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Clinical Research

Normal Pediatric Values of the Subcostal Tricuspid Annular Plane Systolic Excursion (S-TAPSE) and Its Value in Pediatric Pulmonary Hypertension

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ABSTRACT

Background: The clinical value of determination of right ventricular (RV) function in adults using echocardiographic determination of the subcostal tricuspid annular plane systolic excursion (S-TAPSE) has previously been reported. We aim to provide representative, normal reference values for S-TAPSE in the pediatric age group. Moreover, validation of abnormal S-TAPSE values in children with impaired RV function, such as pulmonary hypertension (PH), is intended.

Methods: We propose a prospective echocardiographic study in 658 healthy children and in 27 children with PH (age: 1 day to 18 years; BSA 0.2-2.0 m^2). We correlated the effects of body surface area (BSA) on S-TAPSE values of our healthy subjects and children with PH. S-TAPSE values were compared with apically derived TAPSE values.

Results: S-TAPSE values ranged from a mean of 0.65 ± 0.16 cm in healthy neonates to 1.79 ± 0.33 cm in 18-year-old healthy adolescents. S-TAPSE values increased with increasing age ($P = 0.841$, $P < 0.001$), body weight ($P = 0.852$, $P < 0.001$), body length ($P = 0.846$, $P < 0.001$), and BSA ($P = 0.851$, $P < 0.001$) in a nonlinear way in our healthy patients group. No difference in healthy male and female patients could be observed. In our 27 patients with PH (age range: 0.6 to 15.7 years) the median BSA specific S-TAPSE z-score ranged from −3.24 to 1.10, depending on restraint of RV function.

RÉSUMÉ

Introduction : On a auparavant rapporté la valeur clinique de la détermination de la fonction du ventricule droit (VD) chez les adultes au moyen de la détermination de l'excursion systolique du plan de l'anneau tricuspide (S-TAPSE) en coupe sous-costale par échocardiographie. Nous avons pour objectif de fournir les valeurs de référence normales représentatives de la S-TAPSE du groupe d'âge en pédiatrie. Nous avons également pour objectif la validation des valeurs anormales de la S-TAPSE chez les enfants montrant une détérioration de la fonction du VD comme l'hypertension pulmonaire (HP).

Méthodes : Nous proposons une étude prospective échocardiographique de 658 enfants en bonne santé et de 27 enfants atteints de HP (âge : de 1 jour à 18 ans; surface corporelle [SC] 0,2-2,0 m^2). Nous avons corrélé les effets de la SC aux valeurs de la S-TAPSE des sujets en bonne santé et des enfants atteints de HP. Nous avons comparé les valeurs de la S-TAPSE aux valeurs de la TAPSE en coupe apicale.

Résultats : Les valeurs de la S-TAPSE allaient d'une moyenne de 0,65 ± 0,16 cm chez les nouveau-nés en bonne santé à une moyenne de 1,79 ± 0,33 cm chez les adolescents de 18 ans en bonne santé. Les valeurs de la S-TAPSE augmentaient avec l'avancement en âge ($P = 0{,}841$, $P < 0{,}001$), le poids corporel ($P = 0{,}852$, $P < 0{,}001$), la longueur du corps ($P = 0{,}846$, $P < 0{,}001$) et la SC ($P = 0{,}851$,

Right ventricular (RV) systolic function majorly contributes to hemodynamic stability in critically ill patients.[1] Therefore, echocardiographic assessment of RV function aids valuable information in a variety of conditions, including post-cardiotomy RV dysfunction, as well as acute or chronic RV systolic dysfunction (RVSD). RVSD as a prognostic factor has recently been reported in critically ill patients.[1] This highlights the importance of RV function being characterized in detail in patients with expected RVSD.

