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## Pulmonary Artery Acceleration Time Provides a Reliable Estimate of Invasive Pulmonary Hemodynamics in Children

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### Abstract

**Background**—Pulmonary artery acceleration time (PAAT) is a non-invasive method to assess pulmonary hemodynamics, but lacks validity in children. This study sought to evaluate the accuracy of Doppler echocardiography (DE) derived PAAT in predicting right heart catheterization (RHC) derived pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR) and compliance in children.

**Methods**—Prospectively acquired and retrospectively measured DE derived PAAT and RHC derived systolic PAP (sPAP), mean PAP (mPAP), index PVR (PVRi) and compliance were compared by regression analysis in a *derivation* cohort of 75 children (median age, 5.3 years; 1.3–12.6) with wide ranges of pulmonary hemodynamics. To account for heart rate variability, PAAT was adjusted for right ventricle ejection time (RVET) and corrected by the RR interval. Regression equations incorporating PAAT and PAAT:RVET from the *derivation* cohort were then evaluated for the accuracy of its predictive values for invasive pulmonary hemodynamics in a *validation* cohort of 50 age- and weight- matched children with elevated PAP and PVR.

**Results**—There were significant inverse correlations between PAAT and RHC derived mPAP ( $r = -0.82$ ) and PVRi ( $r = -0.78$ ) and direct correlation ( $r = 0.78$ ) between PAAT and pulmonary compliance in the *derivation* cohort. For detection of pulmonary hypertension ( $PRVi > 3 \text{ WU} \times \text{m}^2$  and  $\text{mPAP} > 25 \text{ mmHg}$ ),  $\text{PAAT} < 90 \text{ msec}$  and  $\text{PAAT:RVET} < 0.31$  resulted in a sensitivity of 97% and a specificity of 95%. In the *derivation* cohort, the regression equations relating PAAT with

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mPAP and PVRi were:  $mPAP = 48 - 0.28 \times PAAT$  and  $PVRi = 9 - 0.07 \times PAAT$ . These PAAT integrated equations predicted RHC measured pulmonary hemodynamics in the *validation* cohort with good correlations ( $r = 0.88, 0.83$  respectively), small biases ( $<10\%$ ), and minimal coefficient of variation ( $<8\%$ ).

**Conclusions**—PAAT inversely correlates with RHC measured pulmonary hemodynamics and directly correlates with pulmonary arterial compliance in children. The study established PAAT based regression equations in children to accurately predict RHC derived PAP and PVR.

### Keywords

Pulmonary artery acceleration time; pulmonary hypertension; pediatrics; echocardiography

## INTRODUCTION

The assessment of pulmonary hemodynamics is critical in the diagnosis and management of cardiopulmonary diseases in children.<sup>1-3</sup> Right heart catheterization (RHC) remains the gold standard investigation for determining pulmonary vascular resistance (PVR) and pulmonary artery pressures (PAP).<sup>1-5</sup> However, the increased risk of an invasive procedure accompanied with radiation exposure and the frequent need for general anesthesia makes the RHC use as a screening or monitoring tool in children with significant cardiopulmonary disease problematic.<sup>1,6,7</sup> Doppler echocardiography (DE) is widely used in clinical practice as a surrogate for RHC for PAP quantification using the maximum Doppler velocity of tricuspid regurgitation. However, recent studies in children and adults comparing Doppler velocity of tricuspid regurgitation and RHC methods have revealed clinically relevant discrepancies between Doppler-estimated and catheter measured PAP.<sup>1,8-10</sup> This problem is compounded by the fact that in significant number of children the Doppler velocity of tricuspid regurgitation is either absent or insufficient to measure.<sup>1-3,8-10</sup>

There is a clinical need for a noninvasive method, other than Doppler velocity of tricuspid regurgitation, to accurately predict PAP, PVR, and pulmonary arterial compliance in children. Pulmonary artery acceleration time (PAAT) is a quantitative method used to study the blood flow velocity characteristics in the RV outflow tract (RVOT) in response to changes in ventricular mechanical performance and pulmonary vascular load and compliance.<sup>4,5,11,12</sup> A number of adult studies have shown a strong, inverse correlation between PAAT and invasively measured pulmonary hemodynamics<sup>3-5,12-14</sup> but there are limited studies in children.<sup>2,11,15-18</sup> Currently, PAAT is not used clinically to evaluate pulmonary hemodynamics in pediatric patients because its validity in children has not been demonstrated.

We hypothesized that PAAT would accurately predict RHC measured pulmonary hemodynamics in pediatric patients. The aim of this study was to evaluate the correlations of DE measured PAAT with RHC derived PAP and PVR in children to establish and validate regression equations that utilize PAAT to estimate these invasive measurements.

## METHODS

### Study Design

In this study, we performed pulmonary hemodynamic assessment by DE and RHC in two cohorts of pediatric patients: (1) A *derivation cohort* to assess the correlations between DE measured PAAT and RHC measured PAP for the establishment of PAAT based regression equations, and (2) A *validation cohort* to substantiate these PAAT based regression equation for their accuracy in predicting invasive measured pulmonary hemodynamics. In each cohort, DE and RHC were performed both simultaneously under the same loading and sedation conditions, as well as non-simultaneously to represent typical clinical condition in both cohorts.

### Derivation Cohort

The *derivation* cohort consisted of 75 children (ages 1 to 18 years) who presented to the Saint Louis Children's Hospital (Missouri, USA) cardiac catheterization laboratory for clinically indicated RHC between November 2011 and December 2013. DE and RHC were performed simultaneously (n=50 children) or within six hours (n=25 children) of each other (DE followed by RHC). The data was prospectively acquired and retrospectively analyzed. The 50 children who underwent simultaneous DE and RHC were recruited from a previous study reported by our group,<sup>1</sup> in whom the invasive pulmonary hemodynamics and PAAT were not reported. Children included in the study had wide range of right heart pressures and diagnoses including pulmonary arterial hypertension due to idiopathic, heritable, or connective tissue diseases etiology, lesions with left-to-right shunt, and orthotopic heart transplant (OHT), representing the spectrum of cardio-pulmonary diseases seen in clinical practice (Table 1). Children with single ventricle physiology, a mechanical tricuspid valve, RVOT obstruction, left heart diseases, arrhythmias, pulmonary insufficiency, or on pulmonary vasodilators were excluded.<sup>1</sup> Informed, written parental consent was obtained for all subjects and assent was obtained for all subjects >12 years of age. The institutional review board at Washington University School of Medicine approved all components of the study.

