Normal Reference Values and *z* Scores of the Pulmonary Artery Acceleration Time in Children and Its Importance for the Assessment of Pulmonary Hypertension

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Background—Pulsed-wave Doppler determination of the pulmonary artery acceleration time (PAAT) as a surrogate for pulmonary artery pressure was found to be of clinical value for assessment of pulmonary hypertension (PH) with studies to date exclusively performed in adults. This study aims to provide representative, normal reference values for PAAT in children of all ages. Moreover, we validated abnormal PAAT values in 54 children with PH.

Methods and Results—We conducted a prospective echocardiographic study in 756 healthy children (aged 1 day to 18 years) and in 54 children with PH. Possible associations of age, body length, body weight, body surface area, and heart rate on PAAT were investigated. The PAAT correlated positively with age (r=0.848), body length (r=0.871), body surface area (r=0.856), and body weight (r=0.825) and negatively with heart rate (r=−0.906). PAAT increased with age (neonates: median: 81 ms, range: 53–104; 18th year of life: median: 151 ms, range: 107–187). Receiver operating characteristic analysis for detecting PH patients using age-specific z scores showed an excellent performance of PAAT (P<0.001; area under the curve, 0.98; 95% confidence interval, 0.97–0.99) with a best cutoff score according to Youden index of −1.565 (sensitivity: 92%, specificity: 96%). PAAT values of PH patients negatively correlated (ρ=−0.497) with pulmonary vascular resistance.

Conclusions—The PAAT normal reference values and z scores we provide here will be useful to identify children with a shortened PAAT. Abnormal PAAT values with scores <−2 were predictive of PH. **(*Circ Cardiovasc Imaging*. 2017;10:e005336. DOI: 10.1161/CIRCIMAGING.116.005336.)**

Key Words: body surface area ■ body weight ■ child ■ echocardiography ■ heart rate

Doppler measurements of the pulmonary artery acceleration time (PAAT) are commonly used to estimate pulmonary artery pressure (PAP). Back in the 1980s, it was shown that in adult patients with PAAT values <100 ms, there is a linear inverse relationship between the PAAT and the mean PAP (mPAP).[1–5] However, an increased heart rate (HR) is suspected to shorten the PAAT. In adults, the PAAT was shown to correlate strongly with mPAP[1] and can be measured in adults and in children.[1,6] After years of fading interest, more recently, PAAT research gained again more interest. Indeed, PAAT seems to correlate with PAP and pulmonary vascular resistance (PVR).[7–11] A shorter PAAT suggests elevated PAP and PVR and, consequently, a larger afterload for right ventricular (RV) ejection. Lanzarini et al[12] found that a PAAT value <93 ms identified 67.4% of patients with pulmonary hypertension (PH). In healthy adults, the PAAT is suggested to be >110 ms.[13,14] In children, the HR and, therefore, the HR-dependent PAAT, clearly differ from the HR in adults. To date, the possible associations of age, body length (BL), body weight (BW), body surface area (BSA), and HR on PAAT values have not been appropriately analyzed in children. Importantly, to date, normal PAAT reference values for healthy children are missing, so that a comparison between decreased PAAT values in children with PH with age-related normal values could not have been performed. The aim of our study was to determine normal z score values for PAAT and possible associations of PAAT with age, BL, BW, BSA, and HR in a large healthy pediatric cohort. To the best of our knowledge, this study is the first to provide data on representative, normal, pediatric PAAT values with according z scores that will be useful for noninvasive diagnostic care. We hypothesized that impaired PAAT variables (defined as z score more

See Clinical Perspective

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negative than −2) may be an additional marker for the hemodynamic relevance of a PH in children compared with normative values and, therefore, related PAAT values in our PH kids to the normative values.

Methods

Healthy Study Group

Our study group consisted of 756 healthy children (415 male; 341 female). The study subjects were recruited prospectively from healthy children referred to our cardiology service for evaluation of a heart murmur or a family history of heart disease. Only echocardiograms with an official reading of normal cardiovascular anatomy and function, or normal cardiovascular anatomy with patent foramen ovale with a diameter of ≤2 mm and trivial left-to-right shunt, were accepted for analysis. In line with our clinical experience in this study, PAAT measurements were possible in >99% of our patients. A patent foramen ovale <2 mm is unlikely to change RV loading conditions in a way that PAAT is substantially influenced. Only subjects whose physical examination was judged as being normal were included. The study group ranged from neonates to adolescents (aged 1 day to 18 years; BW: 2.4–95.0 kg; BSA: 0.18–2.19 m^2), including 113 neonates (0–28 days old) and 121 infants (1–12 months old; Table 1). All patients with a congenital heart disease (CHD) such as pulmonary stenosis, acquired heart diseases, chest and thoracic spine deformities, or chromosomal syndromes were excluded. Patients with patent ductus arteriosus were also excluded because ductal left-to-right shunt flow causes turbulence within the PA and may, therefore, influence PAAT measurements. The normal pulsed-wave Doppler profile is smooth, without notching of the Doppler envelope. A notch is associated with increased PVR among a cohort of PH patients,[15] and, therefore, patients with a notched Doppler envelope were excluded from analysis of the healthy cohort. Patients were examined in a resting state. Infants were allowed to be bottle fed during the examination. In our children of the healthy cohort, we confirmed a normal left ventricular ejection fraction, measured using the Simpson formula, a normal age-related mitral annular plane systolic excursion,[16] as well as a normal RV size[17] and RV systolic function[18,19] by including only patients with normal age-related RV size parameters, and normative tricuspid annular plane systolic excursion (TAPSE) and RV tricuspid annular peak systolic velocity values.

Table 1. Demographics of Our 756 Healthy Children

	n	Male, Median (Min–Max)	Female, Median (Min–Max)
BW			
Neonates	113	3.2 (2.4–4.7)	3.0 (2.6–4.6)
Infants	116	5.6 (2.5–11.0)	5.7 (2.4–9.7)
Toddler	125	14.0 (7.5–26.0)	12.0 (5.4–18.0)
Preschool children	55	19.0 (12.0–25.0)	17.5 (13.5–24.0)
School children	135	30.0 (18.3–60.0)	29.0 (15.0–52.0)
Adolescents	207	63.0 (39.0–95.0)	52.0 (15.5–88.0)
BL			
Neonates	113	51.0 (45.0–57.0)	51.0 (43.0–55.0)
Infants	116	58.0 (47.0–81.0)	60.0 (46.0–75.0)
Toddler	125	94.0 (72.0–112.0)	87.5 (56.0–107.0)
Preschool children	55	110.0 (98.0–123.0)	107.5 (100.0–123.0)
School children	135	137.0 (108.0–166.0)	136.0 (108.0–163.0)
Adolescents	207	174.0 (146.0–193.0)	162.0 (98.0–180.0)
BSA			
Neonates	113	0.21 (0.18–0.27)	0.21 (0.18–0.26)
Infants	116	0.30 (0.18–0.49)	0.31(0.18–0.44)
Toddler	125	0.60 (0.39–0.87)	0.53 (0.29–0.73)
Preschool children	55	0.76 (0.58–0.92)	0.73 (0.64–0.89)
School children	135	1.07 (0.74–1.66)	1.05 (0.67–1.49)
Adolescents	207	1.75 (1.29–2.19)	1.54 (0.65–2.02)

Demographics of the healthy study population. We used the following classification: neonates, day of life 1–28; infants, 1–12 mo of age; toddler, >12 mo to 4 y of age; preschool children, >4 to 6 y of age; school children, >6 to 12 y old; adolescents, >12 to 18 y of age. BL indicates body length; BSA, body surface area; and BW, body weight.

PH Study Group

The PH study group consisted of 54 children with PH: 33 children with pulmonary arterial hypertension (PAH) associated with CHD, 11 patients with PH associated with bronchopulmonary dysplasia, and 10 patients with idiopathic PAH (median age: 5.0; range 3 months to 18.0 years; 35 male, 21 female; BSA: 0.21–1.94 m^2). The PH patients with CHD included patients with post-tricuspid left-to-right shunts such as ventricular septal defects and AV septal defects but no patients with isolated atrial septal defect. The respective CHDs were surgically repaired in all patients at a mean age of 5.6 months (range: 0.6–15.1 months). None of our patients had Eisenmenger syndrome. The baseline characteristics and congenital heart defects of the PH patients are shown in Table 2. Patients with severe AV valve regurgitation or conduit regurgitation were excluded from the study. WHO functional class was determined by 2 independent pediatric cardiologists, who were responsible for the medical care of the patients. At time of enrollment, all patients were clinically stable without change of medications within the preceding 4 months. All PH associated with bronchopulmonary dysplasia patients had measurable mild-to-moderate tricuspid regurgitation (TR) so that TR jets could be well interrogated with continuous wave Doppler. The RV systolic pressure was assessed by TR velocity calculated by applying the modified Bernoulli equation.[20] TR velocity >2.8 m/s is considered a reasonable cutoff to define elevated pulmonary pressure in the absence of pulmonary stenosis.[21] TR jet velocities predicted at least as half-systemic systolic RV pressure in all of our PH associated with bronchopulmonary dysplasia patients. All patients from the idiopathic PAH and PAH-CHD subgroups underwent cardiac catheterization which remains the gold standard for diagnosing PH. PH was defined as a mPAP ≥25 mm Hg at rest, a pulmonary capillary wedge pressure <15 mm Hg, and a PVR ≥3 mm (Wood units [WU]×m^2 BSA).[22] By directly measuring pressures and indirectly measuring flow, we determined markers such as cardiac output (using Fick principle), mixed venous oxygen saturation, and mPAP (Table 2).

Image Acquisition

To minimize variability, a strict institutional protocol for image acquisition was used for this prospective study. Age, BW, BL, BSA, and HR were measured at the time of echocardiography, and the BSA was calculated using the Mosteller formula.[23] The echocardiographic measurement of the PAAT (Doppler probe position) and HR is shown in Figure 1.

