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CLINICAL INVESTIGATIONS

Right ventricular base/apex ratio in the assessment of pediatric pulmonary arterial hypertension: Results from the European Pediatric Pulmonary Vascular Disease Network

Martin Koestenberger[1] | Alexander Avian[2] | Andreas Gamillscheg[1] | Hannes Sallmon[3] | Gernot Grangl[1] | Ante Burmas[1] | Sabrina Schweintzger[1] | Stefan Kurath-Koller[1] | Gerhard Cvirn[4] | Georg Hansmann[5]

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

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

[3]Department of Pediatric Cardiology, Charité–Universitätsmedizin Berlin, Berlin, Germany

[4]Centre of Physiological Medicine, Medical University Graz, Graz, Austria

[5]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany

Correspondence
Martin Koestenberger, MD, Department of Pediatrics, Medical University Graz, Auenbruggerplatz 34/2, A-8036 Graz, Austria
Email: martin.koestenberger@medunigraz.at

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Background: Echocardiographic determination of RV end-systolic base/apex (RVES b/a) ratio was proposed to be of clinical value for assessment of pulmonary arterial hypertension (PAH) in adults.

Hypothesis: We hypothesized that the RVES b/a ratio will be affected in children with PAH and aimed to correlate RVES b/a ratio with conventionally used echocardiographic and hemodynamic variables, and with New York Heart Association (NYHA) functional class.

Methods: First we determined normal pediatric values for RVES b/a ratio in 157 healthy children (68 males; age range, 0.5–17.7 years). We then conducted an echocardiographic study in 51 children with PAH (29 males; age range, 0.3–17.8 years).

Results: RVES b/a ratio was lower compared with age- and sex-matched healthy controls ($P < 0.001$). In children with PAH, RVES b/a ratio decreased with worsening NYHA class. RVES b/a ratio inversely correlated with RV/LV end-systolic diameter ratio ($\rho = -0.450$, $P = 0.001$) but did not correlate with RV systolic function parameters (eg, tricuspid annular plane systolic excursion) and correlated with cardiac catheterization–determined pulmonary vascular resistance index ($\rho = -0.571$, $P < 0.001$). ROC analysis unraveled excellent performance of RVES b/a ratio to detect PAH in children (AUC: 0.95, 95% CI: 0.89–1.00, $P < 0.001$).

Conclusions: The RVES b/a ratio decreased in children with PAH compared with age- and sex-matched healthy subjects. The RVES b/a ratio inversely correlated with both echocardiographic and hemodynamic indicators of increased RV pressure afterload and with NYHA class, suggesting that RVES b/a ratio reflects disease severity in PAH children.

KEYWORDS

Echocardiography, End-Systolic Base/Apex Ratio, Pediatric, Pulmonary Arterial Hypertension, Right Ventricle

1 | INTRODUCTION

Right ventricular (RV) pressure overload causes not only RV dysfunction, but also cardiac remodeling, RV–left ventricular (LV) interaction, and LV diastolic dysfunction in pediatric and adult pulmonary arterial hypertension (PAH).[1–4] An accurate assessment of RV size and function is therefore critically important for guiding treatment and clinical monitoring in PAH patients of all ages.[5,6] The role of echocardiography in the diagnosis and clinical follow-up of children with PAH has evolved and expanded in recent years.[7–9] In particular, echocardiographically determined RV end-systolic and RV end-diastolic diameters can easily be obtained and therefore may be used as noninvasive measures of RV size and geometry in children with PAH.[10] A novel RV end-systolic basal-apical ratio (RVES b/a ratio) recently has been

demonstrated to be a simple reproducible prognostic marker in adults with PAH.[11] However, to date, neither normal RVES b/a ratio values for healthy children nor data for those with PAH are available. A simple index that would incorporate the dilatation of the RV and estimating the RVES b/a will add relevant information on the typical features of an RV "under pressure" in pediatric PAH.

The aim of this study was first to determine normal values for the RVES b/a ratio for children and to assess the indicative strength of this ratio in children with PAH. In addition, we aimed to elucidate correlations between this variable and conventional echocardiographic RV main body dimensions, hemodynamic variables, and New York Heart Association (NYHA) functional class. We hypothesized that the RVES b/a ratio would be decreased in children with PAH vs controls and would decrease in proportion to RV afterload due to the progressive dilation of the RV "under pressure."

