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

Samir Sarikouch, MD; Brigitte Peters, MD; Matthias Gutberlet, PhD; Birte Leismann; Andrea Kelter-Kloeppe, RN; Hermann Koerperich, PhD; Titus Kuehne, PhD; Philipp Beerbaum, MD

Background—Cardiac MRI is important in the treatment of children with congenital heart disease, but sufficient normative data are lacking. For ventricular volumes and mass, we sought to deliver reference centiles and to investigate sex effects.

Methods and Results—We included 114 healthy children and adolescents, uniformly distributed spanning an age range of 4 to 20 years, as required by the Lambda-Mu-Sigma method to achieve a percentile distribution, thus avoiding arbitrary age categories. Subjects underwent axial volumetry (1.5-T scanner) using standardized 2D steady-state free-precession and flow protocols. Percentiles were computed for age 8 to 20 years (99 subjects) because breath-holds were more consistent in this group. When indexed for body surface area or height, the centile curves of ventricular volumetric parameters showed allometric increase until adolescence, when a plateau was reached, with values comparable to published adult reference data. In contrast, ventricular mass centiles increased without plateau. There was a significant sex difference, with centiles reflecting larger values in boys than in girls (P<0.05) when ventricular volumes were indexed to body surface area or height but not when indexed to weight (exception: mass). There was excellent agreement of axial and short-axis volumetry and of volumetric and flow-derived stroke volumes.

Conclusions—Percentiles for ventricular volumes and mass in healthy children have been established to serve as reference values in pediatric heart disease. Significant sex differences were noted when indexing volumes to body surface area or height. Unisex centiles related to weight may be considered for chamber volumes albeit not for mass. (Circ Cardiovasc Imaging. 2010;3:65-76.)

Key Words: heart disease ■ pediatrics ■ MRI ■ volumetry

The diagnosis of an enlarged or hypertrophied heart has important implications for the treatment of children with congenital or acquired heart disease. To this end, cardiac MRI has evolved as an important noninvasive diagnostic tool, particularly in the noninvasive quantitative assessment of the right ventricle.1 Cardiac MRI is generally considered the reference standard for the assessment of ventricular dimensions, function, and mass in terms of accuracy and reproducibility,2 and this is reflected by class I–II recommendations for the clinical use of cardiac MRI by recent consensus panels.3

Although these recommendations explicitly include determination of ventricular size and cardiac function, data are sparse regarding these parameters in healthy children.4,5 Moreover, since these smaller series were published, spoiled gradient-echo cine (cine-GRE) sequences have been replaced by steady-state free-precessing (cine-SSFP) protocols, which are faster and provide improved image contrast based on a higher signal-to-noise ratio and reduced sensitivity to flow turbulence. As a result of the inherently improved myocardial–to–blood pool contrast, cardiac volumetric data obtained by SSFP sequences have been shown to differ significantly from those derived by cine-GRE sequences in that they provide larger end-diastolic volumes and smaller values for ventricular mass when directly compared with previous spoiled gradient-echo techniques.6,7 More recent work has used cine-SSFP protocols to yield pediatric cardiac reference...
values in 60 children, divided into age groups of 8 to 11 years, 12 to 14 years, and 15 to 17 years. However, a general problem in the interpretation of such data is the fact that cardiac growth is known to be allometric, that is, the relation between the size of the heart and the body changes from infancy to adulthood. Moreover, such allometric growth is likely to be different between the sexes. This renders any age group definition somewhat arbitrary because sex differences in the speed of maturation and cardiac growth are not accounted for, thus limiting the scientific and clinical value of age group–based reference data.

What is required is a definition based on the calculation of percentiles because this approach avoids the disadvantages of subjective age group definitions. Therefore, within the German Competence Network for Congenital Heart Disease, we sought to create a larger database for healthy children using standardized contemporary cine-SSFP and flow imaging techniques. To compute reference centile curves, we used the LMS method described in detail by Cole (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation).

This method uses a penalized likelihood technique to derive age-dependent percentiles of target variables and thereby uses the sample elements more efficiently than the use of a classification into more or less artificial age groups.

Age and sex distribution of the study group was calculated before start of the study, intentionally including even younger children (4 to 7 years) for mathematical calculation of the initial slope of the percentile curves. The final percentile curves, however, were restricted to cover the age span of 8 to 20 years because only in this age group, consistent breath-hold performance can be expected.

The goal was to provide a statistical calculation of age- and sex-dependent percentiles for ventricular volumes and mass to serve as reference values for cardiac MRI.