Echocardiographic Protocol

Echocardiograms were performed using a commercially available echocardiographic system (Sonos iE33; Philips, Andover, MA) using transducers of 5–1, 8–3, and 12–4 MHz depending on patient age, size, and weight. Images were recorded digitally and analyzed using off-line software (Xcelera Echo; Philips Medical Systems, The Netherlands). Pulmonary artery flow was measured by placing the

Table 2. Demographics of Our 54 Children With PH

All PH Patients	n or Median (range)
Fulfilled inclusion criteria, n	54
Female, n (%)	21 (39)
Age at baseline, y (range)	5.4 (0.4–18.2)
Body weight, kg (range)	17.4 (3.8–83.7)
Body length, cm (range)	107 (51–190)
BSA, m^2, range	0.21–1.96
WHO functional class	
I, n	10
II, n	29
III, n	15
Medication	
Bosentan, n	6
Bosentan+sildenafil, n	9
Macitentan, n	5
Macitentan+sildenafil, n	8
Sildenafil, n	11
Calcium antagonists, n	4
Furosemide, n	14
Warfarin, n	8
Variables	
TRV, m/s	3.9 (2.8–5.7)
TRV/RVOT VTI ratio	0.36 (0.16–0.98)
% of systemic pressure, %	71 (39–143)
mPAP, mean±range, mm Hg	36.5 (28–57)
PVR, mean±range, WU	5.4 (3.5–18.4)
PAH-CHD	
n	33
TRV, m/s	3.8 (2.9–5.0)
TRV/RVOT VTI ratio	0.37 (0.17–0.67)
% of systemic pressure, %	68 (39–112)
mPAP, mean±range, mm Hg	28 (19–56)
PVR, mean±range, WU	6.7 (0.9–24.2)
Diagnosis	
AVSD, n	19
VSD, n	18
PA with VSD, n	8
TA, n	5
TAPVR, n	4
iPAH	
n	10
TRV, m/s	4.5 (3.3–5.6)
TRV/RVOT VTI ratio	0.46 (0.18–0.72)
% of systemic pressure, %	89.5 (52–119)
mPAP, mean±range, mm Hg	39 (30–61)
PVR, mean±range, WU	14.7 (5.8–29.7)
PH-BPD	
n	11
TRV, m/s	3.4 (2.7–4.7)
TRV/RVOT VTI ratio	0.31 (0.21–0.55)
% of systemic pressure, %	54 (41–75)

Demographic data of PH patients. Age of our patients at baseline is the age at inclusion in the study. Subgroups of patients (PAH-CHD, iPAH, and PH-BPD) are given. AVSD indicates AV septal defect; BSA, body surface area; iPAH, idiopathic PAH; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RVOT, right ventricular outflow tract; TA, tricuspid artery; TAPVR, total anomalous pulmonary venous return; TRV, tricuspid regurgitation velocity; and VTI, velocity time integral (VTI).

pulsed-wave Doppler sample volume at the center of the transpulmonary valve jet just distal to the pulmonary valve, obtained from the short-axis view. From this envelope, we measured the PAAT as the interval between the onset of ejection and the peak flow velocity in accordance with the previous studies,[7,24] defined as the time from the onset to maximal velocity. The time intervals between cardiac catheterization and echocardiography ranged from 0 to 7 days. All data were measured from 3 well-trained observers (M.K., G.G., and A.G.) by 3 to 5 consecutive beats and averaged as previously recommended.[13]

Statistics

For data analysis, SPSS 20 and SAS 9.4 were used. Reliability of both the interobserver and intraobserver measurements was analyzed in 115 healthy patients by a random effects model analysis of variance (intraclass correlation coefficient). Interobserver reliability was 0.995 (95% confidence interval [CI], 0.993–0.996). Bland–Altman plot for interobserver reliability showed a minor bias of +0.31 with limits of agreement of −4.80 to 5.42 ms (Figure 2). Within the Bland–Altman plot, the bias is calculated by the mean difference in PAAT values obtained by 2 independent observers. The limits of agreement are calculated by adding (upper limits of agreement) or subtracting (lower limits of agreement) $1.96 \times SD_{Difference}$ to the bias. As previously described, only 1 averaged value for each child was used for further analysis. Data are presented as median and range or mean and 95% CI. After plotting the data of healthy children and adolescents and calculating Pearson correlation coefficients for the association of PAAT with age, HR, BSA, BL, and BW were calculated. In a second step, regression analysis was used to estimate PAAT from age, BL, BW, and BSA separately. If scatterplots of PAAT with age, BL, BW, or BSA showed a nonlinear change additional to these parameters, the relevant predictors were squared and also included in the model. Furthermore, we also examined the impact of sex and the interaction of sex with age, BL, BW, and BSA within these models. These parameters were analyzed by multivariate stepwise linear regression analysis. Significance level for entry into the model and for staying in the model was 0.15. White test and Breusch–Pagan test were used to examine for heteroscedasticity. Using these tests, it was determined whether the SD of the residuals varied across the range of values for the independent variable. When significant heteroscedasticity was detected, weighted least square methods were used. The resulting residuals were examined, and tests for normality were applied to determine whether data points followed a normal distribution (Anderson–Darling test and

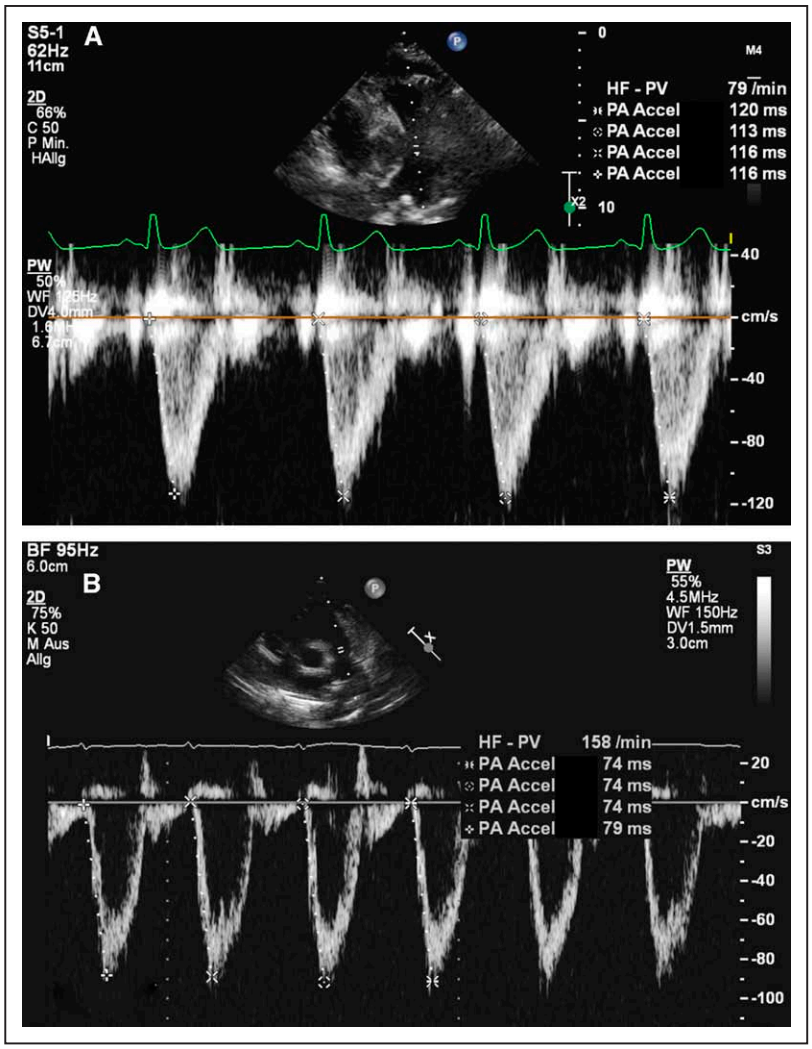

Figure 1. Pulmonary artery acceleration time (PAAT) determination. Parasternal short-axis view. PAAT was measured in ms from onset of flow to attainment of peak velocity. Representative pulmonary artery flow velocity profile in the main pulmonary artery in a 8-y-old female schoolchild (**A**), and in a 2-d-old newborn infant (**B**). The acceleration to peak flow velocity in early systole is marked by the white lines. Mean PAAT of 117 and 75 ms, respectively, is normal for this specific age group of normal subjects. HF indicates heart rate; PA, pulmonary artery; PA accel, PAAT; and PV, pulmonary vascular.

Kolmogorov–Smirnov test). Examination of residuals was crucial for the development of z scores that would accurately predict the normal ranges. The same analysis was performed to calculate age-, BL-, BW-, and BSA-specific HR z scores within our children. To analyze the resulting z scores ability to detect PH patients, a group of patients with previously diagnosed PH was included. Sensitivity and specificity for a cutoff value of −2 was calculated. For this cutoff score (z score=−2), contour plots were drawn. Therefore, for each age and HR, the PAAT value corresponding with a z score of −2 was calculated. Furthermore, receiver operating characteristic curves were plotted, and the area under the curve with corresponding 95% CIs was calculated. To find the best cutoff score for detecting PH patients, the Youden index (calculated as follows: J=Sensitivity+Specificity−1) was calculated. The Youden index gives the value which maximizes sensitivity and specificity at the same time.

Ethics

This study complies with all institutional guidelines related to patient confidentiality and research ethics, including institutional review board approval of the Ethics Board of the Medical University of Graz. There are no financial or other potentially conflicting relationships to disclosure.

