Invasive haemodynamics predict outcomes in paediatric pulmonary artery hypertension

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Abstract

Background: Invasive haemodynamics are often performed for initiating and guiding pulmonary artery hypertension therapy. Little is known about the predictive value of invasive haemodynamic indices for long-term outcomes in children with pulmonary artery hypertension. We aimed to evaluate invasive haemodynamic data to help predict outcomes in paediatric pulmonary artery hypertension. *Methods:* Patients with pulmonary artery hypertension who underwent cardiac catheterisation (2006–2019) at a single centre were included. Invasive haemodynamic data from the first cardiac catheterisation and clinical outcomes were reviewed. The combined adverse outcome was defined as pericardial effusion (due to right ventricle failure), creation of a shunt for pulmonary artery hypertension (atrial septal defect or reverse Pott's shunt), lung transplant, or death. *Results:* Among 46 patients with a median [interquartile range (IQR)] age of 13.2 [4.1–44.7] months, 76% had CHD. Median mean pulmonary artery pressure was 37 [28–52] mmHg and indexed pulmonary vascular resistance was 6.2 [3.6–10] Woods units $\times$ m^2. Median pulmonary artery pulsatility index was 4.0 [3.0–4.7] and right ventricular stroke work index was 915 [715–1734] mmHg mL/m^2. After a median follow-up of 2.4 years, nine patients had a combined adverse outcome (two had a pericardial effusion, one underwent atrial level shunt, one underwent reverse Pott's shunt, and six died). Patients with an adverse outcome had higher systolic and mean pulmonary artery pressures, higher diastolic and transpulmonary pressure gradients, higher indexed pulmonary vascular resistance, higher pulmonary artery elastance, and higher right ventricular stroke work index (p < 0.05 each). *Conclusion:* Invasive haemodynamics (especially mean pulmonary artery pressure and diastolic pressure gradient) obtained at first cardiac catheterisation in children with pulmonary artery hypertension predicts outcomes.

Pulmonary artery hypertension in children in the United States has a prevalence of 26–33 cases per million children.[1] Pulmonary artery hypertension associated with CHD accounts for nearly half of this population (15.6 cases per million children), and idiopathic pulmonary artery hypertension accounts for about 4.4 cases per million.[2] The 5-year survival is ~74% and similar in both subgroups according to one registry study.[3] Patients with pulmonary artery hypertension admitted to paediatric critical care units have high mortality (10%) in comparison with other medical admissions without pulmonary artery hypertension (3.9%).[4] Patients with pulmonary artery hypertension needing invasive ventilation and vasoactive infusions have more than fivefold greater mortality than those who did not.[4] Clinical worsening has been validated as an end point for randomised controlled trials in adult pulmonary artery hypertension therapies.[5–7] Clinical worsening components included events such as hospitalisations, the need for additional therapy, worsening function, lung transplantation, or death. These could be used as suitable end point in paediatric prognostic studies.[8]

Predictors of mortality and morbidity in pulmonary artery hypertension are important to counsel patients/families and guide therapy decisions. Evidence of right ventricular failure, progression of symptoms, WHO functional class ¾,[3,9,10] and elevated brain natriuretic peptide levels[11–13] have been associated with a higher risk of death in children with pulmonary artery hypertension. Six-minute walk distance and functional class are non-invasive surrogate end points that predict long-term outcomes in adults with pulmonary artery hypertension.[14] However, they are difficult to reliably perform in children.[15,16] In a large registry study, older age at diagnosis, lower cardiac index, higher indexed pulmonary vascular resistance, and lack of response to acute vasoreactivity testing were reported to be associated with higher mortality in children with pulmonary artery hypertension.[3] Invasive haemodynamic parameters are usually performed in children at the time of diagnosis or therapy change for pulmonary artery hypertension. Some of these parameters such as mean pulmonary artery pressure/mean

systemic arterial pressure ratio >0.75, mean right atrial pressure >10 mmHg, and indexed pulmonary vascular resistance >20 WUi have also been associated with a higher risk in few studies.[17,18] We aimed to evaluate several directly measured and calculated indices obtained from the initial cardiac catheterisation to predict mid-term outcomes in children with pulmonary artery hypertension.

Materials and methods

This was a single-centre retrospective study conducted at the University of Minnesota Masonic Children's Hospital from 2006 to 2019. Charts were screened based on International Classification of Diseases (ICD) 9 (CM 416.0) and ICD 10 (I27.0, I27.2) codes for pulmonary artery hypertension in our Pediatric Cardiology database. Additional patient data that could not be pulled from the database were accessed through Epic medical record and Pediatric Catheterization Database (PedsCath). Pulmonary artery hypertension was defined as mean pulmonary artery pressure ≥ 25 mmHg at rest, with a mean pulmonary capillary wedge pressure ≤ 15 mmHg and indexed pulmonary vascular resistance ≥ 3 Wood units $\times$ m^2 measured during heart catheterisation.[19] Patients aged less than 18 years at the time of catheterisation were included. Children with pulmonary arterial hypertension (group 2.4) associated with post-capillary obstructive lesions (pulmonary vein stenosis, cor-triatriatum, mitral stenosis, and coarctation) or single ventricles were excluded (Figure 1). The patients included in this study were predominantly in groups 1 (elevation in pulmonary artery pressure with normal pulmonary capillary wedge pressure and includes idiopathic, heritable, HIV, portal hypertension, or CHD) and 3 (developmental lung disorders including BPD, congenital diaphragmatic hernia, and Down syndrome in the absence of CHD), according to the 4th World Symposium Pulmonary Hypertension classification from 2008.[19]

Demographics, clinical data, and haemodynamics measurements from the first cardiac catheterisation after diagnosis of pulmonary artery hypertension were obtained from the medical records. Clinical variables at baseline included pulmonary artery hypertension subgroup, underlying CHD (in pulmonary artery hypertension-CHD), medications at the time of catheterisation, and N-terminal pro-brain natriuretic peptide within 2 months before or after catheterisation.

