A Multicenter Study of Three-dimensional Echocardiographic Evaluation of Normal Pediatric Left Ventricular Volumes and Function

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Abstract

Background: Three-dimensional echocardiography (3DE) evaluation of left ventricular (LV) volume and function in pediatrics compares favorably with cardiac magnetic resonance imaging. The aim of this study was to establish from a multicenter, normal pediatric z-score values of 3DE left ventricular volumes and function. Methods: Six hundred and ninety-eight healthy children (ages 0 to 18 years) were recruited from five centers. LV 3DE was acquired from the 4-chamber view. A vendor independent software analyzed end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and ejection fraction (EF) using semi-automated quantification. Body surface area (BSA) based z-scores were generated. Intraobserver and interobserver variability were calculated using intraclass correlation (ICC) and repeatability coefficient (RC). Results: Z-scores were generated for ESV, EDV, and SV. The ICC for intraobserver variability for EDV, ESV, and SV were 0.99, 0.99, and 0.99 respectively. The ICC for interobserver variability for EDV, ESV, and SV were 0.98, 0.94, and 0.98 respectively. The RC for intraobserver and interobserver variability for LV EF was 4.39% (95% CI: 3.01, 5.59) and interobserver was 7.08% (95%CI: 5.51, 8.42). Conclusions: We report pediatric Z-scores for normal LV volumes using the semi-automated method from five centers, enhancing its generalizability. 3DE evaluation of LV volumes and EF in pediatric patients is highly reproducible.

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Results: Z-scores were generated for ESV, EDV, and SV. The ICC for intraobserver variability for EDV, ESV, and SV were 0.99, 0.99, and 0.99 respectively. The ICC for interobserver variability for EDV, ESV, and SV were 0.98, 0.94, and 0.98 respectively. The RC for intraobserver and interobserver variability for LV EF was 4.39% (95% CI: 3.01, 5.59) and interobserver was 7.08% (95%CI: 5.51, 8.42).

Conclusions: We report pediatric Z-scores for normal LV volumes using the semi-automated method from five centers, enhancing its generalizability. 3DE evaluation of LV volumes and EF in pediatric patients is highly reproducible.

Key words: Three-dimensional echocardiography, left ventricular volume, left ventricular function, normal data

INTRODUCTION

Quantification of left ventricular size and function from echocardiography is important in the diagnosis, prognosis, and management of pediatric heart disease.[1] With rapid improvement in technology, three-dimensional echocardiography (3DE) evaluation of left ventricular (LV) volume and function in pediatrics compares favorably with magnetic resonance imaging (MRI)[2-5]. However, a multicenter trial to generate normative 3DE z-scores in a large pediatric population would be desirable for clinical use.

A multicenter trial would provide important information regarding 3DE LV volumes and function in children of various ages and sizes. Such a large-scale study would also allow for generation of normative data in pediatric patients. Thus, the aim of this study is to establish normal z-score values in this unique population using 3DE volumes and function in a multicenter trial.

METHODS:

Study population

Three-dimensional LV datasets were obtained from healthy subjects from 5 pediatric centers from 2014-2019. Inclusion criteria were normal subjects (ages 0 to 18 years) who presented for routine clinical care for heart murmur, chest pain, or syncope. These subjects had echocardiographic evidence of structurally and functionally normal hearts. Exclusion criteria were similar to the Pediatric Heart Network normal echocardiographic database.[6] Patients with cardiac abnormalities (except for patent foramen ovale, trivial branch pulmonary stenosis, or inaudible patent ductus arteriosus), Kawasaki disease, cardiomyopathy, exposure to anthracyclines, cardiac transplantation, chronic systemic disease, and preterm infants <37 weeks gestation were excluded. Consents and waiver of consents were obtained based on the individual institutional ethics boards and data use agreements were obtained from each center to Children's Hospital Colorado which served as the core laboratory for the study. All 3DE datasets were anonymized and sent to the core laboratory for analysis.