**Methods**

**Study Population and Design**

During a period of 26 months, we prospectively enrolled 114 children and adolescents (59 female and 55 male; mean age, 12.4±3.8 years; median age, 11.9 years; age range, 4 and 20 years), 12.4 children and adolescents (59 female and 55 male; mean age, 12.4±3.8 years; median age, 11.9 years; age range, 4 and 20 years), in 84 children (4 to 7 years) end-expiratory breath-holds were used, with breath-holds between 5 and 10 seconds for the VCG-gated SSFP. The procedure followed the standardized protocol of the MRI project of the German Competence Network for Congenital Heart Defects published on the network web site (www.kompetenznetz-ahf.de/en/research/mri). In a subgroup of 29 children (mean age, 12.58±3.81 years), additional short-axis acquisition was performed using the same sequence, covering the ventricles with 12 to 14 slices, and analyzed in comparison to axial volumetry.

Additionally, quantitative phase-contrast flow measurements were conducted in all subjects to ensure consistency by cross-checking to volumetry. Orthogonal angulated flow measurements in the pulmonary artery (in the middle position between the valve and the valvulostomy and the ascending aorta (1 to 2 cm distal of the aortic bulbus) were performed using a standard, retrospectively gated gradient-echo sequence with 30 to 40 heart phases corresponding to a temporal resolution ranging between 17 to 25 ms; 1-k-space line per phase; repetition time/echo time/flip angle, 15 ms/6.5 ms/30°; velocity-encoded value, 150 cm/s; number of signal averages, 2; slice thickness, 6 mm; acquisition matrix, 144×128; acquired spatial resolution, 2.1×2.1×6 mm; and through-plane, free-breathing phase-contrast-MRI protocol, as evaluated in children with left-to-right shunt.

**MRI Analysis**

Semiautomatic threshold-based volumetric analysis using validated customized software and analysis of stroke volumes in the main pulmonary artery and the ascending aorta was performed by 1 experienced observer. For interobserver variances, 10% of the data were analyzed by a second experienced observer within the cardiac MRI core laboratory of the Competence Network for Congenital Heart Defects. Both observers undergo regular joint consensus training on image reading for improved interobserver and intraobserver performance. Furthermore, intraobserver variance was determined in 24 children, and interexamination variance was determined in 8 children (2 separate examinations). The subgroups for interobserver, intraobserver, and interexamination variability were chosen independently from each other.

After defining the end-systolic and end-diastolic heart phases, an auto-level function was applied for automatic endocardial contour detection (threshold=mean value of the signal intensity defined in a region-of-interest in the ventricular lumen and myocardial septum). If necessary, a manual adaptation of the window/level values was allowed. Manual correction of crucial areas could be performed. A phase-to-phase cine modus was used to avoid partial volume effects at valve planes and the inferior heart. For axial volumetry, particular attention was paid to the semilunar and for short-axis volumetry to the aortocvalve and for right ventricle valve level. Papillary muscles and trabecular structures were excluded from the ventricular lumen but added to the myocardial muscle mass. The epicardial borders were drawn manually (Figure 1).

We determined volumes of the left and right ventricles at end-systole and end-diastole, thus measuring end-diastolic and end-systolic volumes. Stroke volume was calculated as the difference between the diastolic and systolic volumes. Ejection fraction, expressed as a percentage, was calculated as the ratio of stroke volume to end-di-

---

**MRI Technique**

All examinations were performed on a 1.5-T whole-body MR scanner (Philips Medical Systems, Intera, R11; maximum gradient performance, 30 mT/m; slew rate, 150 T·m⁻¹·s⁻¹). A 5-element cardiac phased-array coil was used for signal acquisition, and the body coil was used for signal transmission. A VCG-gated balanced gradient-echo sequence (SSFP) was applied to cover the whole heart. Therefore, 25 to 35 axial slices with 1 to 2 slices per breath-hold, no gap, with repetition time/echo time/flip angle, 2.8 ms/1.4 ms/60°; acquisition matrix, 160×160; number of averages, 1; SENSE reduction factor, 2 (phase-encode); and 5 to 13 k-space lines per phase corresponding to a gating width of 14 to 36 ms with an acquisition resolution of 2.0 to 2.5×1.5 to 1.8 mm were collected. Depending on the patient’s heart rate and physical constitution 25 to 35 phases (no heart phase interpolation) were acquired. A 5-mm slice thickness was used in children weighing <30 kg, whereas a 6-mm slice thickness was used for children weighing >30 kg. For younger children, end-inspiratory breath-holds and for older children (>7 years) end-expiratory breath-holds were used, with breath-holds between 5 and 10 seconds for the VCG-gated SSFP. The procedure followed the standardized protocol of the MRI project of the German Competence Network for Congenital Heart Defects published on the network web site (www.kompetenznetz-ahf.de/en/research/mri).
astolic volumes. The volumes were indexed by dividing them by BSA, height, or body weight. Muscular mass was calculated separately for the free wall of the right ventricle, the interventricular septum, and the left ventricle including the septum, by determining the volume of the particular structure in end-diastole and then multiplying by a factor of 1.05 g/mL.

