardiac catheterisation data with acute vasodilator testing for idiopathic pulmonary arterial hypertension patients

	n	Syncope[#]	n	Non-syncope[¶]	p-value
Baseline					
Mean RAP mmHg		7 (5–10)		6 (5–8)	0.45
Mean PAP mmHg		54 (40–69)		52 (37–76)	0.90
sPAP/sSAP		0.81 (0.58–1.00)		0.84 (0.55–1.10)	0.74
PVRi WU·m^2		16.7 (9.3–24.8)		11.0 (5.5–20.2)	0.10
Rp/Rs	28	0.75 (0.60–1.00)	31	0.7 (0.40–1.10)	0.51
CI L·min^{-1}·m^{-2}		2.7 (2.0–3.4)	34	3.55 (2.8–4.6)	**0.0047**
AVT with iNO			34		
Mean RAP mmHg	24	7 (4.5–8.5)	27	6 (5–8)	0.72
Mean PAP mmHg		44 (27–64)		41 (31–57)	0.88
sPAP/sSAP	33	0.70 (0.40–0.93)	33	0.70 (0.46–0.91)	0.63
PVRi WU·m^2	32	13.2 (5.7–18.9)	33	8.1 (3.6–12.2)	**0.037**
Rp/Rs	18	0.50 (0.30–0.72)	19	0.45 (0.25–0.90)	0.93
CI L·min^{-1}·m^{-2}	33	3.3 (2.5–3.7)	33	3.8 (2.7–5.3)	**0.013**
AVT responders (Barst)		12 (35)		8 (23)	0.19
AVT responders (Sitbon)		6 (18)		5 (14)	0.70

Data are expressed as median (interquartile range) or n (%). Bold p-values represent statistically significant differences. n: number of patients; RAP: right atrial pressure; PAP: pulmonary artery pressure; sPAP/sSAP: ratio of pulmonary artery/systemic arterial systolic pressure; PVRi: indexed pulmonary vascular resistance; Rp/Rs: ratio of pulmonary vascular resistance/systemic vascular resistance; CI: cardiac index; AVT: acute vasodilator testing; iNO: inhaled nitric oxide. [#]: n=34; [¶]: n=35.

APAH-CHD

Of the 89 APAH-CHD patients, 60 had significant post-tricuspid shunts and were excluded from the haemodynamic and survival analysis. Among those included in the analysis, three out of 34 (9%) of APAH-CHD patients had syncope and haemodynamically significant shunts – two with large secundum atrial septal defects (ASDs) and one with a superior sinus venosus defect. The other four patients with

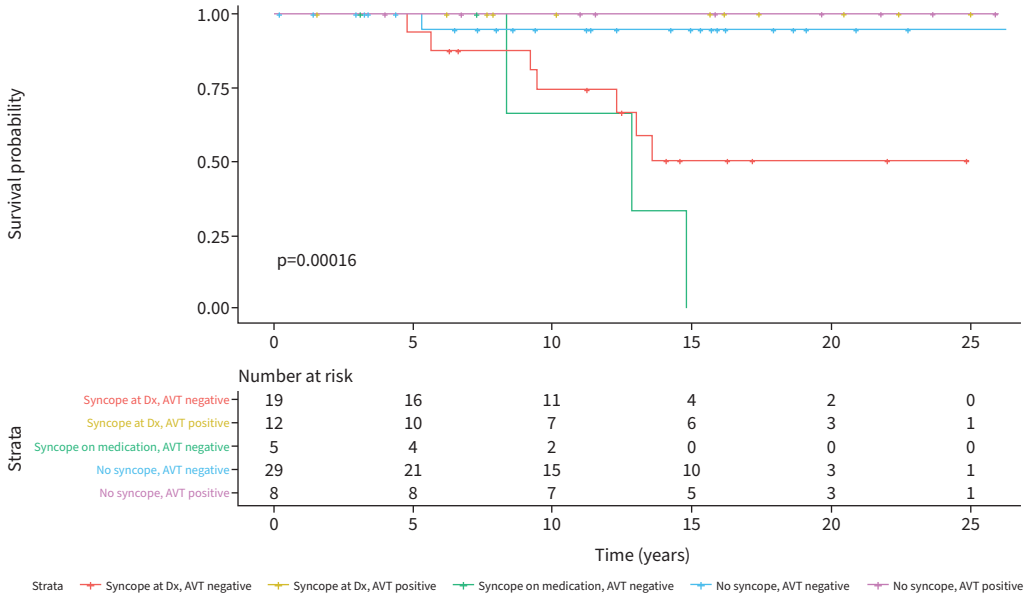

FIGURE 3 Survival of idiopathic pulmonary arterial hypertension patients stratified by syncope and acute vasodilator testing (AVT) response. All patients with idiopathic pulmonary arterial hypertension who responded to AVT had 100% survival regardless of syncope. Those with syncope and without response to acute vasodilator testing had the worst survival. Dx: diagnosis.

APAH-CHD and syncope had only small residual atrial level shunts after repair. Four APAH-CHD patients without syncope had unrepaired shunts at the time of diagnosis including three with large secundum ASDs and one with a partial atrioventricular septal defect. Eight patients with APAH-CHD were vasoresponders, one of whom had syncope.

