Pulmonary Arterial Capacitance Index Is a Strong Predictor for Adverse Outcome in Children with Idiopathic and Heritable Pulmonary Arterial Hypertension

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Objectives To evaluate the clinical utility of pulmonary artery capacitance index (PACi) in the assessment of disease severity and prognostic value in children with idiopathic and heritable pulmonary arterial hypertension (PAH).

Study Design PACi is defined as the ratio of stroke volume index over pulmonary pulse pressure. A retrospective study was performed to compare PACi, brain natriuretic peptide (BNP), 6-minute walk distance, New York Heart association (NYHA) functional class, and adverse outcomes (hospitalization due to heart failure, lung transplantation, and cardiac mortality) in 72 Japanese children (10 ± 3.6 years) with idiopathic and heritable PAH.

Results PACi had significant correlations with pulmonary vascular resistance index (r =–0.73, P < .0001), BNP levels (r = –0.40, P = .0008), and 6-minute walk distance (r = 0.57, P < .05). Statistically significant differences in PACi were observed between NYHA functional class II vs combined III and IV (median; 1.1 vs 0.6 mL/mm Hg/m^2, respectively, P < .05). There were 25 of 72 (35%) children who had an adverse event including initiation of hospitalization due to heart failure, lung transplantation, and death. Cumulative event-free survival rate was significantly lower when PACi was <0.85 mL/mm Hg/m^2 (log-rank test, P < .0001).

Conclusions PACi correlated with BNP and NYHA functional class and may serve as a strong prognostic marker in children with idiopathic and heritable PAH. *(J Pediatr 2017;180:75-9).*

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling, leading to right ventricular (RV) failure and cardiac death.[1-3] Obliteration of the pulmonary vascular bed by cell proliferation and thrombosis leads to increasing vascular stiffness, decreasing compliance, and worsening RV function.[4-6] Pulmonary arterial capacitance index (PACi) is defined as stroke volume index divided by pulmonary artery pulse pressure. PACi reflects the pulmonary vascular compliance with each RV contraction and improves characterization of RV afterload beyond pulmonary vascular resistance. Therefore, PACi is a useful marker in the assessment of the RV-pulmonary arterial coupling and may be associated with RV failure. Recent published studies have demonstrated that reduced PACi was associated with cardiac mortality in adults with PAH.[7-9]

Although previous studies in pediatric patients with various forms of PAH have demonstrated the clinical application of PACi in children with idiopathic and heritable PAH,[10,11] its prognostic value and correlation with disease severity have not been investigated fully. The aim of this study was to assess the clinical utility of PACi for evaluating disease severity and predicting outcomes in children with idiopathic and heritable PAH.

Methods

We retrospectively reviewed hemodynamic data evaluated by cardiac catheterization and clinical data of 72 children diagnosed with idiopathic and heritable PAH. All children (18 years or younger of age at diagnosis) were followed at Toho University Omori Medical Center (Tokyo, Japan) between 1998 and 2015. Patients with associated PAH due to congenital heart disease, secondary to left-sided obstructive lesions (pulmonary venous hypertension), or persistent pulmonary hypertension of the newborn were excluded. The diagnosis of idiopathic and heritable PAH was

BNP	Brain natriuretic peptide
NYHA	New York Heart Association
PACi	Pulmonary arterial capacitance index
PAH	Pulmonary arterial hypertension
PVR	Pulmonary vascular resistance
PVRi	Pulmonary vascular resistance index
RV	Right ventricular
6MWD	6-minute walk distance

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established according to echocardiography, blood test including autoantibodies and liver function, pulmonary function tests, pulmonary ventilation-perfusion scans, genetic testing, and catheterization. All children were enrolled in a protocol approved by the institutional review board at Toho University Omori Medical Center.

New York Heart Association (NYHA) functional class was evaluated in children who were 6 years of age or older, and a 6-minute walk distance (6MWD) was performed in children who were 5 years of age or older. Brain natriuretic peptide (BNP) levels, 6MWD, echocardiography, and assessment of NYHA functional class were evaluated within 3 days of right heart catheterization.