2 | METHODS

2.1 | Healthy pediatric control study group

Our healthy control study group consisted of 157 children without any significant health condition (68 male; 89 female; age range, 0.5–17.7 years; Table 1). For comparison of our healthy subjects with the PAH group, 51 healthy subjects were matched according to sex and age (0–<1 year: ±2 months, 1–<4 years: ±6 months, 4–18 years: ±1 year) to our PAH patients. These 51 healthy subjects had comparable body weight and body surface area (BSA) when compared with the 51 children with PAH. The control 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. All patients with congenital heart disease (CHD) such as pulmonary stenosis, acquired heart diseases, chest and thoracic spine deformities, or chromosomal syndromes were excluded. Pulmonary artery Doppler notch can be associated with increased pulmonary vascular resistance (PVR) in pulmonary hypertension (PH) patients,[12] and therefore patients with a "notched" Doppler envelope were excluded from analysis of the healthy cohort. In our healthy cohort, we confirmed that all control children had normal left ventricular ejection fraction, pulmonary artery acceleration time,[13] RV dimensions,[14] tricuspid annular plane systolic excursion (TAPSE),[15] and tricuspid annular peak systolic velocity (S′).[16]

TABLE 1 Demographic data of children (all ages) with either no PH (healthy) or PH (IPAH, PAH-CHD, PH-BPD)

	Healthy Children		
	Whole Group	Age-/Sex-Matched Group	Children With PH
Age[a]	9.0 (0.5–17.7)	5.4 (0.12–17.70)	5.4 (0.25–17.86)
N	157	51	51
Female sex	89 (56.7)	22 (43.1)	22 (43.1)
Weight, kg	30.0 (3.0–98.0)	20.5 (4.0–75.0)	16.6 (3.2–70.0)
Length, cm	134 (49–188)	115 (49–177)	106 (46–185)
BSA, m^2	1.07 (0.20–2.21)	0.80 (0.24–1.92)	0.70 (0.20–1.90)

Abbreviations: BSA, body surface area; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; PH, pulmonary hypertension; PH-BPD, PH secondary to bronchopulmonary dysplasia; PH-CHD, pulmonary hypertension associated with congenital heart disease. Data are presented as n (%) or median (IQR).
[a] Age of patient at baseline is the age at inclusion in the study.

2.2 | Pediatric PAH study group

The PAH study group consisted of 51 children with PAH (29 male, 22 female): 22 children with PAH associated with congenital heart disease (PAH-CHD),[17] 16 patients with PH associated with bronchopulmonary dysplasia (PH-BPD),[18] and 13 patients with idiopathic PAH (IPAH; age range, 0.3–17.8 years; Table 2).[2] PAH patients with CHD included patients with posttricuspid left-to-right shunts, such as ventricular septal defects and atrioventricular septal defects; and with pretricuspid shunts, such as atrial septal defect; but no patients had repaired right ventricular outflow tract or residual pulmonary stenosis. The respective CHDs had been surgically repaired in all patients at a mean age of 5.9 months (range, 0.34–13.9 months). NYHA functional class was determined by 2 independent pediatric cardiologists who were responsible for the medical care of the patients. At the time of enrollment, all patients were clinically stable without change of medications within the preceding 4 months. The baseline characteristics are shown in Table 2.

2.3 | Hemodynamic assessment

Cardiac catheterization was performed within 3 months of inclusion into the study. In fact, invasive hemodynamic measures were obtained within a week of the study echocardiogram in 78% of the PAH patients. All IPAH and PAH-CHD patients underwent cardiac catheterization. PAH was defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest, a pulmonary capillary wedge pressure ≤ 15 mm Hg, and a pulmonary vascular resistance index (PVRi) >3 mm WU × m^2 (iWU).[19] By directly measuring pressures and indirectly measuring flow, we determined markers such as Qs, mixed venous oxygen saturation, and mPAP (Table 2). None of the PAH patients had a significant intracardiac shunt. All PH-BPD patients had measurable mild to moderate tricuspid regurgitation (TR) so that TR jets could be well interrogated with continuous-wave Doppler and did not undergo cardiac catheterization. A TR velocity > 2.8 m/s was considered a reasonable cutoff to define elevated pulmonary pressure in the absence of pulmonary stenosis.[20] The time interval between cardiac catheterization and echocardiography ranged from 0 to 7 days.

