


Pediatric Cardiac Magnetic Resonance Reference Values for Biventricular Volumes Derived From Different Contouring Techniques

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Background: Measurement of ventricular volumes and function using MRI is an important tool in pediatric congenital heart disease. However, normal values for children are sparse and analysis methods are inconsistent.

Purpose: To propose biventricular reference values in children for two MRI postprocessing (contouring) techniques.

Study Type: Retrospective.

Subjects: A total of 154 children from two institutions (13.9 ± 2.8 years; 101 male) that were referred for a clinical MRI study.

Field Strength/Sequence: 1.5 T; balanced steady-state free precession (bSSFP) sequence.

Assessment: Left ventricular (LV) and right ventricular (RV) end-diastolic and end-systolic volumes (LVEDV, LVESV, RVEDV, RVESV) and end-diastolic and end-systolic myocardial mass (LVEDMM, LVESMM, RVEDMM, RVESMM) were measured from short-axis images using two contouring techniques: 1) papillary muscles, trabeculations and the moderator band were included in the ventricular blood volume and excluded from the myocardial mass, 2) papillary muscles, trabeculations and the moderator band were excluded from the ventricular volume and included in the ventricular mass.

Statistical Tests: Univariable and multivariable linear regression models were used to evaluate relationships between sex, weight, height, body surface area (BSA) and age and volumetric results. Reference graphs and tables were created with the LMS-method. Contouring techniques were compared by intraclass correlation, regression analysis and Bland–Altman plots. A P value < 0.05 was considered statistically significant.

Results: Height and BSA were significantly associated with LVESV (method 1) and with LVEDV and RVEDV (method 2). LVESV (method 2), RVESV (both methods), RVEDV (method 1), and LVEDMM and RVEDMM (both methods), showed significant associations with height and weight. LVSV and RVSV (both methods) were significantly associated with BSA and weight. RVESV (method 1) was significantly associated with age. Gender showed significant associations for all parameters.

Data Conclusion: The proposed pediatric reference values can be used in the diagnosis and follow-up of congenital or acquired heart disease and for research purposes.

Evidence Level: 3

Technical Efficacy: Stage 2

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Ventricular volume and function assessment by MRI has gained increasing popularity in pediatric patients with acquired and congenital heart disease and complements echocardiography and cardiac catheterization.¹ Left and right ventricular (LV, RV) chamber assessment can be performed from both short-axis and axial cine stacks but for the left ventricle, short-axis cines are preferred according to recent recommendations.² LV and RV trabeculations and papillary muscles are often included in the ventricular volume in routine clinical practice although the recommendations suggest that for the LV, they should ideally be included in the myocardial mass.² Whatever contouring method is preferred, it should be kept in mind that ventricular results differ between methods and that only reference values derived from the same approach should be used.^{2,3}

Reference values for LV and RV volumes and systolic function parameters for children are important for accurate image interpretation and clinical management.^{2,4} Several studies have published biventricular reference values but have not considered different ventricular contouring methods.^{5–7}

Thus, the aim of this study was to create pediatric reference values for two contouring methods derived from short-axis cine stacks and to perform a comparison between them.

Methods

Study Population

A general informed consent for the use of routinely acquired clinical data for retrospective research studies was signed by all parents or legal guardians, as appropriate.

The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

MRI examinations of healthy children between January 2016 and December 2019 were included from two institutions as described in previous work from this group.⁸ A total of 145 MRI data sets were acquired at one center and 9 data sets at the other site.

Indications for MRI examinations were⁸: 1) nondiagnostic echocardiographic scan, 2) uncertainty about the anatomical structures on echocardiography, 3) syncope, or 4) chest pain with low pre-scan probability of being cardiac in origin. A detailed overview of indications for echocardiography and subsequent MRI examinations is shown in Table 1.

Exclusion criteria were⁸: 1) congenital or acquired heart disease, 2) arterial hypertension, 3) medication for arterial hypertension, 3) other types of disease that involve structural and functional abnormalities of the heart, and 4) pregnancy.

MR Image Acquisition

All MRI examinations were performed at 1.5 T and with the same scanner type in both institutions (MAGNETOM Aera, Siemens Healthineers, Erlangen, Germany). Short-axis cine stacks fully covering both ventricles from the base to the apex

TABLE 1. Indications for Echocardiography and MRI

Echocardiography (<i>n</i> = 154)	MRI (<i>n</i> = 154)
Palpitations (<i>n</i> = 35)	Nondiagnostic echocardiographic examination (<i>n</i> = 7)
Cardiac murmur (<i>n</i> = 16)	Uncertainty about the cardiac anatomy and myocardial structure on echocardiography (<i>n</i> = 101)
Chest pain (<i>n</i> = 46)	Chest pain with low prescan probability of being cardiac in origin (<i>n</i> = 46)
Syncope and dizziness (<i>n</i> = 45)	
Other indications for echocardiography	
<ul style="list-style-type: none"> • Shortness of breath (<i>n</i> = 2) • Exercise induced fatigue (<i>n</i> = 1) • Abnormal fetal echocardiography (<i>n</i> = 1) • High-level athlete (<i>n</i> = 4) • Persistent ductus arteriosus after coil occlusion (<i>n</i> = 1) • Abdominal discomfort (<i>n</i> = 1) • Asthma (1) • Family history of atrial septal defect (<i>n</i> = 1) 	

were acquired with a retrospectively ECG-gated balanced steady-state free-precession (SSFP) sequence. The sequence parameters were as follows: repetition time (TR)/time to echo (TE) = 30.6/1.17 msec, flip angle 73°, number of reconstructed cardiac phases 25, field of view 250–420 mm (according to patient size), matrix size 192 × 144 mm, slice thickness 5–8 mm, slice gap 2 mm and temporal resolution 30 msec.

MR Image Analysis

Short-axis cine images were analyzed with validated software (Version 5.12.1; cvi42, Circle Cardiovascular Imaging, Calgary, Canada). All measurements were performed by one observer with 1–2 years of experience in cardiac MRI (SH) and reviewed by a pediatric cardiologist with 16 years of experience in cardiac MRI (IV).

Two different contouring techniques were applied to measure the following parameters: 1) LV and RV end-diastolic and end-systolic volumes (LVEDV, LVESV, RVEDV, RVESV) as well as LV and RV stroke volume (LVSV, RVSV), 2) LV and RV ejection fraction (LVEF, RVEF), and 3) LV and RV end-diastolic and end-systolic myocardial mass (LVEDMM, LVESMM, RVEDMM, RVESMM).

Using *contouring method 1*, the papillary muscles, myocardial trabeculations, and the moderator band were

included in the ventricular blood volume and excluded from the myocardial mass. Semiautomatic contour detection for LV endo- and epicardial borders was used with subsequent manual corrections. RV endo- and epicardial contours were drawn manually.