Directly measured indices

Baseline haemodynamic measurements included mean right atrial pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, pulmonary arterial systolic pressure, pulmonary arterial diastolic pressure, heart rate, systemic pressure, systemic saturation, and oxygen consumption (VO2). VO2 was measured by indirect calorimetry (CCM Express®, Medgraphics Corp, St Paul, Minneapolis, USA) if >10 kg[20,21] or assumed by LaFarge.[22]

Calculated indices

1. Indexed systemic cardiac output (Qsi) and pulmonary blood flow (Qpi) were calculated by the Fick method.[23]
2. Pulmonary vascular resistance was calculated by dividing transpulmonary gradient (mean pulmonary artery pressure – pulmonary capillary wedge pressure) by pulmonary blood flow indexed (Wood units $\times$ m^2).[24]
3. Pulmonary artery compliance was calculated as stroke volume/(pulmonary artery systolic pressure – pulmonary artery diastolic pressure).[25,26] Pulmonary arterial compliance allows for passive arterial expansion during right ventricular systole to accept a large portion of the stroke volume while also allowing for arterial recoil, allowing blood flow to continue during diastole. The change in cross-sectional area or volume over a change in pressure at a particular vessel length is used to calculate compliance.
4. Right ventricular stroke work index was calculated as [mean pulmonary artery pressure – mean right atrium (RA) pressure] $\times$ stroke volume index, where the stroke volume index was calculated as the cardiac index divided by the heart rate.[27,28]
5. Pulmonary artery elastance was calculated as pulmonary artery systolic pressure/stroke volume.[29]
6. Pulmonary artery pulsatility index was calculated as (systolic pulmonary artery pressure – diastolic pulmonary artery pressure)/mean RA pressure.[30]
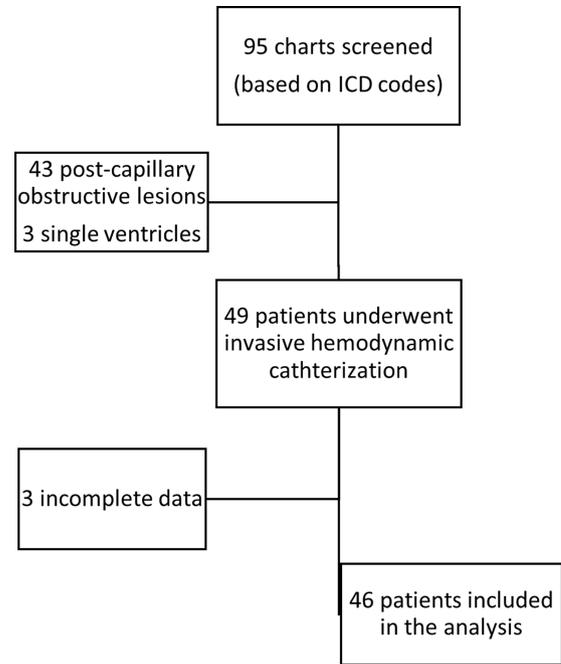
Pulmonary vasodilator testing

According to our institutional protocol, acute vasoreactivity testing was performed in most patients after baseline haemodynamic measurements confirmed the diagnosis of pulmonary artery hypertension. Most pulmonary vasodilator testing was performed using 40 ppm inhaled nitric oxide (iNO) and 100% O$_2$. In those who were on vasodilator therapy, Epoprostenol (n = 2) or Treprostinil (n = 1) in addition to iNO and O$_2$ were used.

Follow-up and outcomes

Patient information was included up until the most recent clinic visit or hospitalisation documented in the electronic medical records. The primary outcome was lung transplantation or death. Secondary outcomes were the creation of reverse Pott's shunt or atrial septostomy, right ventricular dysfunction, or pericardial effusion from right heart failure at the last follow-up. The

Figure 1. Study flow sheet showing patients included in the analysis.

combined adverse outcome was defined as any of the primary or secondary outcomes.

Statistical analysis

Participant characteristics were summarised using median and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables. Continuous variables were compared between groups using the Wilcoxon rank-sum test. Time from catheterisation to adverse outcome was reported using the Kaplan–Meier estimator and the log-rank test. Receiver operating characteristic analysis was used to examine sensitivity, specificity, and area under the receiver operating characteristic curve of each potential baseline predictor of adverse outcomes. Analyses were conducted using R version 4.0.4.

The study was approved by the University of Minnesota institutional review board (IRB).

