Original Article

Real-time 3D-echocardiography of the right ventricle—paediatric reference values for right ventricular volumes using knowledge-based reconstruction: a multicentre study

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Background: Real-time 3D echocardiography is a promising method for non-invasive assessment of right ventricular performance in children with congenital heart disease. Volume quantification using knowledge-based reconstruction (KBR) enables the calculation of right ventricular dimensions by matching endocardial landmarks with a reference library of right ventricular shapes. However, paediatric reference values for volumes based on KBR are missing. Aim of this study was to establish reference values for right ventricular volumes in a large paediatric population using 3D echocardiography and KBR.

Methods: In a multicentre prospective-design study, 545 healthy children and adolescents (age range, 1 day to 216 months) underwent 3D echocardiography of the right ventricle using two different vendors (iE33, Philips or Vivid 7, GE). Volume analysis was performed by a semiautomatic quantification software (VMS, Ventripoint Diagnostics Ltd., Washington, US). Reference centiles were computed using Cole's LMS method and the gamlss package in R. For vendor comparison, 3D datasets were recorded subsequently in 20 subjects using both ultrasound devices.

Results: 3D datasets of 406/545 (74.5%) subjects provided an adequate image quality. Right ventricular volumes had a significant association with age, body size and sex. We created sex-specific percentiles indexed to body surface area (BSA). Intra- and interobserver-variation for all volume calculations were excellent with intraclass correlation coefficients (ICCs) between 0.973–0.998. Agreement of both vendors showed slightly higher end-diastolic and stroke volumes (bias ± standard deviation 2.2%±6.8% respectively 4.5%±8.1%) and smaller end-systolic volumes (–0.9±10.3%) using Philips datasets.

Conclusions: Calculation of ventricular volumes by KBR allows reliable non-invasive assessment of right ventricular volumes with excellent intra- and interobserver variations. The calculated percentiles based on a large paediatric population serve as a reference and may facilitate the use of real-time 3D echocardiography for the analysis of right ventricular size and function.

Keywords: 3D echocardiography; reference values; children; right ventricle; volumetry; knowledge-based reconstruction (KBR)

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Introduction

The accurate assessment of right ventricular (RV) volume and function is of fundamental importance for clinical decision making and follow-up in paediatric cardiology. Both, volume, and function, have been shown to be major indicators of symptoms and survival in patients with acquired and congenital heart disease (CHD) such as corrected tetralogy of Fallot, hypoplastic left heart syndrome or pulmonary hypertension (1-6). Unfortunately, as a result of its complex shape and location behind the sternum exact echocardiographic assessment is challenging.

While cardiac magnetic resonance (CMR) imaging is currently the gold standard for RV quantification (7), echocardiography is more accessible in a clinical setting, less time consuming and comparatively cheaper. Echocardiography rarely requires sedation even in young children and has hardly any contraindications. Two-dimensional echocardiography (2DE), however, is not reliable in the estimation of RV size and function (8-11). The complex crescent shape of the right ventricle cannot be visualised in single two-dimensional views. Real-time three-dimensional echocardiography (RT3DE) has emerged as a promising clinical alternative, being more accurate than 2DE (6,8-12). Current post-processing software using semiautomatic border tracing may underestimate RV volumes and ejection fraction (EF) (13,14). Therefore, knowledge-based reconstruction (KBR) has been developed on a model-based approach to overcome some of the limitations of endocardial border tracing. In an individual dataset, distinct anatomical structures of the right ventricle are identified in different planes. These anatomic landmarks are used to create a three-dimensional reconstruction of the RV cavity with the aid of a of a database catalogue. The catalogue includes various geometrical shapes of the RV which exist in the normal heart as well as various forms of CHD (15,16). Ventricular dimensions are then calculated from the reconstruction. This method has been evaluated with good results for CMR, 2DE, and RT3DE including both healthy subjects without structural or functional anomalies and such with CHD and has been shown to improve the computation of the right ventricle (15-20). For the quantification of volumes in RT3D datasets KBR has been validated with CMR and has been shown to be accurate, reliable, and reproducible (15).

Reference values for RV volumes and ejection fraction are essential for accurate detection and evaluation of pathologies. The aim of this study was to establish reference values for right ventricular volumes in a large paediatric population using RT3DE and KBR.

Methods

Study group

In a multicentre prospective design 545 children and adolescents were enrolled to undergo RT3DE of the RV. The group consisted of 282 (52%) boys and 263 (48%) girls. The age range of the whole group was 1 day to 216 months with a median age of 90.0 months. All subjects were in sinus rhythm, had normal results on standard echocardiography, and did not participate in competitive sport activities. Body weight and height were measured and body surface area (BSA) was calculated by the Haycock formula (21).

The examinations were performed at three centres within Germany after standardisation of the acquisition procedure and operator training (21). The accuracy of the different imaging equipment and platforms was verified using calibrated phantoms. The data were subsequently quantified in a core-laboratory at one centre.

The study was approved by the local ethics institutional review committees (Registration No. 226/06 and No. 20/10) and by the representative boards of all participating centres and conformed to the principles of the Declaration of Helsinki as well as German law. Informed written consent was obtained from all participants and/or their legal guardians before participation.