At cardiac catheterization, the patients underwent mild sedation with the use of midazolam without mechanical ventilation. Right heart catheterization was performed with a balloon-tipped, flow-directed Swan-Ganz catheter and systemic arterial catheter for monitoring. Hemodynamic measurements included right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, systemic blood pressure, and oxygen saturation. Accordingly, we calculated pulmonary vascular resistance index (PVRi) (mean pulmonary artery pressure minus pulmonary capillary wedge pressure divided by cardiac index) and pulmonary vascular resistance/systemic vascular resistance index ratio. Cardiac output was obtained by the Fick method by use of the LaFarge estimation, and cardiac index was calculated. PACi was expressed as the stroke volume/pulmonary artery pulse pressure indexed to body surface area (mL/mm Hg/m^2). Stroke volume was calculated as cardiac output divided by heart rate and pulmonary pulse pressure expressed as the difference between the systolic and diastolic pulmonary artery pressures. Acute pulmonary vasodilator testing also was tested with 100% of oxygen, and we evaluated response to oxygen as a vasodilator agent. Cardiac catheterization was performed at time of diagnosis except for 2 patients with NYHA functional class IV. For these patients, hemodynamic variables were evaluated at 2 and 3 months after diagnosis, respectively, because of disease severity.

Statistical Analyses

Categorical values are expressed as percentages and continuous variables as means with SDs for data with a normal distribution and median and range for non-normally distributed data. A composite outcome included hospitalization due to heart failure, lung transplantation, and cardiac mortality. Only the first adverse event was considered in each patient. The correlations with 6MWD, echocardiographic data, BNP levels, and hemodynamic variables were determined with the Pearson correlation coefficient. Mann-Whitney *U* test was used for PACi between NYHA functional class II and III or IV and PACi between patients with and without adverse events. Differences between the hemodynamic data including PACi before and after acute vasoreactivity testing were performed with a paired *t* test or Wilcoxon signed-rank test, as appropriate. The receiver operating characteristic curve was calculated from a logistic regression to assess optimal cut-off values for the prediction of the adverse outcome. The Kaplan-Meier method was used to approximate the adverse events with the log-rank test. The association between baseline variables and adverse events was evaluated with multivariable Cox proportional hazards analysis. The factors entered into the Cox regression models for composite outcomes included age, sex, idiopathic or familial, follow-up periods, BNP levels, 6MWD, NYHA functional class, treatment (use of epoprostenol), hemodynamic variables, and PACi at diagnosis. The level of statistical significance was defined as a *P* value of .05. Analyses were conducted with Statmate III for Windows (Atoms Co, Tokyo, Japan).

Results

Table I presents the clinical characteristics of the pediatric patients. Overall, 55 patients with idiopathic PAH and 17 with heritable PAH were enrolled. The age at diagnosis was 9.8 ± 3.7 years, with 38 male and 34 female patients. In all, 50 children (69%) were administrated epoprostenol infusion therapy during follow-up, and the remaining 22 children received oral vasodilators.

Correlation with BNP, 6MWD, Echocardiographic Measurements, and Hemodynamics

All children had plasma BNP levels performed, and 6MWD was measured in 63 patients (**Table I**). Nine children were not evaluated for 6MWD because of severe PAH or age younger than 5 years. PACi had significant but weak correlations with plasma BNP levels and 6MWD (r = -0.40, P = .0008; r = 0.57, P = .005, respectively) (**Figure 1**; available at www.jpeds.com). Among echocardiographic measurements, only tricuspid regurgitation velocities had significant negative correlation with PACi (r = −0.59, P < .0001), whereas there were no significant associations between PACi and other measures, such as RV myocardial performance index, tricuspid annular plane systolic excursion, and tricuspid e′ velocity (r = −011, P = .45; r = 0.17, P = .22; r = 0.18, P = .20, respectively). In addition, PACi had a significant correlation with hemodynamic measurements

Table I. Demographic data of study populations

Characteristics	
Idiopathic/heritable	55/17
Age at diagnosis, y, mean ± SD	9.8 ± 3.7
Age at evaluation, y, mean ± SD	10 ± 3.6
Sex, male/female	38/34
Laboratory data	Median (range)
BNP, pg/mL	53.6 (3.5-1380)
6MWD, m, ≥5 y (n = 63)	407 (165-595)
NYHA functional class, ≥6 y (n = 63)	Class II; 19 III; 42, IV; 2
Hemodynamics by right heart catheterization	Mean ± SD, median (range)
Mean right atrial pressure, mm Hg	8 ± 4
Systolic pulmonary artery pressure, mm Hg	96 ± 25
Diastolic pulmonary artery pressure, mm Hg	51 ± 17
Mean pulmonary artery pressure, mm Hg	68 ± 19
PVRi, unit·m^2	19.9 (7.1-43.0)
Pulmonary/systemic vascular resistance ratio	0.92 (0.27-1.77)
Cardiac index, L/min/m^2	3.0 (2.0-5.2)