Results

Patient characteristics

Among 95 charts screened based on ICD codes, 43 with post-capillary obstructive lesions, 3 with single-ventricle physiology, and 3 with incomplete catheterisation data in the medical chart were excluded. Therefore, 46 patients were included in the study for analysis (Fig. 1). The median [interquartile range (IQR)] age of the study cohort was 13.4 [5.8–54.7] months and 57% were males. Five patients had idiopathic pulmonary artery hypertension and 15 had pulmonary artery hypertension-CHD. Nineteen patients with CHD also had associated developmental lung disorders (Table 1). Most of the pulmonary artery hypertension associated with CHD was in patients with intra- or extracardiac shunts. Of note, two patients developed pulmonary artery hypertension of unknown aetiology post-operatively after cardiac surgery for partial anomalous pulmonary venous return and tetralogy of Fallot, respectively. At the time of the first catheterisation, 37% of patients were on medications (eight patients on one medication and nine on more than one medication). Monotherapy consisted of either home oxygen or inhaled nitric oxide or phosphodiesterase-5 inhibitor (sildenafil in 11; tadalafil in 1). Dual or triple therapy consisted of an endothelin receptor antagonist (bosentan in 2, ambrisentan in 1) and/or prostacyclin (treprostinil in 1) in addition to monotherapy. The median duration of medications before the first catheterisation was 78 [26–269] days in 13 patients. The exact duration of therapy was unknown in 4 of 17 patients. Median N-terminal pro-brain natriuretic peptide within 2 months of cardiac catheterisation was 2540 [584–4398] ng/L in 28 patients.

Haemodynamics

The median mean pulmonary artery pressure was 37 [28–52] mmHg and indexed pulmonary vascular resistance was 6.2 [3.6–10.0] WUi, which are elevated and consistent with pulmonary artery hypertension. Median pulmonary artery elastance was higher in patients with combined adverse outcomes compared to those without adverse outcomes (3.4 [1.1–3.9] versus 1.3 [1.0–1.8] mmHg/mL/m^2, p = 0.03). In the entire cohort, median pulmonary artery compliance was 1.4 [IQR 0.9–1.7] mL/mmHg, right ventricular stroke work index was 915 [715–1734] mmHg mL/m^2, and median pulmonary artery pulsatility index was 4.0

[3.0–4.7], with no significant difference comparing patients with versus without adverse outcomes.

Outcomes

After a median [IQR] follow-up of 2.4 [0.8–5.2] years in the entire cohort, nine patients had the combined adverse outcome: one underwent an atrial level shunt, one a reverse Pott's shunt, one had a pericardial effusion, and six died. No patient in this cohort underwent lung transplantation. Moreover, the two patients who had atrial septostomy and a reverse Pott's shunt also had moderately diminished right ventricle function with pericardial effusion. Moderately diminished right ventricle function and pericardial effusion were documented in one of the six patients who died. Right ventricular failure as evident from systolic dysfunction and pericardial effusion were the criteria for performing atrial shunt or reverse Pott's shunt. The patient who underwent atrial shunt creation had previously undergone late repair of a ventricular septal defect (VSD) after sildenafil therapy for 6 months. The patient who had reverse Pott's had severe pulmonary artery hypertension despite maximal therapy with sildenafil, remodulin, and right ventricle dysfunction. He was deemed to be an unsuitable candidate for heart–lung transplantation. The cause of death in the six patients was a pulmonary hypertensive crisis – five in the hospital and one out of the hospital, whose parents chose comfort care. The 1-, 2-, and 3-year combined adverse outcome in our cohort was 11, 17, and 20%, respectively. The Kaplan–Meier estimates include right-censoring as a result of being lost to follow-up. Diagnoses of nine patients with combined adverse outcome are as follows: six had pulmonary artery hypertension associated with CHD (five with more than one level shunt and one VSD). One patient each had porto-pulmonary hypertension, idiopathic pulmonary artery hypertension, and mixed restrictive/obstructive lung disease.

Predictors of outcomes

Comparison of directly measured and calculated haemodynamic variables among the 9 patients who had a combined adverse event versus the remaining 37 who did not are shown in Table 2. The median pulmonary artery mean pressure of the patients who had the combined adverse outcome was significantly higher than those who did not (54 [44–69] versus 34 [28–45] mmHg, p = 0.003). Likewise, the transpulmonary gradient and the indexed pulmonary vascular resistance were significantly elevated in the adverse outcome group at 40 [34–55] mmHg and 10.4 [8.3–24.0] WUi, respectively. The patients who had a combined adverse outcome had higher pulmonary artery pressures (systolic, diastolic, and mean), higher diastolic pressure gradient, higher transpulmonary gradients, higher indexed pulmonary vascular resistance, higher pulmonary artery elastance, and higher right atrial pressure (p < 0.05 each). A pulmonary artery elastance ≥3.15 mmHg/ml had 56% sensitivity and 95% specificity (area under curve (AUC) = 0.74, p = 0.03), while a diastolic pressure gradient ≥24.5 mmHg had 67% sensitivity and 81% specificity (AUC = 0.78, p = 0.009) in predicting the combined adverse outcome (Fig. 2). Table S1 shows the sensitivity and specificity of the haemodynamic parameters.

CHD versus no CHD

Haemodynamic indices of 35 patients with pulmonary artery hypertension associated with CHD were compared to 11 patients

Table 1. Patient characteristics

Variable	Median [IQR] or n [%]
At Baseline	
Age at diagnosis of PAH (months)	13.4 [4.0–47.1]
Age at catheterisation (months)	13.4 [5.8–54.7]
Male	26/46 (57%)
Caucasian	25/46 (54%)
Weight (kg)	9.2 [5.4–15.4]
Height (cm)	72 [58–97]
Diagnosis subgroup	
• PAH associated with CHD	15
• Developmental lung disorder	4
• Both CHD and lung disorder	19
• Idiopathic PAH	5
• Porto-pulmonary hypertension and lung disorder	1
• Mixed restrictive/obstructive lung disease	1
• Both CHD and haematological disorder	1
Underlying CHD	35/46 (76%)
• ASD	5
• PDA	6
• VSD	7
• Combined (more than one level shunt)	10
• AVSD	4
• Dural AV fistula	1
• Post-operative	2
Underlying developmental lung disorder	24/46 (52%)
• Chronic lung disease/bronchopulmonary dysplasia	14
• Congenital diaphragmatic hernia	2
• Down syndrome	12
• Lung hypoplasia	2
• More than one aetiology	6
Medications (at the time of catheterisation)	17/46 (37%)
• Phosphodiesterase-5 inhibitor	12
• Endothelin receptor antagonist	3
• Home oxygen	8
• Prostacyclin	1
• Inhaled nitric oxide	6
NT pro-BNP within 2 months (before or after) catheterisation (n = 28)	2540 [584–4398]
At follow-up	
Duration of follow-up after catheterisation (years)	2.4 [0.8–5.2]
Age at last follow-up (years)	5.0 [2.6–11.1]
Medications (at last follow-up)	22/46 (48%)

