


The right ventricular outflow tract in pediatric pulmonary hypertension—Data from the European Pediatric Pulmonary Vascular Disease Network

Martin Koestenberger MD¹  | Alexander Avian PhD² | Hannes Sallmon MD³ |
Andreas Gamillscheg MD¹ | Gernot Grangl MD¹ | Stefan Kurath-Koller MD¹ |
Sabrina Schweintzger MD¹ | Ante Burmas MD¹ | Georg Hansmann MD, PhD⁴

¹Division of Pediatric Cardiology, Department of Pediatrics, Medical University Graz, Graz, Austria

²Institute for Medical Informatics, Statistics and Documentation, Medical University Graz, Graz, Austria

³Department of Neonatology, Charité – Universitätsmedizin Berlin, Berlin, Germany

⁴Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany

Correspondence

Martin Koestenberger, Division of Pediatric Cardiology, Department of Pediatrics, Medical University Graz, Graz, Austria.
Email: martin.koestenberger@medunigraz.at

Funding information

GH currently receives grant support from the German Research Foundation (DFG; HA 4348/6-1, KFO311).

Objective: The right ventricular outflow tract (RVOT) is pivotal for adequate RV function and known to be adversely affected by elevated pulmonary arterial pressure (PAP) in adults with pulmonary hypertension (PH). Aim of this study was to determine the effects of increased RV pressure afterload in children with PH on RVOT size, function, and flow parameters.

Methods: We conducted a transthoracic echocardiographic study in 51 children with PH (median age: 5.3 years; range 1.5 months to 18 years) and determined the following RVOT variables: RVOT diameter, RVOT velocity time integral (VTI), ratio of tricuspid regurgitation velocity (TRV)/RVOT VTI, and RVOT systolic excursion (SE).

Results: In our pediatric PH cohort, the age-specific RVOT diameter z-score was higher compared to normal values. Deviation from normal RVOT diameter values increased with age, disease severity, and New York Heart Association functional class. Significant correlations were found between RVOT diameter and the RV end-diastolic area and right atrial area. The age-specific RVOT VTI z-score values were significantly lower in children with PH vs healthy controls. The TRV/RVOT VTI ratio increased with rising systolic RV pressure, while the RVOT SE was similar between PH children and control subjects.

Conclusions: In pediatric PH cohort, the RVOT VTI is decreased, and the TRV/RVOT VTI ratio and the RVOT diameter increased compared to healthy subjects. Assessment of RVOT variables, together with established RV parameters, allows for a comprehensive assessment of global right heart size and performance in children with PH.

KEYWORDS

pediatric, pulmonary hypertension, ratio of tricuspid regurgitation/RVOT velocity time integral, right ventricular outflow tract diameter, RVOT velocity time integral

1 | INTRODUCTION

Comprehensive echocardiographic assessment of children and adults with pulmonary hypertension (PH) includes several variables of right ventricular (RV) and right atrial (RA) size, morphology, and

function.^{1–6} However, data regarding the effects of increased right ventricular pressure afterload on RV outflow tract (RVOT) size and systolic function are lacking in children with PH, including those subgroups with pulmonary arterial hypertension (PAH) and PH associated with bronchopulmonary dysplasia (PH-BPD). Guidelines

for adult PH recommended measuring the RVOT diameter as part of the standardized echocardiographic exam (screening/diagnosis, follow-up).⁷ In children, noninvasive techniques to assess pulmonary blood flow are of special interest because such investigations do not require invasive cardiac catheterization, that is not without risk in children with PH.⁸ As the RVOT contributes to RV contraction and its typical pattern in RVs with normal (low) pressure afterload, an altered RVOT function in PH may accompany impaired RV function.⁹ The tricuspid regurgitation velocity (TRV)/RVOT velocity time integral (VTI) ratio, as a reliable measure of pulmonary blood flow in adults with PH,¹⁰ approximates the ratio of pulmonary artery pressure (PAP) to pulmonary blood flow.¹¹ The impact of RV dilation has recently been shown in children with PH,^{12,13} but RVOT values (eg, flow, diameter, and systolic excursion) have not been systematically assessed in pediatric PH.

The aim of this study was to determine RVOT VTI, RVOT diameter, RVOT systolic excursion (SE), and the TRV/RVOT VTI ratio in children with PH to examine the value of these variables in identifying impaired pulmonary blood flow, enlarged size, or reduced systolic function of this part of the RV. In addition, we aimed to elucidate possible correlations between these RVOT variables, conventional RV main body parameters and New York Heart Association (NYHA) functional class. We hypothesized that altered RVOT VTI and diameter values (RVOT dilation defined as z-score > +2) are additional, useful echocardiographic markers for the assessment of PH in children.