### Right Heart Catheterization

Fifty children underwent simultaneous DE and RHC in the cardiac catheterization laboratory under the same sedation and loading conditions and 25 children had the DE performed first without sedation, followed by a sedated RHC within six hours. RHC measured mean PAP (mPAP) and systolic PA (sPAP) using a standard fluid filled catheter. An interventional cardiologist, blinded to the patients' diagnoses and echocardiographic data, analyzed pressure tracings to evaluate pulmonary hemodynamics. Cardiac output (CO) and pulmonary blood flow (Qp) were calculated using standard Fick's method and indexed to body surface area (Qpi). Pulmonary artery compliance (ml/mmHg/m<sup>2</sup>) was calculated as the ratio of stroke volume (Qpi divided by heart rate) to pulmonary artery pulse pressure. PVR (WU) indexed to body surface area (PVRi, WU x m<sup>2</sup>) was derived using pulmonary capillary wedge pressure (PCWP) from the following equation: (mPAP - PCWP)/Qpi. Oxygen consumption was assumed using standard LaFarge's methodology.<sup>19</sup>

## Echocardiography

We acquired two-dimensional and color DE images of the parasternal and apical standard views with the patient in the supine position per the American Society of Echocardiography guidelines.<sup>20</sup> We developed a protocol for PAAT image acquisition and post-processing data analysis (Appendix 1) and tested for variability using reproducibility statistical analysis.<sup>21</sup> A spectral Doppler image was obtained by placing a pulsed Doppler sample volume at the pulmonary valve annulus in the parasternal short-axis view (Figure 1). Maximal alignment of Doppler interrogation with blood flow direction was achieved with the placement of the sample volume at the annulus of the pulmonary valve and not more proximally in the RVOT. PAAT was calculated from a spectral Doppler envelope as the time interval between the onset of systolic pulmonary arterial flow (onset of ejection) and peak flow velocity (Figure 1).

## Confounding Influences

The variables confounding the PAAT measures include imaging acquisition techniques and postprocessing analysis, heart rate variability, influence of right ventricular mechanics and function, and pulmonary compliance.<sup>11,22</sup> We identified and quantified the image acquisition and post process analysis uncertainties with the development of a protocol (Appendix 1). To account for the potential impact of heart rate variability PAAT was corrected for the R-R interval (PAATc) and also adjusted for right ventricle ejection time (RVET) with a ratio of PAAT:RVET.<sup>12,16,23,24</sup> The mean PAAT:RVET ratio from three cardiac cycles were used for data analysis and further corrected by the square root of the R-R interval (PAAT:RVETc).<sup>24</sup> PAAT:RVET and the R-R interval were compared with a linear regression. We measured RV pre-ejection time, RVET, and the ratio of RV pre-ejection time to RVET (PET:RVET) to assess RV mechanics.<sup>25</sup> Pre-ejection time was defined as the interval between the onset of QRS complex to the onset of RV ejection, whereas RVET is defined as the interval between the onset of RV ejection to the cessation of systolic pulmonary arterial flow in the same cardiac cycle (Figure 1).<sup>6,12</sup>

We assessed RV function by two dimensional speckling tracking echocardiography derived global longitudinal systolic strain, a sensitive and reliable measure with published normative values in children.<sup>26</sup> One sonographer measured RV global longitudinal strain in the children who had simultaneous DE and RHC using a protocol previously validated by our group and others.<sup>21</sup>

## PAAT based Regression Equations and Cut-Off Values

In the *derivation* cohort, PAAT and PAAT:RVET were compared with RHC derived mPAP, sPAP, PVR, and PVRi by both linear and logarithmic regression analysis, (P value < 0.01 was considered significant). A receiver operating characteristic (ROC) curve was constructed to determine a cut-off value for PAAT and PAAT:RVET with the best sensitivity to predict pulmonary hypertension defined as elevated PVR values > 2 WU and PVRi > 3 WU x m2, elevated sPAP > 30mmHg, and mPAP > 25 mmHg.<sup>27</sup> The statistical analysis was performed using SPSS version 14.0 (SPSS, Inc., Chicago, IL).

## Validation Cohort

The regression equations utilizing PAAT and PAAT:RVET that were generated in the *derivation cohort* to predict PAP and PVR were subsequently validated in two separate *validation* sub-cohorts: (1) 25 age- and gender-matched pediatric patients with a wide range of pulmonary hemodynamics who were prospectively recruited and underwent simultaneous RHC and DE between January 2014 and December 2014; and (2) 25 age- and gender-matched pediatric patients with pulmonary arterial hypertension who had DE and RHC within seven days of each other were identified from retrospective search of the database for the period between November 2011 and December 2013. We included this retrospective *validation* sub-cohort to demonstrate the applicability of the PAAT based regression equations in routine clinical practice under no sedation. We assessed the predictive value of the PAAT based regression equations to estimate PAP and PVR in both *validation* sub-cohorts, by comparing to the RHC derived pulmonary hemodynamics with 1) Bland-Altman plot analysis (percentage bias and 95% limits of agreement, LOA), 2) intraclass correlation, ICC, and 3) coefficient of variation, CV. A bias < 10%, narrow 95% LOA, a CV < 10%, and an ICC > 0.8 were recognized as measures of minimal variability and positive reliability.<sup>21</sup>

## Reproducibility Analysis

Reproducibility of PAAT measurements was assessed using intra- and inter-observer variability in 60% of the images from the *derivation* and *validation* cohorts. Three observers (P.T.L., M.D.P. and G.K.S.) performed offline analysis using the same measurement protocol and were blinded to the patients' diagnoses, RHC data and each other (Appendix 1).

## RESULTS

### Baseline Patient Characteristics

A total of 125 patients with a wide range of pulmonary hemodynamics were included in this study; 75 children in the *derivation* cohort and 50 children in the *validation* cohort. PAAT measurements were feasible with high degree of reproducibility in all children (Appendix 2). Patients' demographic, cardio-pulmonary diagnosis and baseline hemodynamic data are summarized in Table 1. In the overall cohort, mPAP ranged widely from 12 mmHg to 60 mmHg, PVR ranged from 2 Woods Units (WU) to 10.4 WU, PVRi ranged from 2 WU x m<sup>2</sup> to 18 WU x m<sup>2</sup>. (PCWPs were within normal limits, ranging from 3 mmHg to 9 mmHg; none of the patients had altered pulmonary hemodynamics from left heart disease).

### RHC derived Pulmonary Hemodynamics and PAAT

Table 2 shows group mean values and ranges for RHC derived pulmonary hemodynamic data and DE derived PAAT data for the *derivation* and *validation* cohorts. Figure 2 summarizes the correlation between the RHC derived PAP and PVR with the PAAT by regression analysis.

**Systolic Pulmonary Artery Pressure**—Linear regression analysis between PAAT and PAAT:RVET and sPAP demonstrated inverse correlations for both in all patients ( $r = -0.78$ ,  $-0.80$ ;  $p < 0.001$ ). The relationship between  $\log_{10}$  (sPAP) and PAAT and PAAT:RVET slightly increased the correlation ( $r = -0.79$ ,  $r = -0.82$ , respectively). Patients with sPAP 30

mmHg had significantly lower values of PAAT ( $65 \pm 16$  vs.  $105 \pm 20$  ms,  $p < 0.001$ ) and PAAT:RVET ( $0.25 \pm 0.05$  vs.  $0.37 \pm 0.06$ ,  $p < 0.01$ ) than those with  $< 30$  mmHg. The regression equation relating sPAP and PAAT from our *derivation* cohort data set is:  $sPAP = 64 - 0.39 \times PAAT$ .