Using *contouring method 2*, the papillary muscles, myocardial trabeculations, and the moderator band were excluded from the ventricular blood volume and included in the myocardial mass. Threshold segmentation was used for LV and RV endocardial borders. These contours were manually

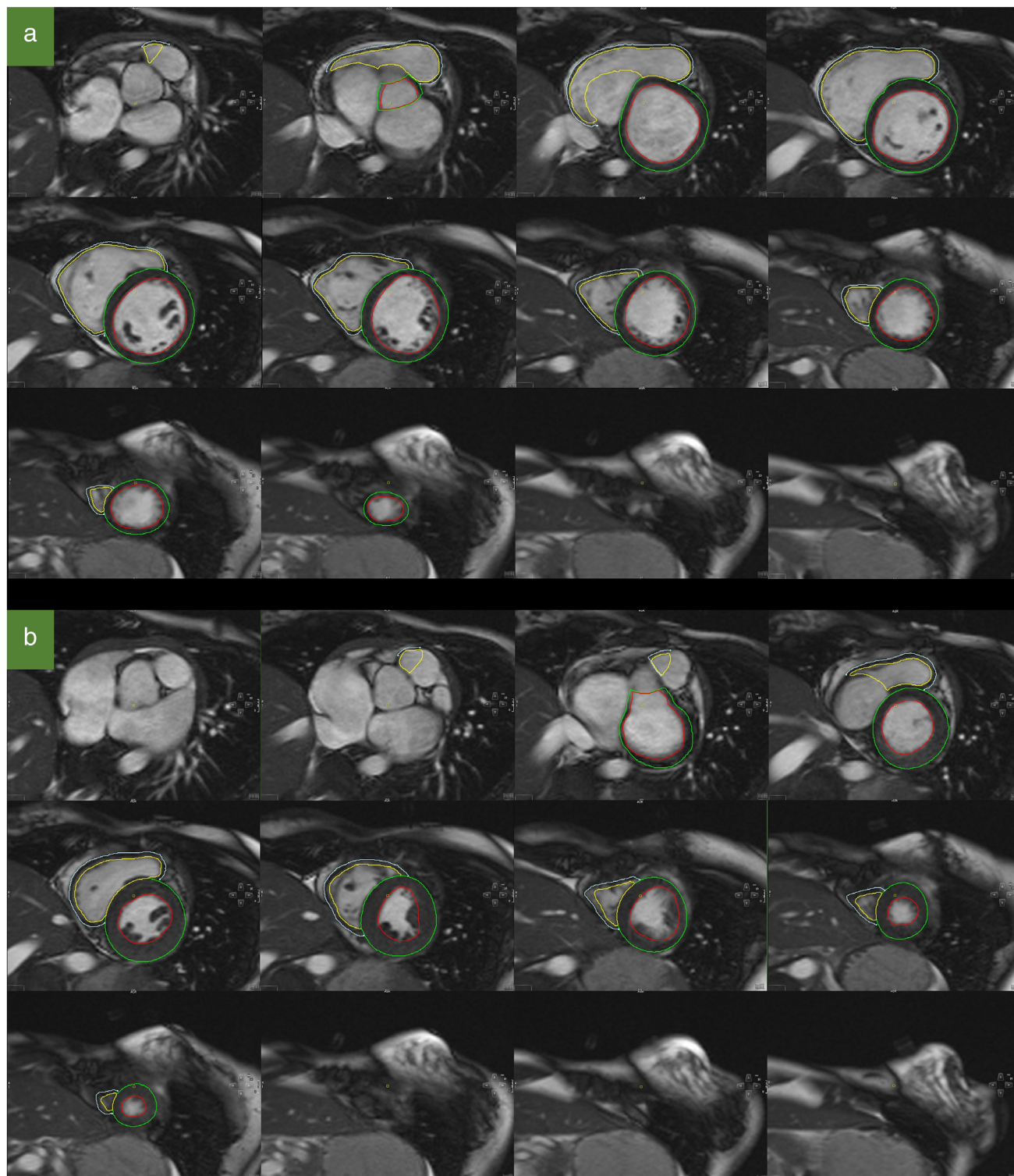


FIGURE 1: Contouring method 1 at end diastole (a) and end systole (b): the papillary muscles, myocardial trabeculations and the moderator band were included in the ventricular volume and excluded from the ventricular mass. Colors: green—LV epicardial contour, red—LV endocardial contour, light blue—RV epicardial contour, yellow—RV endocardial contour (LV: left ventricle, RV: right ventricle).

corrected. RV epicardial borders, papillary muscles and myocardial trabeculations were manually drawn.

Long-axis and axial views were compared with short-axis images in both postprocessing methods

to ensure that atrial and aortic volumes were not included into the ventricular volumes. Examples of images for both contouring methods are shown in Figs. 1 and 2.

