Impact of Gender and Age on Cardiovascular Function Late After Repair of Tetralogy of Fallot
Percentiles Based on Cardiac Magnetic Resonance

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Background—The impact of gender and age on cardiac function by cardiac magnetic resonance (CMR) in repaired tetralogy of Fallot (TOF) is unknown, which limits the value of currently discussed volumetric thresholds and the accuracy of individual follow-up.

Methods and Results—In a nationwide, prospective, 14-center study, 407 consecutive patients with repaired TOF (age, 17.9±8.3 years; range, 8–59 years; 226 male patients) underwent standardized CMR ventricular volumetry and flow quantification (pulmonary artery/ascending aorta). There were no sex differences for age at TOF repair, type of repair, number of prior repair palliations or reinterventions after repair, pulmonary regurgitation fraction, and maximal gradient across the right ventricular outflow tract. Biventricular volumes and mass (indexed to body surface area), available in 380 of 407 patients, respectively, were higher in male patients (P<0.003), but biventricular ejection fraction was higher in female patients (P<0.012). As opposed to reported data of healthy populations, sex-specific reference percentiles computed for an age range of 8 to 40 years (lambda-mu-sigma method) demonstrated (1) an increase of end-diastolic and end-systolic left ventricular volumes, particularly in female patients; (2) an increase of end-systolic right ventricular volumes in both sexes; and (3) a decrease of biventricular ejection fraction in male patients, whereas in female patients, only right ventricular ejection fraction decreased.

Conclusions—Significant gender differences of biventricular volumes, function, and mass by CMR exist late after repair of TOF, suggesting that age and gender cannot be ignored when discussing thresholds. Gender-specific percentiles may present a more relevant framework of reference for an individual patient at a given age and suggest a gradual decline of biventricular systolic function over time.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00266188.

(Circ Cardiovasc Imaging. 2011;4:703-711.)

Key Words: tetralogy of Fallot ■ magnetic resonance imaging ■ ventricular end-diastolic volume ■ ventricular end-systolic volume ■ reference values

Cardiac magnetic resonance (CMR) has evolved as a fundamental cornerstone for postoperative management of tetralogy of Fallot (TOF). Its ability to reliably quantify right ventricular (RV) function and pulmonary valve incompetence in combination with noninvasive angiography of thoracic arteries has influenced therapeutic algorithms. Timing of pulmonary valve replacement in the setting of common severe pulmonary regurgitation currently is usually based on “unisex” RV volume thresholds in combination with clinical signs and symptoms, supplemented by results of exercise testing.

Clinical Perspective on p 711

It has been shown that cardiovascular function by CMR is influenced by gender, age, and normalization to body size parameters in healthy subjects and in acquired heart disease, but such data are lacking in congenital heart disease.
disease, such as TOF after repair. This is a relevant drawback because remodeling of the cardiovascular structures secondary to residual lesions, such as chronic pulmonary incompetence, often is present in these patients, and this latter effect may be misinterpreted if the effects of gender and age on parameters of cardiac function by CMR are ignored. However, as yet, only unisex values are being used in clinical practice, and these are also not normalized for age.

Therefore, we sought to investigate the potential age and gender impact on parameters of cardiac function by CMR and to provide appropriate reference percentiles for repaired TOF in this study. We analyzed CMR data from the image database of the central MRI core laboratory to compute reference data for a recent large cohort of children and mostly adolescents and young adults with repaired TOF recruited from a multicenter study of the German Competence Network for Congenital Heart Defects. We applied the lambda-mu-sigma (LMS)-method by Cole (lambda for the skewness, mu for the median, and sigma for the generalized coefficient of variation) to account for potential data skewness caused by the wide range of phenotypes, surgical approaches, and residual findings. By penalized likelihood techniques, this approach allows for an efficient use of sample elements to derive age-dependent and gender-specific percentiles of target variables of cardiovascular function.

Methods

General Study Setting

The study was registered, designed, performed, and controlled according to current guidelines of good clinical practice (“Follow up of Post-Repair Tetralogy of Fallot”) and approved by all ethics committees of the participating centers. Written informed consent was obtained from all the patients or their caregivers.

An Internet-based information technology infrastructure was implemented to allow for remote data entry, including image data, by the participating institutions, with special emphasis on issues of data protection. All study data were integrated in a central research database. Complete spatial and organizational separation of identifying personal data and study databases was realized.

Data quality was secured by regular independent external monitoring of the participating centers. Moreover, central core laboratories were established for minimization of observer bias error for the imaging modalities of CMR and echocardiography.