RT3DE image acquisition

RT3DE was performed using two different vendors: the iE33 System with an X5-1 or X7-2 transducer (Philips Medical Systems, Best, The Netherlands) or a Vivid 9 System with a V4 transducer (GE Medical Systems, Milwaukee, WI). To depict the entire right ventricle individually apical projections as well as a modified apical view were acquired by angulating the probe upward and toward the left, starting from the position of a standard five-

chamber view, until inflow, outflow, and apex of the right ventricle became visible (15). Full-volume data sets were acquired with a stable transducer position. Older children able to cooperate were asked to perform an end-expiratory breath-hold during acquisition to avoid respiratory motion. Children unable to hold their breath were examined under spontaneous breathing. The mean temporal resolution was 27 volumes/sec (standard deviation SD: ±8.5 volumes/sec) with a mean volume rate per heart beat of 16 (range, 7–35). For a subset of randomly selected subjects, RT3DE scans were acquired during the same session with an iE33 system as well as a Vivid 9 system, without significant change in heart rate or blood pressure in the subjects, and compared for vendor comparison.

Evaluation of RT3DE data

For each subject the RT3DE volume data set of the best image quality was imported to the Ventripoint Medical System (VMS) software (version 1.2.6905.4788, Ventripoint Diagnostics Ltd., Bellevue, WA) and the tool "Right Ventricle" for healthy right ventricles was used for the further computation.

End-systolic and end-diastolic frames were identified in the four-chamber view as the smallest and largest RV-cavity respectively in representative 2DE reformatted planes. The same end-systolic to end-diastolic interval was automatically applied to all other views in the same data set. A set of anatomic landmarks such as the pulmonary valve annulus, the tricuspid valve annulus, apex, interventricular septum, and RV endocardium were then plotted in the end-systolic and end-diastolic data sets. Endocardial landmarks were placed at the bases of trabeculae therefore including them into the RV cavity volumes. A minimum of 11 points were required to create a 3D model. The plotted anatomic landmarks and their 3D special coordinates were then transmitted to a remote server via a secure internet connection and a RV model was created using a knowledge-based reconstruction algorithm referring the plotted points against a catalogue of templates for hearts with normal shapes on the knowledge data base in VMS (*Figure 1*) (15).

The resulting 3D models could be superimposed on the original scan plains and the intersections inspected. In rare cases, where alignment between the surface of the 3D model and either the plotted points or the echocardiographic borders were not satisfactory, points were repositioned, removed, or added as required and the algorithm rerun. The VMS software uses the 3D models to calculate the respective end-systolic and end-diastolic volumes as well as stroke volume and ejection fraction. The use of KBR for the calculation of RV volumes in 3DRT datasets method has already been systematically evaluated by our group (15).

Statistical analysis and construction of centile curves

RT3DE data were quantified by a single investigator (F.S). Intraobserver comparisons were performed with data from randomly selected individuals with the second quantification more than 4 weeks apart and blinded to the results of the first. Interobserver variability was assessed by a second investigator who was blinded to the previous results. All datasets were reanalysed using raw data, starting with the definition of end-diastole and end-systole and position of the landmarks. The correlation was expressed by the intraclass correlation coefficient (ICC) (SPSS version 22, SPSS, Inc., Chicago, IL) and for the assessment of the agreement Bland-Altman analysis was performed (Prism 6, GraphPad Software, Inc., La Jolla, CA). Pearsons correlation was used to correlate relevant continuous variables (Prism 6). For the construction of centile curves, we applied the LMS method by Cole and Green (22). We used the software environment R and the add-on package gamlss for the computation (23,24). As response variable, we chose end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), volumes indexed to BSA and obtained age dependent curves for each response variable. For the training of the curves, the gamlss package allows to vary the degrees of freedom for the penalized splines of the parameters L (Box-Cox power), M (median) and S (coefficient of variation).

Results

The clinical characteristics of our study population are presented in *Table 1*. From a total of 545 individuals 406 could be included in the study, resulting in feasibility of 74.5%. The main reasons for the exclusion of data were incomplete depiction of the RV, insufficient image quality such as indistinct endocardial borders or breathing artefacts (n=88), incomplete demographic data (n=3) or 3D datasets which were not retrievable (n=8). The age and sex distributions are shown in *Figure 2*. Of 406 datasets, 94 were acquired with a GE ultrasound machine. As recently published by our group, image analysis for RT3DE data sets