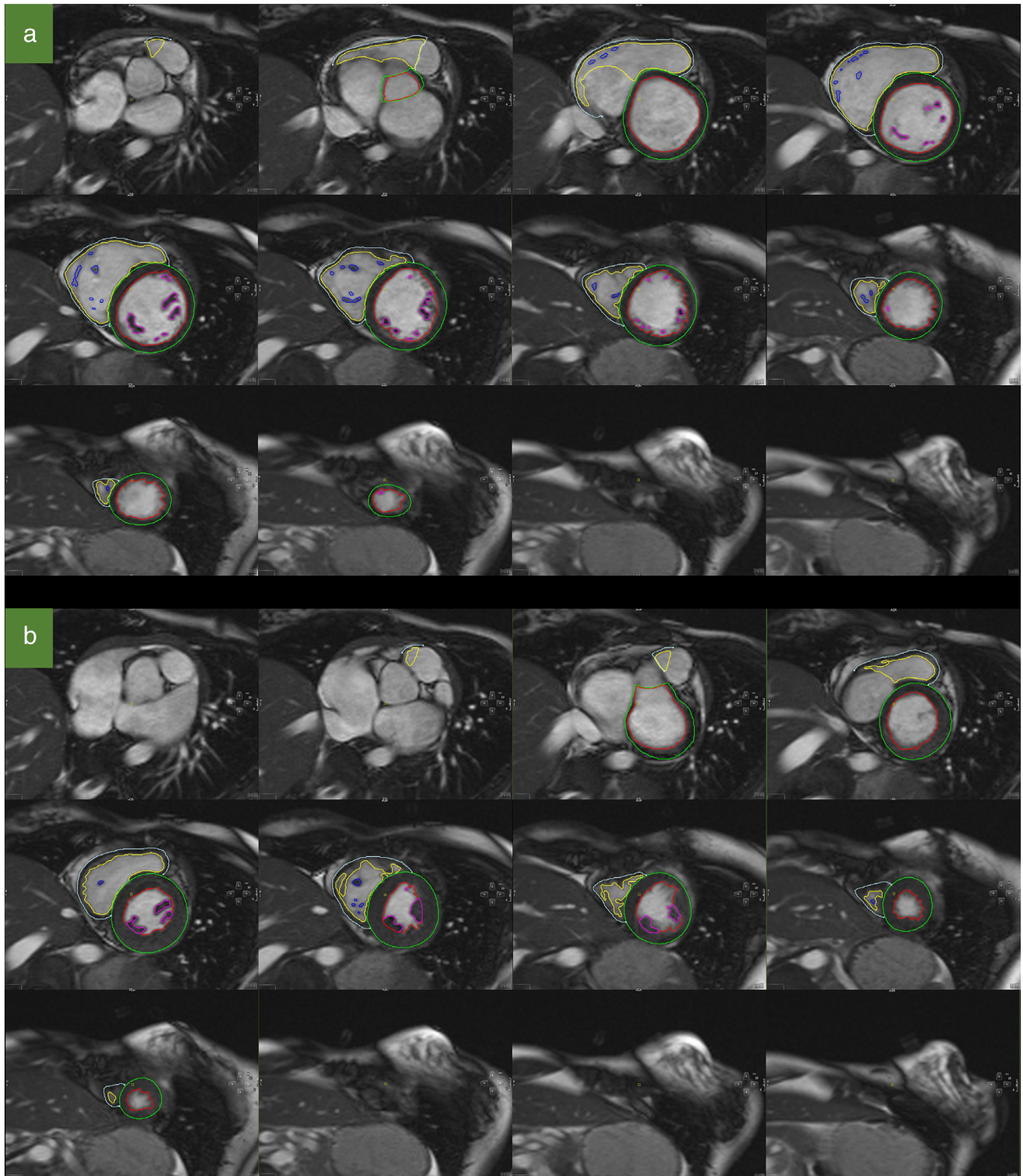


FIGURE 2: Contouring method 2 at end diastole (a) and end systole (b): the papillary muscles, myocardial trabeculations and the moderator band were excluded from the ventricular volume and included in the ventricular mass. Colors: green—LV epicardial contour, red—LV endocardial contour, pink—LV papillary muscles and myocardial trabeculations, light blue—RV epicardial contour, yellow—RV endocardial contour, blue—RV papillary muscles and myocardial trabeculations (LV: left ventricle, RV: right ventricle).

TABLE 2. Subject Characteristics

Parameters	All (<i>n</i> = 154)		Girls (<i>n</i> = 53)		Boys (<i>n</i> = 101)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	13.9	2.8	14.3	2.4	13.6	2.9
Weight (kg)	55.0	15.1	54.3	14.1	55.5	15.7
Height (cm)	162.1	16.0	160.2	11.2	163.2	18.1
BSA (cm ²)	1.6	0.3	1.5	0.2	1.6	0.3
BMI (kg/m ²)	20.6	4.1	21.0	4.7	20.4	3.8
Heart rate (bpm)	74.4	13.4	76.0	10.9	73.5	14.4

BSA = body surface area; BMI = body mass index; bpm = beats per minute.

Statistical Analysis

The software R version 4.0.3 was used for the statistical analyses.⁹ All tests were performed two-sided and a significance level of 0.05 was chosen. Centile curves and tables were generated according to the LMS-method of Cole and Green, where L refers to Box-Cox power, M refers to the mean and S refers to the coefficient of variation.¹⁰ An extended version of this method is implemented in the R package gamlss, which was used for the analysis.¹¹ The influence of factors on the 10 measurements was analyzed for each influence variable separately and in a multiple fashion with linear regression models with and without interactions. The fit of the linear model was assessed with influence factor vs. outcome plots, residual vs. fitted plots, q-q plots, scale-location plots and residual vs. leverage plots. Influence variables were gender, body surface area (BSA), age, body height, and body weight. Model selection in multiple models was performed by backward selection and a *P* value threshold of 0.05.

For the comparison of contouring methods 1 and 2, intraclass correlation (ICC), Bland–Altman plots, and regression lines were used. ICC values were calculated with the R package irr.¹² Because the two methods were applied to all observations and we have a fixed effects model, we applied the parameters model = twoway, type = consistency and unit = single in the command “icc”.¹³ Bland–Altman plots and corresponding measures were calculated.¹⁴

The intraobserver and interobserver variability were evaluated by the ICC. For the intraobserver variability, one of the two observers (S.H.) re-measured ventricular parameters in 30 children. To assess interobserver variability, two independent operators with 1–2 years (S.H.) and 4 years (S.B.G.) of experience performed measurements for both ventricles using both contouring methods in 25 children. ICC values were categorized as follows: 0.50–0.75, moderate; 0.76–0.90, good; >0.90, excellent agreement.¹⁵

Results

Volumetric measurements with both contouring methods were performed in 154 children. Subject demographics are shown in Table 2.

Linear Regression Analysis

Results of the univariable and multivariable linear regression models for the two contouring methods are shown in Table 3. For LVEF and RVEF model quality was insufficient with high dispersion of the values; therefore, no results of regression analysis, percentile curves and tables are given. However, mean and standard deviation for LVEF and RVEF are shown in Table 4.

Univariable linear regression analysis, showed strong associations of gender, BSA, body height, body weight and age on LVEDV, LVESV, LVSV, LVEDMM, RVEDV, RVESV, RVSV, and RVEDMM derived from both contouring methods.

In the multivariable regression analysis, body height and BSA remained in the final model for LVESV from method 1, and for LVEDV and RVEDV from method 2. For global LVESV from method 2, RVESV, RVEDV from method 1, and LVEDMM and RVEDMM from both methods, statistically significant associations were found for body height and body weight. For global LVSV and RVSV, BSA and body weight remained in the multivariable regression model. Gender showed significant associations for all analyzed measurements from both contouring methods. RVESV from method 1 was associated with age in the multivariable model.

Following the multivariable regression analysis, showing that many parameters were strongly associated with height, taking also into account the, centile charts (Figures 3–6 and Figure S1 in Supplement 1) and tables (Tables 1–36 in Supplement 2) were created by height. Because gender had a significant influence for all measurements, centile curves and tables are stratified for boys and girls.