Discussion

Syncope is a predictor of poor outcomes in adults, but this association has not been well studied in children [4]. In the current study, we examined the clinical presentation of paediatric patients with WSPH Group 1 PAH and analysed the association of syncope and vasoresponsiveness to iNO on cardiac catheterisation with outcomes. Patients with syncope had higher rates of AVT response at diagnosis compared to those without syncope and had excellent outcomes with 100% survival over the entire follow-up period. This suggests that in some children syncope may reflect acute pulmonary vasoconstriction to an adverse stimulus and is not associated with poor outcomes, and AVT responsiveness may be associated with excellent outcomes even in the presence of syncope. In this study, children with syncope on medications and negative AVT response had the worst long-term outcomes beyond 10 years, similar to adult studies. It is possible that in children with longstanding PAH and decreased right ventricular function, syncope may have a similar adverse prognostic implication as in adults.

In this cohort of incident and prevalent paediatric patients with PAH, 27% had syncope. Most patients presented with syncope when they were diagnosed with PAH, before starting medication. The proportion of patients with syncope in the current study was similar to that reported in some paediatric studies [7, 10, 14, 15] and more frequent than the rates reported in adult studies [16]. In the current study, patients with syncope were older than those without syncope at the time of diagnosis, as described in previous studies [3, 7]. Syncope was most commonly seen in patients with IPAH; 21% of patients with syncope had APAH-CHD but only five had large shunts and the rest had PAH after shunt closure, which is physiologically similar to IPAH [17–19].

In contrast to the reported incidence by Moledina *et al.* [7], in the current report, children with syncope had higher rates of acute vasoresponsiveness and higher PVRi at baseline, though there were no other significant differences in haemodynamics. Vasoresponders with syncope had similar baseline haemodynamics to non-vasoresponders, and survival was excellent in vasoresponders regardless of syncope, with the only death from sepsis. This was true regardless of cardiac index, suggesting that syncope did not impact long-term outcomes for vasoresponders. In contrast, non-vasoresponsive patients with syncope had significantly worse survival over the whole study period, though this became significant only beyond 10 years of follow-up.

In adults with PAH, syncope is an independent predictor of poor outcomes, as it is nearly always reflective of right heart failure leading to insufficient cardiac output [5]. This appears to hold true in children with syncope without vasoresponsiveness or despite appropriate targeted therapy who have a worse long-term outcome beyond 10 years of follow-up. The children with the worst outcomes were those with syncope while on targeted PH medications. These patients had worse haemodynamics at diagnosis prior to the time of syncope with higher PVRi than those with syncope at the time of PH diagnosis and those without syncope. No patients with syncope on medications were vasoreactive. It is likely that the syncopal episodes in these patients were in fact reflective of progressive disease with worsening pulmonary hypertension and right ventricular failure.

Children with syncope and preserved cardiac function may represent a unique group of patients described in a previous study in 2012 by Barst *et al.*, with highly reactive pulmonary vasculature leading to vasoconstriction with acute decrease in cardiac output in response to adverse stimuli leading to syncope [10]. These patients often are vasoresponders with iNO testing, and when treated with CCBs have excellent long-term outcomes with sustained CCB response [11, 20]. As of the 6th World Symposium on Pulmonary Hypertension (2018), patients with sustained CCB response are now classified in an independent sub-category [4, 21]. Syncope in these patients is likely reflective of a unique haemodynamic phenotype – vasoreactivity – and not of decreased heart function, and therefore does not appear to be associated with poor outcomes, and perhaps should be added to the WSPH classification as another unique subgroup.

In this study we utilised both the Barst/REVEAL criteria [10] and the Sitbon [12] criteria to define vasoreactivity. Several of the vasoreactive patients by Barst criteria did not meet Sitbon criteria due to insufficient decrease in mPAP (>10 mmHg) or due to small decreases in cardiac index. There is ongoing debate over the appropriate criteria to use to determine vasoresponsiveness in children. The more selective

Sitbon criteria may be better predictive of survival compared to REVEAL criteria and may more reliably identify patients who will benefit from treatment with CCB, but further paediatric studies are needed [12]. Vasoresponsiveness using the Sitbon criteria may identify patients who will retain vasoreactivity and have excellent long-term outcomes [4].

Some studies suggest that syncope is less likely in patients with shunts because of having an effective "pop-off", which is part of the rationale for performing an atrial septostomy or reversed Potts shunt in patients with recurrent syncope and RV dysfunction [4]. In this study, while shunts were more common in the non-syncope group compared to those with syncope, 11% of those with syncope had intracardiac shunts as well, despite having a site for pop-off. Interestingly, syncope was more common in our cohort of APAH-CHD patients than in some other studies, and the reason for syncope in patients with Eisenmenger syndrome is not entirely clear [10, 15].

This study was limited by its small sample size; a larger multicentre study would be needed to further examine the difference in outcomes between the subgroups and to study the effect of different AVT criteria on outcomes. However, the advantage of a single centre study is the consistency in treatment strategies for all subjects. Additionally, there may be survival bias given that some patients were diagnosed with PAH significantly before the study period (up to 32 years) and time from diagnosis may reflect some of the mortality noted in the current study. However, the distribution of follow-up times was similar between groups. We did not analyse the impact of RV function by echocardiogram. Quantification of RV function is more accurate using magnetic resonance imaging (MRI) rather than echocardiography. However, due to the era of this study, MRI was not available for many of the patients, and RV function was not included in the risk analysis, which could have enhanced this study. Because of the wide age range of subjects and their inability to perform 6-minute walk tests or cardiopulmonary exercise testing reliably, it was not meaningful to use other risk scores such as the REVEAL lite 2.0 [22]. A risk score system specific to the paediatric age group would be an invaluable resource to appropriately prognosticate children with PAH as proposed by Hansmann *et al.* [23]. Lastly, due to the overall low occurrence of vasoresponsiveness in PAH patients, the study may have been underpowered to detect significant differences between those with and without a positive response. A larger prospective study, including advanced imaging for RV function, may further clarify the implications of syncope in paediatric PAH.

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