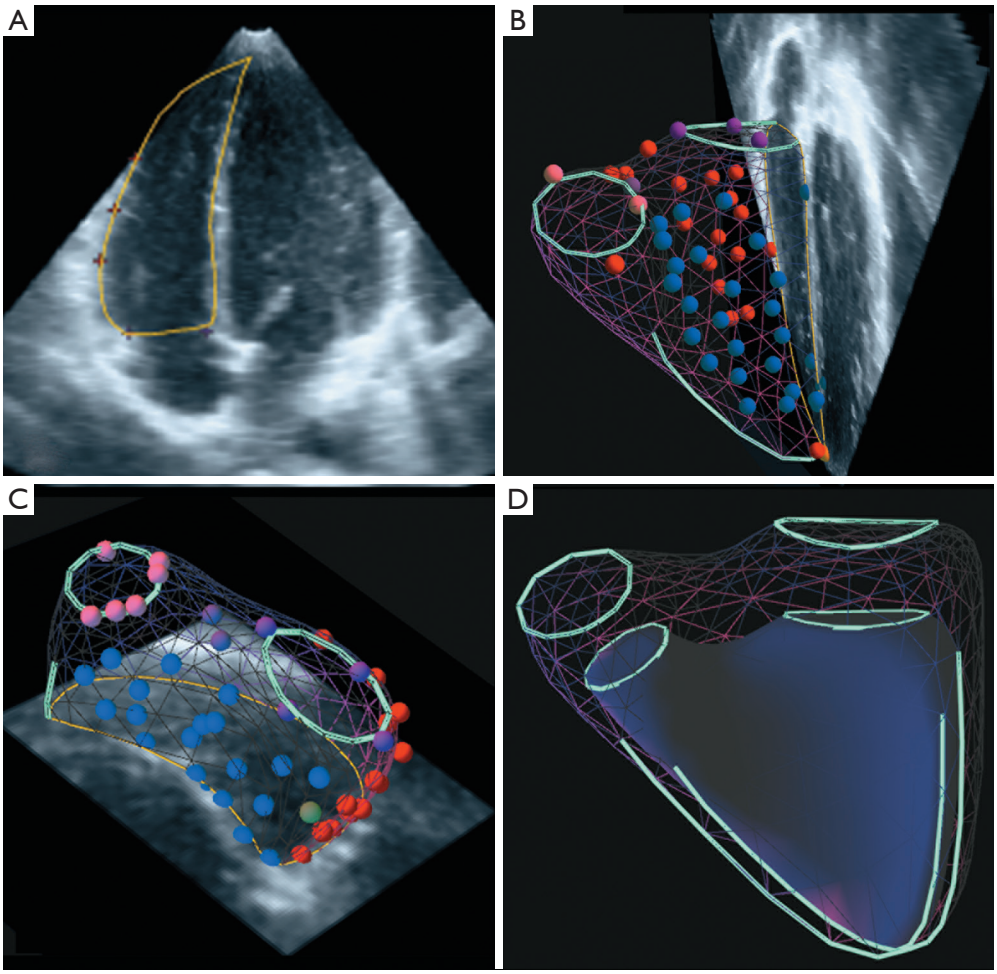

Figure 1 3D right ventricular models based on the Knowledge-Based Reconstruction after setting of anatomical landmarks. (A) Contour model of the RV border (yellow line) superimposed into a 4-chamber view reconstructed from the RT3D full volume, crosses depict the previous placement of landmarks. (B) 3D-model including mesh structure, points, outlines, and borders in a 4-chamber view. (C) Same presentation as b in a short axis view. (D) Combined view of outlines and borders of the 3D-model in end systole (blue) and end diastole (purple mesh). Colour coding: red: RV endocardium, blue: interventricular septum, pink: pulmonic annulus, purple: tricuspid annulus, yellow: apex.

required a mean time of 4 min (15).

Reproducibility

The results of intraobserver and interobserver comparisons are shown in *Table 2* and Figures S1,S2. Intraobserver agreement (*Table 2*, Figure S1) was remarkably good, especially for ESV and EDV resulting in ICCs of 0.999 for both parameters and minimal bias with low limits of agreement (LOA). Interobserver variation (*Table 2*, Figure S2) was slightly higher with the best agreement again for ESV (ICC 0.995) and EDV (ICC 0.996). The second observer's evaluations resulted in generally larger volumes leading to a distinct bias of up to 4.1% between the observers.

Vendor comparison

The comparison of volumes calculated from RT3DE acquired from the same individual both using an iE33 and a Vivid 9 ultrasound system (*Table 3*, Figure S3) likewise showed good results with ICCs of 0.986, 0.992, 0.991 and 0.927 for ESV, EDV, SV and ejection fraction (EF) respectively. Evaluation of scans acquired with the iE33 system resulted in smaller

Table 1 Demographic data of study population

Variables	All subjects	Subjects included in study	Subjects not included in study
Total number	545	406 (74%)	139 (26%)
Female gender	263 (48%)	193 (48%)	70 (50%)
Age mean ± SD (months)	91.2±63.4	95.6±63.0	78.3±62.8
Age range (months)	0.03–216	0.03–216	0.6–210
Weight mean ± SD (kg)	29.7±19.8	30.6±19.6	26.9±19.9
Weight range (kg)	1.9–93	1.9–93	4–86
Height mean ± SD (cm)	123±36.8	125±36.8	116±36.0
Height range (cm)	45–194	45–194	54–190

There were no significant differences between the included and not included groups. SD, standard deviation.

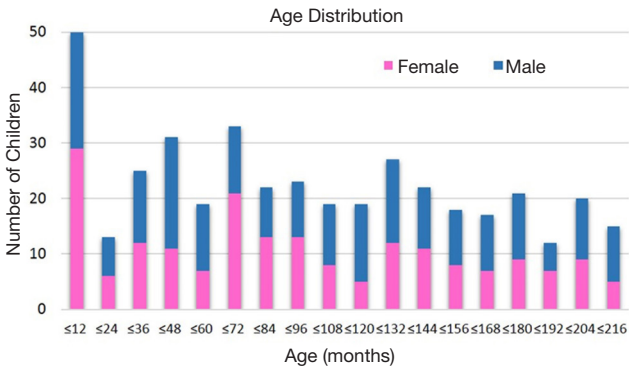

Figure 2 Sex and age distribution of the cohort included.

end-systolic volumes (bias ± SD: −1.1±4.6 mL) but larger end-diastolic volumes (0.7±7.1 mL) and therefore larger stroke volumes (bias 1.7%±4.3%) compared to scans acquired with the Vivid 9 system.