2 | MATERIALS AND METHODS

2.1 | Study population

The study group consisted of 51 children with PH (median age: 5.3 years; range 1.5 months to 18 years; 20 female): 13 had idiopathic PAH (IPAH), 23 children had PH associated with congenital heart disease (PH-CHD), and 15 children had PH associated with bronchopulmonary dysplasia (PH-BPD). The PH patients with CHD included patients with post-tricuspid left-to-right shunts such as ventricular septal defects and AV septal defects (including patients with Down syndrome), and pretricuspid shunts such as atrial septal defect but no patients with repaired RVOT, or residual pulmonary stenosis. The CHDs were surgically repaired in all patients at a mean age of 5.6 months (range: 0.4–14.3 months). Patients with severe AV valve regurgitation or conduit regurgitation were excluded from the study. At time of enrollment, all patients were clinically stable without any change of medications within the preceding 4 months. Infants were allowed to be bottle fed during the examination. The baseline characteristics and CHDs of our PH children are shown in Table 1.

All PH-BPD patients had measurable tricuspid regurgitation (TR) so that TR jets could be reliably interrogated. RV systolic pressure was estimated by CW Doppler of TRV (calculated from the modified Bernoulli equation). TRV >2.8 m/s was considered as the cutoff value to define elevated PAP in the absence of pulmonary stenosis.¹⁴ TR jet velocities predicted at least half-systemic systolic RV pressure in

all of the PH-BPD patients. To calculate the echocardiographic ratio between RV systolic pressure (RVSP) and systemic systolic arterial pressure, we estimated the RVSP (as described above) and measured the systolic arterial pressure in our PH-BPD patients.

2.2 | Hemodynamic assessment

All patients with IPAH or PH-CHD (but not those with PH-BPD) underwent cardiac catheterization which remains the gold standard for diagnosing pulmonary arterial hypertension (PAH). Cardiac catheterization was performed within 3 months of inclusion into the study. In fact, invasive hemodynamics were obtained within a week of the study echocardiogram in 77% of the study patients. PAH was defined as a mPAP \geq 25 mm Hg at rest, a pulmonary capillary wedge pressure \leq 15 mm Hg, and a PVR >3 mm (Wood units [WU] \times m² BSA).³ Systolic pulmonary arterial pressure (sPAP), mean pulmonary arterial pressure (mPAP), mixed venous oxygen saturation, pulmonary vascular resistance index (PVRi), and PVR/systemic vascular resistance (SVR) ratio were determined (Table 1). For calculation of the PAP/SAP ratio, usually the ratio between the mPAP/mSAP is used. Due to the fact that in our PAH-PBD patients respective mPAP values were not available, we calculated the ratio between sPAP/sSAP in our cardiac catheterization measurements. None of the PH patients had significant intracardiac shunt. All children with PH had a normal left ventricular ejection fraction (LVEF), measured using Simpsons formula, and a normal age-related¹⁵ mitral annular plane systolic excursion.

2.3 | Echocardiographic protocol

Echocardiograms were performed using commercially available echocardiographic system using transducers of 5–1, 8–3, and 12–4 MHz depending on patient size and weight. Images were recorded digitally and later analyzed by 1 of the investigators (M.K.) using offline software (Xcelera Echo; Philips Medical Systems, Eindhoven, The Netherlands). Echocardiographic images were considered to be of sufficient quality only if the entire endocardial surface of the RVOT was clearly visualized.

The RVOT proximal diameter was measured using M-mode echocardiography from the parasternal short-axis view at end-diastole. The M-mode echorecording of the RVOT data was measured at end-diastole. The proximal RVOT has the advantage of being the site of measurement for the RVOT SE allowing for both the RV dimension measurement and assessment of systolic RVOT function.

The RVOT SE was measured from the parasternal short-axis view using M-mode echocardiography. Imaging was performed at the level of the aortic valve at the maximal RVOT diameter, with the ultrasound beam perpendicular to the RVOT walls.⁹ The RVOT SE is defined as the systolic excursion of the endocardial surface of the anterior wall of the RVOT relative to the transducer.¹⁶

The RVOT VTI was obtained by placing a PW Doppler sample volume in the proximal RVOT just within the pulmonary valve imaged from the parasternal short-axis view. Importantly, patients must be in sinus rhythm at the time of the echocardiogram. After manually tracing