**Mean Pulmonary Artery Pressure**—Linear regression analysis between PAAT and PAAT:RVET with mPAP, demonstrated robust inverse correlations for both in all patients ( $r = -0.82$ ,  $-0.81$ ;  $p < 0.001$ ). The relationship between  $\log_{10}$  (mPAP) and PAAT or PAAT:RVET slightly increased the correlation ( $r = -0.83$ ;  $r = -0.83$ , respectively). Patients with mPAP  $\geq 25$  mmHg had significantly lower values of PAAT ( $58 \pm 11$  vs.  $100 \pm 23$  ms,  $p < 0.001$ ) and PAAT:RVET ( $0.36 \pm 0.07$  vs.  $0.23 \pm 0.04$ ,  $p < 0.01$ ) than those with  $< 25$  mmHg. The regression equation relating mPAP and PAAT from our *derivation* cohort data set is:  $mPAP = 48 - 0.28 \times PAAT$ .

**Pulmonary Vascular Resistance**—There were good inverse correlations of PAAT and PAAT:RVET with PVR for all patients ( $r = -0.82$ ,  $-0.79$ ,  $p < 0.001$ ). The correlations were similar when PVRi was used in place of PVR ( $r = -0.78$ ,  $r = -0.78$ , respectively). The relationship between  $\log_{10}$  (PVR) and  $\log_{10}$  (PVRi) with PAAT and PAAT:RVET slightly increase the correlation ( $r = -0.85$ ,  $-0.81$ ,  $-0.81$ ,  $-0.80$ ) respectively). Patients with PVRi  $> 3$  WU  $\times$  m<sup>2</sup> had significantly lower values of PAAT ( $68 \pm 17$  vs.  $98 \pm 24$  ms,  $p < 0.001$ ) and PAAT:RVET ( $0.28 \pm 0.05$  vs.  $0.35 \pm 0.07$ ,  $p < 0.01$ ) than those with  $\leq 3$  WU  $\times$  m<sup>2</sup>. The regression equations relating PVR and PVRi to PAAT from our *derivation* cohort data set are:  $PVR = 12 - 0.1 \times PAAT$  and  $PVRi = 9 - 0.07 \times PAAT$ , respectively.

### Predictive Values of PAAT and PAAT:RVET for Pulmonary Hemodynamics

ROC curve analysis was used to determine specific cut-off values of PAAT and PAAT:RVET in predicting elevated pulmonary hemodynamics (Figure 3). For detection of PVR  $> 2$  WU, PVRi  $> 3$  WU  $\times$  m<sup>2</sup>, mPAP  $> 25$  mmHg, and sPAP  $> 30$  mmHg, a PAAT  $< 90$  msec resulted in a sensitivity of 97% and a specificity of 95% with an area under ROC curve (AUC) of 0.98 (0.94 – 0.99, 95% CI). PAAT:RVET  $< 0.31$  resulted in a sensitivity 87% and a specificity of 89% with an AUC of 0.92 (0.84 – 0.99, 95% CI). Only three patients (2%) were misclassified as normal ( $n=2$ ) or abnormal ( $n=1$ ) using the cut-off values. There was no common link in diagnosis or patient characteristics for these patients. For patients with a diagnosis of pulmonary arterial hypertension ( $n=32$ , a PVR  $> 3$  WU, mPAP  $\geq 25$  mmHg, and sPAP  $> 30$  mmHg), a PAAT  $< 88$  msec and PAAT:RVET  $< 0.30$  had a sensitivity 96% and a specificity of 95% with an AUC of 0.92 (0.89 – 0.97, 95% CI). The positive and negative predictive values for elevated PVRi  $> 3$  WU  $\times$  m<sup>2</sup> based on the cut-off value of PAAT  $< 90$  msec was 86% and 82% respectively. RV strain was significantly decreased in patients with PAAT  $< 90$  msec and PAAT:RVET  $< 0.31$  ( $-15.8 \pm 4.5$  vs.  $-20.2 \pm 4.4$ ,  $p < 0.001$ ).

### Validation of Regression Equations

The estimated pulmonary hemodynamic values derived from the PAAT integrated regression equations from the *derivation* cohort when compared to the RHC derived pulmonary hemodynamics in the *validation* cohort yielded strong correlation, small biases  $< 10\%$ ,



narrow LOA, intraclass correlation  $> 0.8$ , and coefficient of variation  $< 10\%$  in both *validation* cohorts (Table 3). There was minimal variation in analysis when gender, age, blood pressure, and body surface area were included in the regression plots. The comparisons were significantly less reliable at the extreme values of PAAT, as expected.<sup>5</sup> With ROC curve analysis, a PAAT  $< 40$  msec and a PAAT:RVET  $< 0.23$  detected PVR  $> 8$  WU, PVRi  $> 10$  WU  $\times$  m<sup>2</sup>, mPAP  $> 45$  and sPAP  $> 65$  mmHg with a sensitivity of 93% and specificity of 92%. Values of PAAT and PAAT:RVET lower than these thresholds were unpredictable, despite correction with logarithmic regression.

### Cofounding Influences on PAAT

There was no statistically significant correlation between PAAT:RVET ratio and R-R interval ( $r=0.004$ ). Consequently, both PAAT and the ratio of PAAT:RVET were not corrected for R-R interval in the analysis. Pulmonary artery compliance ranged from 0.61 to 4.01 ml/mmHG/m<sup>2</sup> in the cohort (Table 2). There were good linear correlations between PAAT and PAAT:RVET with PA compliance for all patients ( $r= 0.78$ ,  $r= 0.75$ , respectively,  $p < 0.01$ ). RV global longitudinal strain ranged from  $-8\%$  to  $-28\%$  and there were good linear correlations between PAAT and PAAT:RVET with RV strain ( $r = -0.85$  and  $r = -0.82$ , respectively). A PAAT  $< 90$  msec and PAAT:RVET  $< 0.31$ , detected a cut-off value of RV global longitudinal strain  $-16\%$  with a sensitivity of 86% and a specificity of 86% with an AUC of 0.83 (0.79–0.97, 95% CI). Children with RV strain values less than  $-16\%$ , had longer pre-ejection time ( $95 \pm 15$  msec vs.  $60 \pm 12$  msec,  $p < 0.01$ ) and increased ratio of Pre-ejection time:RVET (0.31 vs. 0.25,  $p < 0.01$ ) indicative of longer time required by RV to develop wall tension to overcome the afterload. Because of the linear inter-dependence of PAAT measures with RV strain and PA compliance and in the same direction, both were not taken in account in analysis of PAAT and PAAT:RVET with pulmonary hemodynamics.