Reference values (Figures 3,4)

RV volumes correlate with age (r=0.913–0.938), weight (r=0.953–0.973), height (r=0.913–0.939) and BSA (r=0.952–0.975). The EF showed little correlation with these parameters (r=–0.0999 to –0.129). Comparison between the male and female study population showed significant differences in RV volumes indexed for BSA (P<0.001) with significant larger volumes being observed in boys (*Table 4*, differences >9%). Consequently, separate centile curves were created for both sexes and are presented as absolute age-dependent values, as well as volumes indexed to BSA (*Figures 3,4*). Figure S4 depict sex-specific centile curves related to height. Significant sex differences were not found concerning the EF.

Discussion

This prospective multicentre study provides gender-specific paediatric reference values for RV volumes and ejection fraction in a large population of healthy children without structural or functional anomaly from birth to 18 years of age using state-of-the-art RT3DE and KBR.

The main findings of this study are the sex differences in RV volumes, which seem to be present even in very young children and a strong correlation of RV volumes with demographic and anthropometric parameters.

In addition, we found KBR to be a reliable, vendor-independent, and reproducible post processing method for the quantification of right ventricular volumes acquired by 3DRTE.

Maturational changes and gender differences in RV volumes

Cardiac measures are known to be related to body size in the maturating child. The continuous growth and hormone status before, during and after puberty influence the chamber sizes (25-27). In cardiovascular medicine, it has been shown helpful to adequately scale RV volumetric parameters to body size (28). Our own findings indicate a strong correlation of RV volumes with BSA and match with findings by current studies. Therefore, we present our ventricular volumes indexed for BSA with the additional benefits of better visualising a large volume range of 1.1 to

Table 2 Intra- and interobserver variability expressed as relative and absolute mean ± SD, LOA (Bland-Altman analysis), and ICCs with 95% CI

Variables	Bias ± SD (%)	95% LOA (%)	Bias ± SD (mL)	95% LOA (mL)	ICC	95% CI
Intraobserver (n=28)						
ESV	0.1±4.1	−7.9 to 8.1	−0.3±1.9	−4.0 to 3.3	0.999	0.997 to 0.999
EDV	0.4±3.7	−6.8 to 7.6	0.1±4.3	−8.2 to 8.5	0.999	0.997 to 0.999
SV	0.6±5.5	−10.2 to 11.4	0.5±3.6	−6.5 to 7.5	0.997	0.994 to 0.999
EF	–	–	0.04±1.5	−3.1 to 3.1	0.973	0.941 to 0.987
Interobserver (n=21)						
ESV	−4.1±6.2	−16.2 to 8.1	1.7±2.5	−3.2 to 6.6	0.995	0.980 to 0.998
EDV	−1.8±6.1	−13.8 to 10.3	1.2±5.4	−9.4 to 11.9	0.996	0.990 to 0.998
SV	−0.1±9.6	−18.9 to 18.7	−0.4±5.5	−11.2 to 10.3	0.987	0.967 to 0.995
EF	–	–	0.9±2.7	−6.3 to 4.5	0.878	0.702 to 0.950

LOA, limits of agreement; ICC, intraclass correlation coefficient.

Table 3 Vendor comparison expressed as relative and absolute mean ± SD, LOA (Bland-Altman analysis), ICCs with 95% CI, and Philips (iE 33) *vs.* GE (Vivid)

Vendor-comparison (n=20)	Bias ± SD (%)	95% LOA (%)	Bias ± SD (mL)	95% LOA (mL)	ICC	95% CI
ESV	−0.9±10.3	−21.0 to 19.2	−1.1±4.6	−10.1 to 8.0	0.986	0.965 to 0.995
EDV	2.2±6.8	−11.1 to 15.5	0.7±7.1	−13.2 to 14.6	0.992	0.980 to 0.997
SV	4.5±8.1	−11.4 to 20.3	1.7±4.3	−6.6 to 10.1	0.991	0.976 to 0.996
EF	2.4±5.0	−7.4 to 12.2	1.4±2.9	−4.2 to 7.0	0.927	0.815 to 0.971

208.5 mL and comparability with former studies (29). Rather than presenting comparisons by arbitrary age categories we aimed to deliver centile curves using Coles LMS method (22), which graphically present the distribution of a parameter over the whole age range of the sample.

Studies about sex differences in paediatric RV volumes are relatively scarce. However, our findings are in agreement with a number of previous studies. Sarikouch *et al*. (30) found that sex differences are important when treating children and adults with CHD. In another study, the same group (29) found significant sex differences in RV volumes indexed to BSA and height for 99 subjects aged 8 to 20 years using cardiac MRI. They concluded that volumes are higher in boys than girls. Interestingly, the observed sex difference was noticeable but not statistically significant, when only the younger children aged 8 to 15 years were analysed. The larger sample size and younger subjects of our study may account for the sex difference being more pronounced even in the younger age groups. Sex differences in adult RV volumes have been well observed (31-33), yet, maybe more surprisingly studies on other RV parameters such as valve diameters also suggest the existence of sex differences even before puberty (34,35).