TABLE 1 Demographic data of our children with pulmonary hypertension

Demographic data	n or median (range)
All PH patients	
Fulfilled inclusion criteria (n)	51
Female (%) (n)	20 (39)
Age at baseline (range) (y)	5.3 (0.13–17.9)
Body weight (range) (kg)	16.6 (3.0–72.0)
Body length (range) (cm)	106 (48–185)
BSA range (m ²)	0.70 (0.20–1.92)
WHO functional class	
I (n)	17
II (n)	20
III (n)	7
Medication	
Bosentan (n)	5
Bosentan + sildenafil (n)	7
Macitentan (n)	8
Macitentan + sildenafil (n)	10
Sildenafil (n)	16
Calcium antagonists (n)	3
Selexipag (n)	2
Variables	
TRV (m/s)	4.1 (2.8–5.9)
TRV/RVOT VTI ratio	0.30 (0.19–0.69)
mPAP (mean ± range; mm Hg)	39 (27–90)
PVRi (mean ± range; WU)	6.2 (2.3–29.9)
PH-CHD (n)	23
TRV (m/s)	3.8 (2.9–5.0)
TRV/RVOT VTI ratio	0.29 (0.19–0.69)
sPAP/sSAP (%)	74 (40–106)
mPAP (mean ± range; mm Hg)	37 (27–56)
PVRi (mean ± range; WU)	4.6 (2.3–16.0)
Diagnosis	
AVSD (n)	10
VSD (n)	9
ASD (n)	3
IPAH (n)	13
TRV (m/s)	4.5 (3.3–5.6)
TRV/RVOT VTI ratio	0.33 (0.19–0.56)
sPAP/sSAP (%)	89 (42–119)
mPAP (mean ± range; mm Hg)	46 (29–90)
PVRi (mean ± range; WU)	8.6 (3.6–29.9)
PH-BPD (n)	15
TRV (m/s)	3.4 (2.7–4.7)
TRV/RVOT VTI ratio	0.27 (0.21–0.41)
% of systemic pressure (%)	64 (40–88)

(Continues)

TABLE 1 (Continued)

Demographic data	n or median (range)
mPAP (mean ± range; mm Hg)	35 (27–54)
PVRi (mean ± range; WU)	6.7 (3.4–15.5)

BSA = body surface area; mPAP = mean pulmonary artery pressure; PVRi = pulmonary vascular resistance indexed; PH-CHD = PH secondary to congenital heart disease; PH-BPD = PH secondary to bronchopulmonary dysplasia; IPAH = idiopathic PAH; RVOT = right ventricular outflow tract; sPAP = systolic pulmonary artery pressure; sSAP = systolic systemic artery pressure; TRV/RVOT VTI ratio; tricuspid regurgitation velocity/RVOT velocity time integral ratio; WU = Wood units.

the PW Doppler spectrum, RVOT VTI values were measured by applying the calculation package of the ultrasound unit and are equal to the area enclosed by the baseline and Doppler spectrum.¹⁷

The peak TRV was measured using CW Doppler in the apical four-chamber view. The highest velocity obtained from multiple views was used. Subsequently, the TRV/RVOT VTI ratio was calculated. Data are presented as mean and standard deviation or median and range for continuous data, and absolute and relative frequency for categorical data, respectively. Age-adjusted RVOT VTI z-scores were calculated according to a previous study.¹⁷

Tricuspid annular peak systolic velocity (S') was obtained by the following method: Pulsed-wave tissue Doppler imaging was performed using transducer frequencies of 3–8 MHz with spectral Doppler filters adjusted until a Nyquist limit of 15–20 cm/s. S' during systole were recorded and analyzed offline.¹⁸

The RV end-diastolic basal diameter (EDb-d) was measured as the distance between the RV free wall and septum, just distal to the tricuspid annulus. The RV end-diastolic mid-cavity diameter (EDm-d) is measured in the middle third of the RV at the level of the LV papillary muscles, both measured in the apical four-chamber view. The measurements of the RVEDb-d, RVEDm-d, and RVED area (RVEDa) were performed at end-diastole. The RA area is traced at the end of ventricular systole (largest volume) from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area between the leaflets and annulus, following the RA endocardium, excluding the IVC and SVC and the RA appendage.

Tricuspid annular plane systolic excursion (TAPSE) was measured by 2D echocardiography-guided M-mode recordings from the apical four-chamber view with the cursor placed at the free wall of the tricuspid annulus as previously described.¹⁹

2.4 | Image acquisition

To minimize variability, a strict institutional protocol for image acquisition for the measurement of RVOT dimensions was used. Age, body weight (BW), body length (BL), and body surface area (BSA) were measured at time of echocardiography, and BSA was calculated using the Mosteller formula.²⁰ The echocardiographic measurement of the RVOT variables in children with PH is shown in Figure 1.