Tricuspid annular plane systolic excursion (TAPSE) significantly correlates with the RV ejection fraction. It is easy to determine and its' accuracy and reproducibility have been reported. Moreover, TAPSE may be used as a prognostic marker in PH patients and is validated in the pediatric age

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Conclusion: The provided S-TAPSE normal reference values and z-scores may assist to identify children with impaired RV function. Abnormal S-TAPSE values will help to identify impaired RV function in pediatric patients with PH.

$P < 0{,}001$) d'une manière non linéaire dans notre groupe de patients en bonne santé. Nous n'avons pu observer aucune différence entre les patients et les patientes en bonne santé. Chez nos 27 patients atteints de HP (tranche d'âge : de 0,6 à 15,7 ans), le Z-score de la S-TAPSE propre à la SC médiane allait de−3,24 à 1,10, selon la contrainte de la fonction du VD.

Conclusion : Les valeurs de référence normales de la S-TAPSE et les scores z fournis peuvent contribuer à déceler les enfants montrant une détérioration de la fonction du VD. Les valeurs anormales de la S-TAPSE contribueront à la détection de la détérioration de la fonction du VD des patients en pédiatrie atteints de HP.

group. [2-7] However, especially with patients in intensive care units (ICUs), it is not uncommon that the tricuspid annulus motion is inadequately visualized in an apical 4-chamber view.

Recently, the feasibility of the subcostal tricuspid annular plane systolic excursion (S-TAPSE) in critically ill patients was described by Díaz-Gómez et al.[8] S-TAPSE can be used alternatively to TAPSE to estimate RV function in critically ill patients, especially when the apical view is limited or adequate cursor alignment is not possible with the tricuspid annulus.

In healthy adults, the S-TAPSE is suggested to be −0.26 cm compared with TAPSE.[8] At present, no normal values of S-TAPSE exist for healthy children, and therefore a comparison between decreased S-TAPSE values and age-related normal values in pediatric patients with PH was unfeasible. We aimed to determine normative z-score values for S-TAPSE and associations of S-TAPSE with age, body lengths (BL), body weight (BW), body surface area (BSA), and heart rate (HR) in a large healthy pediatric cohort. This is the first study to provide data on representative normal pediatric S-TAPSE values and according z-scores. We hypothesized that impaired S-TAPSE variables (defined as z-score more negative than −2) may help to assess hemodynamic relevance of PH in pediatric patients when compared with BSA-related normative values of S-TAPSE.

Methods

We propose a prospective cohort study primarily aiming to establish S-TAPSE age-specific normative values and z-scores for healthy children and adolescents aged up to 18 years.

Healthy study group

The study subjects were recruited prospectively from children referred to our cardiology service for evaluation of heart murmur or a family history of heart disease. Only echocardiograms with official readings of "normal cardiovascular anatomy and function" or "normal cardiovascular anatomy with patent foramen ovale (PFO) with a diameter of less than or equal 2 mm and trivial left-to-right shunt" were accepted for analysis. A PFO of less than 2 mm is unlikely to change RV-loading conditions in a way that S-TAPSE is substantially influenced. Only children whose physical examination was judged to be normal were included. All patients with congenital heart disease—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 may alter measurement of S-TAPSE values. The normal PW Doppler profile of the PA is smooth, without "notching" of the Doppler envelope. A notch is associated with increased PVR among a cohort of PH patients,[9] and therefore patients with "notched" Doppler envelopes 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 children of the "healthy cohort," we confirmed a normal left ventricular ejection fraction (LVEF), measured using the Simpson formula, a normal age-related pulmonary artery acceleration time (PAAT),[9] and normal age-related RV systolic function[10,11] by including only patients with normative TAPSE and RV S` values. TAPSE refers to apically derived measurement, as described in the literature.[11]