Knowledge based reconstruction

The KBR method has been evaluated with good results to quantify RV volumes from sequential 2DE datasets for healthy right ventricles. Also, various pathologies such as Tetralogy of Fallot, ventricular septal defects, transposition of great arteries after palliative surgery and pulmonary hypertension have been analysed with the KBR method (16-20,36-38). In combination with RT3DE it also compares favourably to other RT3DE software, usually based on semiautomatic border tracing in accuracy and reproducibility (15,39). Difficult border delineation due to blurring of the endocardium has led to systematic underestimation of RV volumes using border tracking. The underestimation was found to be more pronounced in larger or irregular right ventricles, such as in patients

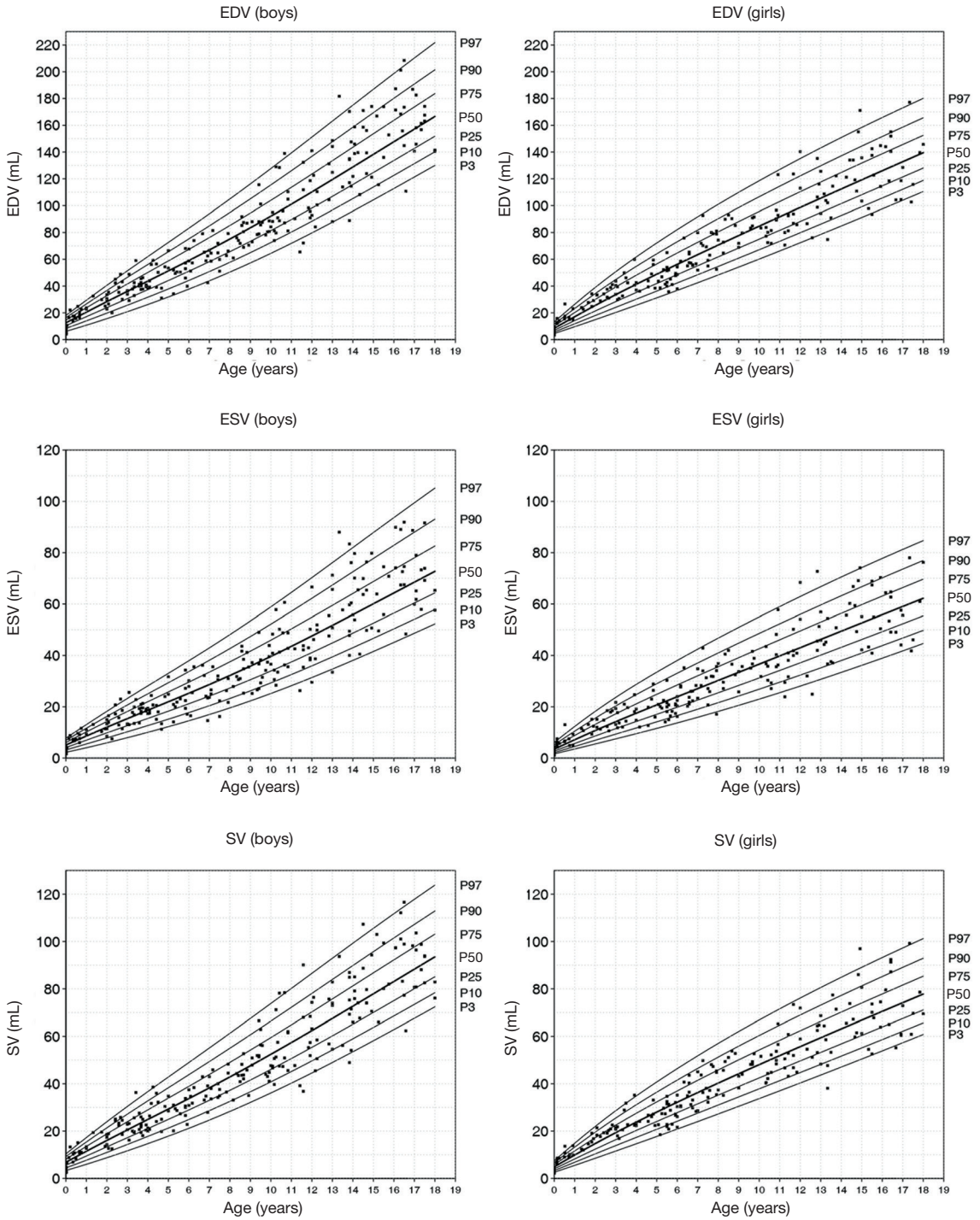

Figure 3 Gender-specific percentiles for with EDV, ESV, and SV in relation to age. P indicates the percentile value, e.g., P50 = 50th percentile value. EDV, end-diastolic volumes; ESV, end-systolic volumes; SV, stroke volume.