Patient Cohort

Between April 2005 and March 2008, patients aged >8 years with repaired TOF were consecutively recruited in a multicenter setting on an outpatient basis without sedation or anesthesia. We included classical TOF with antegrade flow across the pulmonary valve and toward the pulmonary arteries as well as Fallot-type pulmonary atresia with ventricular septal defect to represent the extreme variant of the spectrum of TOF. Centers were instructed to include patients consecutively and in an unsellected manner to avoid major selection bias. Exclusion criteria comprised additional severe heart defects, such as atrioventricular canal, presence of major aortopulmonary collateral arteries, or absent pulmonary valve syndrome, as well as noncardiac clinically relevant disorders, such as malignant or systemic inflammatory diseases.

Details of surgical repair, including any palliative procedures before repair, were recorded where available. Physical examination results were documented as well as results from standard 12-channel ECG and 24-hour Holter monitoring. Exercise tests were performed according to a standardized, predefined protocol either by treadmill or by bicycle spiroergometry, depending on institutional availability.

Cardiac Magnetic Resonance

The standardized CMR protocol as used within the network has been published recently. Briefly, a balanced steady-state free-precession gradient-echo sequence retrospectively gated to ECG (SSFP cine) was used for biventricular volumetric analysis (axial, n = 273; short-axis orientation, n = 107), and free-breathing phase-contrast cine MRI was used for through-plane flow measurements in the main pulmonary artery and ascending aorta (www.kompetenznetz-ahf.de/en/research/mri).

After de-identification for data protection, all image data were transmitted by Web upload using a secured Internet connection to the MRI core laboratory for quality control and blinded image reading by 2 highly trained observers employed by the MRI core laboratory of the network. Both readers underwent repeated, thorough consensus training as published with coreading of image data on screen using a dedicated teleradiological set-up.

Volumetric analysis for end-diastolic and end-systolic ventricular size, ventricular mass, and flow measurements was performed using dedicated customized software capable of handling data of different vendors.

Echocardiography

Echocardiography consisted of a standard 2D echo protocol, including (color) Doppler echocardiographic assessment of tricuspid regurgitation, pulmonary regurgitation and stenosis, and associated valvular disease, which was available in all participating institutions. All echocardiographic data were centrally reviewed by 3 experienced readers.

Statistical Analysis

Descriptive statistical analysis was performed for all relevant data. Prespecified subgroups were defined by age at correction, influence of prior palliation, type of correction, and gender. Significance of the observed differences between groups was tested with a 2-sided Student t test when appropriate. P < 0.05 was considered statistically significant. Reference centile curves were computed with the LMS method by Cole, using LMS version 1.27 software (Institute of Child Health; London, UK). This method describes the distribution of the target parameter at a given age by normal approximation after a Box-Cox transformation. The name for the LMS method is derived from the (age-dependent) estimates of the 3 variables [lambda (Box-Cox power) and mu and sigma (mean and coefficient of variation after transformation)]. The estimation of these variables as a function of age uses a penalized maximum likelihood approach where 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).

We limited the Fallot-specific percentile computation to the age span of 8 to 40 years because of the age distribution of participating subjects, with small numbers aged >40 years (Figure 1) and used data from patients >40 years only for computation of the percentile ending slopes.

Results

Overall Characteristics of the Study Cohort

A total of 407 patients from 14 centers in Germany were consecutively included between April 2005 and March 2008 as a nationwide representative sample of repaired TOF. Mean age at enrollment was 17.9 ± 6.3 years (median, 16.0 years; range, 8–59 years). Male subjects comprised 55.5% of the sample, and this gender distribution was similar for different age groups; 365 (90%) patients had classical TOF and 42 (10%) had TOF with pulmonary atresia.

Figure 1 shows the age distribution of the study population and a breakdown regarding severity of TOF morphology, palliation, age at repair, and mode of repair, including gender subgroups. Male patients (n = 226) outnumbered female pa-
Patients (n=181) by a ratio of 1.25:1, as is known from epidemiological studies in TOF. There were no significant gender differences regarding age at palliation and repair or with regard to the mode of repair (Table). Mean weight at corrective surgery was 11.7±7.7 kg for male patients and 10.9±5.3 kg for female patients (P=0.304). The Table summarizes the global information on patient metric data for the whole population and for both sexes, respectively, listing data on New York Heart Association functional class, results from 12-lead ECG and 24-hour Holter monitoring, and a summary of quantitative findings from echocardiography, CMR, and metabolic exercise testing.

**Age at Repair**

In 120 of 407 (30%) patients, the heart defect was repaired during the first year of life. Of the 407 patients, corrective operation was during the second year of life in 110 (27%) patients; between 2 and 5 years of life in 102 (25%), between 5 and 12 years of life in 59 (15%), and beyond 12 years of life in 13 (3%). Age at study entry of each group was significantly different (17.1±7.9 years; 19.7±8.7 years; 23.0±9.8 years). Mean age at repair was 2.98±4.04 for male patients and 3.18±3.70 years for female patients (P=0.867).