## DISCUSSION

This study presents DE derived PAAT as a TR-independent reliable measure of pulmonary hemodynamics in children. It defines a quantitative relationship between PAAT and RHC-derived pulmonary hemodynamics and shows that (1) PAAT is easily obtainable and reproducible in children, (2) PAAT inversely correlates with RHC derived pulmonary arterial pressures and vascular resistance and directly correlates with pulmonary arterial compliance, and (3) PAAT based regression equations reliably predict a wide range of RHC derived pulmonary hemodynamics. The novel finding derived from the quantitative relationship between PAAT and invasive pulmonary hemodynamics demonstrate that a shorter PAAT of  $<90$  msec and PAAT:RVET  $< 0.31$  reliably detect the triad of elevated PVR, decreased pulmonary arterial compliance, and RV dysfunction with high degree of sensitivity and specificity in children.

Our study reveals that PAAT is a comprehensive quantitative index of pulmonary hemodynamics in children and represents the result of a dynamic interaction between RV mechanical performance and pulmonary vascular load and arterial compliance in children.<sup>28</sup> PAAT predictably shortens with increasing PVR and the degree of shortening is inversely related to the magnitude of the PVR that holds over a wide range of resistances. When PAAT

is modified to take into account heart rate (PAAT:RVET) the correlation is further enhanced. Thus, a PAAT of  $< 90$  msec and PAAT:RVET  $< 0.31$  detected patients with pulmonary hypertension (a PVRi  $> 3$  WU  $\times$  m<sup>2</sup> and a mPAP  $> 25$  mmHg) with high degree of sensitivity and specificity. However, PVR alone does not represent the total afterload to the RV, because it does not take into account the “impedance” to the forward pulsatile blood flow from backward pressure wave reflections from multiple bifurcations of the pulmonary circulation.<sup>29</sup> In pulmonary vascular disease the noncompliant nature of the distal vascular bed causes impedance to increase and forward blood flow to decelerate early in systole as the reflected pressure wave front reaches the pulmonary trunk prematurely, causing an early systolic deceleration and early peaking of flow velocity in the pulmonary artery. Therefore, the time to peak velocity in the pulmonary artery decreases and PAAT shortens (Figure 1b).<sup>30</sup>

The degree of arterial wave reflection is not only determined by vascular resistance, but predominantly by large and medium vessel stiffness, and the geometry of the pulmonary vasculature.<sup>31</sup> In this study, the children with low pulmonary arterial compliance (as measured by the ratio of stroke volume/PA pulse pressure) also demonstrated a shortening of the PAAT. This suggests that PAAT integrates the pulsatile phenomena of pulse wave propagation causing “impedance.” Thus, PAAT shortening may indicate the presence of an underlying pulmonary arterial disease in children.

We further observed that children with a cutoff value of PAAT  $< 90$  msec had decreased RV strain values, suggesting that shorter PAAT is also associated with differing degrees of RV dysfunction in patients with pulmonary hypertension, which parallels the relationship of PAAT with PVR and pulmonary arterial compliance. This implies that RV afterload is a major contributor to the observed differences in RV function.<sup>32</sup> Intuitively, the development of significant decreased RV function might lead to a slower rise in ejection velocities early in systole and a longer PAAT. However, in the setting of depressed RV function and elevated pulmonary vascular resistance, we observed a longer pre-ejection time and ratio of pre-ejection time to RVET that reflects the increased time needed by the RV to develop the wall tension necessary to overcome the elevated afterload. This suggests that the impaired ventricular contraction alone might not cause an early deceleration of pulmonary systolic flow if the pulmonary vascular bed is normal.<sup>30</sup> The combined effect of depressed RV function, altered pulmonary hemodynamics, and decreased vascular compliance leads to increased pre-ejection time (elevated ratio of PET:RVET) and a shorter PAAT.<sup>25</sup>

This is the first study in children, to our knowledge, depicting the novel finding of shorter PAAT association with the triad of elevated PVR, decreased pulmonary arterial compliance, and RV dysfunction. PAAT represents the interactive changes in ventricular mechanical performance, pulmonary vascular load and compliance in children.

### **PAAT Derived Equations of Pulmonary Hemodynamics**

Studies in children have previously evaluated PAAT as an echocardiographic measure of PAP, but with inconsistent results and lack of obvious reliable “cut-off” values to establish sensitive interrelation between DE derived PAAT and RHC derived pulmonary hemodynamics.<sup>2,11,15–18</sup> Kosturakis et al. demonstrated PAAT as a discriminator between



patients with elevated PAP and normal PAP; with PAAT showing moderate inverse correlation with elevated PAP ( $r = -0.62$ ).<sup>16</sup> However, Ebeid et al.<sup>15</sup> showed less robust correlation ( $r$  ranged from  $-0.41$  to  $-0.7$ ), and Cooper et al.<sup>18</sup> showed no correlation between PAAT and invasive pulmonary hemodynamic measures in children with ASD or a VSD. Cevik et al. performed DE and RHC in children and described PAAT(c) cut-off values of 124 msec that identified children with pulmonary arterial hypertension (with a sensitivity of 79% and specificity of 73%).<sup>2</sup> These studies consisted of small patient cohorts, were performed under differing loading conditions between the measurements of PAAT and RHC measurements of pulmonary hemodynamics, and did not perform reproducibility analysis. In comparison, our study established and validated, with multiple and consistent reliability tests (separate *derivation* and *validation* cohorts) “cutoff values” of PAAT and PAAT:RVET to predict elevated pulmonary hemodynamics with high levels of sensitivity and specificity that were lacking in previous studies in children. This is also the first study in children to describe regression equations that utilized PAAT to estimate PVR and PVRi.

### Extremes of PAAT

We observed a deviation from the straight line in points with extremely high PAP and PVR, with the curve resembling a logarithmic function (Figures 2).<sup>2,5</sup> It appears that the relationship between PAAT and pulmonary hemodynamics may be curvilinear at the extremes.<sup>30</sup> We therefore performed logarithmic transformation of each pulmonary hemodynamic derived measure and found only slight improvement in correlation with PAAT and PAAT:RVET. Similar to Kitabatake et al. and Cevik et al, we feel that the both the linear and logarithmic regression equations will not accurately predict the exact invasive pulmonary hemodynamic values with extremely low PAAT.<sup>2,5</sup> Even when the correlation coefficients are reasonable ( $>0.8$ ), there is enough scatter in the plots in this study and previous studies to preclude confidence in the accuracy of results at the extremes. Moreover, the scatter is largest at the highest pulmonary pressures and resistance, where prediction matters most. To account for this limitation, we subsequently used ROC analysis to determine that a PAAT value less than 40 ms or a PAAT:RVET less than 0.23 predicted a mPAP  $> 45$  mmHg and a PVRi  $> 9$ . Although the PAAT based regression equations cannot precisely predict the invasive measures at the extremes, we have demonstrated that a novel clinically relevant “cut-off value” can be used instead to detect markedly elevated pulmonary hemodynamic measures.