Results

In the 756 healthy children and adolescents studied, the median PAAT increased from 81 ms (range: 53–104; HR: 131, range: 101–162) in newborns to 151 ms (range: 107–187; HR: 66, range: 47–99) in 18th year of life in a nonlinear fashion (Figure 3). PAAT positively correlated with age (P<0.001; r=0.848) and negatively with HR (P<0.001; r=−0.906; Figure 3). PAAT also positively correlated with BSA (P<0.001; r=0.856), BL (P<0.001; r=0.871), and BW (P<0.001; r=0.825; Figures 4 through 6; Figure I in the Data Supplement). Stepwise multiple regression analysis revealed that 74.8% of the variance in PAAT could be explained by age (age: P=0.034, age^{½}: P<0.001) and sex (females had shorter PAAT than males; P=0.049). In all of the 3 other models (BL, BW, and BSA), only the linear and the square root term were significant. These models could explain 76% (BSA), 77.0% (BL), and 75% (BW) of the variance in PAAT. For calculating the age-specific z scores, the following formula can be used:

$$PAAT_{z-score_{(age)}} = \frac{PAAT - \left(77.38 + 0.72 * age + 13.88 * \sqrt{age} + 2.02 * sex\right)}{12.87 + 0.17 * age}$$

with PAAT as the measured PAAT value, age in years, and for female sex=1, male sex=0. Age-, BSA-, BL-, and BW-specific PAAT values according to our model and corresponding values for ±1 and ±2 SD are given in Tables 3 through 6. The average PAAT values in healthy females reach the presumed

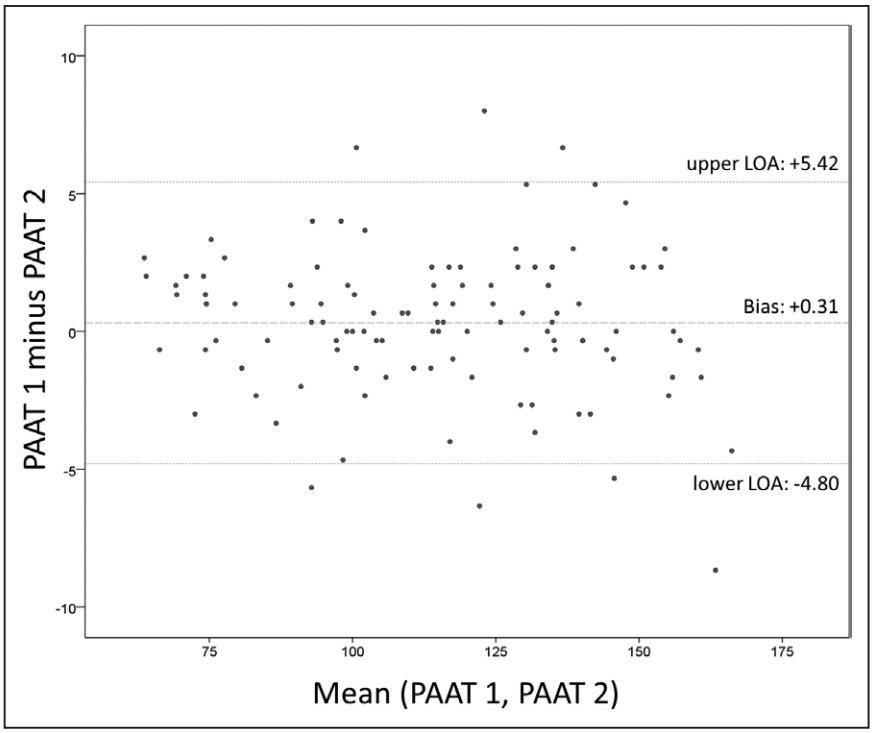

Figure 2. Bland–Altman plot for interobserver reliability showing a minor bias of +0.31 with limits of agreement (LOA) of −4.80 to 5.42. Within the Bland–Altman plot, the bias is calculated by the mean difference in pulmonary artery acceleration time (PAAT) values obtained by 2 independent observers. The LOA are calculated by adding (upper LOA) or subtracting (lower LOA) $1.96 \times SD_{Difference}$ to the bias.

normal adult PAAT cutoff value of 100 ms with an age of 2.3 years (males: 2.7 years). The lower bound of girls' normal values (−2 SD) reaches this value with an age of 10.3 years (males: 11.1 years; Figure 3). In both sexes, this cutoff value is reached with a mean BSA of 0.54 m^2, a mean BL of 88.8 cm, and mean BW of 12.1 kg (Figures 4 through 6). The interobserver reliability was 0.995 (95% CI 0.993–0.996), tested in 25 individuals.

In the 54 PH patients studied (median age: 5.0; range: 3 months to 18.0 years; 35 male, 21 female), PAAT values increased with age ($P<0.001$; $r=0.71$; Figure 7) and age age-specific z scores decreased with age ($P<0.001$; $r=-0.595$), showing a more pronounced deviation from normal values in older children. PAAT values in the PH group showed a positive correlation with TAPSE ($P<0.001$; $r=0.818$) and S′ ($P<0.001$; $r=0.622$), and a negative correlation was observed with PVR ($P=0.011$; $\rho=-0.497$; Figures II through IV in the Data Supplement). We also used as cutoff point a PAAT z score of >−2 to investigate the ability of lower than z score −2 PAAT values in detecting children with a PH. Using this cutoff score (z score more negative than −2.0), 37 out of our 54 PH patients (70%) were identified as having an impaired PAAT (sensitivity: 70%, specificity: 99%, positive predictive value: 79%, and negative predictive value: 98%). The PAAT values in children with PH inversely correlated with the ratio of systemic systolic arterial pressure/pulmonary arterial pressure ($P<0.001$; $r=-0.570$). Receiver operating characteristic analysis for detecting PH patients, using age-specific z scores, showed an excellent performance of the variable PAAT ($P<0.001$; area under the curve, 0.98; 95% CI, 0.97–0.99) with a best cutoff score according to the Youden index of −1.565 (sensitivity: 92%, specificity: 96%, positive predictive value: 61%, and negative predictive value: 99%).

PAAT strongly, negatively correlated with HR ($P<0.001$; $r=-0.906$); also age-specific z scores of PAAT and HR are significantly correlated ($P<0.001$; $r=-0.623$). Therefore, the

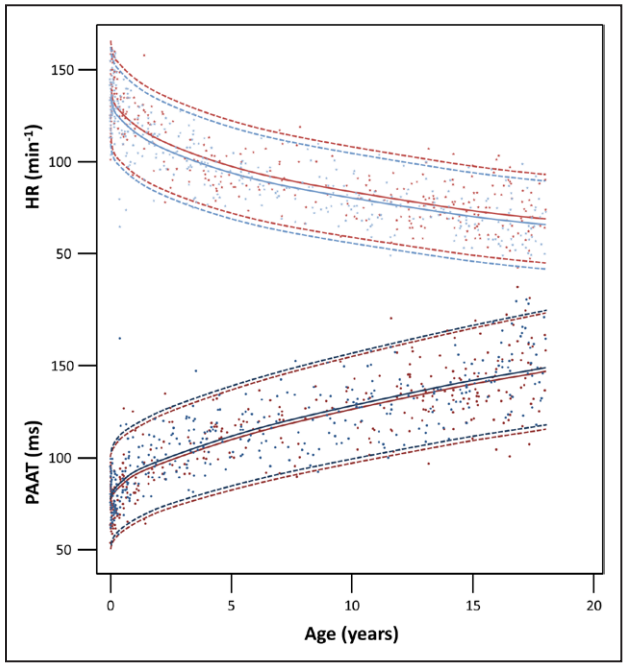

Figure 3. Age (in y) vs mean value of pulmonary artery acceleration time (PAAT) parameters ±2 SDs (z) and age vs mean heart rate (HR) ±2 z. Because HR z scores and PAAT z scores are different between boys and girls, these values are given for girls (red) and boys (blue) separately. HR values are given in lighter colors (girls: light red; boys: light blue) and PAAT values in darker colors (girls: light red; boys: light blue). The mean is given as the solid line. The ±2 z lines are given as the black broken line. Mean and ±2 z score results from regression analysis of healthy subjects.

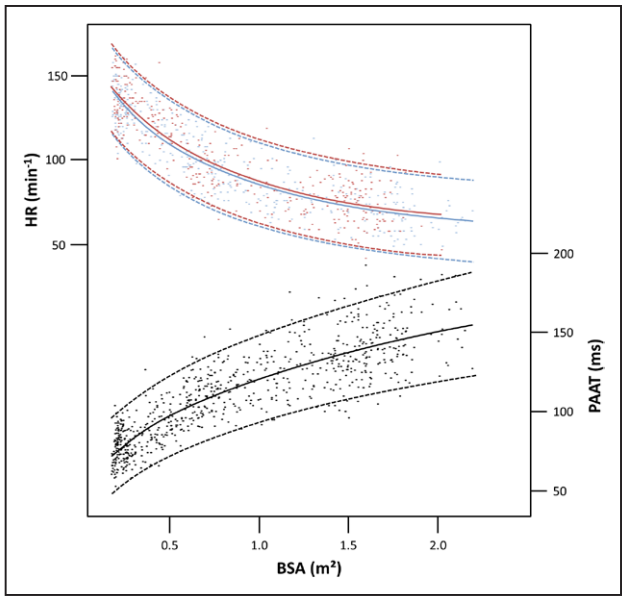

Figure 4. Body surface area (BSA) vs mean value of pulmonary artery acceleration time (PAAT) ±2 SDs (*z*) and age vs mean heart rate (HR) ±2 *z*. Because HR *z* scores are different between boys and girls, these values are given for girls (red) and boys (blue) separately. PAAT values are given for both sexes in black. The mean is given as the black solid line. The ±2 *z* lines are given as the black broken line. Mean and ±2 *z* score results from regression analysis of healthy subjects.

association of PAAT with HR is not only driven by age-specific changes of these values. To include this fact, we provided a contour plot combining both HR and age for the detection of PH. Figure 8 shows PAAT values 2 SD below the expected PAAT value for a given age and HR.

Discussion

To the best of our knowledge, this is the first study providing age-related normal PAAT reference values and *z* scores in a large cohort of healthy, representative children and adolescents. We found that PAAT values increased with increasing age, BSA, BL, and BW. In addition, PAAT inversely correlated with HR in the healthy cohort and the ratio of systolic systemic/pulmonary arterial pressure in a smaller validation cohort of children with PH. As expected, the normative PAAT values in the adolescents were similar to adult PAAT reference data and above the adult normal cutoff value of 100 ms.[8–11]

PAAT is the interval in ms from the onset of ejection to the peak flow velocity and is used for the estimation of PVR in adults.[7] Normative PAAT values in adults ranged from 136 to 153 ms.[9,11] The PAAT is affected not only by PAP, but also by pulmonary blood flow and pathological changes in the pulmonary vascular bed.[2,15,25] Hemodynamic constraints such as increased resistance, elevated pressure, and loss of compliance cause a more rapid increase and a reduction in flow velocity, resulting in a more triangular-shaped Doppler profile. In some cases, the Doppler profile may be notched.[2] The normal pulsed-wave Doppler profile in the RVOT is smooth, without notching of the Doppler envelope. A notch is associated with increased PVR among a cohort of adults with PAH.[15] Even when a reliable TR signal (envelope) is lacking, PAAT measurement is possible in 99% of patients, thereby providing an alternative estimation of PAP and PVR in adults.[7] In a study by Maeba et al,[14] PAAT normalized within a maximum of 19 months

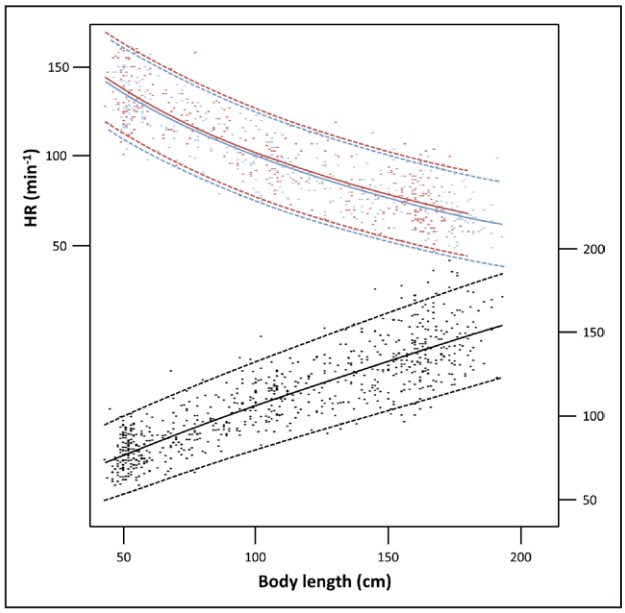

Figure 5. Body length (BL) vs mean value of pulmonary artery acceleration time (PAAT) ±2 SDs (*z*) and age vs mean heart rate (HR) ±2 *z*. Because HR *z* scores are different between boys and girls, these values are given for girls (red) and boys (blue) separately. PAAT values are given for both sexes in black. The mean is given as the black solid line. The ±2 *z* lines are given as the black broken line. Mean and ±2 *z* score results from regression analysis of healthy subjects.