TABLE 3. Univariable Linear Models for the Influence Variables

Influence variable	Contouring Method	Beta	Standard Error	P value
LVEDV (mL)				
Gender, reference male	M1	−21.21	6.20	0.00081
	M2	−22.64	6.04	0.00025
BSA (m ²)	M1	111.38	6.07	<0.0001
	M2	105.97	6.32	<0.0001
Body height (cm)	M1	1.95	0.11	<0.0001
	M2	1.88	0.11	<0.0001
Body weight (kg)	M1	1.92	0.13	<0.0001
	M2	1.82	0.13	<0.0001
Age (years)	M1	8.77	0.84	<0.0001
	M2	8.39	0.84	<0.0001
LVESV (mL)				
Gender, reference male	M1	−9.84	3.35	0.0038
	M2	−9.25	2.92	0.0019
BSA (m ²)	M1	53.04	3.91	<0.0001
	M2	44.44	3.59	<0.0001
Body height (cm)	M1	0.041	0.016	0.013
	M2	0.81	0.061	<0.0001
Body weight (kg)	M1	0.91	0.080	<0.0001
	M2	0.76	0.073	<0.0001
Age (years)	M1	4.50	0.46	<0.0001
	M2	3.76	0.42	6.8×10^{-16}
LVSV (mL)				
Gender, reference male	M1	−13.51	3.60	0.00025
	M2	−13.39	3.63	0.00031
BSA (m ²)	M1	62.35	3.86	<0.0001
	M2	61.53	4.00	<0.0001
Body height (cm)	M1	1.07	0.070	<0.0001
	M2	1.07	0.072	<0.0001
Body weight (kg)	M1	1.08	0.080	<0.0001
	M2	1.06	0.083	<0.0001
Age (years)	M1	4.61	0.52	3.1×10^{-15}
	M2	4.63	0.53	3.2×10^{-15}
LVEDMM (g)				
Gender, reference male	M1	−15.32	4.20	0.00037
	M2	−16.12	4.83	0.0011

TABLE 3. Continued

Influence variable	Contouring Method	Beta	Standard Error	P value
BSA (m ²)	M1	74.55	4.26	<0.0001
	M2	83.82	5.02	<0.0001
Body height (cm)	M1	1.25	0.081	<0.0001
	M2	1.40	0.096	<0.0001
Body weight (kg)	M1	1.32	0.087	<0.0001
	M2	1.49	0.10	<0.0001
Age (years)	M1	5.75	0.59	<0.0001
	M2	6.47	0.68	<0.0001
RVEDV (mL)				
Gender, reference male	M1	-26.02	7.13	0.00036
	M2	-22.40	6.15	0.00037
BSA (m ²)	M1	126.67	7.23	<0.0001
	M2	107.38	6.43	<0.0001
Body height (cm)	M1	2.20	0.13	<0.0001
	M2	1.89	0.11	<0.0001
Body weight (kg)	M1	2.20	0.15	<0.0001
	M2	1.86	0.14	<0.0001
Age (years)	M1	10.11	0.97	<0.0001
	M2	8.48	0.85	<0.0001
RVESV (mL)				
Gender, reference male	M1	-13.25	3.79	0.00061
	M2	-9.78	2.91	0.00099
BSA (m ²)	M1	62.75	4.28	<0.0001
	M2	45.37	3.53	<0.0001
Body height (cm)	M1	1.10	0.076	<0.0001
	M2	0.82	0.060	<0.0001
Body weight (kg)	M1	1.09	0.087	<0.0001
	M2	0.78	0.071	<0.0001
Age (years)	M1	5.38	0.51	<0.0001
	M2	3.93	0.41	<0.0001
RVSV (mL)				
Gender, reference male	M1	-12.77	3.77	0.00091
	M2	-12.62	3.68	0.00078
BSA (m ²)	M1	63.92	4.10	<0.0001
	M2	62.01	4.04	<0.0001
Body height (cm)	M1	1.10	0.074	<0.0001
	M2	1.07	0.073	<0.0001

TABLE 3. Continued

Influence variable	Contouring Method	Beta	Standard Error	P value
Body weight (kg)	M1	1.11	0.085	<0.0001
	M2	1.08	0.083	<0.0001
Age (years)	M1	4.73	0.55	7.9×10^{-15}
	M2	4.55	0.54	2.3×10^{-14}
RVEDMM (g)				
Gender, reference male	M1	-4.74	1.42	0.0011
	M2	-7.81	2.29	0.00084
BSA (m ²)	M1	23.70	1.58	<0.0001
	M2	35.83	2.78	<0.0001
Body height (cm)	M1	0.42	0.027	<0.0001
	M2	0.63	0.048	<0.0001
Body weight (kg)	M1	0.41	0.033	<0.0001
	M2	0.62	0.056	<0.0001
Age (years)	M1	1.92	0.20	<0.0001
	M2	2.99	0.33	3.6×10^{-16}

Influence variables that remained significant in the multivariable linear model are shown in bold.

Beta = coefficient of the linear model; BSA = body surface area; LVEDMM = left ventricular end-diastolic mass; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular stroke volume; M1 = contouring method 1; M2 = contouring method 2; RVEDMM = right ventricular end-diastolic mass; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVSV = right ventricular stroke volume.

Comparison of Contouring Methods

LVEDV, LVESV, RVEDV, and RVESV from contouring method 1 (including papillary muscles and trabeculations into the ventricular volume) were significantly higher compared to those from contouring method 2, whereas LVEDMM, LVESMM, RVEDMM, RVESMM, LVEF, and RVEF from contouring method 2 were significantly higher compared to values derived by method 1 (Table 4). RVSV from method 2 was significantly lower compared to RVSV from method 1 (Table 4), but there was no difference ($P = 0.27$) for LVSV between the two contouring methods (Table 4).

LV and RV volumetric parameters from the two contouring methods were also compared with Bland–Altman plots (Figure S2 and S3 in Supplement 1). The mean difference and the lower and upper limits of agreement (LOA) were as follows: LVEDV 9.35 mL (−2.42, 21.12), LVESV 9.11 mL (0.09, 18.12), LVSV 0.33 mL (−6.83, 7.48), LVEDMM −9.76 g (−21.73, 2.22), RVEDV 21.53 mL (1.83, 41.24), RVESV 15.61 mL (−0.65, 31.88), RVSV 5.92 mL (−5.33, 17.17), RVEDMM −14.5 g (−28.68, −0.32). Furthermore, regression lines are shown to describe the relationship between the methods (Figure S2 and S3 in Supplement 1). Bland–Altman plots showed greater

differences between the methods with larger LV and RV volumes and higher RV and LV mass (Figure S2 and S3 in Supplement 1).

Reproducibility

Results for both contouring methods are shown in Supplement 2 (Table 37). Intraobserver variability was good to excellent for most parameters, only RVEF from method 2 showed moderate intraobserver variability (ICC = 0.71).

Interobserver variability proved to be good to excellent for the majority of volumetric parameters. Moderate results were found for LVEF (ICC = 0.66) and RVEDMM (ICC = 0.65) derived from method 1 and for RVEF from both methods (ICCs = 0.63 and 0.74 for methods 1 and 2, respectively).

Discussion

In this study, pediatric MRI reference values for two ventricular contouring methods were suggested. The centile curves and tables provided are intended to improve the reporting of cardiovascular MRI studies in children and adolescents.