PH study group

The PH study group consisted of children with pulmonary arterial hypertension (PAH) associated with congenital heart disease (PAH-CHD). The patients with PH and CHD included patients with post-tricuspid left-to to-right shunts such as ventricular septal defects (VSD) and atrioventricular septal defects but no patients with isolated atrial septal defect (ASD). The respective CHDs were surgically repaired in all patients at a mean age of 5.6 month (range: 0.6 to 15.3 months). None of our patients had Eisenmenger syndrome. Patients with severe atrioventricular valve regurgitation or conduit regurgitation were excluded from the study. World Health Organization (WHO)-functional class was determined by 2 independent pediatric cardiologists who were responsible for the daily medical care of the patients. At time of enrollment, all patients were clinically stable without change of medications within the preceding 4 months. The RV systolic pressure was assessed by tricuspid regurgitation velocity (TRV) calculated by applying the modified Bernoulli equation.[12] TR velocity greater than 2.8 m/s is considered a reasonable cut-off to define elevated pulmonary pressure in the absence of pulmonary stenosis.[13] TR jet velocities predicted at least as half-systemic systolic RV pressure in all of our patients with PH-bronchopulmonary dysplasia (BPD). PH was defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg at rest, a pulmonary capillary wedge pressure (PCWP) $<$ 15 mm Hg, and a pulmonary vascular resistance (PVR) $\geq$ 3 mm (Wood units x m^2 BSA [WU]) [14] in 22 of our 27 patients with PH-CHD (81%). By directly measuring pressures and indirectly measuring flow, we determined

markers such as cardiac output (using Fick`s principle), mixed venous oxygen saturation, and mPAP.

Image acquisition in echocardiography

To minimize variability, a strict institutional protocol for image acquisition was used for this prospective study. Echocardiograms were performed using a commercially available echocardiographic system (Epiq 5C, Philips, Andover, Massachusetts) using transducers of 5-1, 8-3, and 12-4 MHz, depending on patient age, size, and weight. Images will were recorded digitally and analyzed using off-line software (Intellispace Cardiovascular, Philips Medical Systems, The Netherlands). A 2-dimensional examination of the subcostal 4-chamber view was obtained and a counterclockwise rotation made to create the subcostal short-axis view where these structures are identified: right atrium and RV, tricuspid annulus, and inferior vena cava. Finally, the cursor will be aligned in real time with the tricuspid annulus to obtain a linear measurement in centimetres from end-diastole to end-systole (tricuspid annular kick) with M-mode echocardiographic imaging (Fig. 1). The brightness was adjusted to improve the contrast of the M-mode signal from the tricuspid annulus and the background.

We recorded S-TAPSE, TAPSE, PAAT, S`, and LVEF in all patients at the same visit to correlate values. Measurements of TAPSE, PAAT, S`, and LVEF were performed as previously reported.[6,11,15,16]

Sample size considerations

In our clinic we examine about 6000 patients each year, including 200 suffering from impaired RV function. According to our experience in other projects, approximately 40% of these patients fulfill inclusion criteria (n = 2400), and at least 30% of these patients agree to participate in studies. Therefore, we expected to include 700 healthy and involving 40 patients with PH or impaired RV function within the study period of 1 year. To evaluate the appropriateness of this sample size, the precision (SE) of a reference interval was analyzed according to Altman.[17] Using 700 patients the width of the 95% confidence interval for the limits of the reference interval is 0.25 z-scores; 499 patients would be sufficient for a width of less than 0.3 z-scores, and 1123 would be necessary for a width of less than 0.2.

Statistics

For data analysis SPSS 24 (IBM Corporation, Armonk, New York) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina) were used. Data are presented as mean ± standard deviation (SD). In a first step, the correlation structure among age, BSA, and S-TAPSE was analyzed with Pearson's correlation coefficient or Spearman's correlation coefficient, as appropriate. BSA was calculated using the Haycock formula.[18] Of several different formulas to calculate BSA, the Haycock formula seems to be the best fit for BSA calculation and correlation in pediatric echocardiographic normative values, as it least over- or underestimates BSA in children.[19] Differences in S-TAPSE values between healthy male and female patients were analyzed using Mann–Whitney U Test. Regression was used to estimate S-TAPSE from BSA and sex. Models using logarithmic ($y = a + \beta_1 \ln[x]$) and square root ($y = a + \beta_1 x^{0.5}$) relations were tested. White test and Breusch-Pagan test were used to for heteroscedasticity. When significant heteroscedasticity was detected, weighted least square methods were used. Each value was weighted by the inverse residual of the linear regression. To test for normal