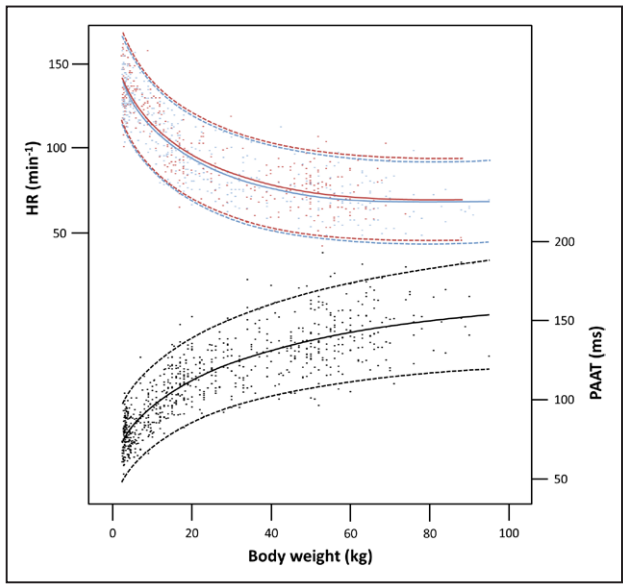

Figure 6. Body weight (BW) vs mean value of pulmonary artery acceleration time (PAAT) ±2 SDs (*z*) and age vs mean heart rate (HR) ±2 *z*. Because HR *z* scores are different between boys and girls, these values are given for girls (red) and boys (blue) separately. PAAT values are given for both sexes in black. The mean is given as the black solid line. The ±2 *z* lines are given as the black broken line. Mean and ±2 *z* score results from regression analysis of healthy subjects.

Table 3. Age-Specific PAAT Values and Corresponding Values for ±1 and ±2 SD

PAAT												
Age	Female						Male					
	HR	−2 SD	−1 SD	Mean	+1 SD	+2 SD	HR	−2 SD	−1 SD	Mean	+1 SD	+2 SD
Mo												
1st	132.4	54.5	67.4	80.2	93.1	106.0	135.4	52.5	65.3	78.2	91.1	104.0
2nd	129.2	56.6	69.5	82.4	95.3	108.1	132.3	54.6	67.5	80.4	93.2	106.1
3rd	127.1	58.1	71.0	83.9	96.8	109.7	130.1	56.0	68.9	81.8	94.7	107.7
4th–6th	123.9	60.3	73.2	86.1	99.1	112.0	127.0	58.3	71.2	84.1	97.1	110.0
7th–12th	118.9	64.0	76.9	89.9	102.9	115.9	121.9	61.9	74.9	87.9	100.9	113.9
Y												
2nd	112.0	69.2	82.3	95.5	108.6	121.7	115.0	67.2	80.3	93.4	106.6	119.7
3rd	105.4	74.5	87.8	101.1	114.4	127.7	108.4	72.5	85.8	99.1	112.4	125.7
4th	100.3	78.9	92.4	105.9	119.3	132.8	103.3	76.9	90.4	103.8	117.3	130.8
5th	96.0	82.8	96.4	110.1	123.7	137.3	99.1	80.8	94.4	108.0	121.7	135.3
6th	92.3	86.3	100.1	113.9	127.7	141.5	95.4	84.2	98.1	111.9	125.7	139.5
7th	89.0	89.5	103.5	117.4	131.4	145.4	92.1	87.5	101.4	115.4	129.4	143.4
8th	86.1	92.5	106.6	120.8	134.9	149.1	89.1	90.5	104.6	118.8	132.9	147.1
9th	83.4	95.3	109.6	124.0	138.3	152.6	86.5	93.3	107.6	121.9	136.3	150.6
10th	81.0	98.0	112.5	127.0	141.5	156.0	84.0	96.0	110.5	125.0	139.5	154.0
11th	78.7	100.6	115.3	129.9	144.6	159.2	81.7	98.6	113.2	127.9	142.6	157.2
12th	76.6	103.1	117.9	132.7	147.6	162.4	79.6	101.0	115.9	130.7	145.5	160.4
13th	74.6	105.4	120.5	135.5	150.5	165.5	77.6	103.4	118.4	133.4	148.4	163.5
14th	72.7	107.8	122.9	138.1	153.3	168.5	75.8	105.7	120.9	136.1	151.3	166.4
15th	71.0	110.0	125.3	140.7	156.0	171.4	74.0	108.0	123.3	138.7	154.0	169.4
16th	69.3	112.2	127.7	143.2	158.7	174.2	72.4	110.1	125.7	141.2	156.7	172.2
17th	67.8	114.3	130.0	145.7	161.3	177.0	70.8	112.2	127.9	143.6	159.3	175.0
18th	66.3	116.3	132.2	148.1	163.9	179.8	69.4	114.3	130.2	146.0	161.9	177.8

The values in the table are shown as follows: for each age group, the estimated mean and ±2 *z* scores according to the regression analysis of the PAAT are shown. The range ±2 *z* scores represent the expectable normal intervals of deviation for a certainty level of 95%. Formula for calculating the expected PAAT values according to regression analysis results: $\text{PAAT} = z_\alpha * (12.87 + 0.17 * \text{age}) + (77.38 + 0.72 * \text{age} + 13.88 * \sqrt{\text{age}} + 2.02 * \text{sex})$, where PAAT, expected PAAT value according to the age group and sex. z_α, 0 for calculating the expected mean, −2 for calculating the PAAT value 2 SD below the mean and +2 for calculating the PAAT value 2 SD above the mean; age, in y; sex, males=0, females=1. Within each age group, the mean age was used for the calculation. For example, for the age group 13th y, the actual age of 12.5 y was used. The range ±2 *z* scores represent the expectable normal intervals of deviation for a certainty level of 95%. Furthermore, the mean HR for each age group is shown. If a PAAT value of 100 is measured in a girl (aged 10.5 y), the corresponding values are given in the line 11th y. It can be seen this value is slightly below the −2 SD values (−2 $SD_{girls,11th\ year}$: 100.6 ms) for girls. The same values (PAAT: 100 ms) measured in a boy of the same age is slightly above the −2 SD value (−2 $SD_{boys,11th\ year}$: 98.6 ms) for the corresponding age group. HR indicates heart rate; and PAAT, pulmonary artery acceleration time.

after PAP normalization due to pulmonary thromb-endarterectomy in adults with chronic thromboembolic PH. In adults, a PAAT ≤90 ms was shown to have 84% sensitivity and 85% specificity in identifying patients with PVR ≥3 WU.[9] PAAT values of 85 ms ≤100 ms have also been described to be associated with elevated PVR (>3 WU) and elevated PAP values (systolic pulmonary artery pressure>38 mm Hg and mPAP>25 mm Hg).[11] A cutoff for PAAT of 100 ms for normal versus abnormal resulted in a sensitivity of 89% and a specificity of 84% for the detection of systolic PAP above 38 mm Hg.[8] For detection of mPAP above 25 mm Hg, a cutoff for PAAT of 100 ms resulted in similar sensitivity and specificity.[8] In a case series of patients with moderate-to-severe TR and suspected to have PH, 2 did not have PH and their PAAT values were 125 and 150 ms, respectively.[26] Mean PAAT values were 94 ms in PH patients and 131 ms in those without PH in this study.[26] Authors also show that PAAT measurements were possible to perform in about 99% of all patients.[26] PAAT is shortened with increasing HR at normal and mildly elevated PAPs.[27] At any given HR in the adult population studied, PAAT shortened as the PAP increased up to a mean of >25 mm Hg.[27]

It is important to create normal values for the pediatric age group because pediatric cardiologists, unlike their adult colleagues, need to have indexed measurements to age, BSA, BL, BW, and HR because of the high variability

Table 4. BSA-Related *z* Scores for PAAT Are Shown

BSA, m^2	HR	PAAT		
		−2 SD	Mean	+2 SD
0.2	137.8	50.8	75.1	99.5
0.3	126.2	59.2	84.0	108.8
0.4	117.1	66.1	91.3	116.5
0.5	109.7	72.0	97.6	123.2
0.6	103.4	77.1	103.2	129.3
0.7	98.1	81.7	108.2	134.7
0.8	93.4	85.8	112.8	139.8
0.9	89.3	89.7	117.1	144.5
1	85.7	93.2	121.0	148.9
1.1	82.5	96.4	124.7	153.0
1.2	79.6	99.5	128.2	156.9
1.3	77.1	102.3	131.5	160.7
1.4	74.9	105.0	134.6	164.2
1.5	72.8	107.6	137.6	167.7
1.6	71.1	110.0	140.5	170.9
1.7	69.5	112.3	143.2	174.1
1.8	68.1	114.4	145.8	177.1
1.9	66.8	116.5	148.3	180.1