Previous studies on ventricular MRI normal values in children have used different approaches and contouring

TABLE 4. Comparison of Volumetric Parameters Between Contouring Methods

Parameters	Method 1		Method 2		P value*
	Mean	SD	Mean	SD	
LVEDV (mL)	137.7	39.7	128.3	27.7	<0.001
LVESV (mL)	59.0	20.2	49.9	17.7	<0.001
LVSV (mL)	78.7	22.1	78.3	22.3	0.27
LVEDMM (g)	80.1	25.7	89.9	29.4	<0.001
LVESMM (g)	81.0	26.6	90.5	29.7	<0.001
LVEF (%)	57.5	5.2	61.4	5.6	<0.001
RVEDV (mL)	142.5	43.7	120.9	37.7	<0.001
RVESV (mL)	64.5	23.1	48.8	17.7	<0.001
RVSV (mL)	78.0	23.0	72.1	22.1	<0.001
RVEDMM (g)	29.4	8.7	43.9	14.0	<0.001
RVESMM (g)	25.8	8.8	34.9	12.7	<0.001
RVEF (%)	55.2	5.3	59.8	5.9	<0.001

LVEDMM = left ventricular end-diastolic mass; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESMM = left ventricular end-systolic mass; LVSV = left ventricular stroke volume; RVEDMM = right ventricular end-diastolic mass; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; RVESMM = right ventricular end-systolic mass; RVSV = right ventricular stroke volume.

*P values are derived from the paired samples *t*-test.

methods.^{3,5-7,16} However, it has been shown in several studies that results from varying contouring methods can give different volumetric results.¹⁶⁻¹⁹ Therefore, the decision about the best matching normal values should take postprocessing methods into account.² Most studies on pediatric ventricular normal values have used a short axis stack for volume and function analysis and have excluded papillary muscles and trabeculations from the blood pool.^{6,7,16} Only Sarikouch et al used axial cine stacks, but they also excluded papillary muscles and large trabeculations from the ventricular blood volume.⁵

In clinical routine, however, ventricular trabeculations and papillary muscles are commonly included into the ventricular blood volume although they correspond to myocardial tissue.² Nevertheless, there is still discussion about excluding papillary muscles and trabeculations from the ventricular volume and until now, both methods have been acceptable.² As suggested by Urzua Fresna et al, it is therefore probably best to use the institution's most reproducible contouring method.¹⁷ It must also be mentioned that different software vendors have different segmentation tools and that this can particularly impact volumetric results when myocardial trabeculations and papillary muscles are included into the blood pool. Therefore, reference values derived from method

2 should only be used when analysis is performed with the same software as used for this study or software applications using an identical segmentation function.

With regard to the available pediatric normal values, studies using a simple approach by including trabeculations into the blood pool are lacking. We therefore tried to close this gap and also confirmed that the two contouring methods give significantly different results for biventricular volumes and EF.^{3,17-19} Another reason for providing additional normal values for a simple approach is that from our experience until recently, software tools for semi-automatic or automatic contour delineation in children especially with congenital heart disease commonly did not work as well as in adults. For high volume centers, a simple contouring method is therefore to be preferred. Recently, a number of fully automated deep-learning segmentation techniques have been validated and these have shown strong agreement with manual segmentation in children and adults with congenital heart disease.^{19,20} This has potential to improve clinical workflow, but importantly it is based on volumetric analysis which includes papillary muscles and trabeculations in the ventricular volumes.^{20,21}

Linear regression analysis showed significant associations of LV and RV volumetric parameters with studied parameters

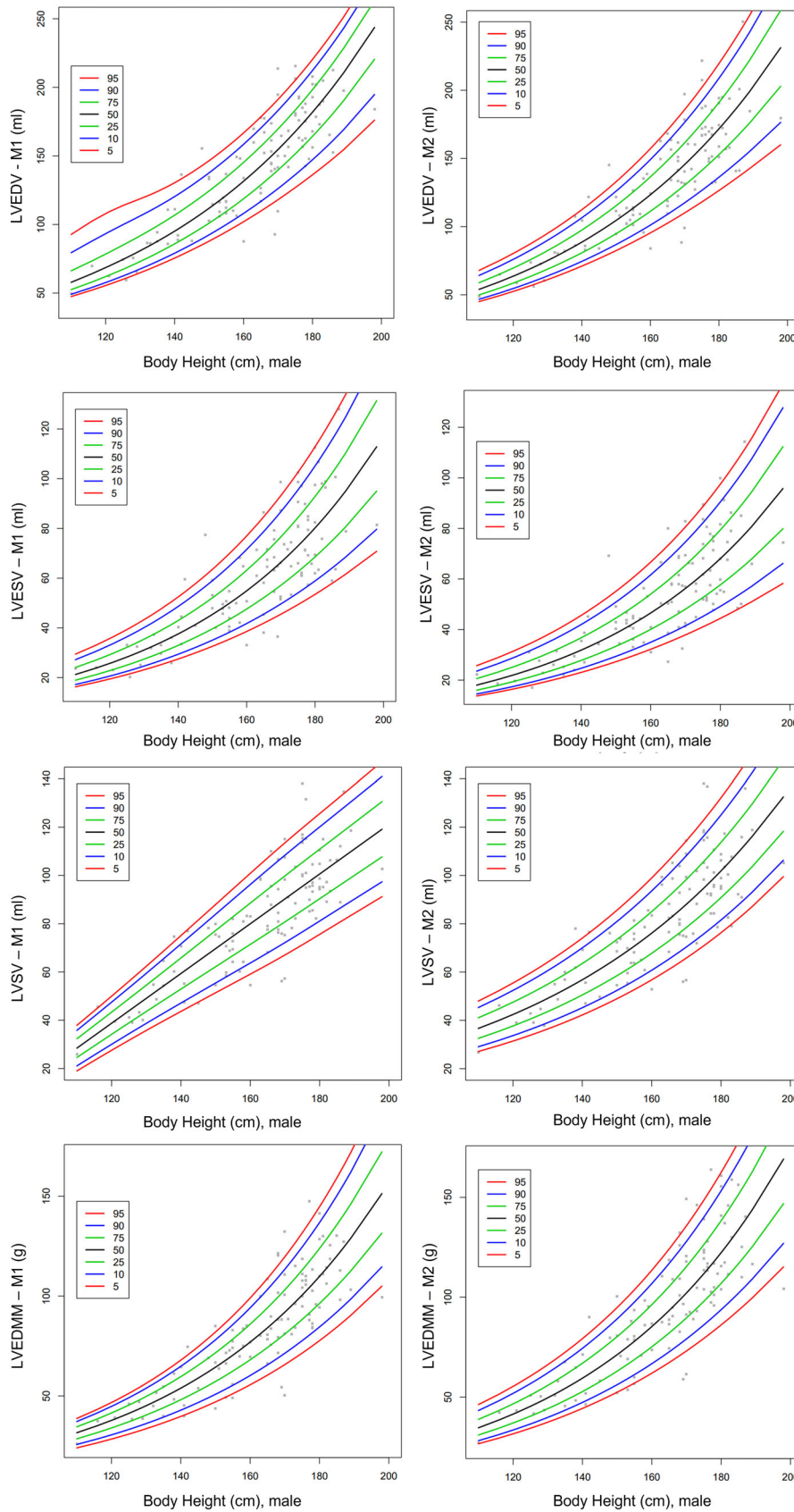


FIGURE 3: Centile charts for boys showing LVEDV, LVESV, LVSV, and LVEDMM by body height for both contouring methods (M1 and M2). The colors correspond to the given centiles. LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; LVSV = left ventricular stroke volume; LVEDMM = left ventricular end diastolic mass.