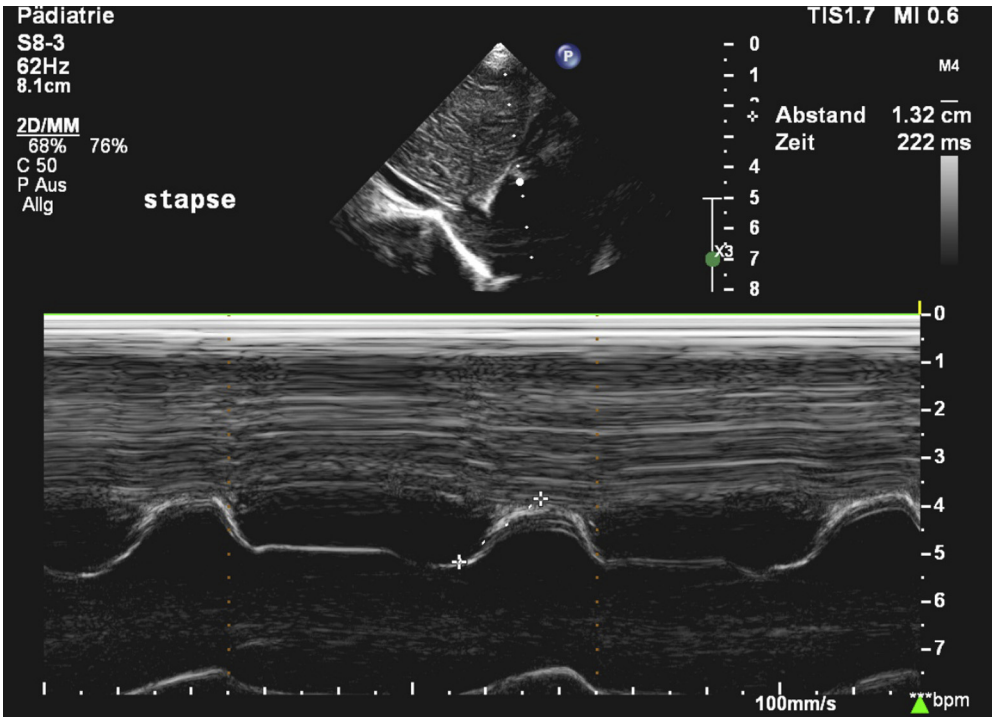

Figure 1. Echocardiographic determination of S-TAPSE using M-Mode from the subcostal view.

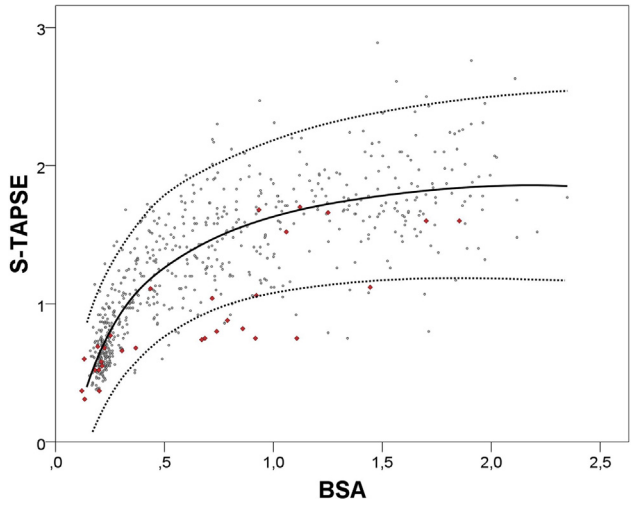

Figure 2. S-TAPSE values of 658 healthy pediatric patients (**grey circles**) and 30 pediatric patients with PH (**red diamonds**). With the expected S-TAPSE value according to the BSA value (**black line**) with ± 2 standard deviation (**broken lines**).