The values in the table are shown as follows: for each BSA, the estimated mean and ±2 *z* scores according to the regression analysis of the PAAT are shown. Formula for calculating the expected PAAT values according to the regression analysis results: $\text{PAAT} = z_\alpha * (11.72 + 2.20 * \text{BSA}) + \left(32.73 - 11.79 * \text{BSA} + 100.08 * \sqrt{\text{BSA}}\right)$, where PAAT: expected PAAT value for the defined BSA value; z_α: 0 for calculating the expected mean, −2 for calculating the PAAT value 2 SD below the mean and +2 for calculating the PAAT value 2 SD above the mean. The range± 2 *z* scores represent the expectable normal intervals of deviation for a certainty level of 95%. BSA indicates body surface area; and PAAT, pulmonary artery acceleration time.

of age-dependent growth. Ambiguous results have been reported on the relevance of correction for HR of PAAT in the pediatric age group with groups showing no relevance on HR correlations to pulmonary hemodynamics,[6,28] although others found an influence of HR correction in children on the estimation of PVR and PAP.[29,30] For example, for a 10-year-old healthy boy, we would expect an HR of 80 bpm and, therefore, a PAAT of 128 ms. If this boy has a high HR of 120 bpm, we would expect a reduced PAAT of 104 ms. In our opinion, with an HR above the +2 SD, the PAAT should not be used for any prediction of PH. Although an age- and sex-specific cutoff score of −2 works good for children above an age of 10 years, in younger children, a substantial amount is diagnosed false negative. This poor performance of a cutoff score is because of the fact that PAAT of PH children is more deviated from normal values in older children. A correlation of PAAT to variables of systolic RV function (TAPSE and S′) and PVR in our PH patients showed that the PAAT correlates strongly and positively with TAPSE (P<0.001; r=0.818) as a surrogate of longitudinal RV systolic function and moderately with S′ (P<0.001; r=0.622), whereas a negative correlation was observed with PVR (P=0.011; ρ=−0.497). It is likely that PAAT will be dependent not only on mPAP but also on longitudinal systolic RV function, as judged by TAPSE. However, we have to state that TAPSE can be overestimated in adult PH patients when global contractility, including

Table 5. BL-Related *z* Scores for PAAT Are Shown

BL, (cm)	HR	PAAT		
		−2 SD	Mean	+2 SD
50	135.7	53.3	76.9	100.5
55	131.2	56.2	80.0	103.9
60	127.0	59.0	83.1	107.3
65	123.0	61.7	86.2	110.6
70	119.2	64.4	89.2	113.9
75	115.7	67.1	92.1	117.1
80	112.3	69.7	95.0	120.3
85	109.0	72.3	97.9	123.5
90	105.9	74.8	100.7	126.6
95	103.0	77.3	103.5	129.7
100	100.1	79.8	106.2	132.7
105	97.4	82.2	109.0	135.7
110	94.8	84.7	111.7	138.7
115	92.2	87.1	114.4	141.7
120	89.8	89.4	117.0	144.7
125	87.4	91.8	119.7	147.6
130	85.2	94.1	122.3	150.5
135	83.0	96.4	124.9	153.4
140	80.8	98.7	127.5	156.3
145	78.8	101.0	130.1	159.1
150	76.8	103.3	132.6	162.0
155	74.9	105.5	135.2	164.8
160	73.0	107.8	137.7	167.6
165	71.2	110.0	140.2	170.4
170	69.4	112.2	142.7	173.2
175	67.7	114.4	145.2	176.0
180	66.0	116.6	147.7	178.8
185	64.4	118.8	150.2	181.5
190	62.9	121.0	152.6	184.3

The values in the table are shown as follows: for each BL, the estimated mean and ±2 *z* scores according to the regression analysis of the PAAT are shown. Formula for calculating the expected PAAT values according to the regression analysis results:

$$\text{PAAT} = z_\alpha * (10.35 + 0.03 * \text{BL}) + \left(29.42 + 0.33 * \text{BL} + 4.37 * \sqrt{\text{BL}}\right),$$

where PAAT: expected PAAT value for the defined BL value; z_α: 0 for calculating the expected mean, −2 for calculating the PAAT value 2 SD below the mean and +2 for calculating the PAAT value 2 SD above the mean. The range ±2 *z* scores represent the expectable normal intervals of deviation for a certainty level of 95%. BL indicates body length; and PAAT, pulmonary artery acceleration time.

Table 6. BW-Related *z* Scores for PAAT Are Shown

BW, kg	HR	PAAT		
		−2 SD	Mean	+2 SD
3	137.2	50.1	75.3	100.5
4	132.1	54.0	79.4	104.7
5	127.7	57.4	82.9	108.3
6	123.9	60.4	86.0	111.5
7	120.6	63.1	88.8	114.4
8	117.5	65.6	91.3	117.1
9	114.8	67.8	93.7	119.5
10	112.2	69.9	95.9	121.8
15	101.9	78.5	105.0	131.5
20	94.2	85.2	112.2	139.2
25	88.3	90.6	118.1	145.6
30	83.6	95.0	123.1	151.1
35	79.8	98.8	127.4	155.9
40	76.7	102.1	131.2	160.2
45	74.3	104.9	134.5	164.1
50	72.3	107.3	137.4	167.6
55	70.8	109.4	140.1	170.7
60	69.6	111.3	142.4	173.6
65	68.8	112.9	144.6	176.2
70	68.3	114.3	146.5	178.7
75	68.0	115.5	148.2	180.9
80	67.9	116.5	149.8	183.0

The values in the table are shown as follows: for each BW, the estimated mean and ±2 *z* scores according to the regression analysis of the PAAT are shown. Formula for calculating the expected PAAT values according to the regression analysis results: $\text{PAAT} = z_\alpha * (12.46 + 0.05 * \text{BW}) + (46.54 - 0.70 * BW + 17.82 * \sqrt{\text{BW}})$, where PAAT: expected PAAT value for the defined BW value; z_α: 0 for calculating the expected mean, −2 for calculating the PAAT value 2 SD below the mean and +2 for calculating the PAAT value 2 SD above the mean. The range ±2 *z* scores represent the expectable normal intervals of deviation for a certainty level of 95%. BL indicates body length; BW, body weight; and PAAT, pulmonary artery acceleration time.

longitudinal and radial strain, and strain rate is not.[31] Other factors also associated with PAAT were not investigated in this study. In children, PVR and mPAP were shown to have high associations with PAAT.[32] If these parameters may explain a substantial amount of the remaining variance cannot be answered within this study.

In children, a PAAT >124 ms was formerly suggested as cutoff value to distinguish between healthy subjects and PH patients.[32] In children with PH compared with children without PH, differences were found in PAAT (119±39 versus 136±29 ms) values, respectively.[6] Nevertheless, to date, no sufficient normative data for the complete pediatric age group are available, given the fact that a neonate will not have a similar PAAT as an adolescent. In the children with PH studied, the PAAT values were significantly shortened compared with healthy subjects. Receiver operating characteristic analysis for detecting PH patients, using age-specific *z* scores, showed a good performance of the PAAT. In contrast to adolescents, in a substantial proportion of infants with PH, the PAAT values were within the ±2 SD normative values. Therefore, the PAAT data in neonates and young infants should be interpreted with caution, because of the high variability in body size, pulmonary blood flow, and PVR in this particular age group. Nevertheless, determination of the PAAT could be an important variable during follow-up investigations of pediatric PH patients as it has been shown for adults.[33]

For clinical practice, PAAT values from now on can be judged as being normal, or abnormally impaired (shortened), for example, in children with PH. As a noninvasive parameter to detect impaired pulmonary blood flow in children with PH, we suggest including PAAT determination in echocardiographic protocols when evaluating children with a suspected PH. Moreover, echocardiographic assessment of PAAT values can assist in the evaluation of PH patients in routine follow-up and may reduce costs by decreasing the number of more advanced investigations such as cardiac magnetic resonance imaging.[34]

A limitation of PAAT determination in CHD is the impaired reliability in patients with left-to-right shunts.[25] Therefore, patients with shunts and persistent ductus arteriosus were excluded from our study. In our healthy pediatric study population, we confirmed a normal RV size and systolic function by including only patients with normal age-related RV size, RVOT size, TAPSE, and RV S′.[17–19,35–37] Proper placement of the Doppler cursor in the middle of the pulmonary artery from the parasternal short-axis view and accurate alignment of the long axis of the main PA are both important steps in the use of PAAT measurement. The number of our pediatric PH patients was small, and the possible influence of differences in treatment, including surgery in the PAH-CHD patient population, cannot be excluded.

To the best of our knowledge, this is the first systematic assessment of PAAT in a large cohort of healthy children by transthoracic echocardiography to date. In conclusion,

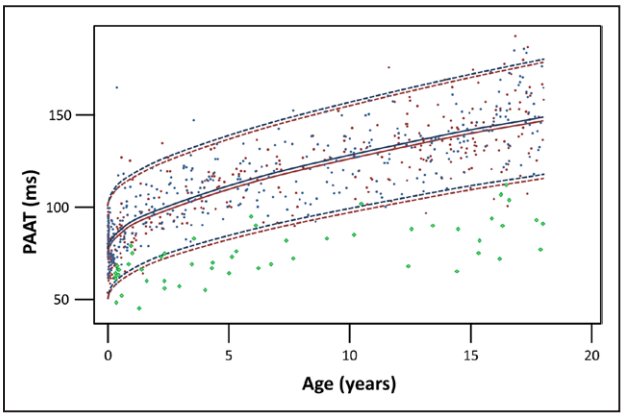

Figure 7. Age (in y) vs pulmonary artery acceleration time (PAAT). Observed individual PAAT values (circles), age- and sex-dependent mean values (solid line) ±2 SDs (broken lines) for healthy girls (red) and boys (blue), and individual PAAT values (green diamonds) of pulmonary hypertension patients are given. Mean and ±2 *z* score results from regression analysis of healthy subjects.