2.4 | Image acquisition

To minimize variability, a strict institutional protocol for image acquisition was used for this study. Age, body weight, body length, and BSA were measured at time of echocardiography. BSA was calculated using the Mosteller formula.[21]

2.5 | Echocardiographic protocol

Transthoracic echocardiograms were performed with a commercially available echocardiographic system (Sonos iE33; Philips Medical Systems, Leiden, The Netherlands), using transducers of 5–1, 8–3, and 12–4 MHz, depending on patient age and size. Images were recorded

TABLE 2 Demographic and clinical data of PAH patients

All PAH Patients	
Met inclusion criteria	51
NYHA class	
I	20
II	22
III	9
PH medication	
Bosentan	7
Bosentan + sildenafil	8
Macitentan	7
Macitentan + sildenafil	9
Sildenafil	14
Calcium antagonists	3
Selexipag	3
Variables	
RV b/a ratio	1.31 (1.03–2.18)
RV/LV ratio	1.03 (0.57–2.00)
sPAP/sSAP ratio, %	74 (40–119)
mPAP	42 (27–90)
PVRi	7.40 (2.30–29.9)
Subgroup: PAH-CHD, n = 22	
RV b/a ratio	1.29 (1.03–2.0)
RA area	12.81 (4.00–25.6)
RV/LV ratio	0.99 (0.57–1.35)
sPAP/sSAP ratio, %	75 (40–119)
mPAP	38 (27–56)
PVRi	5.31 (2.30–12.1)
Subgroup: IPAH, n = 13	
RV b/a ratio	1.23 (1.08–1.45)
RA area	17.94 (8.80–39.1)
RV/LV ratio	1.26 (0.85–2.0)
sPAP/sSAP ratio, %	88 (54–119)
mPAP	52 (32–90)
PVRi	10.79 (3.20–29.9)
Subgroup: PH-BPD, n = 16	
RV b/a ratio	1.41 (1.22–2.18)
RA area	5.9 (1.60–13.1)
RV/LV ratio	0.91 (0.71–1.46)
sPAP/sSAP ratio, %	62 (40–88)
mPAP	37 (27–54)
PVRi	7.7 (3.4–15.5)

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; LV, left ventricle; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAH-CHD, PAH associated with congenital heart disease; PH-BPD, pulmonary hypertension secondary to bronchopulmonary dysplasia; PVRi, pulmonary vascular resistance index; RVES b/a, right ventricular end-systolic base to apex ratio; RA, right atrium; RV, right ventricle; sPAP, systolic pulmonary artery pressure; sSAP, systolic systemic artery pressure. Data are presented as n or median (IQR).

digitally and analyzed by offline software (Xcelera Echo; Philips Medical Systems). All measures were averaged over 3 cycles and analyzed according to guidelines by 2 blinded certified readers.[22]

In the apical 4-chamber view, the RV internal diameter at the base (RVES b) was measured just apical to the tricuspid annulus at end-systole as a horizontal line from endocardium of the RV free wall to endocardium of the interventricular septum, orthogonal to the axis of the interventricular septum (IVS). The apical internal diameter of the RV (RVES a) was measured at the level of the distal end of the moderator band during end-systole as a horizontal line from endocardium of the RV free wall to endocardium of the interventricular septum, again perpendicular to the axis of the IVS. The ratio of basal diameter to apical diameter was calculated at end-systole (defined as the time frame preceding tricuspid valve opening; in most instances, the time of the end of the T wave) and measured 3 times, and their average was reported.

The TAPSE reflects the longitudinal excursion of the tricuspid annulus toward the apex (ie, longitudinal RV systolic function) and is measured with M-mode in the apical 4-chamber view.[15] The S′ was recorded and analyzed offline.[16] The RV/LV end-systolic diameter ratio is a variable that correlates well with invasive hemodynamic measures.[23]

The estimation of systolic PAP (PASP) is based on the peak velocity of the tricuspid regurgitation jet (TRV). The simplified Bernoulli equation and continuous-wave Doppler are used to assess velocity within the TRV jet: Right ventricular systolic pressure (RVSP) describes the relationship of TR and RVSP as surrogate of PASP in the absence of a RV outflow tract obstruction or pulmonary artery stenosis. The mean PAP (mPAP) can be calculated from the PA systolic pressure as mPAP = 0.61 × PASP +2 mm Hg. The latter formula could allow the use of Doppler measurements to raise the suspicion for PAH, applying the accepted definition of pediatric PH as mPAP ≥25 mm Hg and a pulmonary vascular resistance index >3.0 WU × m^2 for biventricular circulations.[24]

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.