### Influence of heart rate

We assessed the impact of the heart rate on PAAT measures by adjusting the PAAT by the RVET and correlating each by the R-R interval. We plotted the R-R interval against the PAAT:RVET. Similar to Subhedar et al.<sup>33</sup> and Fitzgerald and Evans<sup>22</sup>, we did not demonstrate a statistically significant correlation between these variables and concluded that inclusion of the corrected ratio was considered unnecessary. As the HR increases, both PAAT and RVET may shorten, and PAAT may underestimate PVR and PAP. However, Kosturakis et al observed that although RVET and PAAT decrease with increasing heart rate, the ratio of PAAT:RVET was uninfluenced by heart rate.<sup>16</sup> Other studies have shown that for a heart rate less than 60 or greater than 100, the PAAT needed to be corrected for heart rate to improve correlation.<sup>4-6,12,23</sup> We adjusted for the heart rate with the ratio of PAAT:RVET,

and validated equations that showed good relationships with PAP and PVR in children with heart rates that range between 55 and 150.

### Clinical Implications

The assessment of pulmonary hemodynamics includes evaluation of both pressure and resistance. The echocardiographic assessment of pulmonary hypertension in adults, children, and even preterm infants with chronic lung disease often begins with evaluation of the presence of the Doppler velocity of tricuspid regurgitation. Doppler velocity of tricuspid regurgitation, when present, is advantageous in certain clinical situations (i.e. in children with large intracardiac left to right shunts), however “a method which allows data collection in only a minority of subjects may not be the best for describing physiological and pathological changes.”<sup>34</sup> Furthermore, in the absence of a high quality Doppler velocity of tricuspid regurgitation, the ability to quantitatively assess PAP and PVR (using the Abbas equation<sup>35</sup>) non-invasively is limited. PAAT measures have been reported in adults and children in multiple studies, but by properly validating a quantitative relationship between PAAT and RHC derived pulmonary hemodynamic parameters in both simultaneous and clinically relevant situations, our study provides a clinically applicable non-invasive screening tool to estimate both PAP and PVR in children with a wide range of pulmonary hemodynamics. We observed that a PAAT < 90 msec and PAAT:RVET < 0.31 would identify most patients with mPAP > 25 and PVRi > 3 WU x m<sup>2</sup> in different clinical scenarios in children, and is similar to published results in adults.<sup>2,6,14,36</sup> PAAT is not meant to replace invasive catheterization as the standard reference method, but it offers an effective screening tool for pediatric patients on whom to select for invasive assessment, or be an alternative monitoring tool in patients who cannot undergo catheterization because of their clinical condition, and should be considered when Doppler velocity tricuspid regurgitation is absent.<sup>37</sup>

### Strengths and Limitations

Several factors may affect the duration of the PAAT and lead to inaccurate values, including heart rate, cardiac output, RV function, and imaging technique. To account for the variations we developed a protocol to acquire and analyze PAAT that will improve its reliability in children across a diverse range of disease states. PAAT measures most likely differ in the presence of significant intra-cardiac left to right shunts.<sup>15</sup> In our study 20 patients (13%) had an ASD, but its presence did not appear to affect the duration of the PAAT when accounted for in the analysis. However, this study was not powered to account for the impact of an ASD on PAAT, and the true influence of shunts is an area for further investigation.<sup>34</sup> We elected to use RV strain as a measure of RV function, but future work should assess the relationship between other measures of RV function (i.e. tricuspid annular plane systolic excursion, fractional area of change, dP/dt) and PAAT measures.

The *derivation* and *validation* cohorts intentionally included a heterogeneous patient population with several different diagnoses. The PAAT based regression equations were validated with simultaneous and non-simultaneous DE and RHC so that they would account for and be applicable across a wide range of abnormal pulmonary hemodynamics and loading conditions in clinical pediatric practice, a fact that sets this study apart from

previous work and further validates the relationships. The inclusion of heart transplant patients introduced a separate potential bias, as these patients typically have sutures at the anastomosis of the recipient with donor pulmonary arteries that influence PA compliance. However, the regression equation held their validity, and PAAT was not affected by discrete stiffening of the main pulmonary artery at the site of anastomosis.

## CONCLUSIONS

PAAT is feasible in children and inversely correlates with RHC derived pulmonary hemodynamics. The study establishes and validates PAAT based regression equations in children to estimate RHC derived sPAP, mPAP, PVR, and PVRI. These predictive relationships permit PAAT to be considered as a noninvasive tool for reliably estimating and monitoring pulmonary hemodynamics in children.

## Acknowledgments

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## Abbreviations

<b>DE</b>	Doppler echocardiography
<b>PAAT</b>	pulmonary artery acceleration time
<b>PAP</b>	pulmonary artery pressure
<b>PCWP</b>	Pulmonary capillary wedge pressure
<b>PVR</b>	pulmonary vascular resistance
<b>PVRI</b>	pulmonary vascular resistance index
<b>RHC</b>	right heart catheterization
<b>RVET</b>	right ventricle ejection time
<b>RVOT</b>	right ventricle outflow tract

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## Appendix 1: Protocol for Pulmonary Artery Acceleration Time Image Acquisition and Postprocessing Data Analysis

Measurements: Pulmonary artery acceleration time and right ventricle ejection time

## A) Optimize image acquisition

- Mode: Fundamental imaging mode. Center frequency of 4–12 MHz. Two-dimensional grey scale images acquired.
- Views: Pulsed-wave Doppler interrogation of the proximal pulmonary artery was performed in the parasternal short-axis view (Figure 1) as proposed by the American Society of Echocardiography.
- A spectral Doppler image obtained by placing a pulsed Doppler sample volume at the pulmonary valve annulus. The sample volume was placed at the annulus of the pulmonary valve and not more proximally in the RV outflow tract to maximally align blood flow and Doppler interrogation.
- ECG tracing on screen – minimize artifacts.
- Store/Record: Three consecutive cardiac cycles. A minimum of three Doppler spectral flow velocity envelopes is stored for analysis to account for respiratory variation.
- Morphology: The Doppler spectral flow velocity envelope needs to meet three criterion to be considered acceptable for analysis: (1) Clear onset of the Doppler spectral flow velocity envelope, (2) Clearly demarcated edges of the Doppler spectral flow velocity envelope avoiding modal frequency, and (3) Three consecutive well-defined Doppler spectral signals across the RVOT.
- Image archiving and storage: Store the two-dimensional cine loop images as enhanced DICOM digital loops for off-line analysis.

