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Active right atrial emptying fraction predicts reduced survival and increased adverse events in childhood pulmonary arterial hypertension☆,☆☆

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ABSTRACT

Background: Right atrial (RA) function has been studied rarely in childhood pulmonary arterial hypertension (PAH). We sought to determine if RA and right ventricular (RV) area changes measured by echocardiography predicted outcomes.
Methods: We reviewed data from children with PAH undergoing cardiac catheterization and echocardiography. RA and RV areas were obtained from the apical 4-chamber view. Clinical worsening indicated initiation of parenteral prostanoid therapy, heart and/or lung transplantation, Potts shunt surgery or death.
Results: We studied 57 children (27 females), median age 3 years (range 0.30–17 years), body surface area 0.56 m2 (0.2–1.8), follow up 3 years (0.21–8.35), time to clinical worsening was 1.14 years (0.03–6.14) and mortality was 1.55 years (range 0.88–4.95). We determined from receiver operator curves that RA active emptying fraction (RA EaF) ≥60% predicted clinical worsening (sensitivity 78%, specificity 69%, AUC 0.7) and mortality (sensitivity 100%, specificity 65%, AUC 0.82). RV fractional area change (RVFAC) <25% predicted clinical worsening (sensitivity 72%, specificity 79%, AUC 0.85) and death (sensitivity 67%, specificity 69%, AUC 0.77). The combination of RA EaF ≥60% and RVFAC <33% were best predictors of clinical worsening (sensitivity 72%, specificity 82%, partial AUC 0.65) and mortality (sensitivity 100%, specificity 77%, partial AUC 0.75).
Conclusion: In childhood PAH, RA EaF ≥ 60% and RVFAC <25% were associated with poor outcomes. RA EaF ≥60% and RVFAC <33% were best predictors of clinical worsening and may be useful markers in children with PAH who require closer observation and more intensive therapy.

1. Introduction

Clinical deterioration in children with pulmonary arterial hypertension often accompanies worsening right ventricular function. Increased right atrial pressure, measured at cardiac catheterization, or the echocardiographic and clinical surrogates, may coexist with decreased right ventricular function and herald a poor prognosis. [1,2] However, in children increased right atrial pressure may occur late in disease progression. [3–6] Recent studies suggest that right atrial compensatory mechanisms are apparent before clinical and echocardiographic signs of right ventricular dysfunction in adults with pulmonary arterial hypertension. [7–11] There are important phenotypic and hemodynamic differences between adults and children with pulmonary arterial hypertension. [5,6,12,13] Cardiac catheterization is considerably more challenging in infants and young children than in adults with pulmonary arterial hypertension and non-invasive risk assessment

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may be of huge benefit. Therefore, we sought to determine if right atrial and right ventricular area changes measured by echocardiography influence event free survival and mortality in childhood pulmonary arterial hypertension.

2. Methods

Informed and signed consent was obtained from each subject as part of a prospective registry and non- invasive evaluation study of the pediatric pulmonary hypertension service. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the University of Alberta Human Research Committee.

We undertook a retrospective review of the collected data from all children with pulmonary arterial hypertension undergoing diagnostic cardiac catheterization and echocardiography on the same day. We evaluated data collected between April 2008–April 2016 on all new (incident) patients presenting with pulmonary hypertension in whom the diagnosis of PAH was confirmed at the cardiac catheterization.

We included all children with a mean pulmonary arterial pressure ≥ 25 mmHg and a pulmonary arterial occlusion or left atrial pressure ≤ 15 mmHg according to the definition of pulmonary arterial hypertension. [14,15] We excluded children with pulmonary vein stenosis and atrial septal defects.

Clinical worsening was defined as initiation of parenteral prostanoid therapy, lung transplantation, heart and lung transplantation, Potts shunt surgery or death. The date of cardiac catheterization was considered the first day of follow up. Event free survival was described from the date of cardiac catheterization until clinical worsening occurred.