Flow data analysis was performed offline on a computer workstation using a customized computer algorithm for semiautomatic vessel border detection as described in detail and validated by Beerbaum et al.16 to optimize measurement reproducibility and accelerate image analysis.

Statistical Analysis

Descriptive statistical analysis was performed for all relevant data. Pearson correlation coefficients and Bland-Altman analysis were calculated to compare volumetry and quantitative flow data as well as axial versus short-axis volumetry. The coefficient of variation was calculated to study the percentage of variability of the measurements. Significance of the observed differences between groups was tested with a 2-sided Student t test when appropriate. A probability value of <0.05 was considered statistically significant.

Reference centile curves were computed with the LMS method by Cole, using the software LMS, version 1.27, from the Institute of Child Health (London, United Kingdom).14,15 This method describes the distribution of the target parameter at a given age by normal approximation after a Box-Cox transformation. The (age-dependent) estimates L, M, and S for the 3 parameters lambda (Box-Cox power), mu, and sigma (mean and coefficient of variation after transformation) provide the name for this method. The estimation of these parameters as function of the age uses a penalized maximum likelihood approach, in which the penalty term is composed from integrals over the squared second derivatives expressing the smoothness of the curves. Cubic splines are used to assess the function in between the considered distinct values of the age (full years). This process is controlled by 1 smoothing parameter for each of the L, M, and S curves. The authors give recommendations for the choice of the smoothing parameters dependent on the range of age, on the range of the observed parameter, and on the sample size. Based on the L, M, and S curves, the centile curves can be derived. Age and sex distribution of the study group was calculated before start of the study, intentionally including children as young as possible. Because of a possibly reduced reproducibility for very young children, the results are presented only in the age span from 8 to 20 years (represented by 99 children), using the children <8 years of age for an improved estimation of the initial slope (Figure 2).

Results

Subject Characteristics

All 114 children were able to fully cooperate during the examinations. No sedation or anesthesia was used. Examinations lasted between 25 and 40 minutes, and MRI quality was deemed sufficient for study purposes in all cases. Body weight, height, and BMI (body weight in kilograms; height in centimeters) are summarized for the total population and for age subgroups (8 to 15 years, 16 to 20 years) in Table 1.

Percentile Analysis Versus Age

Group-Based Analysis

Using the LMS method, reference centile curves were computed for ventricular volumes and mass separately for boys and girls from 8 to 20 years because of the observed

Figure 1. Volumetric analysis. A, Axial images for volumetric analysis of end-diastolic volumes of the left and right ventricles. B, Short-axis images for volumetric analysis of end-diastolic volumes of the left and right ventricles. C, Axial volumetry of the free walls of the right and left ventricles and the interventricular septum. D, Short-axis volumetry of the free walls of the right and left ventricles and the interventricular septum.

Sarikouch et al  Sex-Specific Pediatric CMR Percentiles 67

Downloaded from http://circimaging.ahajournals.org/ by guest on October 19, 2017
significant differences in the population when indexed for BSA and height (Table 2).

Interestingly, when indexing for weight, such sex difference was only noted for ventricular mass parameters but not for ventricular volumes (see below). We present percentile curves for BSA and weight in this report. Percentile curves related to height were not included because the noted sex differences and curve forms were similar to the BSA-related percentiles. When analyzing pediatric patients (age 8 to 15 years) versus adolescents/young adults (age 16 to 20 years), sex differences were noted in both age groups (see Tables 2 and 3) but only became significant in the older group.

Effect of Sex on Relation Between Ventricular Volumes and Body Size

Ventricular volumes indexed to the BSA were, in the whole group, ~10% to 15% higher in boys than in girls; this sex difference was statistically significant for most volumetric parameters—only the left ventricular end-systolic volume was not statistically significant. Ejection fractions of the right and left ventricles showed no relevant sex difference. This sex difference for ventricular volumes indexed to the body surface was notable but smaller (4% to 7%) when only the age group between 8 to 15 years was considered, and the sex differences were not statistically significant. For the young adult group (age, 16 to 20 years), the sex significance was substantive and significant for most parameters; only the right ventricular end-systolic volume was not statistically significant (Table 2).

The sex difference in general for the ventricles was also statistically significant when volumes were indexed for height. For this form of indexing ventricular volumes of boys were ~15% to 20% higher than in girls (Table 3). Again, this sex difference was notable but smaller (0% to 6%) when only the age group between 8 to 15 years was considered, and the sex differences were not statistically significant. For the young adult group, the sex difference was substantial and highly significant (Table 3).