3D dataset acquisition and analysis

Real-time 3DE image acquisitions of the LV from the 4-chamber view were performed using echocardiographic ultrasound platforms (GE Vivid E9/E95; Vingmed Ultrasound, Horten, Norway, iE33/EPIQ; Philips Medical Systems, Andover, MA, USA, and/or Siemens SC2000, Siemens Medical Solutions, Malvern, PA, USA). 3D datasets were excluded by the core lab if any portion of LV endocardial borders or LV apex were not well visualized in the 3D dataset. LV end diastolic and end systolic volumes (EDV and ESV), stroke volumes (SV), and ejection fraction (EF) were generated after manually editing the contours to define the LV endocardial borders using semi-automated method (4D LV Analysis, TomTec Imaging Systems version 4.0, Unterschleissheim, Germany). The core laboratory performed intraobserver (LL – measured 6 months apart) and interobserver (LL and PNJ) variability in 20 randomly selected datasets.

Statistical analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR). BSA was calculated using Haycock's method [7]. To build the z-model of a parameter (i.e., ESV, EDV, and SV), we selected an optimum exponent, α, of the index parameter (parameter/BSA$^\alpha$) such that: 1) The index parameter satisfactorily follows a normal distribution and 2)The index parameter does not depend upon BSA. Z-score was then calculated as

$Z = \frac{[\left(\frac{\text{parameter}}{\text{BSA}^\alpha}\right) - (\text{mean value of indexed parameter})]}{\text{SD of indexed parameter}}$.[6] Normality of an indexed parameter was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov tests, Q-Q plot, skewness and kurtosis. Dependence of the indexed parameter on BSA was evaluated with a test of the slope of the linear regression of the indexed parameters on BSA. We conducted grid search with a 0.001 step size to find the optimum exponent, α, and chose the one that maximized the sum of p-value for Shapiro-Wilk test and the p-value of testing the slope of index parameter vs. BSA. During the model development, diagnostic analysis was conducted using leave-one-out method. Few data points with extreme values that influences the distribution of indexed parameter were excluded from the final z-model development. After the optimum z-score model has determined, association of indexed parameter with age and gender were further examined with respectively linear regression and Student t-test. Gender specific z-scores model hence developed because there was a difference between genders in indexed parameter. A two-sided p-value <0.05 was considered statistically significant. Intraobserver and interobserver variability for LV EDV, ESV, and SV were calculated using intraclass coefficient (ICC). Repeatability coefficient (RC) was used to assess intraobserver and interobserver variability for LV EF. Confidence interval (CI) for RC was calculated using percentile method with 5000 Bootstrap samples. Statistical analysis was performed using SAS version 9.4 (SAS institute, Cary, NC).

RESULTS:

Study Subjects

Six hundred fifty-eight subject studies were sent to the core lab for analysis. Five hundred twenty-three (79%) LV 3D datasets were able to be traced at the core lab. The median (IQR) patient age was 10 (5 to 14) years. Eighteen percent (96/523) of the patients were [?] 3 years of age. The mean BSA was 1.2 $\pm$ 0.5

m^2. There were 291 males (56%) and 232 females (44%). The age range and feasibility of study subjects in different age groups are reported in Table 1. The mean±SD for LV EF is 59.8±3.2%.

Z-score generation

Normative pediatric z-score generation was performed on the 523 LV 3D datasets. The optimum exponents are shown in Table 2 as well as the mean and SD of indexed parameters. Figure 1 demonstrates the normative data and z-score for ESV, EDV, and SV. As can be seen the EDV, ESV and SV volumes did not have a linear relationship with BSA, but rather a slight concave curvilinear relationship.

Interobserver and interobserver variability

The ICC for intraobserver variability for EDV, ESV, and SV were 0.99, 0.99, and 0.99 respectively. The ICC for interobserver variability for EDV, ESV, and SV were 0.98, 0.94, and 0.98 respectively. The intraobserver and interobserver RC for LV EF was 4.39% (95% CI: 3.01, 5.59) and 7.08% (95%CI: 5.51, 8.42).