## B) Pulmonary artery acceleration time analysis

- Pulmonary artery acceleration time (PAAT) and the right ventricle ejection time (RVET) are measured from each Doppler spectral flow velocity envelope. All the values used for analysis represent the average of three consecutive cardiac cycles to account for respiratory variation in pulmonary flow.
- PAAT is calculated from the spectral Doppler image at the pulmonary valve annulus. PAAT is defined as the interval between the onset of systolic pulmonary arterial flow (onset of ejection) and peak flow velocity (Figure 1).
- Right ventricle ejection time (RVET) is measured from the interval between the onset of RV ejection to the point of systolic pulmonary arterial flow cessation (Figure 1).
- The ratio of the PAAT to RVET is calculated by dividing the acceleration time by the right ventricular ejection time.
- The mean PAAT:RVET ratio from three waveforms was used for subsequent data analysis.
- Exclusion: Non-measurable Doppler signal across the right ventricle outflow tract by color Doppler at the time of data acquisition, or an inadequate Doppler



spectral flow velocity envelope that lacked the appropriate morphology, brightness, or sharply defined edges.

## Appendix 2: Reproducibility Analysis

	Bland Altman		ICC	P value	CV	Correlation	
	Bias (%)	LOA	Coefficient (95% CI)		(%)	R value	P value
Intra- observer							
PAAT	4%	-1.6 – 1.6	0.97 (0.94–0.98)	0.01	2.7%	0.97	0.001
PAAT:RVET	5%	-0.3 – 0.3	0.90 (0.84–0.94)	0.04	4.4%	0.92	0.04
Inter- observer							
PAAT	7%	-4.8 – 4.7	0.93 (0.89–0.96)	0.03	3.9%	0.93	0.03
PAAT:RVET	7%	-0.3 – 0.5	0.90 (0.85–0.94)	0.04	4.5%	0.91	0.04

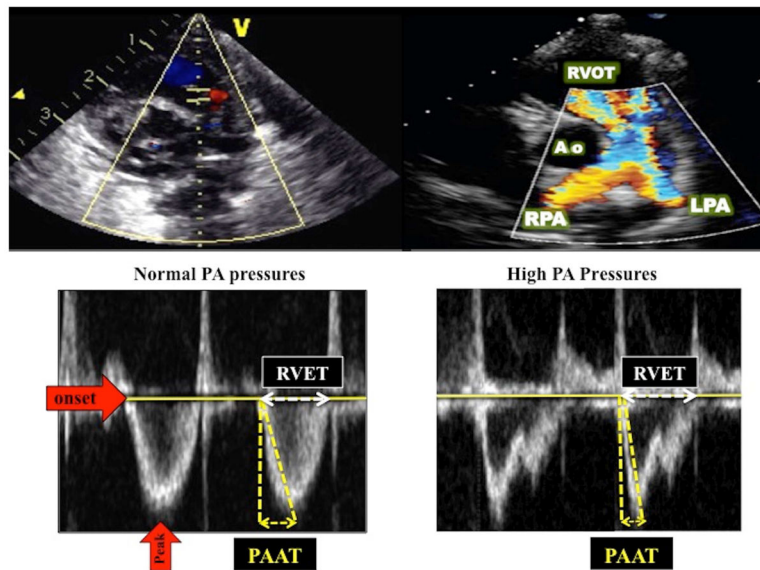
LOA, limits of agreement; Correlation, Pearson's correlation

PAAT, Pulmonary acceleration time (msec)

RVET, Right ventricle ejection time (msec)

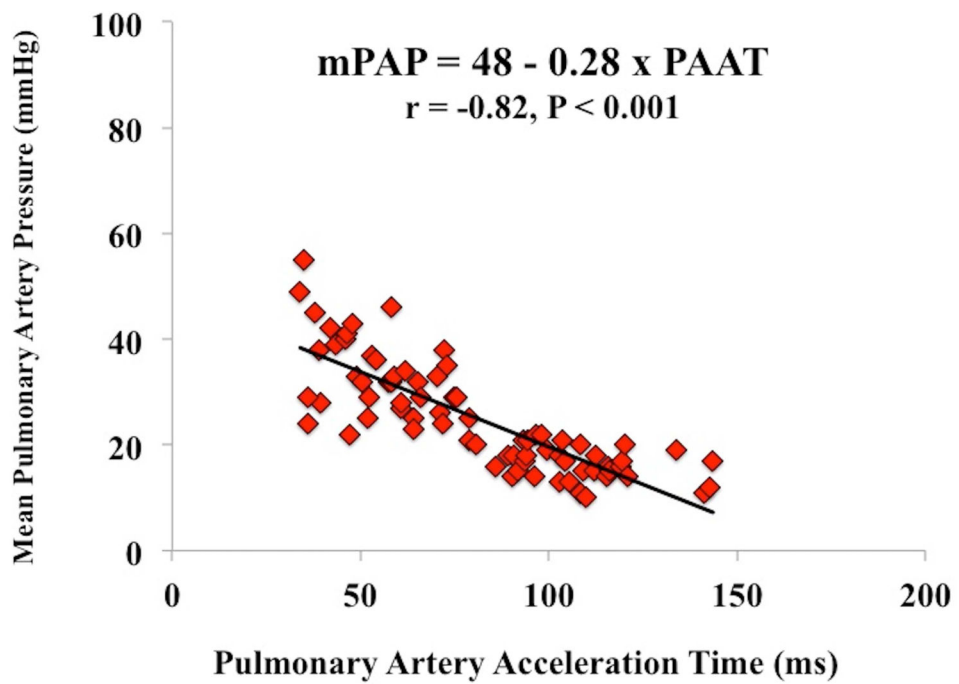
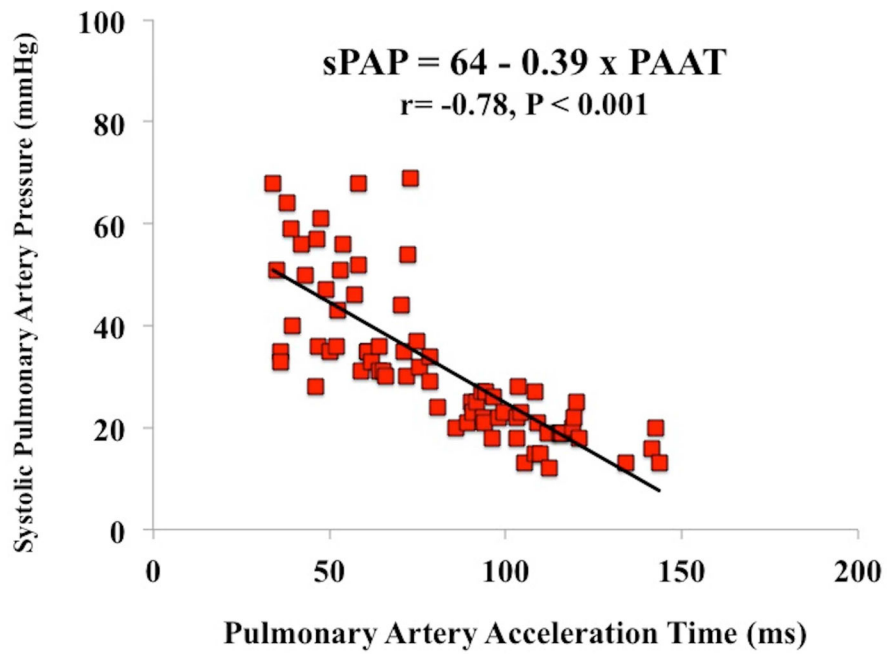
ICC, Intraclass correlation coefficient