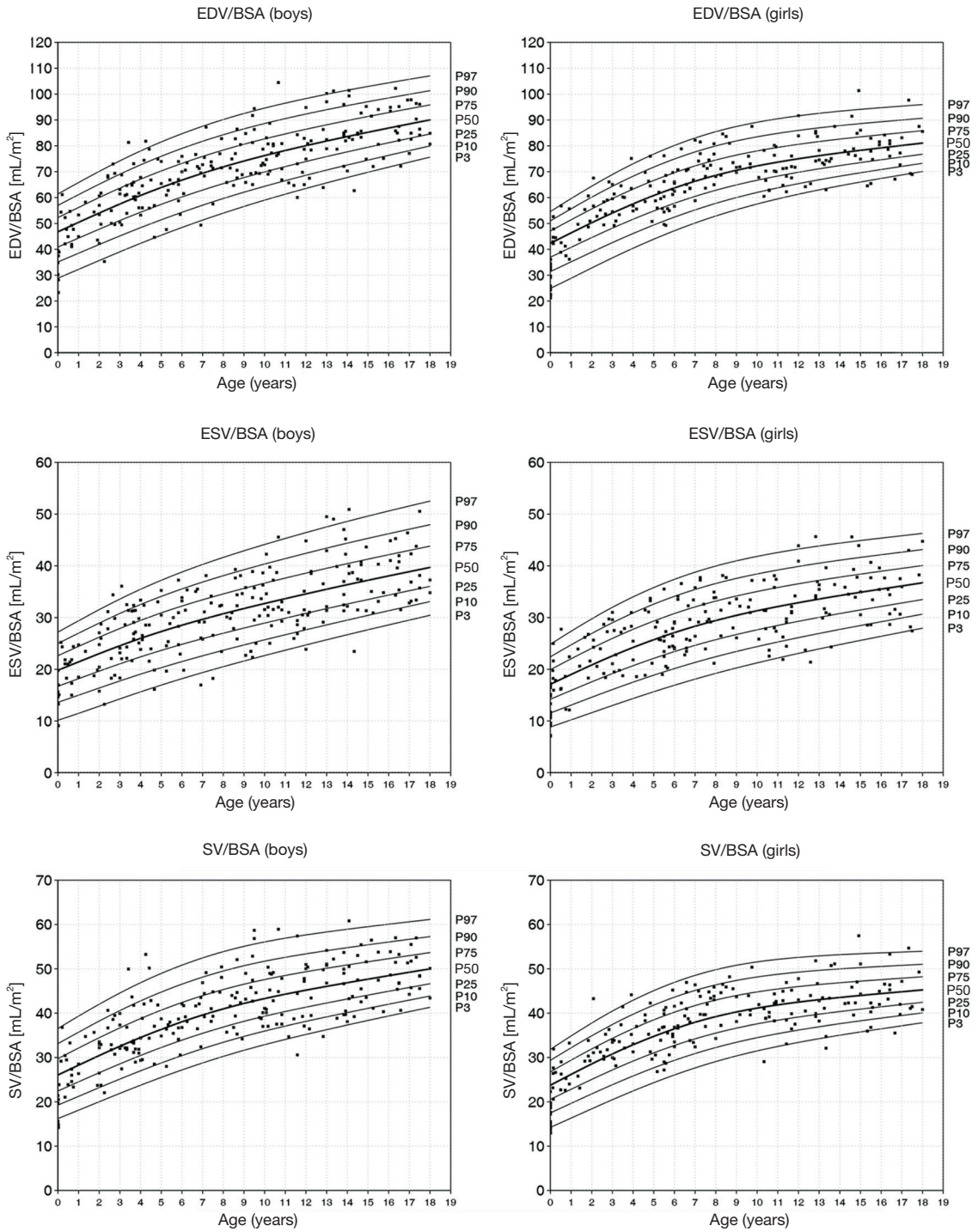

Figure 4 Gender-specific percentiles for with EDV, ESV, and SV indexed to BSA in relation to age. P indicates the percentile value, e.g., P50 = 50th percentile value.

Table 4 Effect of gender on RV-Volumes indexed for body surface area and EF

Variables	ESV/BSA (mL/m^2)	EDV/BSA (mL/m^2)	SV/BSA (mL/m^2)	EF (%)
Girls (n=193)	27.7±8.0	64.3±15.8	36.6±9.0	57.1±5.0
Boys (n=213)	30.4±8.1	70.5±16.0	40.1±9.2	56.9±4.9
Difference (%)	9.3	9.1	9.1	0.4
Significance, P	0.0008	0.0001	0.0001	0.709

Volumes and ejection fraction expressed as mean ± SD. EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume.

with CHD (13). To avoid these issues, the KBR method allows the investigator to define anatomic RV landmarks, which are identified and verified on multiple 2D slices extracted from the RT3DE full volume (*Figure 1*). RV volumes are subsequently calculated using a reference database for representative normal and pathological RV shapes, taking into account the irregular shapes of diseased right ventricles. This approach intends to reduce the impact of reduced spatial resolution. In this regard, the drawbacks of conventional software might be overcome. Nevertheless, datasets with poor image quality, reduced spatial or temporal resolution or incomplete depiction of the complete right ventricular cavity cannot assessed by any software.

Our previous findings (15) suggest that the KBR method results in highly accurate and reproducible RV volumetry in both healthy and diseased individuals and positively compares with other approaches (13,14,39).

In contrast to reports on software using semiautomatic contour finding algorithms (21,40) image acquisition by different vendors did not have a significant impact on volumetric results. Inter-vendor variability was within the same range as inter-observer variability (41) (Figures S2,S3). This permits usage of reference centiles for RT3D datasets of both vendors. It seems reasonable that image quality seems far more relevant for calculation of ventricular volumes than the influence of different ultrasound machines.

Clinical implications

Differentiating physiological from pathological right ventricular sizes not only at one given time but also on longitudinal follow-up is of paramount importance in clinical decision making as well as for evaluation and follow-up after therapeutic interventions. The centiles obtained were established for the normal configurated right ventricle and can serve as reference values for conditions with a regular shaped right ventricle. These are found in pulmonary hypertension, atrial septal defect before and after closure, pulmonary stenosis, and pulmonary regurgitation, after arterial switch of transposition of great arteries, cardiomyopathy and after cardiac transplantation.

The percentiles provided by our study may be useful to detect pathological development of RV sizes and determine its scale while also providing a basis for further research concerning RV proportions in healthy individuals and such with heart disease. In the future, RT3DE may represent an alternative to CMR.