Hemodynamic data at cardiac catheterization were collected as described before. [16,17] All subjects were anesthetized, intubated and mechanically ventilated. We measured right atrial, pulmonary arterial, systemic arterial and pulmonary arterial occlusion pressures or left atrial pressures with fluid filled catheters zeroed to the level of the posterior axillary line. In children with systemic to pulmonary shunts we calculated pulmonary and systemic flow using the Fick principle with directly measured oxygen consumption using either the Amis 2000 mass spectrometer or Innocor™ inert gas rebreathing unit based on gas analysis of the breath-by-breath method (Innovision, Odense, Denmark). [18] In children without shunts, thermodilution cardiac output was measured using a triple-lumen balloon-tipped Swan-Ganz catheter (Edwards Life Sciences, Irvine, CA, USA) as described. [19] Pulmonary and systemic vascular resistances were calculated using standard formulas and indexed to body surface area. Transpulmonary gradient was calculated as mean pulmonary artery pressure minus mean left atrial or pulmonary artery occlusion pressure. Diastolic pressure gradient was calculated as diastolic pulmonary artery pressure minus mean left atrial or pulmonary artery occlusion pressure. Pulmonary artery capacitance index was calculated using the method of Sajan et al. [20]

Echocardiograms were undertaken using the Philips IE33 system (Philips Medical Systems, Bothell, Washington). The echocardiographic images were analyzed offline with Xcelera Client Imaging System (Philips Medical Systems, Andover, MA, USA) independently by two pediatric cardiologists blinded to the identity of the subject's echocardiogram. One pediatric cardiologist was blinded to the clinical course of the subjects and completely uninvolved in the clinical pediatric pulmonary hypertension service or with reviewing the patients or their echocardiograms as part of a clinical responsibility or assessment. The right atrial and right ventricular areas, indexed to body surface area, were obtained by tracing the endocardial surface in the apical four-chamber view in accordance with established guidelines. [21] We measured right atrial (RAA max, RAA min) and ventricular areas (RVA max, and RVA min) at end systole and at end diastole. Additionally, we measured right atrial area at the onset of the p wave (RAA p). Each variable was analyzed twice and averaged. These indices were tested for intra-observer variability and inter- observer variability with measurements repeated more than one month apart. We constructed Bland Altman plots to determine the bias of the right atrial and ventricular area measurements and to determine if individual measurement differences lay between the limits of agreement. We determined the 95% confidence intervals for the bias and for the precision of the limits of agreement. [22] We calculated the coefficient of measurement variation (expressed as a percentage) by dividing the absolute difference between measurements by the average of the 2 measurements.

We calculated the following indices of right atrial and ventricular function (indexed to body surface area) from the areas obtained by tracing the echocardiographic images as follows:

$$\text{RA area change (RAAC)} = \text{RAA max} - \text{RAA min}$$

$$\text{RA fractional area change (RAFAC)}\% = \text{RAA max} - \text{RAA min} \div \text{RAA max} \times 100$$

$$\text{RV fractional area change (RVFAC)}\% = \text{RVA max} - \text{RVA min} \div \text{RVA max} \times 100$$

$$\text{RA passive emptying area (RA Ep)} = \text{RAA max} - \text{RAA p}$$

$$\text{RA active emptying area (RA Ea)} = \text{RAA p} - \text{RAA min}$$

$$\text{RA passive emptying area fraction}\%\text{(RA EpF)} = \text{RA Ep} \div \text{RAAC} \times 100$$

$$\text{RA active emptying area fraction}\%\text{(RA EaF)} = \text{RA Ea} \div \text{RAAC} \times 100$$

We performed statistical analysis of the data using the R project for statistical computing (R 3.3.1,2016 Vienna, Austria). The discrete variables were expressed as numbers and percentages and continuous variables as mean with standard deviation or median with range as appropriate for the data distribution.