2.7 | Statistical analysis

Data are presented as mean ±2 SD. A linear regression model (predictor age) was built to predict RVES b/a ratio values of all healthy children and adolescents. Data were examined for heteroscedasticity to determine whether the SD of the residuals varied across the range of values for the independent variable. The resulting residuals (differences between observed data and predicted values from the model) were examined and tests for normality were done to determine whether they conformed to a normal distribution. Examination of residuals was crucial for the development of *z*-scores that would accurately predict the normal ranges.

To test the final models, their ability to identify children with PH was analyzed. Therefore, sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for a cutoff score of +2 SD were calculated. The best cutoff value according to the Youden index was calculated. PH patients were compared with age- and sex-matched healthy controls using the *t* test or Mann–Whitney *U* test, as appropriate. Associations were analyzed using Spearman rank

correlation coefficient or Pearson correlation coefficient, as appropriate. A P value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS software, version 24 (IBM Corp., Armonk, NY).

3 | RESULTS

In the 157 healthy children, the mean RVES b/a ratio was 1.87 ±0.22. The normal values of the RVES b/a ratio slightly increased with increasing age (r = 0.20, P = 0.011) and body length (r = 0.17, P = 0.036) and showed a nonsignificant trend toward an increase with BSA (r = 0.16, P = 0.05). Age-specific RVES b/a ratio z-score values were calculated using the following formula: RVES $b/a_{\text{age-specific } z\text{-value}}$ = (1.796 + 0.008 × age) / 0.216.

In the PAH study group (n = 51), both the basal and apical diameter of the RV were significantly enlarged (RVES b: median 3.3, interquartile range [IQR]: 2.8–4.4; RVES a: median 2.7, IQR: 2.11–3.4), whereas in the healthy control group the RVES basal diameter was approximately twice as high as the RVES apical dimension (RVES b: median 2.5, IQR: 1.9–2.9; RVES a: median 1.4, IQR: 1.0–1.6; Figure 1).

In the 51 PAH children, the RVES b/a ratio (median: 1.3, IQR: 1.2–1.4) was significantly lower compared with the 51 age- and sex-matched healthy controls (PAH pediatric patients age-specific z-values: −2.49 ±0.99; age- and sex-matched healthy controls age-specific z-values: −0.09 ±1.04; P < 0.001; Figure 2).

When using a RVES b/a ratio cutoff value of <−2 SD to investigate whether lower values indicate PAH in children, 43 out of 51 PAH children were identified as having a decreased RVES b/a ratio (sensitivity: 84.3%, specificity: 98.0%, PPV: 97.7%, NPV: 86.2%).

A receiver operating characteristic (ROC) analysis on the accuracy for detecting PAH in children showed an excellent performance of the novel RVES b/a ratio (AUC: 0.95, 95% CI: 0.89–1.00, P < 0.001). The best cutoff score, according to the Youden index, was an age-specific z-value of −1.58 (sensitivity: 92.2%, specificity: 98.0%, PPV: 97.9%, NPV: 92.6%). ROC analysis of absolute RVES b/a ratio values showed similar results (AUC: 0.95, 95% CI: 0.90–1.00, P < 0.001) with a best cutoff score of 1.488 (sensitivity: 92.2%, specificity: 98.0%, PPV: 97.9%, NPV: 92.6%).

RVES b/a ratio inversely correlated to the RV/LV end-systolic diameter ratio (ρ = −0.450, P = 0.001) but did not correlate with the RV systolic function parameters TAPSE (ρ = 0.217, P = 0.127), and S′ (ρ = 0.196, P = 0.168).

The RVES b/a ratio values in our PH/PAH children positively correlated with hemodynamic variables determined by cardiac catheterization (eg, the mPAP [ρ = −0.415, P = 0.012] and the PVRi [ρ = −0.571, P < 0.001]).

In addition, in PAH children the RVES b/a ratio values decreased with worsening NYHA functional class (P = 0.008). The lowest RVES b/a ratio was observed in PAH children with NYHA class III (n = 9; median: 1.15, IQR: 1.11–1.24), followed by NYHA class II (n = 22; median: 1.30, IQR: 1.22–1.35) and NYHA class I (n = 20; median: 1.33, IQR 1.28–1.36; Figure 3).