distribution of z scores, Anderson-Darling test (A-D test) and Kolmogorov Smirnov test (K-S test) were used. A P value of < 0.05 was considered statistically significant. To analyze interobserver reliability, 2 well-trained observers measured the S-TAPSE in the same patients within a time range of 1 to 5 days. Observers were blinded to previous S-TAPSE values of the patients. For this purpose, 135 patients were randomly selected. For intraobserver reliability, the same 135 patients were assessed by a well-trained observer, who measured the S-TAPSE 3 consecutive times. Of these 3 values, intraobserver reliability was calculated using intraclass correlation coefficient (ICC). No other analytical method besides ICC was used. Inter- and intraobserver variability were found for S-TAPSE with an ICC of 0.98 (confidence interval [CI], 0.97-0.99), $P < 0.001$, and 0.99 (CI, 0.99-1.00), $P > 0.001$. For visualizing the association of BSA, BSA-specific z-scores of S-TAPSE and S-TAPSE contour plots are generated. To analyze the ability of BSA-specific TAPSE z-scores to discriminate pediatric patients with and without PH, ROC analyses were conducted. Furthermore, the best cut-off score, according to Youden index, was calculated. Specificity and sensitivity for this best cut-off score and corresponding 95% CI were calculated.

Results

We included 658 healthy children (344 male, 314 female). The study group ranged from neonates to adolescents (age: 1 day to 18 years; BW: 2.0 kg to 107.0 kg; BSA: 0.15 m^2 to 2.35 m^2), including 152 neonates (0 to 28 days old) and 153 infants (1 to 12 months old). The PH study group consisted of 27 children with PAH associated with congenital heart disease (median age: 4.9; range 0 month to 15.7 years; 16 male, 11 female; BSA: 0.2 to 1.85 m^2).

In line with our clinical experience in this study, S-TAPSE measurements were possible in more than 99% of our patients. With some experience throughout the study, difficulty in assessment of S-TAPSE was equal when compared with assessment of apically derived TAPSE.

Correlation of S-TAPSE with age, BW, BL, and BSA

In our healthy group, S-TAPSE values increased with increasing age ($P = 0.841$, $P < 0.001$), body weight ($P = 0.852$, $P < 0.001$), body length ($P = 0.846$, $P < 0.001$) and BSA ($P = 0.851$, $P < 0.001$) in a nonlinear way. No difference in healthy male and female patients could be observed according to their S-TAPSE values ($P = 0.779$). S-TAPSE values ranged from a mean of 0.65 ± 0.16 cm in