DISCUSSION

This study reports the largest multicenter data collection for development of 3DE z-scores for LV volumes and function in healthy children using the semi-automated quantification method. Seventy-nine percent of the 3D datasets were able to be analyzed at the core laboratory, similar to another multicenter study in the pediatric age group [8]. Krell et al. reported having a feasibility of 74% in their smaller multicenter study. Kuebler et al reported normative LV volume and functional values in 238 pediatric subjects of different age group and body surface area [9]. However, only 14% of their subjects were under the age of 5 (34/238)[9]. Our study is notable in that 27% (141/523) of the subjects were under 5 years and 18% were less than 3 years of age. Hence this study provides important normative 3D LV volumetric data in this very young age group. Cantinotti et al. studied 800 Italian healthy children and reported excellent overall feasibility of 91%; however, feasibility for smaller children with BSA less than 0.5 was 68% to 80% respectively [10].

Prior studies from Kuebler et al. and Cantinotti et al. have described pediatric normative LV volumes and function derived from single centers[9,10]. Our study is a normative data from multiple centers to improve generalizability. The curvilinear relationship between LV volumes and BSA is similar to previous studies finding of LV volumes indexed to the BSA showing a gradual increase from childhood to adolescent years [8-12].

Consistent with prior studies[8,9], our ICC and RC analysis demonstrate that the intraobserver and interobserver variability for 3DE LV volumes were good to excellent. Because the variability of LV EF in a normal population is small with a mean of 59.8±3.2%, the absolute reliability within observer and between observers were assessed using the RC analysis. LV EF intraobserver and interobserver reliability was also similar to previous studies evaluating for reproducibility of this measure.[13-15]

3DE LV EF has been reported to be more accurate and reproducible than 2DE LV EF in adults and children because 3DE does not rely on geometric assumptions and is less affected by 2D limitations such as foreshortening [3,16-20]. These factors are apparent in LV with variable regional and global geometric shapes. Thus, similar to adult centers, 3DE LV volumes and EF should be reported in clinical centers with experience in 3DE [20]. The z-scores generated by this multicenter study will serve as the normative data when evaluating pediatric patients with 3DE.

Limitations

The reasons as to the inability to acquire optimal 3 D date sets in 19% of the subjects was not apparent and needs to be further investigated. As per developing normal Z score values a limitation of the study includes the lack of racial and ethnicity inclusion. The number of subjects between 1- to 2-year-old was low, and future studies need to be done to recruit this age group.

CONCLUSION

This normal pediatric data for LV volumes and function from 3DE provide z-scores calculations derived from a large population of healthy children, spanning ages 0 to 18 years. The multicenter nature of this study increases its generalizability as reference values for pediatric patients in clinical practice. 3DE LV volume assessments is highly reproducible.

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Tables

Table 1: Feasibility of study subjects in different age group

Age (years)	Traceable datasets (N=523) M/F (291/232)	Total in age group (N=658)	Feasibility in age group (%)
<1	51	66	77.3
1	6	9	66.7
2	14	19	73.7
3	25	35	71.4
4	15	17	88.2
5	30	38	78.9
6	24	28	85.7
7	21	27	77.8
8	18	21	85.7
9	35	45	77.8
10	28	34	82.4
11	34	39	87.2
12	31	41	75.6
13	37	42	88.1
14	37	49	75.5
15	41	49	83.7
16	30	39	76.9
17	30	40	75.0
18	16	20	80.0

M = male, F= female

Table 2: Parameters for calculating z-scores.

Parameter	Exponent α	Gender	Mean of index parameter	SD of index parameters
ESV	1.284	F and M	22.744	4.422
		F	21.491	3.936
		M	23.768	4.538
EDV	1.277	F and M	56.874	10.124
		F	53.729	8.705
		M	59.416	10.485
SV	1.278	F and M	34.073	6.230
		F	32.237	5.497
		M	35.547	6.398

Index parameter=Parameter/BSA $^{\alpha}$. EDV = end-diastolic volume, ESV = end-systolic volume, F = female, M = male, SV = stroke volume

Figure Legends

Figure 1: Normative Z-score values for left ventricular volumes. BSA = body surface area, EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume.

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