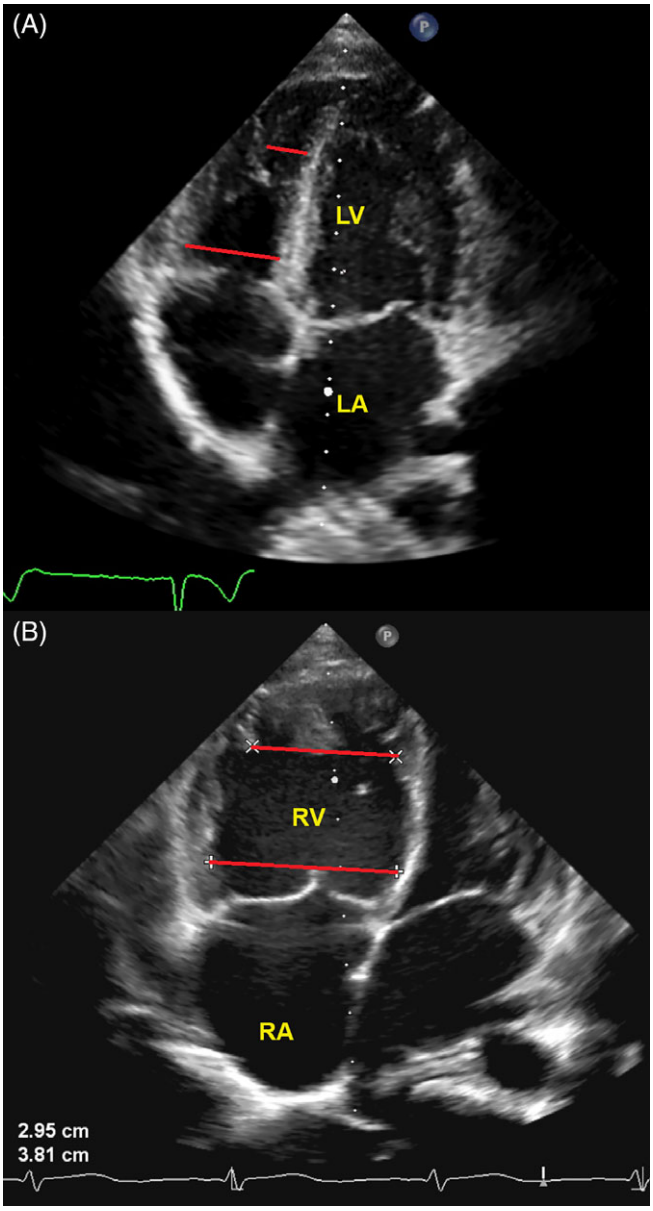

FIGURE 1 (A) An 11-year-old male child with normal RV and LV size and function. (B) An 11-year-old male child with IPAH. The red lines show the end-systolic basal diameter and the end-systolic apical diameter, respectively. The RVES b/a ratio represents a ratio of these 2 RV dimension parameters. Abbreviations: IPAH, idiopathic pulmonary arterial hypertension; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; RVES b/a, right ventricular end-systolic base/apex

4 | DISCUSSION

In this study, we first determined the normative RVES b/a ratio values in healthy children. We then identified the RVES b/a ratio to be decreased in pediatric PAH patients compared with healthy age- and sex-matched control subjects. We found dilation of the RV base and RV apex (a low RV b/a ratio) to be an echocardiographic signature of PAH and showed an association of the parameter with echocardiographically determined RV parameters, with the NYHA functional class, and with invasive hemodynamic variables.

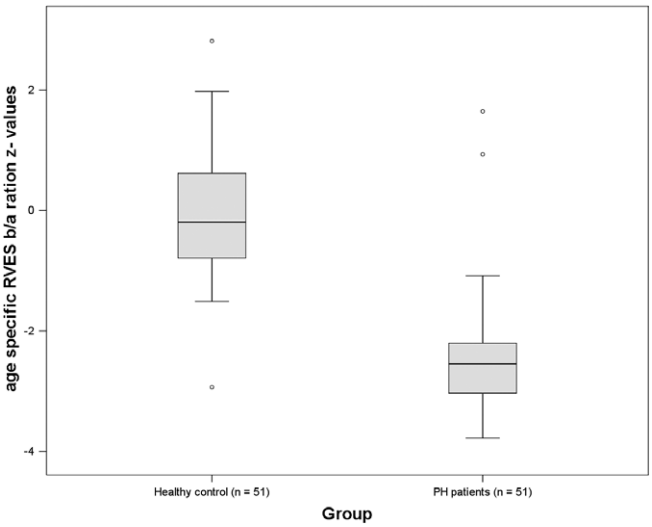

FIGURE 2 Age-specific RVES b/a ratio *z*-values for children with PAH (n = 51) and for age- and sex-matched controls (n = 51). Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RVES b/a, right ventricular end-systolic base/apex