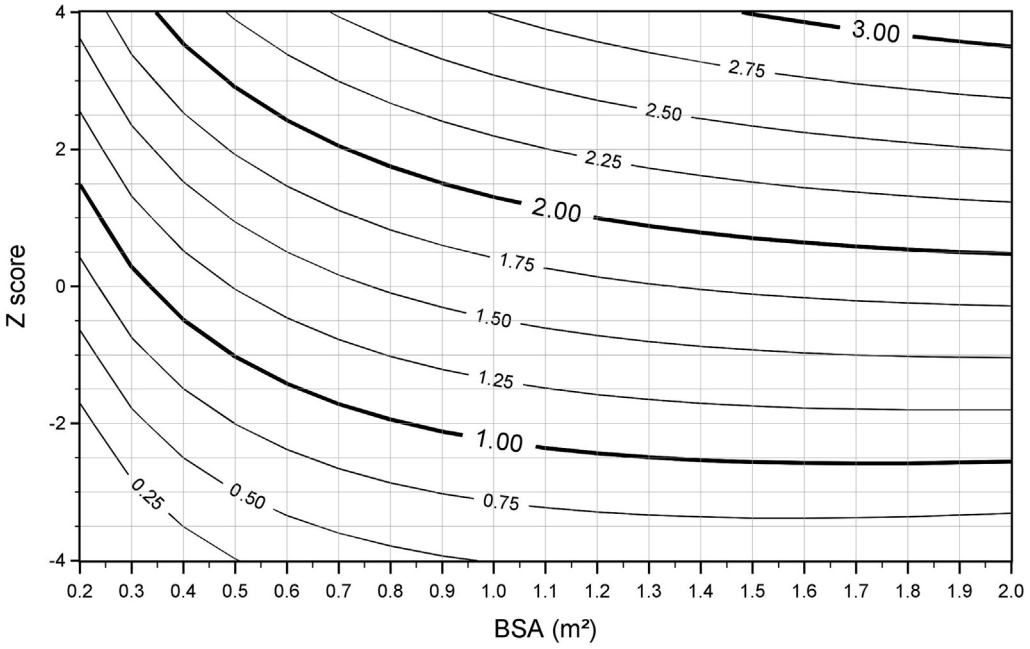

Figure 3. Contour plot for S-TAPSE in healthy patients according to BSA and BSA-specific z-scores. How to read the Figure: Although a S-TAPSE value of 1 corresponds to a z-score of 0 for children with a BSA of 0.35, it corresponds to a z-score of −2 for children with BSA of 0.8.

Table 1. BSA related z-scores for S-TAPSE. For each BSA level, the expected mean (S-TAPSE), ±1SD, and ±2 SD according to the model are shown

BSA	−2SD z-score = −2	−1SD z-score = −1	Expected value z-score = 0	1SD z-score = 1	2SD z-score = 2
0.2	0.18	0.42	0.65	0.89	1.12
0.3	0.45	0.69	0.93	1.17	1.42
0.4	0.62	0.87	1.12	1.37	1.62
0.5	0.75	1.01	1.26	1.51	1.77
0.6	0.85	1.11	1.37	1.63	1.89
0.7	0.92	1.19	1.46	1.72	1.99
0.8	0.98	1.26	1.53	1.80	2.07
0.9	1.03	1.31	1.58	1.86	2.14
1.0	1.07	1.35	1.63	1.91	2.20
1.1	1.10	1.39	1.67	1.96	2.25
1.2	1.13	1.42	1.71	2.00	2.29
1.3	1.15	1.44	1.74	2.03	2.33
1.4	1.16	1.46	1.76	2.06	2.37
1.5	1.17	1.48	1.78	2.09	2.40
1.6	1.18	1.49	1.80	2.11	2.42
1.7	1.18	1.50	1.82	2.13	2.45
1.8	1.19	1.51	1.83	2.15	2.47
1.9	1.19	1.51	1.84	2.16	2.49
2.0	1.18	1.51	1.84	2.17	2.50

BSA calculated using the Haycock formula.
BSA, body surface area; SD, standard deviation; S-TAPSE, subcostal tricuspid annular plane systolic excursion.

neonates to 1.79 ± 0.33 cm in 18-year-old adolescents. Figure 2 shows the final model relating S-TAPSE to BSA, and Figure 3 relating S-TAPSE to BSA-specific z-scores and BSA. Within this model, 73.4% of the variance in S-TAPSE could be explained by BSA. Adding sex did not result in a significant increase of explained variance. The regression equation relating BSA and S-TAPSE is: $S-TAPSE_{pred} = 1.958 + 0.772 * ln(BSA) - 0.325 * BSA$. For calculating Z-scores the residual standard deviation ($S-TAPSE_{res} = 0.2365 + 0.0065 * ln(BSA) + 0.0446 * BSA$) has been used. BSA related z-scores ± 2 SD and ± 3 SD for S-TAPSE are shown in Table 1.