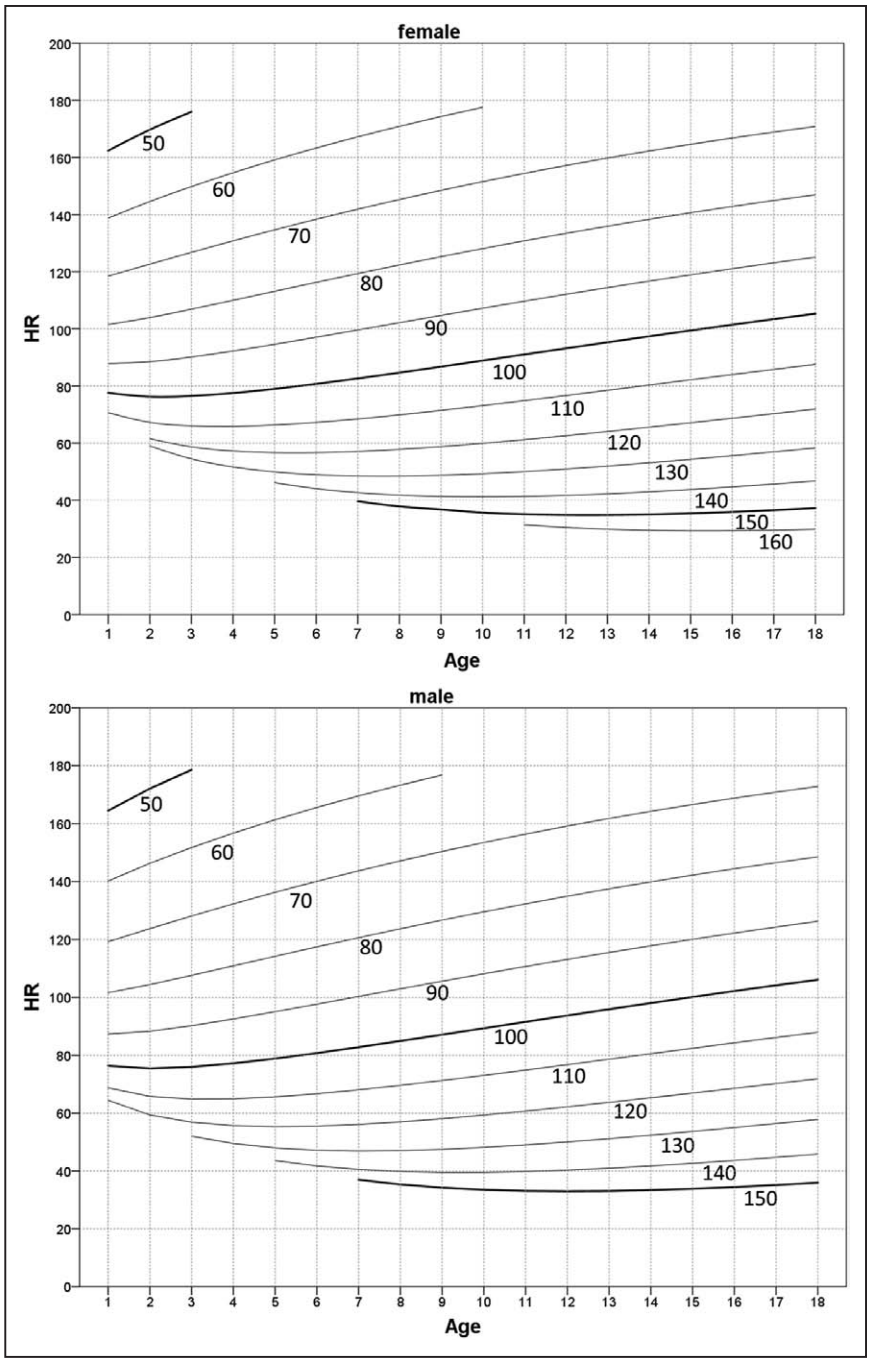

Figure 8. Contour plot showing pulmonary artery acceleration time (PAAT) values 2 SD below expected PAAT according to the heart rate (HR; *y* axis) and age (*x* axis) separately for male and female. For each age and HR, the PAAT value corresponding with a *z* score of –2 was calculated. Within the contour plot, lines for PAAT values of 50, 60, 70 ms, and so on were shown. For example, for a 10-y-old male patient with an HR of 90 bpm, a PAAT value of 100 ms represents a value 2 SD below the expected age and HR-specific value. If a PAAT value below 100 ms is measured this patient has a PAAT value which is >2 SD below the expected PAAT value.

the PAAT normal reference values and *z* scores we provide here will be useful to identify children with a shortened PAAT who may have PH. Abnormal age- and sex-matched PAAT values with scores <−2 were predictive of PH; however, a combination of echocardiographic variables—if present—will most likely increase the predictive strength of these test and should be evaluated in larger cohorts of children with PH.

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Disclosures

None.

References

1. Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation*. 1983;68:302–309.
2. Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, Henry WL. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. *Am J Cardiol*. 1987;59:662–668.

3. Takenaka K, Waffarn F, Dabestani A, Gardin JM, Henry WL. A pulsed Doppler echocardiographic study of the postnatal changes in pulmonary artery and ascending aortic flow in normal term newborn infants. *Am Heart J*. 1987;113:759–766.
4. Martin-Duran R, Larman M, Trugeda A, Vazquez de Prada JA, Ruano J, Torres A, Figueroa A, Pajaron A, Nistal F. Comparison of Doppler-determined elevated pulmonary arterial pressure with pressure measured at cardiac catheterization. *Am J Cardiol*. 1986;57:859–863.
5. Gardin JM, Sato DA, Rohan MK, Shu VW, Allfie A, Gardin SK, Henry WL. Effect of acute changes in heart rate on Doppler pulmonary artery acceleration time in a porcine model. *Chest*. 1988;94:994–997.
6. van Dijk AP, Hopman JC, Klaessens JH, van der Werf T, Daniëls O. Is noninvasive determination of pulmonary artery pressure feasible using deceleration phase Doppler flow velocity characteristics in mechanically ventilated children with congenital heart disease? *Am J Cardiol*. 1996;78:1394–1399.
7. Yared K, Noseworthy P, Weyman AE, McCabe E, Picard MH, Baggish AL. Pulmonary artery acceleration time provides an accurate estimate of systolic pulmonary arterial pressure during transthoracic echocardiography. *J Am Soc Echocardiogr*. 2011;24:687–692. doi: 10.1016/j.echo.2011.03.008.
8. Granstam SO, Björklund E, Wikström G, Roos MW. Use of echocardiographic pulmonary acceleration time and estimated vascular resistance for the evaluation of possible pulmonary hypertension. *Cardiovasc Ultrasound*. 2013;11:7. doi: 10.1186/1476-7120-11-7.
9. Tossavainen E, Söderberg S, Grönlund C, Gonzalez M, Henein MY, Lindqvist P. Pulmonary artery acceleration time in identifying pulmonary hypertension patients with raised pulmonary vascular resistance. *Eur Heart J Cardiovasc Imaging*. 2013;14:890–897. doi: 10.1093/ehjci/jes309.
10. Bech-Hanssen O, Karason K, Rundqvist B, Bollano E, Lindgren F, Selimovic N. Can pulmonary hypertension and increased pulmonary vascular resistance be ruled in and ruled out by echocardiography? *J Am Soc Echocardiogr*. 2013;26:469–478. doi: 10.1016/j.echo.2013.02.011.
11. Bech-Hanssen O, Lindgren F, Selimovic N, Rundqvist B. Echocardiography can identify patients with increased pulmonary vascular resistance by assessing pressure reflection in the pulmonary circulation. *Circ Cardiovasc Imaging*. 2010;3:424–432. doi: 10.1161/CIRCIMAGING.109.913467.
12. Lanzarini L, Fontana A, Campana C, Klersy C. Two simple echo-Doppler measurements can accurately identify pulmonary hypertension in the large majority of patients with chronic heart failure. *J Heart Lung Transplant*. 2005;24:745–754. doi: 10.1016/j.healun.2004.03.026.
13. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786. doi: 10.1016/j.echo.2010.05.010.
14. Maeba H, Nakatani S, Sugawara M, Mimura J, Nakanishi N, Ogino H, Kitakaze M, Iwasaka T, Miyatake K. Different time course of changes in tricuspid regurgitant pressure gradient and pulmonary artery flow acceleration after pulmonary thromboendarterectomy: implications for discordant recovery of pulmonary artery pressure and compliance. *Circ J*. 2007;71:1771–1775.
15. Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, Marzec L, Palevsky HI, Ferrari VA, Forfia PR. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. *Am J Respir Crit Care Med*. 2011;183:268–276. doi: 10.1164/rccm.201004-0601OC.
16. Koestenberger M, Nagel B, Ravekes W, Avian A, Heinzl B, Fritsch P, Fandl A, Rehak T, Gamillscheg A. Left ventricular long-axis function: reference values of the mitral annular plane systolic excursion in 558 healthy children and calculation of z-score values. *Am Heart J*. 2012;164:125–131. doi: 10.1016/j.ahj.2012.05.004.
17. Koestenberger M, Nagel B, Ravekes W, Avian A, Burmas A, Grangl G, Cvirn G, Gamillscheg A. Reference values and calculation of z-scores of echocardiographic measurements of the normal pediatric right ventricle. *Am J Cardiol*. 2014;114:1590–1598. doi: 10.1016/j.amjcard.2014.08.028.
18. Koestenberger M, Nagel B, Ravekes W, Avian A, Heinzl B, Cvirn G, Fritsch P, Fandl A, Rehak T, Gamillscheg A. Reference values of tricuspid annular peak systolic velocity in healthy pediatric patients, calculation of z score, and comparison to tricuspid annular plane systolic excursion. *Am J Cardiol*. 2012;109:116–121. doi: 10.1016/j.amjcard.2011.08.013.
19. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, Cvirn G, Boysen A, Fandl A, Nagel B. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. *J Am Soc Echocardiogr*. 2009;22:715–719. doi: 10.1016/j.echo.2009.03.026.
20. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation*. 1984;70:657–662.
21. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104:2797–2802.
22. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099. doi: 10.1161/CIR.0000000000000329.
23. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098. doi: 10.1056/NEJM198710223171717.
24. Haddad F, Zamanian R, Beraud AS, Schnittger I, Feinstein J, Peterson T, Yang P, Doyle R, Rosenthal D. A novel non-invasive method of estimating pulmonary vascular resistance in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr*. 2009;22:523–529. doi: 10.1016/j.echo.2009.01.021.
25. Matsuda M, Sekiguchi T, Sugishita Y, Kuwako K, Iida K, Ito I. Reliability of non-invasive estimates of pulmonary hypertension by pulsed Doppler echocardiography. *Br Heart J*. 1986;56:158–164.
26. Cowie B, Kluger R, Rex S, Missant C. The relationship between pulmonary artery acceleration time and mean pulmonary artery pressure in patients undergoing cardiac surgery: an observational study. *Eur J Anaesthesiol*. 2015;32:1–6.
27. Mallery JA, Gardin JM, King SW, Ey S, Henry WL. Effects of heart rate and pulmonary artery pressure on Doppler pulmonary artery acceleration time in experimental acute pulmonary hypertension. *Chest*. 1991;100:470–473.
28. Kosturakis D, Goldberg SJ, Allen HD, Loeber C. Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. *Am J Cardiol*. 1984;53:1110–1115.
29. Serwer GA, Cougle AG, Eckerd JM, Armstrong BE. Factors affecting use of the Doppler-determined time from flow onset to maximal pulmonary artery velocity for measurement of pulmonary artery pressure in children. *Am J Cardiol*. 1986;58:352–356.
30. Nakahata Y, Hiraishi S, Oowada N, Ando H, Kimura S, Furukawa S, Ogata S, Ishii M. Quantitative assessment of pulmonary vascular resistance and reactivity in children with pulmonary hypertension due to congenital heart disease using a noninvasive method: new Doppler-derived indexes. *Pediatr Cardiol*. 2009;30:232–239. doi: 10.1007/s00246-008-9316-y.
31. Motoji Y, Tanaka H, Fukuda Y, Sano H, Ryo K, Sawa T, Miyoshi T, Imanishi J, Mochizuki Y, Tatsumi K, Matsumoto K, Emoto N, Hirata K. Association of apical longitudinal rotation with right ventricular performance in patients with pulmonary hypertension: insights into overestimation of tricuspid annular plane systolic excursion. *Echocardiography*. 2016;33:207–215. doi: 10.1111/echo.13036.
32. Levy PT, Patel MD, Groh G, Choudhry S, Murphy J, Holland MR, Hamvas A, Grady MR, Singh GK. Pulmonary artery acceleration time provides a reliable estimate of invasive pulmonary hemodynamics in children. *J Am Soc Echocardiogr*. 2016;29:1056–1065. doi: 10.1016/j.echo.2016.08.013.
33. Cevik A, Kula S, Olgunturk R, Tunaoglu FS, Oguz AD, Saylan B, Cilsal E, Sanli C. Assessment of pulmonary arterial hypertension and vascular resistance by measurements of the pulmonary arterial flow velocity curve in the absence of a measurable tricuspid regurgitant velocity in childhood congenital heart disease. *Pediatr Cardiol*. 2013;34:646–655. doi: 10.1007/s00246-012-0520-4.
34. Alghamdi MH, Grosse-Wortmann L, Ahmad N, Mertens L, Friedberg MK. Can simple echocardiographic measures reduce the number of cardiac magnetic resonance imaging studies to diagnose right ventricular enlargement in congenital heart disease? *J Am Soc Echocardiogr*. 2012;25:518–523. doi: 10.1016/j.echo.2012.01.023.
35. Koestenberger M, Apitz C, Abdul-Khaliq H, Hansmann G. Transthoracic echocardiography for the evaluation of children and adolescents with

suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and D6PK. *Heart*. 2016;102(suppl 2):ii14–ii22. doi: 10.1136/heartjnl-2014-307200.

36. Koestenberger M, Avian A, Ravekes W. Reference values of the right ventricular outflow tract (RVOT) proximal diameter in 665 healthy children and calculation of Z-score values. *Int J Cardiol*. 2013;169:e99–e101. doi: 10.1016/j.ijcard.2013.10.035.
37. Koestenberger M, Ravekes W, Nagel B, Avian A, Heinzl B, Cvirn G, Fritsch P, Fandl A, Rehak T, Gamillscheg A. Reference values of the right ventricular outflow tract systolic excursion in 711 healthy children and calculation of z-score values. *Eur Heart J Cardiovasc Imaging*. 2014;15:980–986. doi: 10.1093/ehjci/jeu041.

CLINICAL PERSPECTIVE

The unique features of pulmonary hypertension (PH) in children and young adults have led to the development of specific recommendations for the early diagnosis and treatment in this age group in North America and Europe. Echocardiographic estimates of right ventricular systolic pressure are calculated from the maximal velocity of the tricuspid regurgitation jet. Unfortunately, there is often insufficient tricuspid regurgitation to reliably quantify the continuous wave Doppler envelope. Recently, pulsed-wave Doppler determination of the pulmonary artery acceleration time as a surrogate for pulmonary artery pressure has gained more interest. However, studies have been performed in adults with relatively stable heart rates. In previous, small studies, significant differences in pulmonary artery acceleration time values had been found in children with PH versus those without PH; however, groups were not matched by age. To the best of our knowledge, we provide here for the first time reference values and *z* scores of the easy-to-measure pulmonary artery acceleration time in a large cohort of children of all ages (n=756). Our pediatric pulmonary artery acceleration time normative data, when incorporated into standard diagnostic practice in the pediatric age group, will lead to an earlier diagnosis and better monitoring of PH and potentially reduce long-term morbidity of children with PH.

Normal Reference Values and *z* Scores of the Pulmonary Artery Acceleration Time in Children and Its Importance for the Assessment of Pulmonary Hypertension

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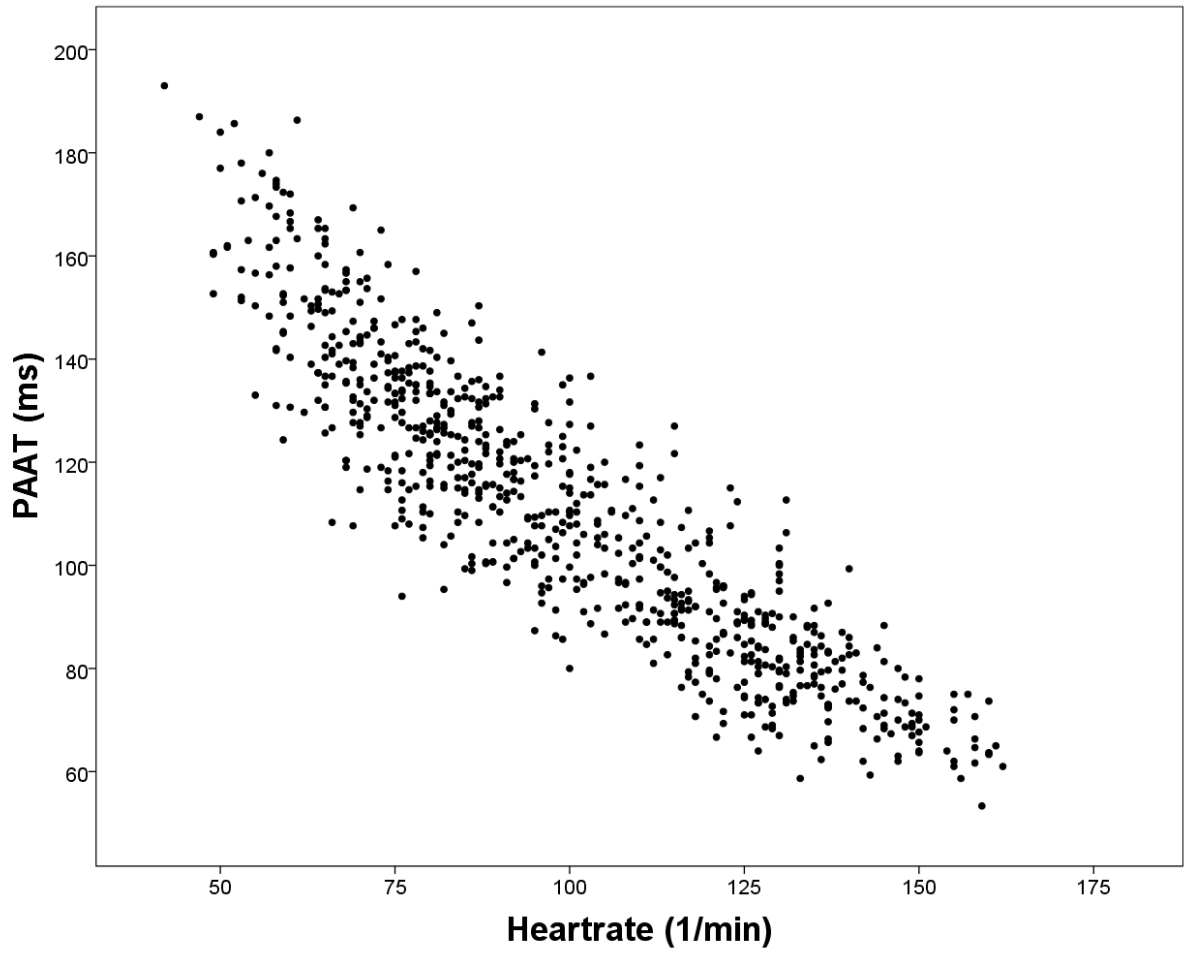
Supplemental Material