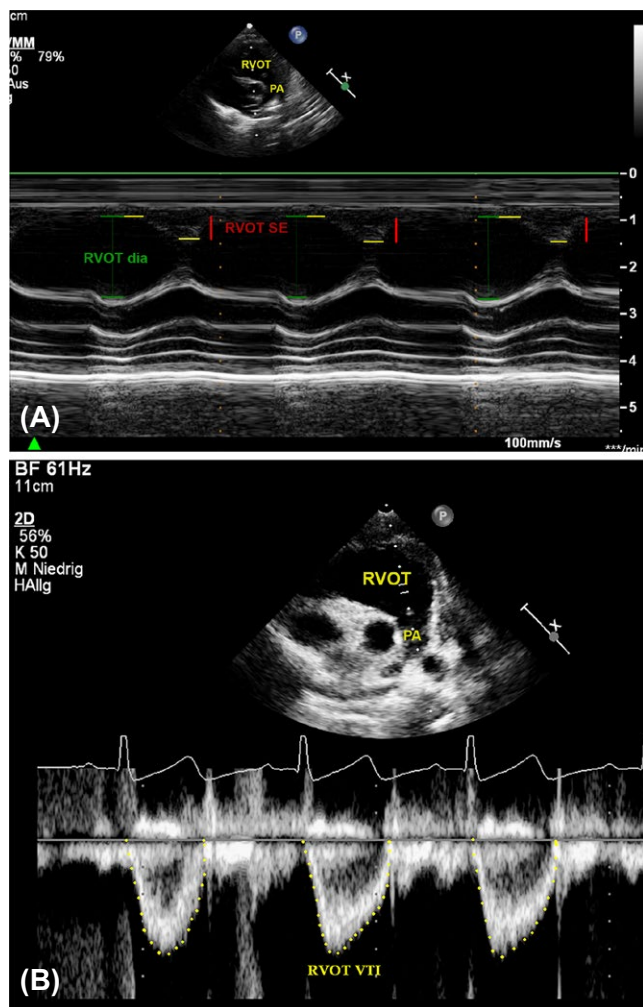


FIGURE 1 A. The RVOT proximal diameter was measured from the parasternal short-axis view; the RVOT SE measures the systolic excursion of the RVOT anterior wall. A representative M-mode image of the RVOT SE and the RVOT diameter in an 11-year-old patient with normal RV and LV function is shown. The absolute longitudinal displacement measure is shown as the red line. The yellow lines mark the upper and lower measure points of the RVOT SE. The vertical green lines mark the upper and lower measure points on the endocardial surface of the RVOT diameter. B. PW Doppler sample volume is placed in the proximal RVOT just below the pulmonary valve to measure RVOT VTI. A decreased RVOT VTI value (marked with a yellow dotted line) of a 14-year-old patient with PH-CHD is shown. Note the enlarged RVOT size. RVOT = right ventricular outflow tract; SE = systolic excursion; VTI = velocity time integral

2.5 | Statistical analysis

Inter-observer and intra-observer reliability of echocardiographic measurements ranges from ICCintra: .97-.99 for intra-observer reliability and from ICCintra: .88-.99 for inter-observer reliability.^{17,21,22}

Data are presented as mean \pm SD. Age-specific z-scores were calculated according to published algorithms (RVOT diameter,²¹ RVOT SE,²² and RVOT VTI¹⁷). One sample *t* test was used to analyze whether age-specific z-scores differ from zero and therefore are

increased or decreased compared to normal age-specific values. The number of patients with increased (z-score >2) or decreased (z-score <-2) age-specific z-scores was reported. Association with parameters of the RV main body were analyzed using Pearson correlation coefficient (*r*) or Spearman correlation coefficient (ρ), as appropriate. Diagnosis groups were compared using ANOVA or Kruskal-Wallis test as appropriated. For post hoc tests for pairwise comparisons Bonferroni correction was used.

2.6 | 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 competing relationships to report.

3 | RESULTS

The RVOT VTI ranged from 5.9 to 18 cm in our PH children, Figure 2. Age-specific RVOT VTI z-score (-1.20 ± 1.6) was significantly lower compared to normal values, $P < .001$. Female and male PH patients had comparable age-specific RVOT VTI z-scores values (1.33 ± 1.79 vs 1.00 ± 1.37 ; $P = .481$). While RVOT VTI in young children were normal, deviation from normal values increased with age and disease severity (correlation age with age-specific RVOT VTI z-score: $\rho = -.639$, $P < .001$). In children from 0 to 3 years of age, the specific RVOT VTI z-scores values were -0.12 ± 1.28 , in children >3 -10 years of age, values were -1.35 ± 1.19 , and in children >10 -18 years of age, the RVOT VTI z-scores values were -2.85 ± 1.14 .

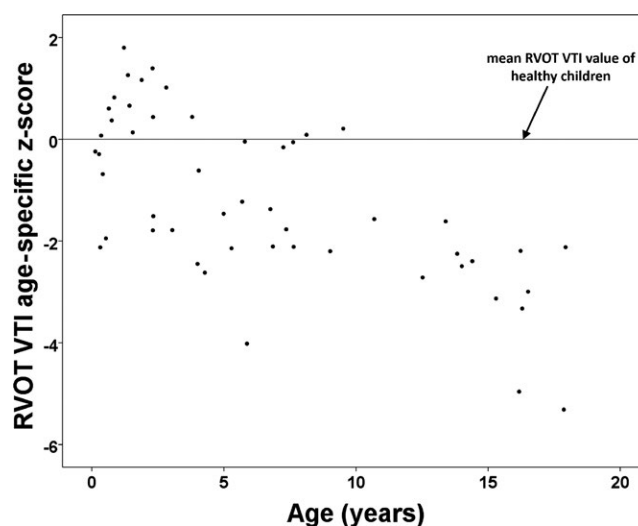


FIGURE 2 Association of RVOT VTI age-specific z-scores with age. A z-score of 0 is indicated by a solid line. This value corresponds to mean RVOT VTI value of healthy children of the same age. The value of +1 corresponds to 1 standard deviation above and -1 to 1 standard deviation below this mean value