In contrast, when indexing volumes to body weight, the sex differences were much smaller, 1% to 5%, and the differences were not significant, neither for the total population nor for the 2 age groups (Table 3).

Effect of Sex on Relation Between Ventricular Mass and Body Size

Muscle mass of the left ventricle, the right ventricle, and the interventricular septum were in general significantly higher for boys than girls when indexed for BSA or height. For the age group from 8 to 15 years, a significant sex difference was only observed for the interventricle septum indexed to

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Girls (n=59)</td>
</tr>
<tr>
<td>Boys (n=55)</td>
</tr>
<tr>
<td>8 to 15 y</td>
</tr>
<tr>
<td>Girls (n=35)</td>
</tr>
<tr>
<td>Boys (n=35)</td>
</tr>
<tr>
<td>16 to 20 y</td>
</tr>
<tr>
<td>Girls (n=13)</td>
</tr>
<tr>
<td>Boys (n=16)</td>
</tr>
</tbody>
</table>
Table 3. Effect of Sex and Age Group on Ventricular Volumes Indexed for BSA

<table>
<thead>
<tr>
<th></th>
<th>RV-EDV, mL/m²</th>
<th>RV-ESV, mL/m²</th>
<th>LV-EDV, mL/m²</th>
<th>LV-ESV, mL/m²</th>
<th>Cardiac Index, L/min/m²*</th>
<th>RV-EF, %</th>
<th>LV-EF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls (n=59)</td>
<td>7.69±1.27</td>
<td>28.6±5.4</td>
<td>48.2±6.8</td>
<td>77.9±10.8</td>
<td>28.5±6.2</td>
<td>49.3±8.1</td>
<td>3.98±0.7</td>
</tr>
<tr>
<td>Boys (n=55)</td>
<td>84.5±12.7</td>
<td>32.5±6.4</td>
<td>52.0±8.4</td>
<td>85.1±13.8</td>
<td>30.5±7.6</td>
<td>54.6±8.2</td>
<td>4.30±0.85</td>
</tr>
<tr>
<td>Difference, %</td>
<td>10</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Significance, P</td>
<td>0.001</td>
<td>0.001</td>
<td>0.01</td>
<td>0.002</td>
<td>0.132</td>
<td>0.001</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>8 to 15 y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls (n=35)</td>
<td>78.3±9.7</td>
<td>29.2±4.6</td>
<td>49.1±6.8</td>
<td>78.7±10.7</td>
<td>28.9±6.1</td>
<td>49.7±8.3</td>
<td>3.94±0.62</td>
</tr>
<tr>
<td>Boys (n=35)</td>
<td>82.9±12.6</td>
<td>31.3±6.1</td>
<td>51.6±8.4</td>
<td>81.9±12.9</td>
<td>28.2±6.7</td>
<td>53.7±8.5</td>
<td>4.42±0.85</td>
</tr>
<tr>
<td>Difference, %</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>(-12)</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Significance, P</td>
<td>0.090</td>
<td>0.117</td>
<td>0.165</td>
<td>0.254</td>
<td>0.613</td>
<td>0.048</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>16 to 20 y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls (n=35)</td>
<td>79.7±10.3</td>
<td>30.4±6.9</td>
<td>49.3±6.3</td>
<td>80.7±9.5</td>
<td>29.0±7.5</td>
<td>51.7±6.8</td>
<td>3.85±0.86</td>
</tr>
<tr>
<td>Boys (n=16)</td>
<td>90.2±10.9</td>
<td>36.1±6.3</td>
<td>54.1±7.3</td>
<td>93.5±10.9</td>
<td>35.9±7.1</td>
<td>57.6±5.9</td>
<td>4.02±0.79</td>
</tr>
<tr>
<td>Difference, %</td>
<td>13</td>
<td>19</td>
<td>10</td>
<td>16</td>
<td>24</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Significance, P</td>
<td>0.014</td>
<td>0.029</td>
<td>0.075</td>
<td>0.003</td>
<td>0.018</td>
<td>0.019</td>
<td>0.571</td>
</tr>
</tbody>
</table>

*Cardiac index was determined by ventricular stroke volume multiplied by mean heart rate.

BSA; masses indexed for height showed no significant sex difference. In contrast, for the young adult group, the sex difference was highly significant when muscle masses were indexed for BSA or height (Table 4).

When ventricular masses were indexed for body weight, the general sex difference appeared smaller but still significant for the interventricular septum and the left ventricle, whereas there was no significant difference between boys and girls for the right ventricle. For the age group 8 to 15 years, only the interventricular septum showed a significant sex difference, whereas the young adult group showed significant differences for the interventricular septum and the left ventricle (Table 4).