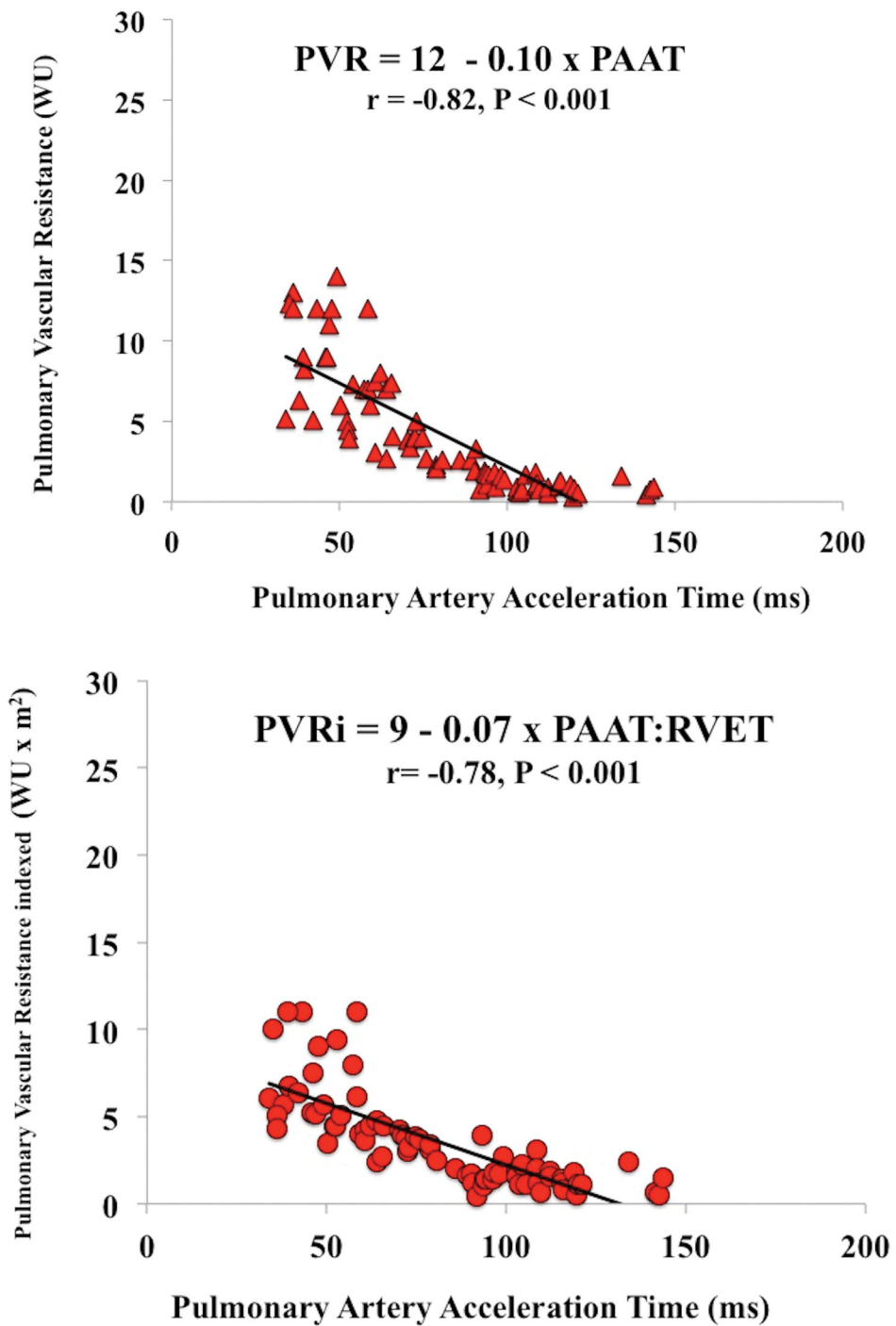
CV, Coefficient of variation



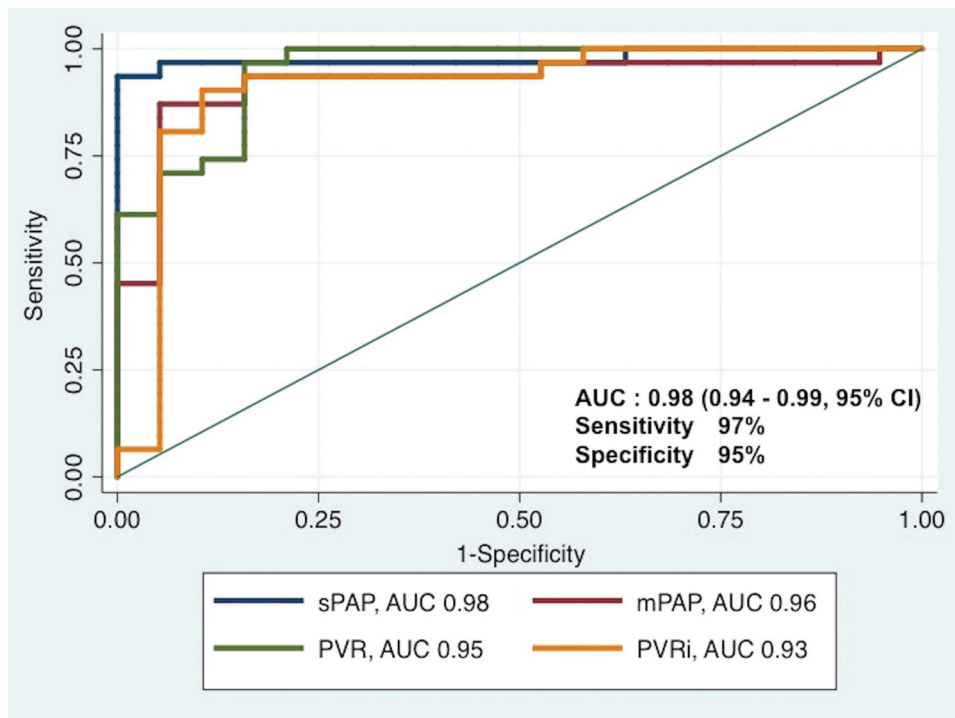
**Figure 1.**

A) Pulmonary artery (PA) velocity curve in a patient with normal PA pressure. PA acceleration time (PAAT) is defined as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity. Right ventricle ejection time (RVET) was measured from the interval between the onset of RV ejection to the point of systolic pulmonary arterial flow cessation. B) PA velocity curve with a shortened PAAT in a patient with high PA pressures. Ao, aorta; RPA, right pulmonary artery; LPA, left pulmonary artery





**Figure 2.** Correlation plots between RHC derived pulmonary hemodynamics and pulmonary artery acceleration time; 2A) Systolic pulmonary artery pressure (sPAP); 2B) Mean pulmonary artery pressure (mPAP); 2C) Pulmonary vascular resistance (PVR); 2D) Pulmonary vascular resistance index (PVRi).