Impact of reference values on the detection of enlarged RVs in a group of children with PH

In our 27 patients (female/male: 11/16 female) with PH (median age: 4.9 years, range: 0 to 15.7 years) the median BSA specific S-TAPSE z-score was −0.72 (range: −3.24 to 1.10).

In the 27 patients with PH-CHD studied, S-TAPSE values increased with age ($P < 0.001$, $P = 0.771$), and BSA specific z-scores decreased with age ($P = 0.044$, $P = -0.391$). S-TAPSE values in the PH-CHD group showed a positive correlation with PAAT ($P = 0.011$, $P = 0.481$), TAPSE ($P < 0.001$, $P = 0.924$) and S' ($P < 0.001$, $P = 0.779$) (Supplemental Fig. S1)

In this group of patients with PH, as well as in the group of healthy children, S-TAPSE was significantly correlated with TAPSE (healthy: $P = 0.952$, $P < 0.001$; PH), S' (healthy: $P = 0.796$, $P < 0.001$) and PAAT (healthy: $P = 0.748$, $P < 0.001$; PH).

Discussion

We intended to assess an easily applicable method that can be applied in the postoperative setting with chest tubes and bandages in place but is still reliable to provide a quick assessment of systolic RV function. It has been shown that the reproducibility of TAPSE measurements is higher compared with other echocardiographic indices of systolic RV function,[6,20] with high specificity and negative predictive power to detect abnormal systolic RV function in adults and children.[11,21-23] The recently developed variable S-TAPSE is much easier to measure than to calculate the RVEF or fractional area change (FAC) in clinical practice.[24] S-TAPSE can be considered a physiologic index of RV function, and testing its significance in the pediatric age group seems worthwhile. This is the first study reporting normal values on S-TAPSE for the pediatric age group ranging from neonates to adolescents.

The tricuspid annulus shows greatest motion along its lateral aspect, as has been shown in healthy adults.[25] The usefulness of TAPSE to diagnose systolic RV dysfunction in children is well established.[11] By providing information not only on the RV output but also on the *vis a fronte* by systolic shortening of the RV, which acts on the systemic venous column, a reduced TAPSE very well reflects severe impairment of RV performance.[21]

The S-TAPSE resembles a modification of TAPSE and can be easily measured irrespective of heart rate.[26] We have provided, for the first time, reference ranges on this new RV function parameter for the pediatric population. Inter- and intraobserver variability were found for S-TAPSE with an intraclass correlation coefficient of 0.98 (CI, 0.97-0.99). Observers were well-trained pediatric cardiologists. However, for interobserver variability, we used colleges not specifically trained on S-TAPSE assessment. These findings suggest that even with little experience, S-TAPSE values can be assessed accurately.

It is important to create normal values for the pediatric age group, as indexed measurements to age, BSA, BL, BW, and HR—owing to the high variability of age-dependent growth— are needed in this particular population.

In this study, we found that S-TAPSE values increase with age and BSA in a nonlinear way. This is in agreement with the behaviour of the TAPSE determined in the 4CV in the pediatric age group.[11] Because of developmental changes, it is accurate not to use a single value throughout the pediatric

population but rather to reference the S-TAPSE to BSA (Fig. 2) to best interpret the results. The clinical importance of this point is illustrated by the 3-fold increase of the z-score of −2 SD of S-TAPSE values from 0.65 cm in a neonate to 1.84 cm in an 18-year-old adolescent (Table 1). S-TAPSE is affected by increasing BSA and by increasing age with a steeper course of the curve in neonates and infants compared with older children and adolescents. Our normal values for S-TAPSE in the older adolescents are very similar to adult S-TAPSE normal reference data available in the literature.[8] In our pediatric study group, we did not find any significant difference of S-TAPSE normal values between male and female patients.