The RVOT diameter ranged from 0.80 to 4.70 cm in our PH children, Figure 3. Age-specific RVOT diameter z-score (1.56 ± 1.74) was higher compared to normal values ($P < .001$). Deviation from normal RVOT diameter values increased with age and disease severity (correlation of age with age-specific RVOT diameter z-score: $\rho = .316$, $P = .025$).

The TRV/RVOT VTI ratio ranged between 0.19 and 0.69 (median = 0.30) in our PH patients. The TRV/RVOT VTI ratio was found to rise with increasing ratio of systolic PAP/systolic systemic arterial pressure (SAP), ($\rho = .852$, $P > .001$), Figure 4.

Right ventricular outflow tract systolic excursion ranged from 0.26 to 1.00 cm in our PH children. Age-specific RVOT SE z-score (median: -0.25 , IQR: -1.67 to 0.58) was comparable to normal values ($P = .081$). Age-specific RVOT SE z-score did not change over time (correlation age with age-specific RVOT SE z-score: $\rho = -.185$, $P = .197$).

The RVOT diameter showed a significant positive correlation with the RV end-diastolic basal (RVEDb) diameter ($\rho = .905$; $P < .001$), to the RVED mid-cavity (RVEDm-c) diameter ($\rho = .883$; $P < .001$), to the RVED area ($\rho = .895$; $P < .001$), and to the right atrial (RA) area ($\rho = .871$; $P < .001$). In addition, a shortening of the established pulmonary artery acceleration time (PAAT) significantly correlated with lower RVOT VTI values ($\rho = .677$; $P < .001$) and higher TRV/RVOT VTI values ($\rho = -.689$; $P < .001$).

The RVOT VTI showed a significant negative correlation with the mPAP ($\rho = -.54$; $P < .001$) and the PVRi ($\rho = -.54$; $P < .01$), while the RVOT diameter and the RVOT SE had no significance correlation with these hemodynamic parameters.

Comparing RVOT variables between the different disease entities (IPAH, PH-CHD, and PH-BPD), the RVOT VTI, RVOT SE, and TRV/RVOT VTI ratio values were comparable among the groups.

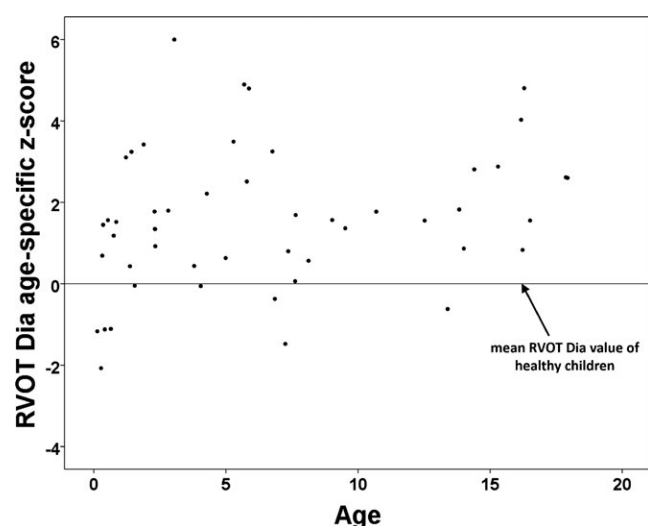


FIGURE 3 Association of RVOT diameter age-specific z-scores with age. A z-score of 0 is indicated by a solid line. This value corresponds to the mean RVOT VTI value of healthy children with the same age. The value of +1 corresponds to 1 standard deviation above and -1 to 1 standard deviation below this mean value

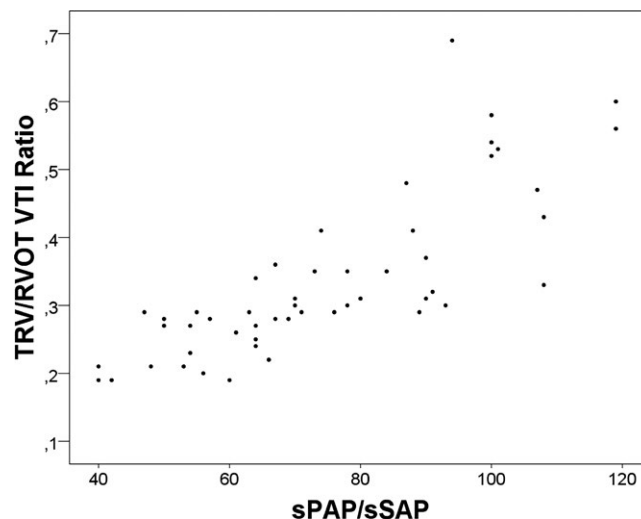


FIGURE 4 Association of the ratio of systolic pulmonary artery pressure (sPAP)/systolic systemic arterial pressure (sSAP) with the TRV/RVOT VTI ratio ($\rho = .852$, $P > .001$). RVOT = right ventricular outflow tract; TRV = tricuspid regurgitation velocity; VTI = velocity time integral

However, significant differences in RVOT diameter values were found. The highest RVOT diameter values were present in children with IPAH, followed by children with PH-CHD, and children with PH-BPD. Differences between all groups were significant as shown in Table 2.