(Continued)

Table 1. (Continued)

Variable	Median [IQR] or n [%]
Outcome variables	
Combined adverse outcome	9/46 (20%)
Death	6
Lung transplantation	0
Atrial septostomy or reverse Pott's shunt	2
Moderately diminished right ventricle function and pericardial effusion at last follow-up	1

IQR = interquartile range, PAH = pulmonary artery hypertension, IPAH/HPAH = idiopathic or hereditary pulmonary arterial hypertension, PAH-CHD = pulmonary arterial hypertension associated with CHD, NT pro-BNP = N-terminal pro-brain natriuretic peptide, ASD = Atrial Septal Defect, VSD = ventricular septal defect, AVSD = atrioventricular septal defect, PDA = patent ductus arteriosus.

without CHD (Table S2). Qpi, pulmonary stroke volume, and pulmonary artery compliance were higher and pulmonary artery elastance was lower in patients with pulmonary artery hypertension associated with CHD ($p > 0.05$).

Discussion

We describe the first comprehensive paediatric evaluation of the relationship between invasive haemodynamic parameters and long-term adverse outcomes in pulmonary arterial hypertension. We found that invasive haemodynamic parameters measured at the time of first cardiac catheterisation after diagnosis of pulmonary artery hypertension can predict adverse outcomes in children. Pulmonary artery pressures (mean, systolic, and diastolic), pulmonary vascular resistance, transpulmonary gradient, diastolic pulmonary gradient, and pulmonary artery elastance were significantly higher in patients who experienced the combined adverse outcome. Pulmonary artery systolic pressure, mean pulmonary artery pressure, and pulmonary artery diastolic pressure each had the highest sensitivity, and pulmonary artery elastance >3.15 mmHg/mL/m^2 had the highest specificity to predict the adverse outcomes. This information can help prognosticate outcomes and possibly guide therapy decisions to help improve outcomes.

In our study, the majority of patients with pulmonary artery hypertension had underlying CHD (76%) and only 11% were idiopathic. These results are similar to two epidemiological studies conducted in the US and a Dutch registry [1,2,31] but different (reporting a higher proportion of idiopathic pulmonary artery hypertension) than other registries.[3,15] There was no significant difference in age, weight, and height between patients who did and did not have an adverse outcome in our study. Low body weight z-score at the time of presentation has been reported to be associated with increased mortality on multivariable analysis.[9] At 4 years from enrolment and 7 years from diagnosis in our study, the survival rate was similar between idiopathic pulmonary artery hypertension or hereditary pulmonary arterial hypertension and CHD-associated pulmonary artery hypertension cohorts.[32] Similarly, no significant difference in combined adverse outcomes could be demonstrated between patients with and without CHD.

Elevated right ventricle afterload leading to right ventricle failure has been thought to be the main determinant of mortality in pulmonary artery hypertension.[33] Right ventricle afterload consists
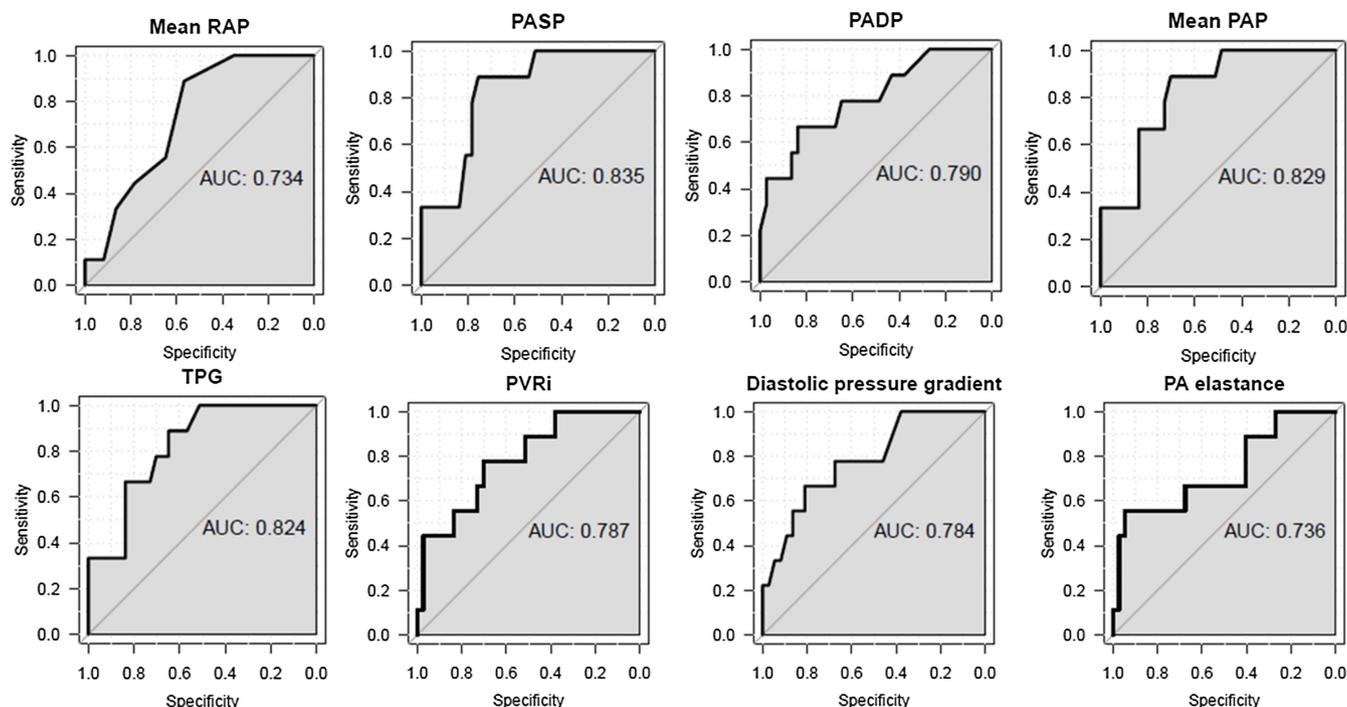
Figure 2. Receiver operating characteristic analysis to examine sensitivity, specificity, and area under the curve for haemodynamic variables.