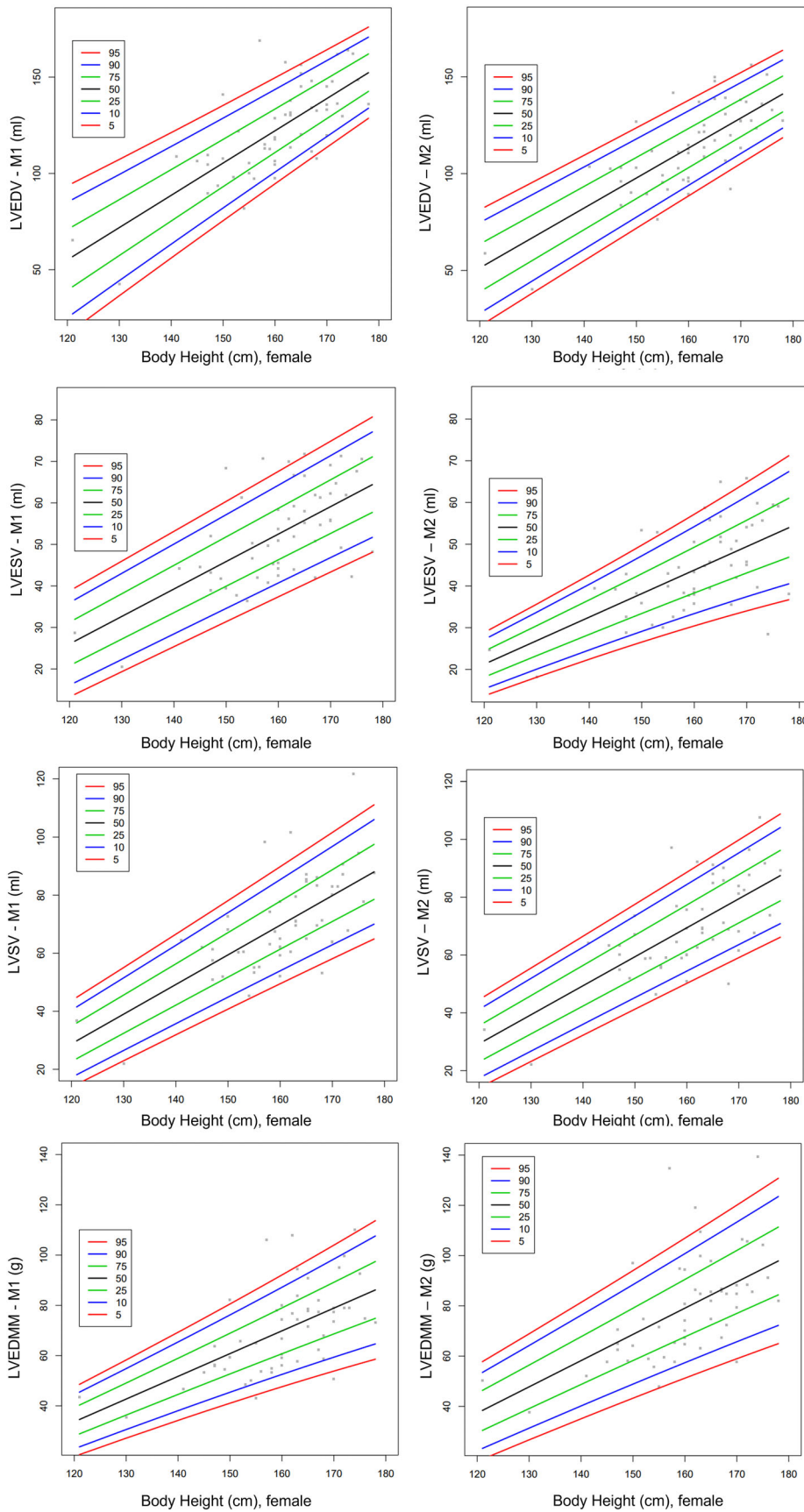


FIGURE 4: Centile charts for girls showing LVEDV, LVESV, LVSV, and LVEDMM by body height for both contouring methods (M1 and M2). The colors correspond to the given centiles. LVEDV = left ventricular end diastolic volume; LVESV = left ventricular endsystolic volume; LVSV = left ventricular stroke volume; LVEDMM = left ventricular enddiastolic mass.