With worsening NYHA functional class (FC), the RVOT diameter ($P = .010$) and the TRV/RVOT VTI ratio ($P = .001$) increased in our children with PH. The RVOT VTI showed only a trend toward a decrease ($P = .055$), and the RVOT systolic excursion (SE) did not significantly change ($P = .536$) with worsening FC. The highest RVOT diameter values, TRV/RVOT VTI ratio, and the lowest RVOT VTI values were observed in children and adolescents with PH being in NYHA FC III [$n = 7$; RVOT diameter z-score: 2.21 (1.56 – 2.81); TRV/RVOT VTI ratio: 0.47 (0.33 – 0.53); RVOT VTI z-score: -2.40 (-4.96 to -1.95)], followed by NYHA FC II [$n = 23$; RVOT diameter z-score: 1.82 (0.86 – 3.49); TRV/RVOT VTI ratio: 0.30 (0.29 – 0.37); RVOT VTI z-score: -1.78 (-2.35 to -1.30)], and followed by NYHA FC I [$n = 21$; RVOT diameter z-score: 0.83 (0.42 – 1.55); TRV/RVOT VTI ratio: 0.25 (0.21 – 0.31); RVOT VTI z-score: -0.16 (-2.11 to -0.21)], respectively.

4 | DISCUSSION

In this study of 51 pediatric patients with PH, we were able to identify the RVOT diameter to be increased, the TRV/RVOT VTI ratio to be increased, and RVOT VTI values to be decreased compared to normative values. With this study, we introduce these RVOT parameters in clinical care of children with PH and demonstrate an association of these parameters with echocardiographic measured RV parameters, with NYHA functional class and invasive hemodynamic variables.

	IPAH	PH-BPD	PH-CHD
RVOT VTI (cm)	12.8 ± 2.9	12.9 ± 2.1	12.0 ± 3.5
RVOT dia (cm)	3.35 ± 0.89 ^{b,c}	1.69 ± 0.53 ^{a,c}	2.61 ± 0.69 ^{a,b}
RVOT SE (cm)	0.68 ± 0.21 ^b	0.49 ± 0.12 ^a	0.62 ± 0.18
TRV/VTI ratio	0.33 (0.29–0.37)	0.27 (0.22–0.34)	0.29 (0.28–0.47)

IPAH = idiopathic pulmonary arterial hypertension; PH-BPD = PH associated with bronchopulmonary dysplasia; PH-CHD = PH associated with congenital heart disease; RVOT VTI = right ventricular outflow tract velocity time integral; RVOTI dia = RVOT diameter; TRV = tricuspid regurgitation velocity; RVOT SE = RVOT systolic excursion.

^aSignificantly different to IPAH.

^bSignificantly different to PH-BPD.

^cSignificantly different to PH-CHD.

Global assessment of all parts of the right heart is difficult owing to the underlying anatomy.²³ The main body of the RV is an integral part of the right heart system but the other parts (RVOT, RA) significantly contribute to right heart performance.²³ RV function is distinct from the LV, in that it has 3 distinctive compartments with different patterns of response to raised pulmonary artery pressure.²⁴ In adult PH patients, RV body and RVOT were dilated and the thin-walled RVOT became progressively dysfunctional as its dimensions increase with an eventual decrease in systolic function.²⁴ Determination of the RVOT movement has been suggested to be an additional marker of RV function in patients with various CHDs.¹⁶ The RVOT SE directly measures the contraction of the RVOT region.²⁵ Parameters of main RV body systolic function such as the TAPSE and the S' have been shown to be useful quantitative measures of longitudinal RV systolic function in adults and children.^{18,26,27} No significant differences in RV systolic function parameters such as TAPSE were found in adults²⁸ and in children with PH as compared to control subjects.²⁹ Combined assessment of RV systolic pressure and RVOT diameter was reported to provide a suitable strategy to exclude PH in patients with advanced lung disease referred for lung transplantation, highlighting the need for multimodal echocardiographic approach which takes into account that RV pressure overload is associated with changes of all right heart structures.³⁰