**Primary Repair Versus Previous Palliation**

Of the 407 patients, 309 (76%) had a primary repair, 80 (20%) had received 1 palliative surgical procedure (shunt) before anatomic repair, and 18 (4%) had 2 palliative procedures. As expected, the age at study entrance of each of these groups was significantly different (primary repair, 17.1±7.9 years; 1 palliative procedure before repair, 19.7±8.7 years; 2 palliative procedures before repair, 23.0±9.8 years).

**Mode of Repair**

Details of intracardiac repair were available in 360 of 407 (89%) patients (male, 203; female, 157; P not significant). Of 360 patients, 198 (55%) were repaired without a transannular patch (TAP) (female, 89; male, 109; P not significant), whereas 82 (22.8%) were repaired by use of a TAP (female, 37; male, 45; P not significant), and another 80 (22.2%) received pulmonary augmentation procedures (female, 31; male, 49; P not significant) in addition to a TAP. Interestingly, patients repaired without TAP were significantly older at study entrance than those with TAP repair (19.2±8.8 versus 15.1±4.6 years, P<0.001). Mean age at repair also was different for the 3 groups (without TAP, 3.7±4.5 years; with TAP, 2.3±2.6 years; with TAP and pulmonary artery plasty, 2.3±3.4 years). Reinterventions after repair but before this study also were recorded. There were no significant
Table. Fallot Study Patient Characteristics by Gender

<table>
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<th></th>
<th>Total</th>
<th>Male Patients</th>
<th>Female Patients</th>
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<td></td>
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<td>Mean±SD</td>
<td>n</td>
<td>Mean±SD</td>
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<td>203</td>
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<td>Without TAP</td>
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<td>109</td>
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<td>63±11</td>
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<td>226</td>
<td>82±10</td>
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<td>22.1</td>
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<td>Sinus rhythm, %</td>
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<td>99.8</td>
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<td>99.1</td>
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<td>Maximum QRS duration, ms</td>
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<td>224</td>
<td>149.9±23.7</td>
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<td>Mean heart rate by 24-h Holter, beats/min</td>
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<td>76.9±10.6</td>
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<td>Exercise testing</td>
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<tr>
<td>Peak oxygen uptake, mL/kg per min</td>
<td>400</td>
<td>31.4±9.1</td>
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<td>34.3±8.1</td>
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<td>Peak oxygen uptake at AT, mL/kg per min</td>
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<td>24.1±10.3</td>
<td>216</td>
<td>26.4±11.2</td>
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<td>Peak heart rate, beats/min</td>
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<td>168.3±21.7</td>
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<td>170.2±19.6</td>
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<td>Echocardiography</td>
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<td>Mean RVOT gradient, mm Hg</td>
<td>304</td>
<td>11.8±8.6</td>
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<td>12.5±8.6</td>
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<tr>
<td>Maximal RVOT gradient, mm Hg</td>
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<td>21.2±15.7</td>
<td>166</td>
<td>22.8±16.1</td>
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<td>2.7±1.1</td>
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<td>2.8±1.1</td>
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<tr>
<td>Maximal aorta gradient, mm Hg</td>
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<td>4.4±3.1</td>
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<td>Aortic regurgitation, grade 0–4</td>
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<td>0.4±0.6</td>
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<td>RV pressure, mm Hg</td>
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<td>RVEDV, mL/m²</td>
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<td>120.4±32.9</td>
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<td>RVESV, mL/m²</td>
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<td>60.9±23.8</td>
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<td>65.2±25.7</td>
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<td>RVEF, %</td>
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<td>50.2±9.3</td>
<td>209</td>
<td>48.4±9.8</td>
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<td>Pulmonary regurgitation (PC-flow), %</td>
<td>319</td>
<td>26.8±18.4</td>
<td>172</td>
<td>26.6±18.7</td>
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<td>RV mass, g/m²</td>
<td>380</td>
<td>34.0±13.7</td>
<td>209</td>
<td>37.2±14.2</td>
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<td>RV mass/volume ratio, g/mL</td>
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<td>0.29±0.12</td>
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<td>0.31±0.14</td>
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<td>80.9±17.1</td>
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<td>83.8±18.5</td>
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<td>LVESV, mL/m²</td>
<td>380</td>
<td>35.1±12.8</td>
<td>209</td>
<td>37.3±14.4</td>
</tr>
</tbody>
</table>

(Continued)
Gender differences regarding the number of reoperations after repair \( (P=0.804) \) and pulmonary valve replacement procedures \( (P=0.744) \).

**Gender Influence on CMR Parameters of Cardiac Function**

CMR data on biventricular function were available in 380 of the 407 patients and were indexed to body surface area, reflecting current clinical practice. For the whole population, male patients had significantly higher masses of both ventricles \( (P=0.001) \) and larger left ventricular (LV) and RV volumes \( (P=0.001–0.003) \). In contrast, female patients had significantly higher ejection fractions (EFs) for both ventricles \( (\text{RVEF}, 52.4\pm8.0 \text{ versus } 48.4\pm9.4 \; [P=0.001]; \text{LVEF}, 58.2\pm8.3 \text{ versus } 56.0\pm8.4 \; [P=0.012]) \).