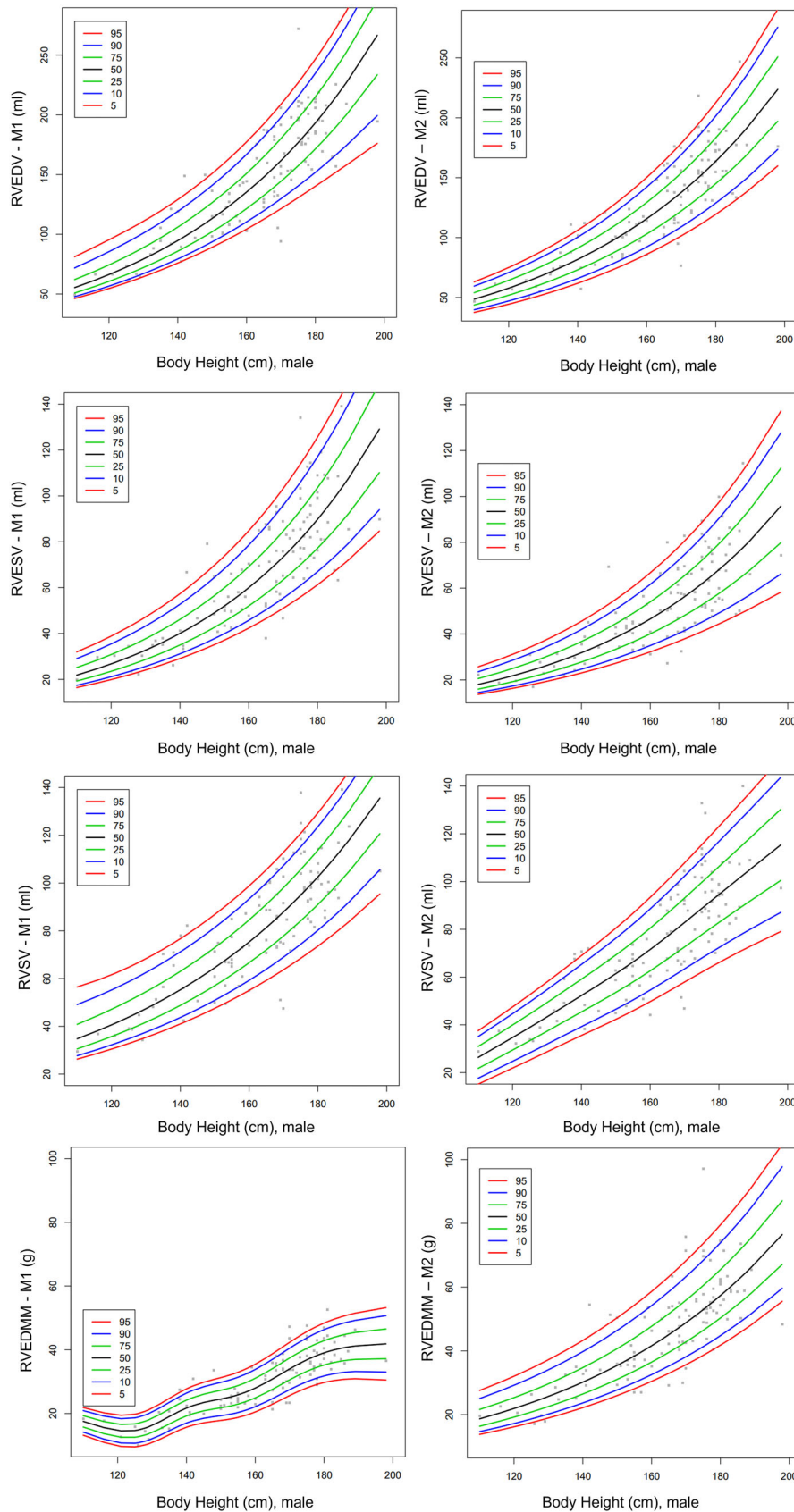


FIGURE 5: Centile charts for boys showing RVEDV, RVESV, RVSV, and RVEDMM by body height for both contouring methods (M1 and M2). The colors correspond to the given centiles. RVEDV = right ventricular end diastolic volume; RVESV = right ventricular end systolic volume; RVSV = right ventricular stroke volume; RVEDMM = right ventricular end diastolic mass.

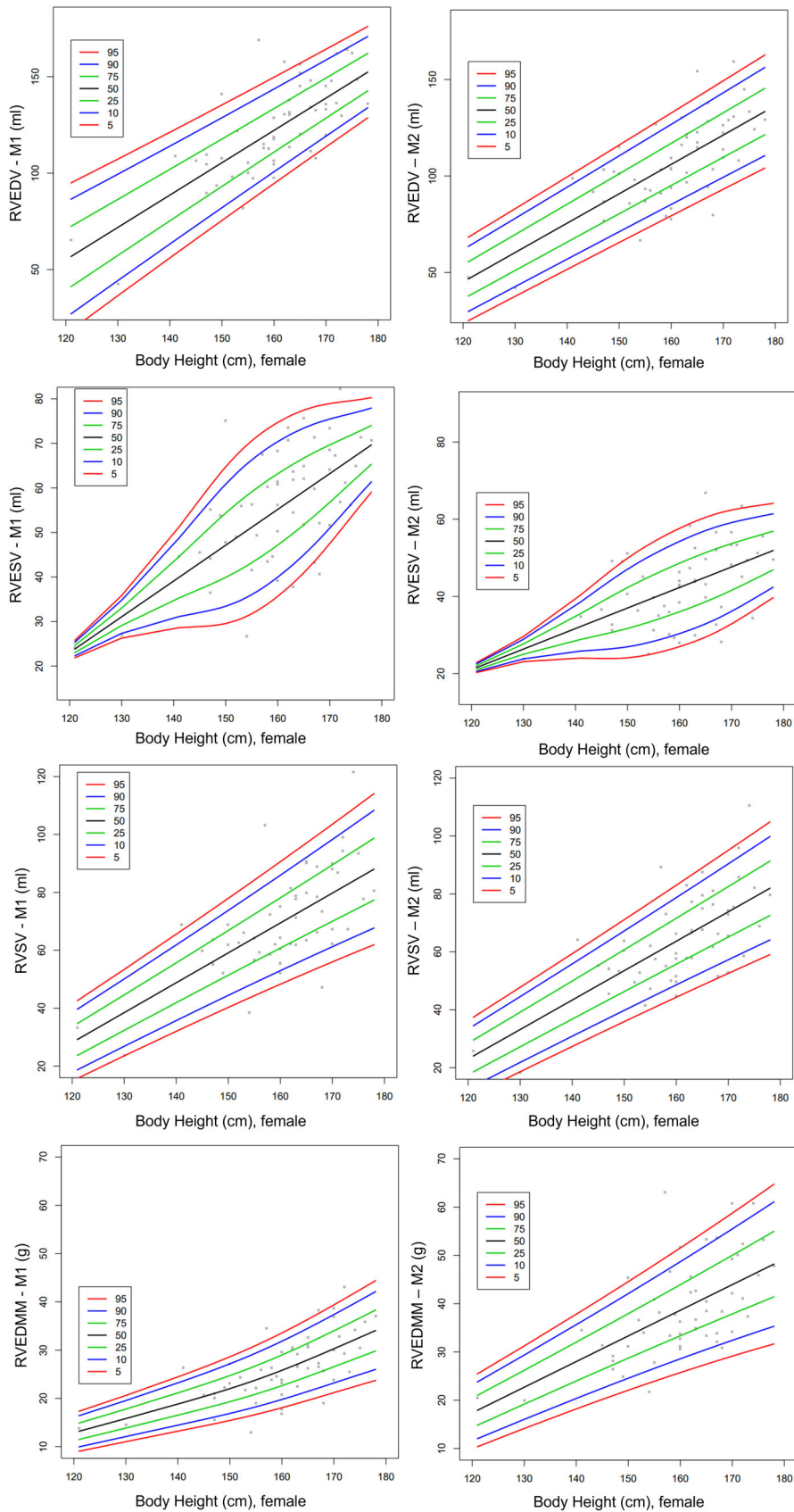


FIGURE 6: Centile charts for girls showing RVEDV, RVESV, RVSV, and RVEDMM by body height for both contouring methods (M1 and M2). The colors correspond to the given centiles. RVEDV = right ventricular end diastolic volume; RVESV = right ventricular end systolic volume, RVSV = right ventricular stroke volume; RVEDMM = right ventricular end diastolic mass.