of static components and pulsatile components. Static components, including mean pulmonary artery pressure and indexed pulmonary vascular resistance, confirm the diagnosis, but their correlation to clinical status and survival has been limited.[3] Moreover, pulmonary artery hypertension leads to right ventricle hypertrophy and elevated pulmonary artery pulsatility index in all patients. This probably accounts for the similar pulmonary artery pulsatility index in the groups with and without adverse events, particularly at the time of cardiac catheterisation when the right ventricle systolic function is preserved.

In a systematic review,[34] the combined hazard ratio was calculated, using random-effects meta-analysis, for variables studied in at least three non-overlapping cohorts. It identified WHO functional class (HR 2.7), N-terminal pro-brain natriuretic peptide (HR 3.2), mean right atrial pressure (HR 1.1), cardiac index (HR 0.7), indexed pulmonary vascular resistance (HR 1.3), and acute vasodilator response (HR 0.3) as significant prognostic factors ($p \leq 0.001$). This is similar to our data in which indexed pulmonary vascular resistance >8.0 Wood units $\times$ m^2 had 78% sensitivity and 70% specificity (AUC = 0.79, $p = 0.009$) and mean right atrial pressure >7.5 mmHg had 89% sensitivity and 57% specificity (AUC = 0.73, $p = 0.03$) in predicting an adverse outcome. However, N-terminal pro-brain natriuretic peptide was not available to us around the time of catheterisation in 18 patients and acute vasoreactivity testing was not performed in 8 cases, limiting our ability to perform an adequate analysis.

Several paediatric studies have demonstrated that lower mean pulmonary artery pressure has been predictive of better survival, both before and after vasodilator therapy.[35–38] In adults with group 1 pulmonary hypertension (PH), increasing diastolic pulmonary gradient (DPG) was strongly associated with increased mortality during 5 years of follow-up, even after risk adjustment.[39] We found that mean pulmonary artery pressure and diastolic pressure gradient (Table S1) were good predictors of an adverse outcome, in agreement with above-mentioned studies. At the time of the study,

a pulmonary artery mean pressure of >25 mmHg was used to define pulmonary artery hypertension. However, we are aware that the criterion is now >20 mmHg.[40]

In a Dutch study, invasive pulsatile parameters such as pulmonary arterial compliance and pulmonary stroke volume were associated with pulmonary artery hypertension disease severity and predicted survival independent of indexed pulmonary vascular resistance.[41] In the same study, higher pulmonary artery compliance ≥ 0.9 mL/mmHg/m^2 was associated with improved survival, independent of WHO functional class, and therapy and was similar to an adult study.[26] In contrast, another study showed that indexed pulmonary arterial compliance either <0.70 mL/mmHg/m^2 or >1.25 mL/mmHg/m^2 was associated with decreased freedom from death or lung transplant.[42] In our cohort, pulmonary artery compliance ≥ 0.93 mL/mmHg had 56% sensitivity and 84% specificity (AUC = 0.68, $p = 0.11$) but was not a predictor of adverse outcomes. These differences could be due to the different disease characteristics; in the Dutch and adult studies, the patients with pulmonary artery hypertension-CHD had advanced irreversible pulmonary artery hypertension. In several paediatric and adult studies, pulmonary stroke volume was shown to be a predictor of survival.[10,43,44] In our study, pulmonary stroke volume was not a predictor of adverse outcomes (AUC = 0.60, $p = 0.35$).