Effect of Age on Ventricular Volumes and Mass

When indexing to BSA and height, there was a steady rise with increasing age of left and right ventricular end-diastolic volumes in girls from 8 to 14 years, when the volumes reached a plateau. In boys, a plateau was reached later, at ~17 years (Figure 3). End-systolic volumes demonstrated a similar, almost parallel increase (Figure 3). Stroke volumes of the left and right ventricles, as derived parameters, displayed the same slope from childhood to adolescence.

Masses of the right ventricle, the interventricular septum, and the left ventricle indexed to the BSA and height rose continuously with age and showed no clear plateau, with a steeper slope in boys (Figure 4).

As indexing ventricular volumes to body weight eliminated largely any sex difference (see above), the resulting unisex percentile curves for right and left ventricular end-diastolic and end-systolic volumes are shown in Figure 5. End-diastolic and end-systolic volumes of both ventricles indexed to body weight exhibited a slight decrease from childhood to adolescence where a plateau at ~14 years was recognized (Figure 5).

Volumetric Versus Flow-Derived Stroke Volumes

There was a highly significant correlation between left ventricular stroke volume derived from volumetry and stroke volume in the ascending aorta established by flow measure-
tions using phase-contrast MRI ($r=0.95$, $P<0.001$). The correlation between right ventricular stroke volume and main pulmonary flow was accordingly significant ($r=0.94$, $P<0.001$). The coefficient of variation was 6.47 for the left ventricle and the right ventricular muscle mass demonstrated the greatest variation (CV-RV-MM, 9.78). The limits of agreement (Bland-Altman analysis) are shown in Table 5.

Axial Volumetry Versus Short-Axis Volumetry
Comparison between axial and short-axis volumetry revealed high and significant correlations with low coefficients of variation (CV) for end-diastolic volumes of the ventricles (CV-RV, 2.23; CV-LV, 2.46). End-systolic volumes displayed more variation than end-diastolic volumes, with a slightly higher variation for the right ventricle (CV-RV, 6.02; CV-LV, 4.68). Muscle mass of the left ventricle and the interventricular septum revealed the same variation as end-systolic ventricular volumes (CV-LV-MM, 5.93; CV-IVS-MM, 6.02). Right ventricular muscle mass demonstrated the highest variation (CV-RV-MM, 9.78). The limits of agreement (Bland-Altman analysis) are shown in Table 6.

Intraobserver, Interobserver, and Interexamination Variances
There was good intraobserver agreement, with the highest variation in the end-systolic volumes of the ventricles and masses of the ventricles. Interobserver comparison showed more variation, with the highest variation also in end-systolic volumes and masses of the ventricles. Interexamination variances demonstrated the greatest variation in the left ventricular end-systolic volume, right ventricular stroke volume, and mass of the right ventricle. Mean differences, limits of agreement, coefficients of variation (each in percent), and the correlation coefficients are shown in Table 7.

Discussion
The relation between the size of the heart and the body is known to be allometric, which means that this relation changes from infancy to adulthood. This makes the generation of normative data challenging. However, the ability to accurately measure volumetric and mass parameters of right and left ventricular function, adequately scaled to body size, is of critical importance both for clinical care and for cardiovascular health research.

Sex Differences in Cardiac Measures in the Developing Child
The impact of sex on such normative data has always been a matter of concern in pediatric cardiology because sex influence is (1) likely to be different before, during, and after puberty, and (2) the timing of the adolescent growth spurt in individuals is different between the sexes. Although data are relatively limited, a number of previous studies suggest the existence of sex differences of cardiac measures even before puberty. In a pathoanatomic series ($n=200$, 0 to 19 years), variables such as heart weight, ventricular wall thickness, and cardiac valve circumferences were found to be usually larger in boys. Moreover, for echocardiographic parameters of heart size, a small sex difference was identified in 7- to 11-year-old children in the Bogalusa Heart Study. Zilberman et al found in a large echocardiographic investigation ($n=748$, 434 boys) using standardized 2D measures that boys had statistically larger valve diameters at all ages. Additional evidence of prepubertal sex differences was identified for diastolic left ventricular function parameters (Doppler echocardiography). These subtle prepubertal sex differences only became statistically significant in larger series. In contrast, a large echocardiographic study in more than 2000 healthy infants and children in central Europe revealed no sex differences, but the authors reasoned that this was probably due to interobserver bias.