Limitations

Limited availability and high cost of CMR as well as the need for sedation in young children were some of the reasons preventing us from subjecting healthy young children in different ages to CMR examination. Therefore, we compared the results of our evaluations to CMR as a reference standard, as recently published by our group [Laser *et al*. (15)] with very good results. In addition, there are several studies comparing RT3DE to CMR measurements in children and adults (13,42-44) generally showing RV volumes to be slightly underestimated by RT3DE. This bias should be taken into account when comparing measurements analysed with different modalities and highlight the need for separate sets of reference values for both methods. While high accuracy and good reproducibility are some of the advantages of 3DE and KBR, we cannot deny that the feasibility of 74.5% demonstrated in our study is comparatively low.

This may be caused in part by the larger number of very young children included in our study population who were unable to cooperate fully or hold their breath during examination and in part by our relatively rigorous criteria, applied to make sure poor quality datasets were excluded to

increase the reliability of the resulting reference values.

Although an ideal sample size to calculate paediatric nomograms has not been established, the selected sample size should be as large as possible whilst still being feasible. Therefore, we conducted a multicentre study using up-to-date 3D equipment and enrolled a large number of subjects, including a relatively high number of neonates and small children, which earlier studies tended to avoid. This very young age group is particularly important because of the rapid growth rate of the children and change in cardiac volumes.

The centiles obtained were established for the normal configurated right ventricle, conditions as atrial switch and tetralogy of Fallot with severe right ventricular dilatation can be evaluated by other shapes of the KBR library. In addition, normal values may vary depending on the ethnic population and therefore need to be adjusted for other ethnic groups.

Conclusions

Calculation of RV volumes in RT3DE datasets by KBR software is feasible. This method allows a reproducible and non-invasive evaluation of the volumetric data in paediatric cardiology.

The centile curves provided are based on a large sample size of healthy children and created in a multicentre approach using different ultrasound machines, state-of-the-art RT3DE and a vendor independent KBR software. These age- and sex-specific references for right ventricular volumes and EF may be useful serving as reference values in clinical practice and research.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-1155). Drs. UH and JB report grants from Kinderherzen, during the conduct of the study. The authors have no other conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of the University of Bonn (Registration No. 226/06) and Bochum (No. 20/10): the registration number of ethics board) and informed consent was taken from all individual participants and their legal guardians before participation.

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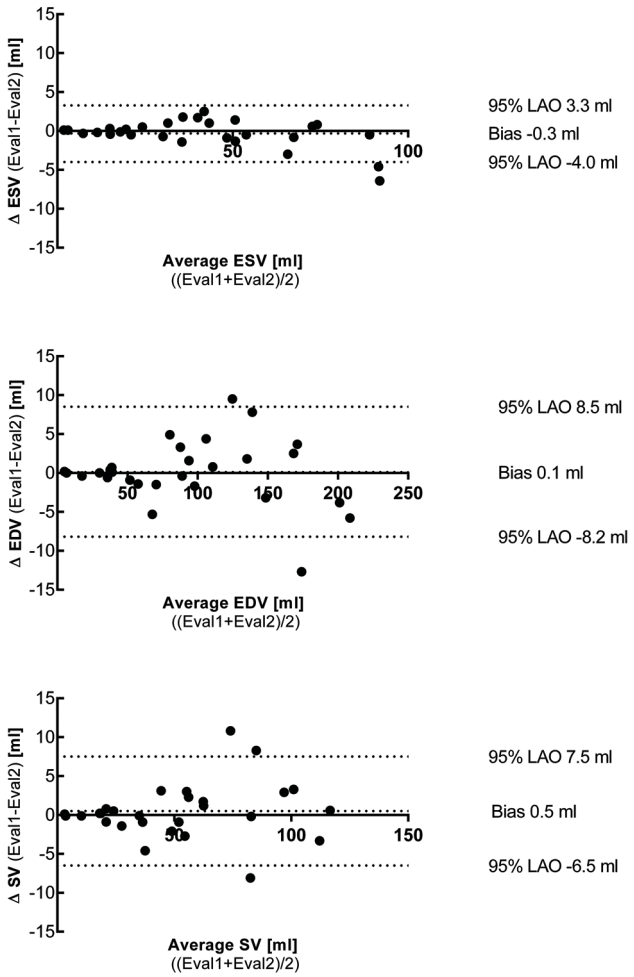

Figure S1 Intra-observer variability. Bland-Altman plots for EDV, ESV, and SV with biases and 95% LOA. EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume; LOA, limits of agreement.