Right ventricular stroke work, the product of mean pulmonary artery pressure and stroke volume, integrates contractility, afterload, and ventricular–vascular coupling. Patients with high right ventricle afterload have high right ventricular stroke work provided ventricular–vascular coupling is unchanged. In one study, higher right ventricular stroke work predicted the need for atrial septostomy and death (29). Right ventricular stroke work and pulmonary artery pulsatility index can be estimated echocardiographically and have a linear correlation with invasively derived values.[45,46] Similarly, in our cohort, right ventricular stroke work index was higher in patients who had combined adverse outcomes (1613 versus 888 g/m^2, $p = 0.24$). But the variables used to derive

Table 2. Haemodynamic measurements

Variables	Overall (n = 46)	Combined adverse outcome (n = 9)	No adverse outcome (n = 37)	p-Value
Directly measured variables				
Age at diagnosis of PAH (months)	13.4 [5.8–54.7]	44.4 [12.0–114]	8.4 [6.0–46.8]	0.23
Weight (kg)	9.2 [5.4 - 15.4]	14 [8–24]	9 [5–15]	0.17
Height (cm)	72 [58 – 97]	97 [71–118]	97 [71–118]	0.16
NT pro-BNP	2540 [584–4398]	2520 [1277-17091]	1478 [351-4056]	0.72
VO^2 (measured/LaFarge)	150 [148–160]	150 [148–168]	150 [148–160]	0.52
Heart rate	120 [105–134]	105 [100–120]	120 [107–134]	0.25
Mean RAP (mmHg)	8 [6–10]	9 [8–11]	7 [6–9]	0.03*
PASP (mmHg)	54 [41–70]	70 [66–91]	47 [40–64]	0.002*
PADP (mmHg)	24 [18–38]	41 [26–52]	21 [17–30]	0.008*
mPAP (mmHg)	37 [28–52]	54 [44–69]	34 [28–45]	0.003*
mPCWP (mmHg)	10 [9–11]	11 [10–13]	10 [9–11]	0.07
Mean SAP	57 [53–67]	62 [55–67]	57 [52–67]	0.58
Calculated variables				
TPG (mmHg)	26 [19–40]	40 [34–55]	24 [18–36]	0.003*
PVRi (Wood units/m^2)	6.2 [3.6–10.0]	10.4 [8.3–24.0]	4.7 [3.5–9.3]	0.009*
Diastolic pulmonary gradient	14 [8–28]	30 [16–38]	12 [7–20]	0.009*
PA elastance indexed (mmHg/mL/m^2)	1.4 [1.0–2.1]	3.4 [1.1–3.9]	1.3 [1.0–1.8]	0.03*
Qpi (L/min/m^2)	4.5 [3.1–5.1]	3.1 [2.4–4.8]	4.5 [3.3–5.4]	0.20
Qsi (L/min/m^2)	3.5 [2.9–4.5]	3.7 [2.8–4.8]	3.4 [3.0–4.4]	0.72
PA pulse pressure (mmHg)	30 [24–36]	37 [29–39]	29 [23–32]	0.09
PSVi (mL/m^2)	38 [26–49]	26 [19–50]	38 [28–46]	0.35
PA compliance indexed (mL/mmHg)	1.4 [0.9–1.7]	0.9 [0.6–1.5]	1.4 [1.0–1.8]	0.11
RVSWI (g/m^2 or mmHg × mL/m^2)	915 [715–1734]	1613 [955–1749]	888 [692–1607]	0.24
PAPi (no units)	4.0 [3.0–4.7]	3.8 [3.2–4.6]	4.1 [3.0–5.2]	0.92

mPAP = mean pulmonary arterial pressure, NT pro-BNP = N-terminal pro-brain natriuretic peptide, PA = pulmonary artery, PASP = pulmonary arterial systolic pressure, PADP = pulmonary arterial diastolic pressure, PAPi = pulmonary artery pulsatility index, PCWP = pulmonary capillary wedge pressure, PSVi = pulmonary stroke volume index, PVRi = indexed pulmonary vascular resistance, Qpi = pulmonary flow index, Qsi = systemic flow index, RAP = right atrial pressure, RVSWI = Right ventricular stroke work index, SAP = systemic arterial pressure, TPG = transpulmonary gradient. *p < 0.05 is significant.

right ventricular stroke work index and pulmonary artery pulsatility index were not routinely measured in our echocardiograms and hence were not evaluated in this study.

Pulmonary artery pulsatility index has been shown to predict right ventricle failure in patients after acute inferior myocardial infarction[47] and after LVAD support.[48,49] Significantly lower pulmonary artery pulsatility index index (0.96 versus 3.6) was documented in patients requiring prolonged inotropes/pulmonary vasodilators after continuous flow-left ventricular assist device (CF-LVAD) placement.[30] Decreased pulmonary artery pulsatility index was shown to also be an independent predictor of mortality in adults with group 1 pulmonary artery hypertension.[50,51] To our knowledge, this is the first report describing pulmonary artery pulsatility index as a potential predictor of adverse outcomes. However, unlike in adult studies, the difference in adverse outcomes between the lowest quartile and the rest of the patients was not significant. This could be because the two adult studies were performed in registry data from the 1980s, and survival in the current era has improved with pulmonary vasodilator therapies. Another reason that pulmonary artery pulsatility index was not a predictor of an adverse outcome could be due to our relatively small sample size.

There are limitations to our study. The number of patients in each diagnostic group is relatively small which limited subgroup analyses of haemodynamic pulmonary artery hypertension indices and adverse outcomes. The retrospective nature is vulnerable to measurement bias. Vasodilator therapy was given to 37% of patients before catheterisation, likely based on clinical status. This could have an impact on baseline haemodynamics and confound association with outcomes. However, statistically significant relationships between various indices and adverse outcomes suggest that they may have clinical utility. In addition, the number of patients with adverse outcomes is lower, which leads to the receiver operating characteristic analysis being underpowered and should be taken into consideration during interpretation.

Conclusion

Invasive haemodynamics performed at initial cardiac catheterisation after diagnosis appears to predict outcomes in paediatric

pulmonary artery hypertension. In particular, higher mean pulmonary artery pressures, pulmonary vascular resistance, right ventricle stroke work, pulmonary artery elastance, and diastolic pressure gradient predict adverse outcomes such as death, creation of Atrial Septal Defect (ASD), reverse Pott's shunt, and pericardial effusion from right ventricle failure. This information may be used in guiding therapy and counselling families. Studies with larger numbers of patients are needed to confirm these findings. Further study could delineate the value of longitudinal measurement of indices in their ongoing clinical management.