(gender, age, BSA, body weight, and body height). Subsequent multivariable regression analysis demonstrated that body height and body weight showed significant associations with volumetric results. Based on these results, and findings from other groups, suggesting that height-based methods of indexing may be preferred,^{22,23} centile charts and tables were generated with respect to gender and height. Although indexing to BSA is commonly used, it is known that extreme weight can affect results and possibly, clinical decision making.²⁴ Therefore, height or calculation of the ideal BSA as suggested by others²⁴ might be more appropriate for indexing of MRI volumetric measurements.

Method 1 showed significantly higher LV and RV volumes, but lower mass compared to method 2 with greater differences between the methods for higher volumetric values. The latter findings are also reported by Riffel et al.³ and confirm that results from different postprocessing methods are not interchangeable and that differences might become more important in subjects with larger ventricles.

Reference tables and graphs for LVEF and RVEF could not be demonstrated because the model quality from multivariable linear regression analysis was insufficient. Therefore, only mean values are given. However, as EF remains largely constant during growth in children and there are no sex differences,^{5,6} we believe that reference tables and graphs for LVEF and RVEF are not important.

Interobserver and intraobserver variability demonstrated good-to-excellent agreement for most volumetric parameters and both contouring methods, suggesting that both methods can be applied with overall good reproducibility.

As an outlook, comparisons of different software solutions for segmentation of myocardial trabeculations and papillary muscles should be performed to establish multivendor reference values for biventricular volumes when papillary muscles are excluded.

Limitations

The number of included subjects is relatively small with less female subjects compared to male participants. In addition, the number of younger children below the age of 10 was relatively small and this altogether might impact on the study results. As it is difficult to recruit normal volunteers, we included children and adolescents who were referred for MRI due to clinical reasons who were, however, finally found to have normal cardiovascular examinations and findings.

Measurements were performed on short-axis cine stacks and similar reference values for axial cine stacks are not provided. However, volumetry from short-axis cine stacks is a common practice in the cardiac centers.

Segmentation of myocardial trabeculations and papillary muscles can be influenced by different segmentation tools from different software vendors. Reference values derived

from method 2 should therefore only be used when analysis is performed with the same software used for this study or software applications using an identical segmentation function.

Finally, reference values for ejection fraction could not be presented because the model quality of the multivariable regression analysis was insufficient.

Conclusions

Pediatric MRI reference values for biventricular volumes and masses for two different MRI contouring methods were developed. Significant differences for volumetric results between the delineation methods were found and this confirms that it is important to use normal values from similar postprocessing methods and to include the method applied into the MRI report.

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References

1. Leiner T, Bogaert J, Friedrich MG, et al. SCMR position paper (2020) on clinical indications for cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2020;22:76.
2. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on standardized post-processing. *J Cardiovasc Magn Reson* 2020;22:19.
3. Riffel JH, Schmucker K, Andre F, et al. Cardiovascular magnetic resonance of cardiac morphology and function: Impact of different strategies of contour drawing and indexing. *Clin Res Cardiol* 2019;108:411-429.
4. Pfaffenberger S, Bartko P, Graf A, et al. Size matters! Impact of age, sex, height, and weight on the normal heart size. *Circ Cardiovasc Imaging* 2013;6:1073-1079.
5. Sarikouch S, Peters B, Gutberlet M, et al. Sex-specific pediatric percentiles for ventricular size and mass as reference values for cardiac MRI: Assessment by steady-state free-precession and phase-contrast MRI flow. *Circ Cardiovasc Imaging* 2010;3:65-76.
6. Buechel EV, Kaiser T, Jackson C, Schmitz A, Kellenberger CJ. Normal right- and left ventricular volumes and myocardial mass in children measured by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2009;11:19.
7. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. *J Magn Reson Imaging* 2009;29:552-559.
8. Krupickova S, Risch J, Gati S, et al. Cardiovascular magnetic resonance normal values in children for biventricular wall thickness and mass. *J Cardiovasc Magn Reson* 2021;23:1.
9. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019.
10. Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. *Stat Med* 1992;11:1305-1319.
11. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *Appl Stat* 2005;54:507-554.

12. Gamer M, Lemon J, Fellows I, Singh P. irr: Various Coefficients of Interrater Reliability and Agreement. R package version 0.84.1 2019. Available from: <https://CRAN.R-project.org/package=irr>
13. Shrout PE, Fleiss JL. Intraclass correlations: Uses in assessing rater reliability. *Psychol Bull* 1979;86:420-428.
14. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310.
15. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016;15:155-163.
16. van der Ven JPG, Sadighy Z, Valsangiacomo Buechel ER, et al. Multi-centre reference values for cardiac magnetic resonance imaging derived ventricular size and function for children aged 0-18 years. *Eur Heart J Cardiovasc Imaging* 2020;21:102-113.
17. Urzua Fresno CM, Folador L, Shalmon T, et al. Prognostic value of cardiovascular magnetic resonance left ventricular volumetry and geometry in patients receiving an implantable cardioverter defibrillator. *J Cardiovasc Magn Reson* 2021;23:72.
18. Chuang ML, Gona P, Hautvast GL, et al. Correlation of trabeculae and papillary muscles with clinical and cardiac characteristics and impact on CMR measures of LV anatomy and function. *JACC Cardiovasc Imaging* 2012;5:1115-1123.
19. Weinsaft JW, Cham MD, Janik M, et al. Left ventricular papillary muscles and trabeculae are significant determinants of cardiac MRI volumetric measurements: Effects on clinical standards in patients with advanced systolic dysfunction. *Int J Cardiol* 2008;126:359-365.
20. Karimi-Bidhendi S, Arafati A, Cheng AL, Wu Y, Kheradvar A, Jafarkhani H. Fully-automated deep-learning segmentation of pediatric cardiovascular magnetic resonance of patients with complex congenital heart diseases. *J Cardiovasc Magn Reson* 2020;22:80.
21. Tran CT, Halicek M, Dormer JD, Tandon A, Hussain T, Fei B. Fully automated segmentation of the right ventricle in patients with repaired tetralogy of Fallot using U-net. *Proc SPIE Int Soc Opt Eng* 2020;11317:113171M.
22. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: Assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. *J Am Coll Cardiol* 1995;25:1056-1162.
23. Maskatia SA, Spinner JA, Nutting AC, Slesnick TC, Krishnamurthy R, Morris SA. Impact of obesity on ventricular size and function in children, adolescents and adults with tetralogy of Fallot after initial repair. *Am J Cardiol* 2013;112:594-598.
24. Simpson SA, Field SL, Xu M, Saville BR, Parra DA, Soslow JH. Effect of weight extremes on ventricular volumes and myocardial strain in repaired tetralogy of Fallot as measured by CMR. *Pediatr Cardiol* 2018;39:575-584.