Echocardiographic investigation of RV size is noninvasive and easily obtainable in children, therefore allowing for repetitive measurements and a longitudinal follow-up.[25,26] A tool to assess RV dimension, the RV/LV end-systolic dimension ratio, was derived to combine a measure of RV size with septal shift secondary to elevated RV pressure.[5,23] Such an RV/LV dimension ratio had been shown to be significantly higher in children with PAH vs healthy controls.[23] In our pediatric PAH cohort, together with a decreased RVES b/a ratio, the RV/LV ratio significantly increased, demonstrating an association of the RVES b/a ratio to established RV-LV size and interaction markers in pediatric PAH.[23]

In contrast to RV dimension changes, the systolic RV function surrogates, TAPSE and S′, showed no significant correlation to the RVES b/a ratio in the PAH cohort. However, RV dimension changes do not automatically reflect RV systolic functional impairment. TAPSE and S′ are only measurements to assess the longitudinal motion of the RV base; they do not provide data on overall RV function and morphology. Mid and apical RV deformation has been shown to correlate with outcomes in children with idiopathic PAH,[27] with RV global and regional longitudinal strain worsened, especially in RV apical segments.[27] Therefore, parameters of RV morphology outperformed measures of RV function (eg, TAPSE) in their ability to predict PAH in the current study. Our finding will likely be clinically significant, as RV systolic function and filling pressures are influenced by RV preload, afterload, and RV contractile function,[28] and they become abnormal much later in PAH progression than RVSP, N-terminal pro-brain natriuretic peptide, or as we show here, the RVES b/a ratio.

As such, a depressed RV function is a final common pathway of any insult to preload, afterload, and contractile function. Dilation of the RV apex (to a greater extent than the RV base so that the RVES b/a ratio is decreased) has been shown to represent a morphologic signature of high PA afterload.[11] The RVES b/a ratio negatively correlated with invasive hemodynamics (eg, PVRi) in our pediatric PH patients, which suggests that RVES b/a ratio decreased with increasing disease severity in pediatric PAH, making it a valuable future diagnostic variable. But further clinical studies (ideally in a multicenter approach) are clearly needed to evaluate the power of this ratio in screening patients for PH. Consistently, the RVES b/a ratio decreased with increasing NYHA functional class in our children with PAH.

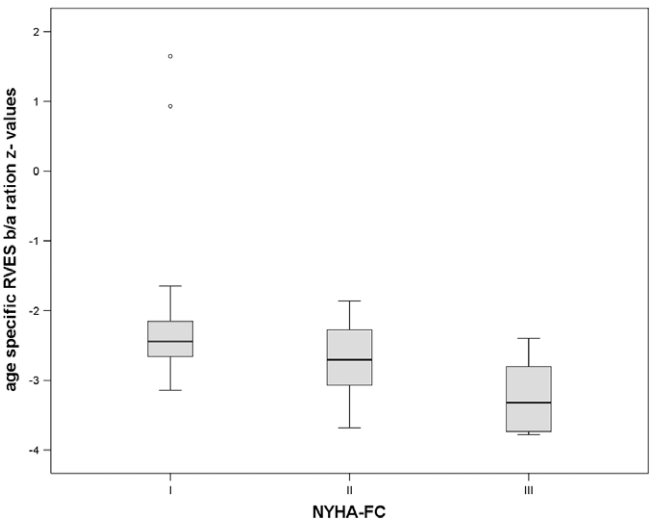

FIGURE 3 Differences in age specific RVES b/a ratio *z*-values between different NYHA FC groups (n = 20 in class I, n = 22 in class II, n = 9 in class III). Abbreviations: FC, functional class; NYHA, New York Heart Association; RVES b/a, right ventricular end-systolic base/apex

5 | CONCLUSION

The RVES b/a ratio normal reference values we provide here will be very useful in initial diagnosis (together with established echocardiographic parameters)[5] and to follow up PAH children. An impaired RVES b/a ratio may indicate the presence of or a deterioration of a PAH.

Conflicts of interest

GH currently receives grant support from the German Research Foundation (DFG; HA 4348/6–1, KFO311). The authors declare no other potential conflicts of interest.

ORCID

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

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