References

1. Li L, Jick S, Breitenstein S, Hernandez G, Michel A, Vizcaya D. Pulmonary arterial hypertension in the USA: an epidemiological study in a large insured pediatric population. Pulm Circ 2017; 7: 126–136. DOI: 10.1086/690007.

2. van Loon RLE, Roofthooft MTR, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 2011; 124: 1755–1764. DOI: 10.1161/CIRCULATIONAHA.110.969584.

3. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension. Circulation 2012; 125: 113–122. DOI: 10.1161/CIRCULATIONAHA.111.026591.

4. Morell E, Gaies M, Fineman JR, et al. Mortality from pulmonary hypertension in the pediatric cardiac ICU. Am J Respir Crit Care Med 2021; 204: 454–461. DOI: 10.1164/RCCM.202011-4183OC.

5. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015; 373: 2522–2533. DOI: 10.1056/NEJMoa1503184.

6. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369: 809–818. DOI: 10.1056/NEJMOA1213917/SUPPL_FILE/NEJMOA1213917_DISCLOSURES.PDF.

7. Galiè N, Barberà JA, Frost AE, et al. Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension. N Engl J Med 2015; 373: 834–844. DOI: 10.1056/NEJMoa1413687.

8. Beghetti M, Brand M, Berger RMF, et al. Meaningful and feasible composite clinical worsening definitions in paediatric pulmonary arterial hypertension: an analysis of the TOPP registry. Int J Cardiol 2019; 289: 110–115. DOI: 10.1016/j.ijcard.2019.04.062.

9. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 2010; 96: 1401–1406. DOI: 10.1136/hrt.2009.182378.

10. van Loon RLE, Roofthooft MTR, Delhaas T, et al. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. Am J Cardiol 2010; 106: 117–124. DOI: 10.1016/j.amjcard.2010.02.023.

11. Bernus A, Wagner BD, Accurso F, Doran A, Kaess H, Ivy DD. Brain natriuretic peptide levels in managing pediatric patients with pulmonary arterial hypertension. Chest 2009; 135: 745–751. DOI: 10.1378/CHEST.08-0187.

12. Lammers AE, Hislop AA, Haworth SG. Prognostic value of B-type natriuretic peptide in children with pulmonary hypertension. Int J Cardiol 2009; 135: 21–26. DOI: 10.1016/J.IJCARD.2008.03.009.

13. van Albada ME, Loot FG, Fokkema R, Roofthooft MTR, Berger RMF. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res 2008; 63: 3–327. DOI: 10.1203/pdr.0b013e318163a2e7.

14. Wronski SL, Mordin M, Kelley K, et al. The role of noninvasive endpoints in predicting long-term outcomes in pulmonary arterial hypertension. Lung 2020; 198: 65–86. DOI: 10.1007/S00408-019-00289-2.

15. Berger RMF, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012; 379: 537–546. DOI: 10.1016/S0140-6736(11)61621-8.

16. Takatsuki S, Dunbar Ivy D. Current challenges in pediatric pulmonary hypertension nih public access. Semin Respir Crit Care Med 2013; 34: 627–644. DOI: 10.1055/s-0033-1356461.

17. Ivy DD, Rosenzweig EB, Lemari JC, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with Bosentan in real-world clinical settings. Am J Cardiol 2010; 106: 1332–1338. DOI: 10.1016/J.AMJCARD.2010.06.064.

18. Douwes JM, van Loon RLE, Hoendermis ES, et al. Acute pulmonary vasodilator response in paediatric and adult pulmonary arterial hypertension: occurrence and prognostic value when comparing three response criteria. Eur Heart J 2011; 32: 3137–3146. DOI: 10.1093/EURHEARTJ/EHR282.

19. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54: S43–S54. DOI: 10.1016/j.jacc.2009.04.012.

20. da Rocha EEM, Alves Véria GF, da Fonseca RBV. Indirect calorimetry: methodology, instruments and clinical application. Curr Opin Clin Nutr Metab Care 2006; 9: 247–256. DOI: 10.1097/01.mco.0000222107.15548.f5.

21. Black C, Grocott MPW, Singer M. Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods. Br J Anaesth 2015; 114: 261–268. DOI: 10.1093/bja/aeu365.

22. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. Cardiovasc Res 1970; 4: 23–30. DOI: 10.1093/cvr/4.1.23.

23. Fagard R, Conway J. Measurement of cardiac output: Fick principle using catheterization. Eur Heart J 1990; 11: 1–5. DOI: 10.1093/eurheartj/11.suppl_I.1.

24. Manohar M, Goetz TE. Pulmonary vascular resistance of horses decreases with moderate exercise and remains unchanged as workload is increased to maximal exercise. Equine Vet J 1999; 117–121. https://pubmed.ncbi.nlm.nih.gov/32119267/.

25. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The critical role of pulmonary arterial compliance in pulmonary hypertension. Ann Am Thorac Soc 2016; 13. DOI: 10.1513/AnnalsATS.201509-599FR.

26. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 2006; 47: 799–803. DOI: 10.1016/J.JACC.2005.09.054.

27. Ibe T, Wada H, Sakakura K, et al. Right ventricular stroke work index. Int Heart J 2018; 59: 1047–1051. DOI: 10.1536/ihj.17-576.