We constructed receiver operating curves (ROC) curves to find the values of RA EaF, RVFAC and both RA EaF *and* RVFAC that might predict event free survival and mortality. We calculated the individual cut-off values for RA EaF and RVFAC, while giving equal weight to specificity and sensitivity, by choosing the point on their respective ROC curves that minimized the Euclidean distance between the top-left corner of the graph and the ROC curve (i.e. the minimum of $\sqrt{}$[False Positive Rate^2 + (1 - True Positive Rate)^2]) for both clinical worsening and mortality. None of our subjects had a RVFAC > 55%, therefore, for the combined values of RA EaF *and* RVFAC, we constructed a partial ROC curve. [23] To obtain the combined cut-off values for RA EaF *and* RVFAC, we generated a single ROC curve for the combination of RA EaF *and* RVFAC by holding RA EaF constant (at the value that best predicted outcome, described above) and sweeping RVFAC. We found the point on the combined ROC curve that minimized the Euclidean distance to the top-left corner of the graph as described for the single case variable. From the partial ROC curve we obtained a partial area under the curve (pAUC) by calculating the AUC and dividing by the maximum false positive rate minus the minimum false positive rate defined in the ROC curve. [23]

The survival distributions and Kaplan Meier curves were compared using a p-value calculated from a log rank test. Unpaired *t*-test was used to compare the echocardiographic and hemodynamic variables. P values ≤0.05 were considered statistically significant. Confidence intervals (5–95%) were calculated for all comparisons.

3. Results

During the study period 74 patients with pulmonary arterial hypertension (27 females: 30 males) as defined above underwent cardiac catheterization. We excluded from analysis 17 subjects (7 with pulmonary vein stenosis, 7 atrial septal defects and 3 with incomplete data). Therefore, we included in the study analysis 57 subjects.

3.1. Etiology of pulmonary arterial hypertension

The etiology of the pulmonary arterial hypertension was as follows idiopathic pulmonary arterial hypertension (n = 17/57 (30%), pulmonary arterial hypertension associated with repaired congenital heart disease (n = 32/57 (56%). The repaired lesions were as follows: patent ductus arteriosus (n = 9/32), atrioventricular (canal) septal defect (n = 8), ventricular septal defect (n = 7), atrial septal defect (n = 6), aortopulmonary window(n = 1), coarctation of aorta (n = 1). The patients with pulmonary arterial hypertension after cardiac surgery were considered for inclusion a median of 1.4 years post surgery (range 0.2–13.5 years). This group included 2 patients with repaired congenital diaphragmatic hernias, as well as, congenital heart disease. There were 4/57 (7%) subjects who had pulmonary arterial hypertension associated with unoperated congenital heart diseases (patent ductus arteriosus (n = 2), ventricular septal defect (n = 2)). None of the 4 subjects with unrepaired defects were considered operable and did not undergo subsequent reparative cardiac surgery. Finally 4/57 (7%) had pulmonary hypertension (with normal pulmonary artery occlusion pressures) associated with bronchopulmonary dysplasia in ex prematurely born subjects.

The 57 subjects' median age was 3 years (range 0.30–17 years), median body surface area was 0.56 m^2 (range 0.2–1.8 m^2) and median follow up period was 3 years (range 0.21–8.35 years). Nine subjects died and 9 patients suffered clinical worsening without death. The subjects' median time interval to clinical worsening was 1.14 years (range 0.03–6.14 years) and to death was 1.55 years (range 0.88–4.95 years). The hemodynamic measurements obtained at cardiac catheterization and the echocardiographic variables measured are shown in Table 1.

We found from the ROC curves, optimized for both sensitivity and sensitivity, that RA EaF ≥ 60% predicted clinical worsening with a sensitivity of 78% and specificity of 69% (AUC = 0.70) and mortality with a sensitivity of 100% and specificity of 65% (AUC 0.82) (Fig. 1). We found that RVFAC <25% predicted clinical worsening with a sensitivity of 72% and specificity of 79% (AUC 0.85) and death with a sensitivity of 67% and specificity of 69% (AUC 0.77). We determined from the overlap between the ROC curves, that the combined values of RA EaF ≥ 60% *and* RVFAC < 33% were the best predictors of clinical worsening