Using the LMS Method for Reference Centile Computation
It is mainly for this reason that we sought to deliver sex-specific percentiles of cardiac MR volumetry in the first place, rather than presenting comparisons by age categories. Hence, we generated reference centile curves for children and adolescents from 8 to 20 years for ventricular volumes and mass using the LMS method described by Cole.
Figure 3. Reference percentile curves for ventricular volumes indexed for BSA for boys and girls. RV-EDV<sub>i</sub> [mL/m<sup>2</sup>] indicates right ventricular end-diastolic volume in mL per m<sup>2</sup> BSA; RV-ESV<sub>i</sub> [mL/m<sup>2</sup>], right ventricular end-systolic volume in mL per m<sup>2</sup> BSA; LV-EDV<sub>i</sub> [mL/m<sup>2</sup>], left ventricular end-diastolic volume in mL per m<sup>2</sup> BSA; LV-ESV<sub>i</sub> [mL/m<sup>2</sup>], left ventricular end-systolic volume in mL per m<sup>2</sup> BSA; P 50, percentile in which 50% of boys or girls of the respective age have smaller or equal ventricular volumes; P 97, percentile in which 97% of boys or girls of the respective age have smaller or equal ventricular volumes.
statistical technique has a number of advantages that render it particularly useful in the pediatric age group. It avoids all more or less artificial age categories, and, unlike regression analyses, LMS does not depend on linear relationships between cardiovascular parameters and body size, and it is well known that these do not exist. An additional parameter also allows the fitting of non-Gaussian distributions. Moreover, LMS-derived centiles can display different ranges of distribution at different time points, whereas regression analyses assume constant ranges of distribution. This makes the LMS method generally suited for parameters of cardiac function with known or suspected sex influence. In children, this is particularly valuable as the generation of normative data are further complicated by the difference in onset and speed of pubertal growth spurt between girls and boys.

**Figure 4.** Reference percentile curves for ventricular masses indexed for BSA for boys and girls. RV-MMi [g/m²] indicates right ventricular mass in g per m² BSA, excluding the septum; IVSi [g/m²], interventricular septum mass in g per m² BSA; LV-tot MMi [g/m²], total left ventricular mass in g per m² BSA, including the septum; P 50, percentile in which 50% of boys or girls of the respective age have smaller or equal ventricular mass; P 97, percentile in which 97% of boys or girls of the respective age have smaller or equal ventricular mass.

**Study Findings: Sex and Age Effects on Ventricular Volumes and Mass**

For the total population, we observed statistically highly significant sex differences when indexing for BSA and for height for ventricular volumes and mass parameters. In keeping with the literature, not surprisingly, these differences were less clear for the younger age group than for the adolescents (Table 2).
Interestingly, when indexing to body weight, there was no significant sex influence for volume parameters both before and after puberty, whereas there still was clear sex effect on mass parameters, particularly after puberty (Table 4). Hence, at least for cardiac volumes such as end-diastolic and end-systolic volume and derived parameters, weight-related unisex reference centiles may be considered for daily practice as shown in Figure 5, knowing, however, that BSA indexing is more popular in pediatric cardiology. For mass parameters, relation to weight, however, does not provide this advantage, and sex-specific centiles are needed here as well (Figure 4).

More generally, ventricular volumes indexed for BSA and height demonstrated allometric growth with steady gentle enlargement from childhood to adolescence, in which end-diastolic and end-systolic volumes reached plateaus comparable to adult reference values.24 Masses of the ventricles and the interventricular septum, also indexed for BSA, exhibited a steady increase without a clear plateau. These results correspond to a recently published cross-sectional study of sex- and age-specific normal values of the left ventricle from adolescence to late adulthood, in which the peak of the end-diastolic volume was found before 20 years of age, but the peak for the left ventricular muscle mass only after 30 years.25

**Volumetric Parameter Measures: Comparison to the Literature**

We observed small but notable differences to the volumetric MRI data for children as published so far. End-diastolic and end-systolic volumes reached plateaus comparable to adult reference values.24 Masses of the ventricles and the interventricular septum, also indexed for BSA, exhibited a steady increase without a clear plateau. These results correspond to a recently published cross-sectional study of sex- and age-specific normal values of the left ventricle from adolescence to late adulthood, in which the peak of the end-diastolic volume was found before 20 years of age, but the peak for the left ventricular muscle mass only after 30 years.25

**Table 5. Phase-Contrast Flow Versus Volumetric Measurements**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean±SD</th>
<th>R</th>
<th>P</th>
<th>CV, %</th>
<th>Lower (±95% CI)</th>
<th>Upper (±95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-SV PC flow, mL</td>
<td>72.65±25.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV-SV vol, mL</td>
<td>74.23±27.8</td>
<td>0.950</td>
<td>&lt;0.001</td>
<td>6.47</td>
<td>−19.14 (−22.0; −16.26)</td>
<td>15.96 (13.09; 18.83)</td>
</tr>
<tr>
<td>RV-SV PC flow, mL</td>
<td>73.4±25.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV-SV vol, mL</td>
<td>71.7±26.1</td>
<td>0.942</td>
<td>&lt;0.001</td>
<td>6.67</td>
<td>−15.90 (−18.78; −13.01)</td>
<td>19.27 (16.38; 22.16)</td>
</tr>
</tbody>
</table>