**Figure 3.** Receiver operator curve analysis to determine specific cut-off values of PAAT in predicting altered pulmonary hemodynamics. For detection of  $PVR > 2$  WU,  $PVRI > 3$  WU  $\times$  m<sup>2</sup>,  $mPAP > 25$  mmHg, and  $sPAP > 30$  mmHg,  $PAAT < 90$  msec resulted in a sensitivity of 97% and a specificity of 95%

**Table 1**

Demographic and Clinical Characteristics of the Patients Undergoing Simultaneous and Non-Simultaneous Right Heart Catheterization and Doppler Echocardiography

Variable	Study Cohort (n = 75)	Validation Cohort (n = 50)
Age (years)	6.0 (1.4 – 14.2)	8.0 (1.2–14.3)
Female	46 (61%)	27 (54%)
Caucasian (%)	84	80
Weight (kg)	20 (11.4 – 48.2)	23 (13.9 – 65)
Body surface area (kg/m <sup>2</sup> )	0.70 (0.43 – 1.35)	0.83 (0.55 – 1.18)
Hemoglobin (mg/dL)	11.1 ± 1.6	11.0 ± 1.9
Heart rate (beats/minute)	104 ± 22 (53 – 155)	104 ± 19 (60 – 144)
Systolic blood pressure (mmHg)*	83 ± 15 (60 – 128)	84 ± 22 (54 – 141)
Diastolic blood pressure (mmHg)*	52 ± 11 (35 – 87)	55 ± 14 (30 – 90)
Mean arterial blood pressure (mmHg)*	63 ± 12 (44 – 103)	67 ± 15 (60 – 144)
Diagnosis		
Orthotopic heart transplantation	22	13
Atrial septal defect	10	3
Pulmonary artery hypertension	32	28
Others	11	6
Reason for right heart catheterization		
Diagnostic	43	43
Right ventricle biopsy	22	5
Atrial septal defect device closure	6	1
Others	4	1

Data are expressed as median (interquartile range) or mean ± SD (range) or numbers (percentage)

\* Simultaneous systemic blood pressure was obtained by arterial catheterization in patients in whom arterial access was clinically indicated or by upper extremity noninvasive cuff measurement.



**Table 2**

## Measures of Pulmonary Hemodynamics

Variable	<i>Derivation Cohort</i>		<i>Validation Cohort</i>	
	Simultaneous (n = 50)	Non-simultaneous (n = 25)	Simultaneous (n = 25)	Non-simultaneous (n = 25)
<i>RHC derived value</i>				
Systolic PAP (mmHg)	32 (21 – 40)	46 (23 – 64)	38 (21 – 76)	42 (22 – 80)
Diastolic PAP (mmHg)	14 (11 – 20)	20 (20 – 32)	13 (10 – 24)	17 (14 – 31)
Mean PAP (mmHg)	26 (17 – 37)	32 (18 – 49)	31 (12 – 47)	38 (18 – 60)
PVR (WU)	3.3 (1.1 – 6.1)	5.6 (2.2 – 10.4)	4.3 (1.5 – 4.5)	7.6 (2.5 – 10.5)
PVRi (WU x m <sup>2</sup> )	3.2 (1.4 – 6.5)	3.9 (3.7 – 18)	4.6 (1.7 – 12)	4.8 (2.7 – 20.7)
PA compliance (ml/mmHg/m2)	1.5 (0.9–3.9)	1.5 (0.6–3.1)	1.1 (0.7 – 2.1)	1.4 (0.8–3.6)
<i>DE derived values</i>				
PAAT (msec)	88 (35 – 115)	69 (40–93)	76 (31– 141)	69 (41 –91)
RVET (msec)	267 (216–345)	269 (207–302)	280 (210–356)	280 (218–306)
PAAT:RVET	0.31 (0.20–0.50)	0.29 (0.20–0.37)	0.31 (0.19–0.46)	0.29 (0.22–0.36)

Data are expressed as mean (minimum and maximum range)

PAP, pulmonary artery pressure

PVR, pulmonary vascular resistance; WU, wood unit

PVRi, pulmonary vascular resistance index

PA compliance, pulmonary arterial compliance, (PA compliance = stroke volume / pulse pressure)

PAAT, pulmonary artery acceleration time

RVET, right ventricle ejection time

Comparison between Right Heart Catheterization derived and Doppler Echocardiographic Predicted Pulmonary Hemodynamics in the Validation Cohort.

**Table 3**

	Bland Altman			ICC	CV (%)		Correlation	
	Bias (%)	LOA	Coefficient (95% CI)		P	R	P	
<i>Simultaneous (n=25)</i>								
sPAP (RHC:DE)	8%	-2.5 - 2.0	0.95 (0.92-0.96)	0.02	5.4%	0.88	<0.01	
mPAP (RHC:DE)	6%	-2.1 - 1.9	0.96 (0.93-0.97)	0.02	3.7%	0.86	<0.01	
PVR (RHC:DE)	7%	-3.3 - 2.6	0.93 (0.89-0.95)	0.03	4.6%	0.84	<0.01	
PVRi (RHC:DE)	8%	-3.1 - 2.9	0.94 (0.90-0.97)	0.01	2.9%	0.83	<0.01	
<i>Non-simultaneous (n=25)</i>								
sPAP (RHC:DE)	9%	-2.3 - 2.2	0.94 (0.92-0.96)	0.03	5.7%	0.82	<0.01	
mPAP (RHC:DE)	7%	-2.2 - 2.0	0.93 (0.91-0.95)	0.02	4.7%	0.84	<0.01	
PVR (RHC:DE)	7%	-3.4 - 2.8	0.91 (0.88-0.94)	0.03	5.6%	0.83	<0.01	
PVRi (RHC:DE)	9%	-3.2 - 3.0	0.96 (0.90-0.98)	0.02	3.9%	0.84	<0.01	

sPAP, systolic pulmonary artery pressure (mmHg)

mPAP, mean pulmonary artery pressure (mmHg)

PVR, pulmonary vascular resistance (WU, wood units)

PVRi, pulmonary vascular resistance index

RHC, right heart catheterization

DE, Doppler echocardiography predicted pulmonary hemodynamic values are the PAAT based regression equations derived from the study cohort: sPAP = 64 - 0.39 x PAAT, mPAP = 48 - 0.28 x PAAT, PVR = 12 - 0.10 x PAAT, and PVRi = 9 - 0.07 x PAAT