When compared with the more commonly known and routinely used TAPSE, we found that magnitude of S-TAPSE values may be estimated by TAPSE values. A regression analysis showed that TAPSE could explain 90% of the variance in S-TAPSE. The resulting regression equation included a small intercept (−0.071) and a regression coefficient of 0.742 for TAPSE. For daily clinical use, a simplification of these estimations to an approximation of TAPSE*0.7 may be useful. This simplification results in a maximal error of −0.09 to 0.05, compared with the more precise estimation, according to the regression analysis (Supplemental Fig. S2). This estimation (TAPSE*0.7) may be used to validate S-TAPSE measurements in clinical echocardiography.

At present, no studies evaluating S-TAPSE measurements in infants and children exist, but there is increasing interest in S-TAPSE measurements in pediatric patients with CHD, especially in patients with CHD after surgical repair in an ICU setting. CHDs known to affect the RV function (eg, tetralogy of Fallot) are of interest to be evaluated for the behaviour of S-TAPSE in the pediatric age group; it seems important to measure S-TAPSE in children with PH. S-TAPSE was impaired in our patients with PH-CHD. However, this value as a single echocardiographic parameter cannot predict PH but must be interpreted together with other echocardiographic parameters predictive of PH, as described above. TAPSE was established as a valuable echocardiographic parameter to assess RV function in the pediatric age group in 2009.[11] Ever since then, TAPSE has been one of the major clinical indicators of RV function in pediatric PH.[27] However, using a single variable has proved to be inadequate for diagnosis and monitoring, and up-to-date RV function research in PH uses multiparametric approaches.[28] Very recently, it has been demonstrated that combining RVEe (=TAPSE/PVRi ratio) and the ratio of TAPSE/pulmonary arterial systolic pressure (PASP) reflects patients' functional capacity and hemodynamics of the individual RV to pulmonary artery unit in children with PH.[29]

TAPSE is vastly independent of HR and therefore very useful in the pediatric age group. Moreover it is accepted to assess systolic RV function in children with PH.[27] We hypothesized that impaired S-TAPSE variables (defined as z-score more negative than −2) may help to assess hemodynamic relevance of PH in children when compared with normative values.

Limitations

Lacking assessment of effects of respiratory preload variations might be a potential limitation to our study. In clinical practice, applying respiratory gaiting to this method would be exhausting. Furthermore, it remains uncertain as to how well S-TAPSE will perform as an index of systolic RV function in pediatric patients with heart disease, compared with other well-established approaches such as myocardial performance index or other RV deformation parameters. Future clinical studies will have to prove the usefulness of S-TAPSE.

Our pediatric PH-CHD cohort was small, and the influence of differences in treatment—including surgery—may not be excluded. Another limitation is the etiologic heterogeneity of the PH group, containing 27 patients with associated CHD. The presence of CHD could influence RV remodelling; also, the BPD group differs from the 2 other groups, with PH occurring earlier in life and generally improving with growth and lung maturation.

It is also important to note that even small differences in the attained echocardiographic plane may result in substantial quantitative differences in area and diameter.[30]

Conclusion

We provide normal S-TAPSE reference values and z-scores that will help to identify children with impaired S-TAPSE (impaired RV function) in conditions such as PH. In summary, our data should provide sturdy normal values throughout the entire pediatric age group. Our results are similar to those of previous studies demonstrating correlations of systolic RV function parameters to age.[26,31,32] Whether the markedly lower S-TAPSE in infants is solely a marker of growth-related changes inside the pediatric population, or a sign of possible altered systolic function in infants due to the immaturity of the ventricular muscle, remains unclear. A z-score of ≤ -0.173 for S-TAPSE, combined with further echocardiographic parameters to evaluate for PH—such as TAPSE or PAAT—may help to identify pediatric patients with PH.

Ethical Considerations

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. The study protocol was approved by the local ethics committee (Ethics Committee Graz, Styria, Austria; EK 29-238 ex 16/17), and informed consent was obtained before inclusion. The study was also registered at the German Registry of Clinical Trials (www.drks.de).

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.online cjc.ca and at https://doi.org/10.1016/j.cjca.2019.01.019.