Under normal physiologic conditions, the pulmonary vascular bed has low impedance and produces only small reflected pressures and flow waves returning to the RVOT after pulmonic valve closure. Measuring blood flow in the RVOT is independent of (subclinical) stenosis of the pulmonary valve. RVOT flow velocity determination is an essential part of the noninvasive investigation of pulmonary blood flow in adult patients.¹⁰ In children with an ASD, the RVOT VTI and RVOT diameter, but not the RVOT SE, have been shown to be significant predictors in estimating the ASD disease severity.³¹ RV dimension and RVOT VTI were shown to be significant predictors of mortality in adult PH patients. Accordingly, prostacyclin treatment facilitated improvements of the RVOT VTI in these adult patients.³²

Right ventricular outflow tract VTI, RVOT diameter, and RVOT SE reference values from healthy children were recently published,^{17,21,22} but a detailed investigation of RVOT size, function, and flow in pediatric PAH has been unavailable to date. In the current

TABLE 2 Data of the pediatric PH subgroups

study, we demonstrate significantly increased RVOT diameter, decreased RVOT VTI, and increased TRV/RVOT VTI ratio values in comparison with normative values. RVOT SE values were not found to be significantly different between pediatric PH patients and age-related normative data.

We observed differences between RVOT variables among the different disease entities (IPAH, PH-CHD, PH-BPD). RVOT diameters were highest in children with IPAH, followed by children with PH-CHD, and lowest in those with PH-BPD. One might argue that these differences indicate a more severe disease in IPAH patients, and in fact, our IPAH patients showed the most pronounced changes during catheter-based hemodynamic assessment. However, it is also possible that different PH disease entities show specific patterns of RVOT affection caused by possible disease-specific hemodynamic differences or by the duration of the disease. Of note, RVOT VTI and TRV/RVOT VTI ratio values did not differ among the different disease entity groups. As an easy to measure, noninvasive parameter to detect impaired pulmonary blood flow in pediatric PH patients, we suggest including the assessment of the RVOT VTI when evaluating patients with PH. Care should be given evaluating the RVOT diameter in patients from the PH-CHD subgroup as in such patients influencing factors of the respective CHD cannot be excluded. Furthermore, finding an RVOT to be significantly enlarged and the RVOT VTI to be significantly decreased in screening investigations of children with suspected PH should lead to a more detailed diagnostic approach (ie, cardiac magnetic resonance imaging or cardiac catheterization). Future studies incorporating a higher number of patients are needed to address these issues.

In conclusion, we found the RVOT diameter to be enlarged, the RVOT VTI to be decreased, the TRV/RVOT VTI ratio increased, while the RVOT SE was not significantly altered compared to controls in our pediatric PH patients. Our study suggests that echocardiographic evaluation of these RVOT parameters provides a useful tool for diagnosis and follow-up RV afterload and performance in children with PH. RVOT and RV main body parameters showed close correlations. Thus, measuring RVOT parameters together with established echocardiographic RV parameters allows for a more detailed assessment of global right heart performance in children with PH. The RVOT values correlated with the NYHA FC of our children with PH, suggesting a potential clinical relevance of this index.

4.1 | Limitations of the study

RVOT imaging by echocardiography is limited by a lack of fixed reference points to ensure optimization of the RVOT. To obtain good reproducibility of the RVOT diameter, RVOT VTI, TRV/RVOT VTI ratio, and RVOT SE values, we performed these measurements only in unambiguous views. Using the RVOT VTI as an estimate of RV flow has the limitation that it assumes a circular geometry of the RVOT; this might be the case in healthy children but not in all children with PH. Although we employed a wide variety of echocardiographic RVOT variables, it is obvious that we would have obtained a more thorough evaluation of the effect of right heart pressure overload on RVOT parameters if we had included echocardiographic techniques such as 3D echo and strain assessment. Our selection criteria resulted in a small cohort of pediatric PH patients of mixed etiologies, however, this study did not allow for a complete and comprehensive evaluation of the impact of a specific PH disease/subgroup on the accuracy of echocardiographic indices.

ACKNOWLEDGMENTS

This manuscript resulted from collaborations within the European Pediatric Pulmonary Vascular Disease Network (www.pvdnetwork.org).