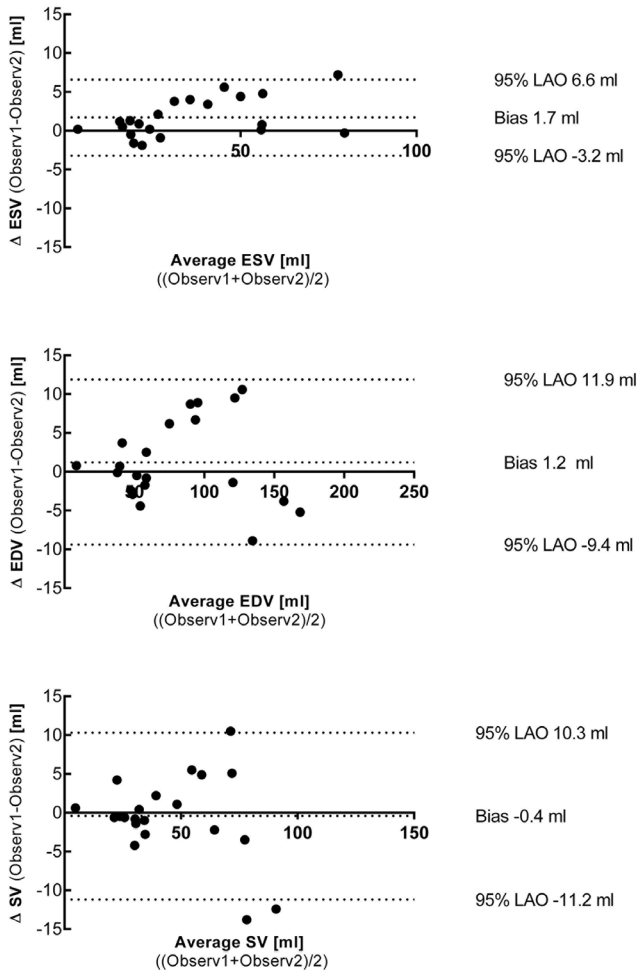

Figure S2 Inter-observer variability. Bland-Altman plots for EDV, ESV, and SV with biases and 95% LOA. EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume; LOA, limits of agreement.

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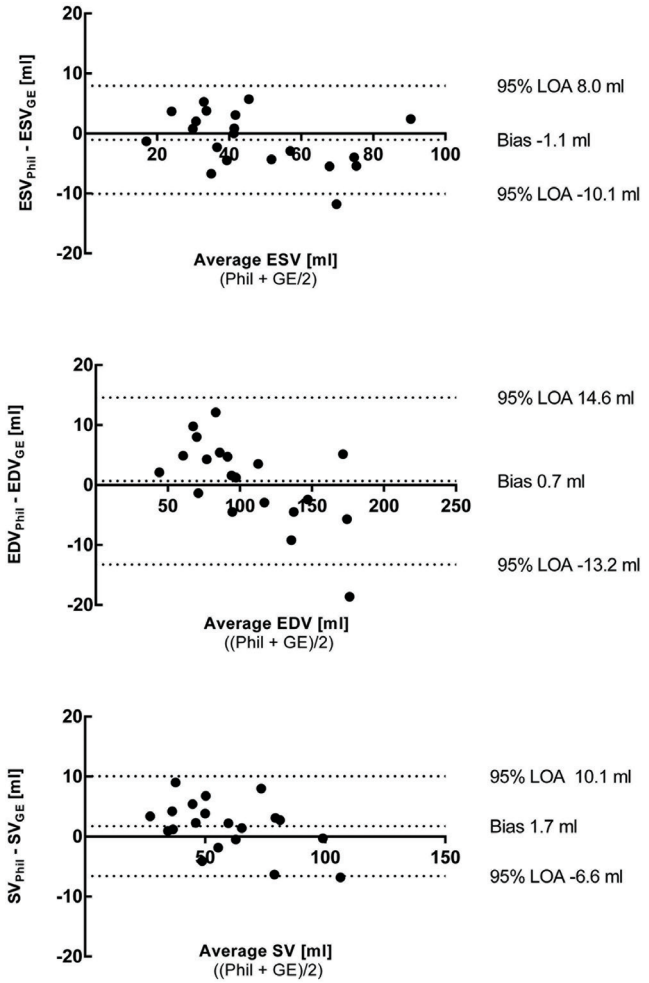

Figure S3 Intra-vendor variability, comparing Philips and GE datasets-Bland-Altman plots for EDV, ESV, and SV with biases and 95% LOA. EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume; LOA, limits of agreement.

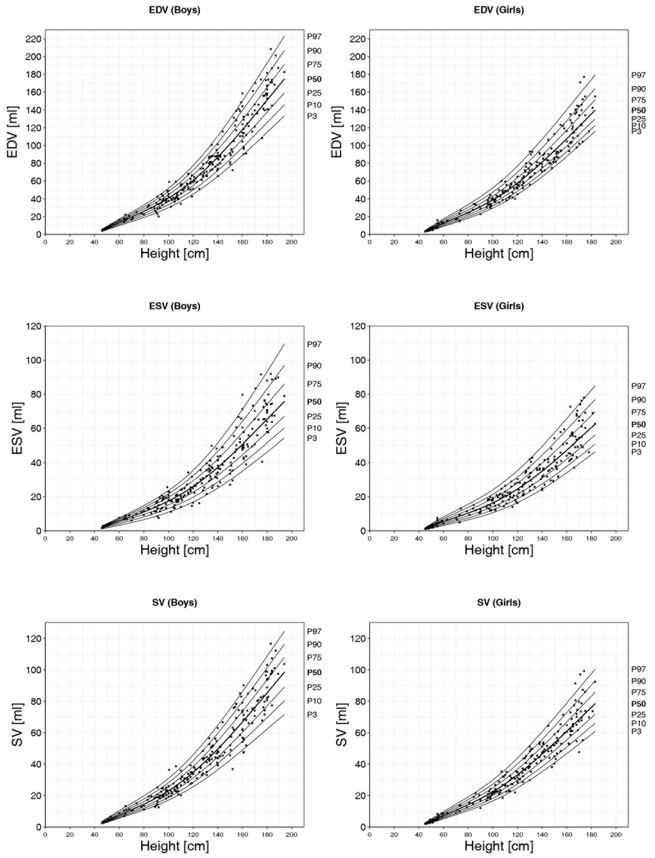

Figure S4 Gender-specific percentiles for with EDV, ESV, and SV in relation to height. P indicates the percentile value, e.g., P50 = 50th percentile value. EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; SV, stroke volume; LOA, limits of agreement.

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