28. Di Maria MV, Younoszai AK, Mertens L, BF Landeck, Ivy D D, 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: 1342–1347. DOI: 10.1136/heartjnl-2013-305298.

29. Silber D, Lachmann J. Invasive hemodynamics of pulmonary disease and the right ventricle. Interv Cardiol Clin 2017; 6: 329–343. DOI: 10.1016/j.iccl.2017.03.004.

30. Aggarwal V, Tume SC, Rodriguez M, et al. Pulmonary artery pulsatility index predicts prolonged inotrope/pulmonary vasodilator use after implantation of continuous flow left ventricular assist device. Congenit Heart Dis 2019; 14: 1130–1137. DOI: 10.1111/chd.12860.

31. Abman SH, Mullen MP, Sleeper LA, et al. Characterisation of paediatric pulmonary hypertensive vascular disease from the PPHNet Registry. Eur Respir J 2022; 59: 2003337. DOI: 10.1183/13993003.03337-2020.

32. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated

pulmonary arterial hypertension (from the REVEAL Registry). Am J Cardiol 2014; 113: 147–155. DOI: 10.1016/j.amjcard.2013.09.032.

33. Lankhaar JW, Westerhof N, Faes TJC, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006; 291: H1731–H1737. DOI: 10.1152/AJPHEART.00336.2006.

34. Ploegstra MJ, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. Int J Cardiol 2015; 184: 198–207. DOI: 10.1016/j.ijcard.2015.01.038.

35. Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999; 99: 1197–1208. DOI: 10.1161/01.CIR.99.9.1197.

36. Clabby ML, Canter CE, Moller JH, Bridges ND. Hemodynamic data and survival in children with pulmonary hypertension. J Am Coll Cardiol 1997; 30: 554–560. DOI: 10.1016/S0735-1097(97)00155-1.

37. Wagner BD, Takatsuki S, Accurso FJ, Ivy DD. Evaluation of circulating proteins and hemodynamics towards predicting mortality in children with pulmonary arterial hypertension. In: Kuwana M (ed). PLoS One. vol. 8, 2013: e80235, DOI: 10.1371/journal.pone.0080235.

38. Evers PD, Quinn P, Critser PJ, Frank BS, Alnoor M, Armsby LB. Prognostic value of longitudinal vasoreactivity in pediatric pulmonary hypertension. Pulm Circ 2022; 12: e12152. DOI: 10.1002/pul2.12152.

39. Mazimba S, Mejia-Lopez E, Black G, et al. Diastolic pulmonary gradient predicts outcomes in group 1 pulmonary hypertension (analysis of the NIH primary pulmonary hypertension registry). Respir Med 2016; 119: 81–86. DOI: 10.1016/j.rmed.2016.08.024.

40. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 53: 1801913. DOI: 10.1183/13993003.01913-2018.

41. 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: 1370–1377. DOI: 10.1016/j.ijcard.2012.12.080.

42. Sajan I, Manlhiot C, Reyes J, McCrindle BW, Humpl T, Friedberg MK. Pulmonary arterial capacitance in children with idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease: relation to pulmonary vascular resistance, exercise capacity, and survival. Am Heart J 2011; 162: 562–568. DOI: 10.1016/j.ahj.2011.06.014.

43. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007; 28: 1250–1257. DOI: 10.1093/eurheartj/ehl477.

44. D'Alonzo GE. Survival in patients with primary pulmonary hypertension. Ann Intern Med 1991; 115: 343–349. DOI: 10.7326/0003-4819-115-5-343.

45. Di Maria MV, Burkett DA, Younoszai AK, Landeck BF, et al. Echocardiographic estimation of right ventricular stroke work in children with pulmonary arterial hypertension: comparison with invasive measurements. J Am Soc Echocardiogr 2015; 28: 1350–1357. DOI: 10.1016/j.echo.2015.07.017.

46. Mirza S, Khalif A, Khodjaev S, et al. Echocardiographic estimation of pulmonary artery pulsatility index in pulmonary hypertension. J Heart Lung Transpl 2019; 38: S492. DOI: 10.1016/j.healun.2019.01.1252.

47. Korabathina R, Heffernan KS, Paruchuri V, et al. The pulmonary artery pulsatility index identifies severe right ventricular dysfunction in acute inferior myocardial infarction. Catheter Cardiovasc Interv 2012; 80: 593–600. DOI: 10.1002/ccd.23309.

48. Morine KJ, Kiernan MS, Pham DT, Paruchuri V, Denofrio D, Kapur NK. Pulmonary artery pulsatility index is associated with right ventricular failure after left ventricular assist device surgery. J Card Fail 2016; 22: 110–116. DOI: 10.1016/j.cardfail.2015.10.019.

49. Kang G, Ha R, Banerjee D. Pulmonary artery pulsatility index predicts right ventricular failure after left ventricular assist device implantation. J Heart Lung Transpl 2016; 35: 67–73. DOI: 10.1016/j.healun.2015.06.009.

50. Mazimba S, Welch TS, Mwansa H, et al. Haemodynamically derived pulmonary artery pulsatility index predicts mortality in pulmonary arterial hypertension. Heart Lung Circ 2019; 28: 752–760. DOI: 10.1016/j.hlc.2018.04.280.

51. Welch TS, Bilchick KC, Kennedy JLW, et al. Hemodynamically derived pulmonary artery pulsatility index predicts adverse clinical outcomes in group 1 pulmonary hypertension. (Analysis of the NIH Pulmonary Hypertension Registry). J Card Fail 2016; 22: S3–S4. DOI: 10.1016/j.cardfail.2016.06.022.