CV indicates coefficient of variation; LV-SV, left ventricular stroke volume; PC, phase-contrast flow; vol, volumetric.
end-systolic volumes were slightly higher than described by Lorenz2 and Helbing.6 These differences may be explained by the use of contemporary SSFP sequences with better blood-myocardium differentiation for the older reference data6 and by threshold-based semiautomatic segmentation versus manual segmentation for newer pediatric data. No clinically significant difference for volumetric parameters was recognizable by the use of short-axis volumetry by Robbers-Visser et al.8 Contemporary SSFP sequences and new segmentation tools may account for the relatively lower myocardial masses of the ventricles observed in this study because computer-assisted segmentation is likely to be more precise than manual border tracing of the endocardium, particularly for the right ventricle. There was a very good correlation to recently published echocardiographic data using 2D and 3D approaches.26

### MR Internal Validation and Observer Variance

In line with Jeltsch et al,27 there was a very high correlation between volumetric-derived and flow-derived stroke volumes, which allowed simple internal quality control of volumetric data. Comparison between axial and short-axis volumetry demonstrated no relevant differences, as reported by Jauhiainen et al28 and in contrast to Alfakih et al, who found short-axis volumes of the right ventricle to be larger in adult volunteers.29 Axial acquisition had the advantage of allowing for additional phasic volumetry of the atria for further studies and has also recently been reported to be more reproducible than short-axis slices for ventricular volumetry in patients with corrected tetralogy of Fallot.30 Intraobserver and interobserver variability demonstrated results comparable to other studies with good agreement for end-diastolic volumes and less agreement for end-systolic volumes and end-diastolic volumes.

### Table 6. Axial Volumetry Versus Short-Axis Volumetry

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>R</th>
<th>P</th>
<th>CV, %</th>
<th>Lower (&lt;95% CI)</th>
<th>Upper (&gt;95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV_EDV, axial, mL/m²</td>
<td>77.11 ± 8.89</td>
<td>0.920</td>
<td>&lt;0.001</td>
<td>2.23</td>
<td>-5.8 (-8.50; -3.18)</td>
<td>10.31 (7.64; 12.96)</td>
</tr>
<tr>
<td>RV_EDV, SA, mL/m²</td>
<td>74.88 ± 10.22</td>
<td>0.924</td>
<td>&lt;0.001</td>
<td>2.46</td>
<td>-5.31 (-7.56; -2.07)</td>
<td>8.30 (6.06; 10.55)</td>
</tr>
<tr>
<td>LV_EDV, axial, mL/m²</td>
<td>76.01 ± 8.81</td>
<td>0.867</td>
<td>&lt;0.001</td>
<td>6.02</td>
<td>-4.44 (-6.46; -2.41)</td>
<td>7.84 (5.81; 9.87)</td>
</tr>
</tbody>
</table>