ORCID

Martin Koestenberger  <http://orcid.org/0000-0003-1766-7859>

REFERENCES

- Koestenberger M, Apitz C, Abdul-Khaliq H, et al. 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 DGPK. *Heart*. 2016;102(Suppl 2):ii14–ii22.
- Hansmann G, Apitz C, Abdul-Khaliq H, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart*. 2016;102(Suppl 2):ii86–ii100.
- Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099.
- Koestenberger M, Hansmann G, Apitz C, et al. Diagnostics in children and adolescents with suspected or confirmed pulmonary hypertension. *Paediatr Respir Rev*. 2017;23:3–15.
- Vonk Noordegraaf A, Haddad F, Bogaard HJ, et al. Noninvasive imaging in the assessment of the cardiopulmonary vascular unit. *Circulation*. 2015;131:899–913.
- Hansmann G. Pulmonary hypertension in infants, children, and young adults. *J Am Coll Cardiol*. 2017;69:2551–2569.
- Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119.
- Beghetti M, Schulze-Neick I, Berger RM, et al. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension). *Int J Cardiol*. 2016;203:325–330.
- Asmer I, Adawi S, Ganaem M, et al. Right ventricular outflow tract systolic excursion. A novel echocardiographic parameter of right ventricular function. *Eur Heart J Cardiovasc Imaging*. 2012;13:871–877.
- Abbas AE, Franey LM, Marwick T, et al. Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. *J Am Soc Echocardiogr*. 2013;26:1170–1177.
- Kouzu H, Nakatani S, Kyotani S, et al. Noninvasive estimation of pulmonary vascular resistance by Doppler echocardiography in patients with pulmonary arterial hypertension. *Am J Cardiol*. 2009;103:872–876.
- Koestenberger M, Nagel B, Ravekes W, et al. Reference values and calculation of z-scores of echocardiographic measurements of the normal pediatric right ventricle. *Am J Cardiol*. 2014;114:1590–1598.
- Ploegstra MJ, Roofthoof MT, Douwes JM, et al. Echocardiography in pediatric pulmonary arterial hypertension: early study on assessing disease severity and predicting outcome. *Circ Cardiovasc Imaging*. 2014;8. pii: e000878.
- McQuillan BM, Picard MH, Leavitt M, et al. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104:2797–2802.
- Koestenberger M, Nagel B, Ravekes W, et al. 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.
- Kutty S, Zhou J, Gauvreau K, et al. Regional dysfunction of the right ventricular outflow tract reduces the accuracy of Doppler tissue imaging assessment of global right ventricular systolic function in patients with repaired tetralogy of Fallot. *J Am Soc Echocardiogr*. 2011;24:637–643.
- Koestenberger M, Nagel B, Ravekes W, et al. Right ventricular outflow tract velocity time integral determination in 570 healthy children and in 52 pediatric atrial septal defect patients. *Pediatr Cardiol*. 2015;36:1129–1134.
- Koestenberger M, Nagel B, Ravekes W, et al. 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.
- Koestenberger M, Ravekes W, Everett A, et al. 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.
- Mosteller R. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.
- 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.
- Koestenberger M, Ravekes W, Nagel B, et al. 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.
- Redington AN. Right ventricular function. *Cardiol Clin*. 2002;20:341–349.

24. Calcuttea A, Lindquist P, Soderberg S, et al. Global and regional right ventricular dysfunction in pulmonary hypertension. *Echocardiography*. 2014;31:164–171.
25. Haddad F, Hunt SA, Rosenthal DN, et al. Right ventricular function in cardiovascular disease, part I: anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation*. 2008;117:1436–1448.
26. Koestenberger M, Nagel B, Ravekes W, et al. Systolic right ventricular (RV) function in pediatric and adolescent patients with TOF: echocardiography versus MRI. *J Am Soc Echocardiogr*. 2011;24:45–52.
27. Koestenberger M, Nagel B, Ravekes W, et al. Tricuspid annular peak systolic velocity (S') in children and young adults with pulmonary artery hypertension secondary to congenital heart diseases, and in those with repaired tetralogy of Fallot: echocardiography and MRI data. *J Am Soc Echocardiogr*. 2012;25:1041–1049.
28. Bussadori C, Di Salvo G, Pluchinotta FR, et al. Evaluation of right ventricular function in adults with congenital heart defects. *Echocardiography*. 2015;32(Suppl 1):S38–S52.
29. Koestenberger M, Nagel B, Ravekes W, et al. Tricuspid annular plane systolic excursion (TAPSE) and right ventricular ejection fraction in pediatric and adolescent patients with tetralogy of Fallot, patients with atrial septal defect, and age-matched normal subjects. *Clin Res Cardiol*. 2011;100:67–75.
30. Nowak J, Hudzik B, Jastrze Bski D, et al. Pulmonary hypertension in advanced lung diseases: echocardiography as an important part of patient evaluation for lung transplantation. *Clin Respir J*. 2017; Jan 4 [Epub ahead of print].
31. Koestenberger M, Ravekes W, Avian A, et al. Right ventricular outflow tract changes in children with an atrial septal defect: focus on RVOT velocity time integral, RVOT diameter, and RVOT systolic excursion. *Echocardiography*. 2016;33:1389–1396.
32. Tonelli AR, Conci D, Tamarappoo BK. Prognostic value of echocardiographic changes in patients with pulmonary arterial hypertension receiving parenteral prostacyclin therapy. *J Am Soc Echocardiogr*. 2014;27:733–741.

How to cite this article: Koestenberger M, Avian A, Sallmon H, et al. The right ventricular outflow tract in pediatric pulmonary hypertension—Data from the European Pediatric Pulmonary Vascular Disease Network. *Echocardiography*. 2018;00:1–8. <https://doi.org/10.1111/echo.13852>