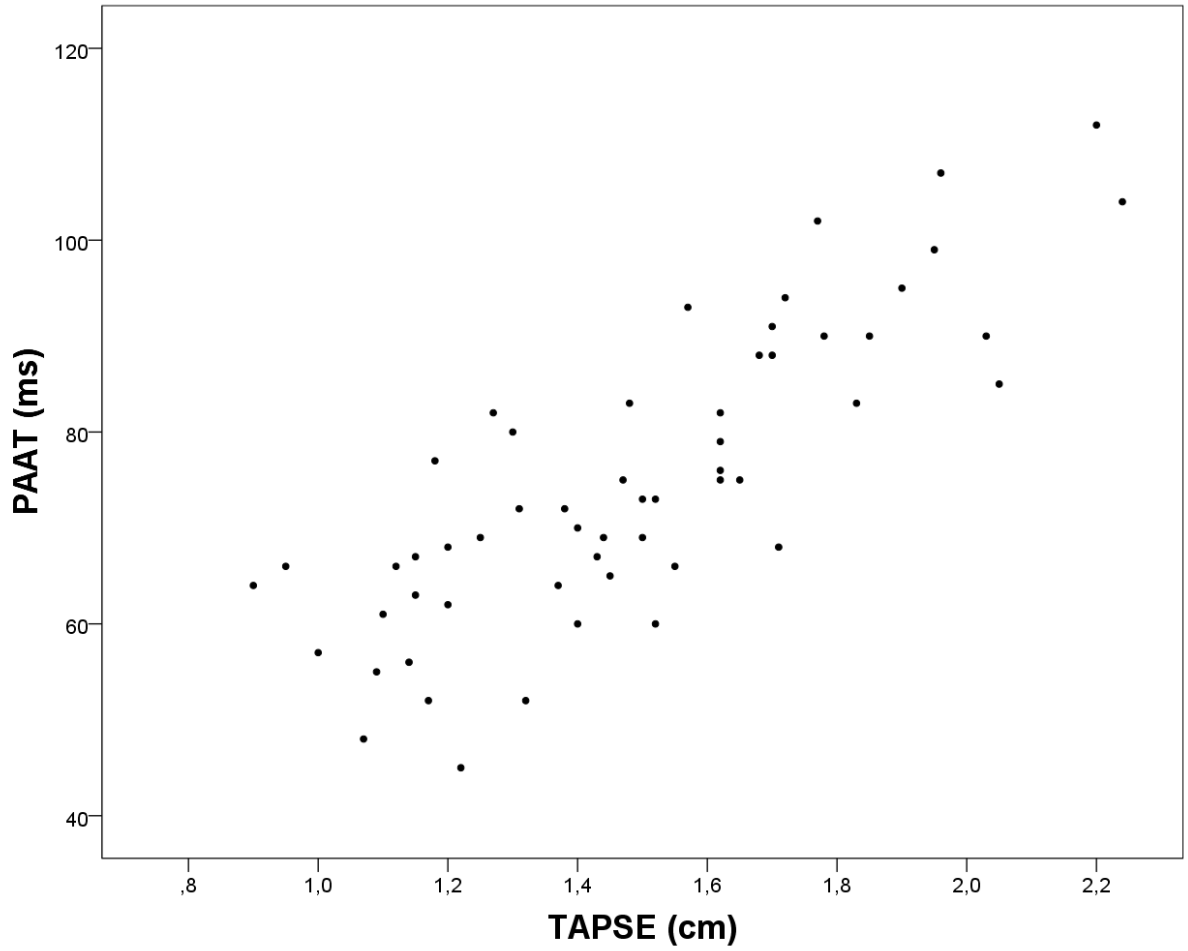
Supplemental Figures and Figure Legends

Supplemental Figure 1:



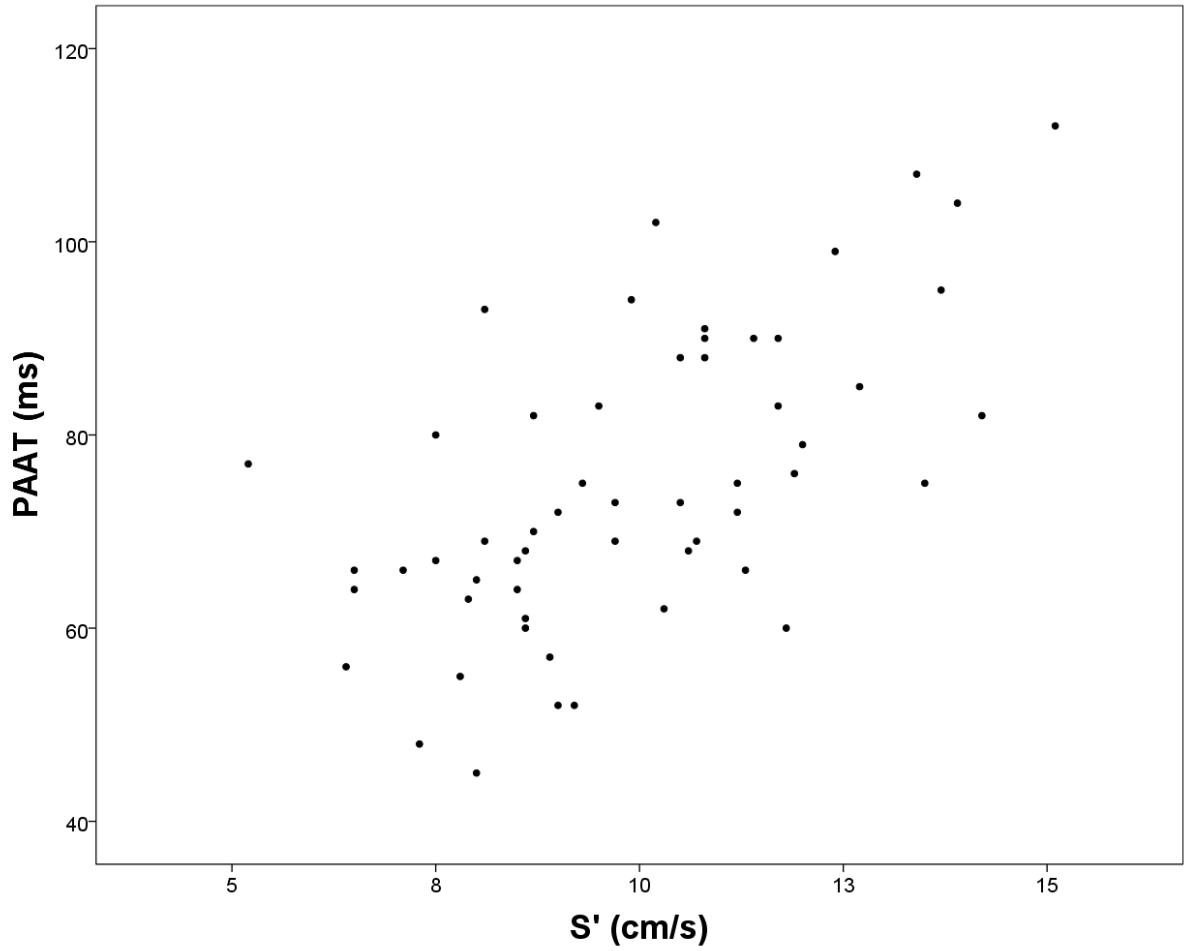
Scatterplot of the association between pulmonary artery acceleration time (PAAT) values and heartrate (HR) in our 756 healthy children ($p < 0.001$, $r = 0.-906$).

Supplemental Figure 2:



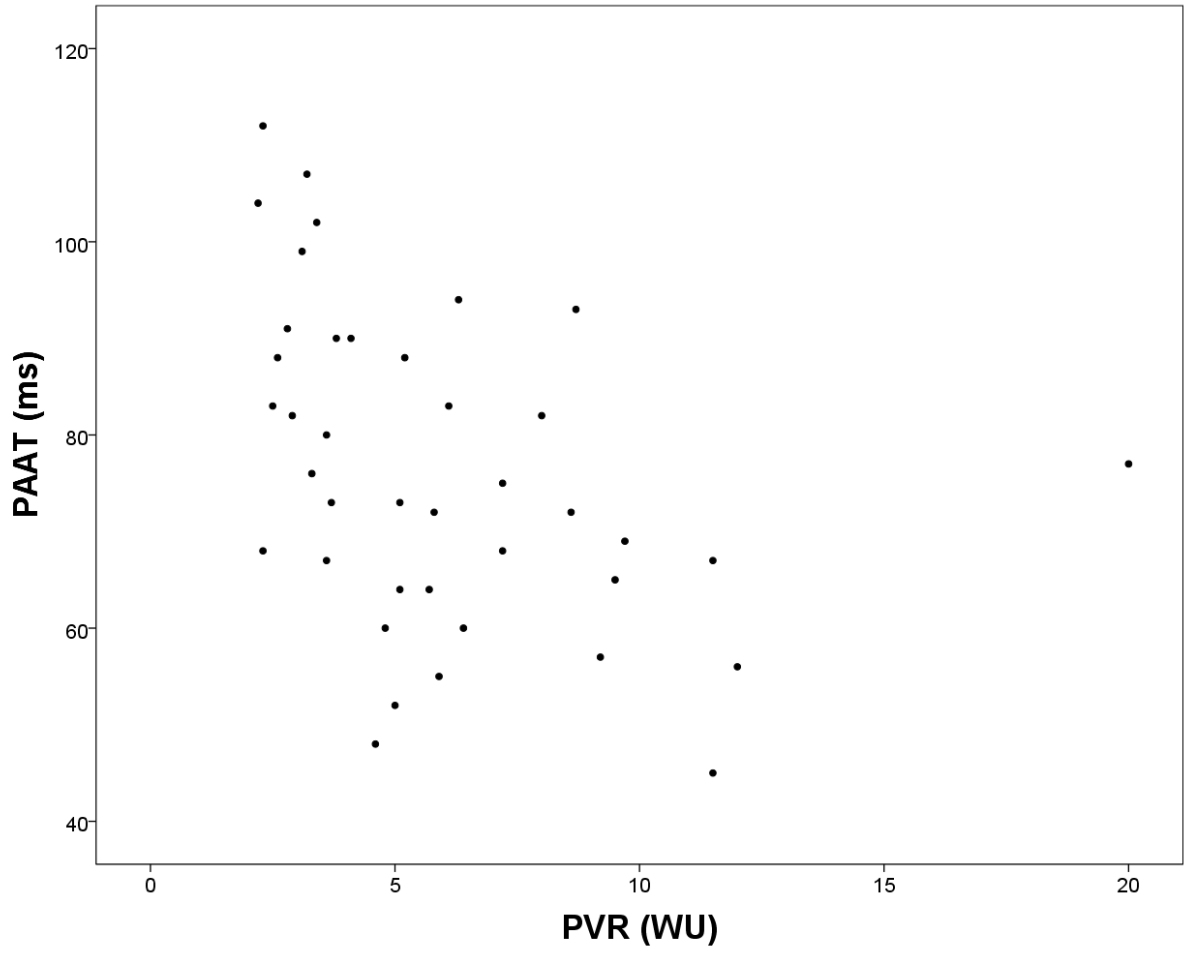
Scatterplot of the association between pulmonary artery acceleration time (PAAT) values and tricuspid annular plane systolic excursion (TAPSE) in our pediatric PH patients ($n = 54$; $p < 0.001$, $r = 0.818$).

Supplemental Figure 3:



Scatterplot of the association between pulmonary artery acceleration time (PAAT) values and tricuspid annular peak systolic velocity (S') in our pediatric PH patients, ($n = 54$, $p < 0.001$, $r = 0.622$)

Supplemental Figure 4:



Scatterplot of the association between pulmonary artery acceleration time (PAAT) values and pulmonary vascular resistance (PVR) in the PH group ($n = 54$, $p = 0.011$, $\rho = -0.497$).