### Table 7. Intraobserver, Interobserver, and IntereXamination Variability

<table>
<thead>
<tr>
<th>Variables</th>
<th>LV-EDV</th>
<th>LV-ESV</th>
<th>LV-SV</th>
<th>RV-EDV</th>
<th>RV-ESV</th>
<th>RV-SV</th>
<th>LV-MM</th>
<th>IVS-MM</th>
<th>RV-MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference</td>
<td>2.6</td>
<td>4.9</td>
<td>1.2</td>
<td>3.1</td>
<td>0.5</td>
<td>4.5</td>
<td>4.6</td>
<td>3.7</td>
<td>2.9</td>
</tr>
<tr>
<td>LOA</td>
<td>-5.9</td>
<td>-6.8</td>
<td>-10.3</td>
<td>-7.6</td>
<td>-16.0</td>
<td>-16.9</td>
<td>-7.5</td>
<td>-10.8</td>
<td>-14.3</td>
</tr>
<tr>
<td>R</td>
<td>0.994</td>
<td>0.994</td>
<td>0.984</td>
<td>0.990</td>
<td>0.979</td>
<td>0.986</td>
<td>0.990</td>
<td>0.991</td>
<td>0.973</td>
</tr>
<tr>
<td>COV</td>
<td>2.6</td>
<td>4.2</td>
<td>2.9</td>
<td>3.5</td>
<td>4.8</td>
<td>4.3</td>
<td>4.6</td>
<td>5.4</td>
<td>6.9</td>
</tr>
<tr>
<td>R</td>
<td>0.994</td>
<td>0.994</td>
<td>0.984</td>
<td>0.990</td>
<td>0.979</td>
<td>0.986</td>
<td>0.990</td>
<td>0.991</td>
<td>0.973</td>
</tr>
<tr>
<td>Interobserver variability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td>3.4</td>
<td>2.5</td>
<td>3.8</td>
<td>8.3</td>
<td>13.1</td>
<td>5.6</td>
<td>-16.2</td>
<td>-6.5</td>
<td>-13.8</td>
</tr>
<tr>
<td>LOA</td>
<td>-8.0</td>
<td>-18.0</td>
<td>-10.1</td>
<td>-6.6</td>
<td>-13.5</td>
<td>-14.6</td>
<td>-57.5</td>
<td>-33.4</td>
<td>-82.2</td>
</tr>
<tr>
<td>R</td>
<td>0.992</td>
<td>0.972</td>
<td>0.985</td>
<td>0.976</td>
<td>0.965</td>
<td>0.957</td>
<td>0.854</td>
<td>0.962</td>
<td>0.658</td>
</tr>
<tr>
<td>COV</td>
<td>3.1</td>
<td>5.4</td>
<td>4.1</td>
<td>6.5</td>
<td>10.8</td>
<td>6.4</td>
<td>14.5</td>
<td>8.4</td>
<td>22.3</td>
</tr>
<tr>
<td>R</td>
<td>0.992</td>
<td>0.972</td>
<td>0.985</td>
<td>0.976</td>
<td>0.965</td>
<td>0.957</td>
<td>0.854</td>
<td>0.962</td>
<td>0.658</td>
</tr>
</tbody>
</table>

Except for the correlation coefficient $R$, all values are given in percentages. LOA indicates limits of agreement; COV, coefficient of variation; $R$, correlation coefficient.
muscle mass with right ventricular variability higher than left ventricular variability.\(^2\)\(^,\)\(^17\) Interexamination agreement was satisfactory, with the highest variability for left ventricular end-systolic volume and right ventricular mass, which correlates to results in adults and supports that MRI can adequately assess ventricular size and function in children.\(^2\)

**Limitations**

The age of the children studied allowed no calculation of percentile curves for infants and toddlers. Reference values for neonates and infants would be of great interest, for example, regarding thresholds for biventricular repair in the setting of ventricular imbalance.

We used accepted modern statistical calculation models to create pediatric reference data for cardiac volumes and mass. Nevertheless, true normative, sex-specific data from birth to adulthood would be preferable, but this would have required including a much larger number of children (\(>1000\)) to ideally also account for ethnic differences. The ideal body size measure to relate volumetric variables to may be neither weight, height, nor BSA. It may well be that—one once a much larger normative database is accumulated—other body size derivatives may prove better suited, and these may also be different for different parameters of cardiac size and function.

**Conclusions**

Age- and sex-specific percentiles for ventricular volumes and mass of healthy children and adolescents from 8 to 20 years have been established by cardiac MRI to serve as reference values in the evaluation of acquired and congenital heart disease. Significant sex differences were noted when indexing volumes to BSA or height. In contrast, indexing ventricular volumes (but not mass) to body weight largely eliminated the sex differences and may therefore be attractive for daily use in pediatric cardiology.

**Acknowledgments**

We thank Anne Gale, ELS, for editorial assistance.

**Sources of Funding**

This study was part of the Magnetic Resonance Imaging Project of the Competence Network for Congenital Heart Defects funded by the German Federal Ministry of Education and Research (FKZ 01G10210).

**Disclosures**

None.

**References**


---

**CLINICAL PERSPECTIVE**

The present study examined a healthy pediatric group large enough to serve as a reference for volumetric cardiac MRI. Age- and sex-specific percentiles for right and left ventricular volumes and mass of healthy children and adolescents from 8 to 20 years of age were established to serve as reference values in the evaluation of acquired and congenital heart disease. Significant sex differences were noted when indexing volumes to body surface area or height. In contrast, indexing ventricular volumes (but not mass) to body weight largely eliminated the sex differences and may therefore be attractive for daily use in pediatric cardiology. An individual patient’s progression of ventricular size in relation to these percentile curves may inform the timing of or the response to medical or surgical treatment. This potentially will facilitate a more accurate diagnosis of ventricular dilation and ventricular hypertrophy by cardiac MRI in this age group, with potential impact on management decisions.
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
Samir Sarikouch, Brigitte Peters, Matthias Gutberlet, Birte Leismann, Andrea Kelter-Kloepping, Hermann Koerperich, Titus Kuehne and Philipp Beerbaum

Circ Cardiovasc Imaging. 2010;3:65-76; originally published online October 9, 2009;
doi: 10.1161/CIRCIMAGING.109.859074
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/3/1/65

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org/subscriptions/