**CMR Percentiles for Patients Aged 8 to 40 Years**

TOF-specific reference percentiles were computed from volumetric CMR data to display percentiles of the range of values that can be expected after repair in patients with TOF aged 8 to 40 years. As a result from the observed significant gender differences for the whole group, percentiles were generated separately for both sexes. Figure 2 summarizes results for the LV, and Figure 3 summarizes results for the RV. All CMR-measured parameters were indexed to body surface area to reflect the current clinical practice.

**LV Parameters**

LV end-diastolic and end-systolic volumes showed a steady gradual increase from childhood to mid-adulthood. This was more evident in female patients with TOF. LVEF demonstrated no clear trend in female patients, whereas in male patients, there was a steady gradual decrease over the decades. LV muscle mass demonstrated a steady gradual increase in female patients over the observed period, whereas muscle mass in male patients rose until age 30 years (Figure 2).

**RV Parameters**

RV end-diastolic volumes exhibited no trend over the observed period in female and male patients, but RV end-systolic volumes increased gradually over the years. Accordingly, RVEF decreased over the observed decades in both sexes and was more pronounced in male patients. RV muscle mass demonstrated no obvious trend over the observed time period (Figure 3).

**Discussion**

We used a prospective multicenter setting and strict methodological standardization to study the impact of age and gender on cardiovascular function by CMR in a large representative contemporary cohort of children and adults with repaired TOF. We consider the reported population representative of current management of repaired TOF in Germany. Population characteristics, including male/female ratio for the whole group and subpopulations, as well as results of 12-lead ECG, Holter monitoring, and imaging studies are in agreement with previously reported data. There were no gender differences for age at TOF repair, type of repair, number of prerepair palliations or postrepair reoperations, pulmonary regurgitation fraction, and maximal gradient across the RV outflow tract.

**Clinical Impact of the Study Findings**

The novelty of the information obtained is 2-fold. First, we documented for the whole group significant gender differences for indexed ventricular volumes and mass. Male patients with TOF had larger indexed volumes and mass of the RV and LV than female patients. This was expected because sex differences of such parameters were previously noted in healthy populations. On the other hand, female patients with TOF had higher EFs in both ventricles than male patients, whereas in healthy patients, no significant sex differences were reported, although hemodynamical burden and clinical history was not different (Table). This presence of obvious gender differences renders unsatisfactory any algorithms for clinical follow-up or research outcome investigations suggesting unisex preoperative thresholds for pulmonary valve replacement. It is likely that an RV end-diastolic volume in a particular patient (eg, 150–180 mL/m² body surface area), as often is used to support a clinical decision over pulmonary valve replacement, should actually be interpreted differently for male and female patients. Ignoring gender may result in female patients experiencing relatively more-severe ven-
Figure 2. Reference percentile curves for LV parameters in repaired tetralogy of Fallot. LV-EDV, indicates left ventricular end-diastolic volume (in mL/m² body surface area [BSA]); LV-EF, left ventricular ejection fraction (%); LV-ESV, left ventricular end-systolic volume (in mL/m² BSA); LV-MM, left ventricular mass (in g/m² BSA), including the septum; P50, percentile where 50% of male or female patients of the respective age have smaller or equal ventricular volumes, EF, or mass; P97, percentile where 97% of male or female patients of the respective age have smaller or equal ventricular volumes, EF, or mass.
Figure 3. Reference percentile curves for RV parameters in repaired tetralogy of Fallot. RV-EDV, indicates right ventricular end-diastolic volume (in mL/m² BSA); RV-EF, right ventricular ejection fraction (%); RV-ESV, right ventricular end-systolic volume (in mL/m² BSA); RV-MM, right ventricular mass (in g/m² BSA), excluding the septum. Other abbreviations as in Figure 2.
tricular dilatation if a unisex threshold was considered as 1 criterion for pulmonary valve replacement. Moreover, for each sex, such a number is very likely to have a different meaning, depending on the patient’s age.

Second, the sex-specific percentiles of volumes and mass between age 8 and 40 years allow, to some extent, an appreciation of the degree of ventricular dilatation and dysfunction in patients with repaired TOF. The presented percentiles may constitute a more realistic framework than any relation of volumetric CMR-derived parameters to values of a normal population. The centiles also reflect the impact of both age and sex on the evolution of these parameters over time. The percentiles suggest a gradual decline in EF for both ventricles in male patients and for the RV only in female patients. In contrast, in healthy populations, the EF of both ventricles increases as both end-diastolic and end-systolic volumes decrease over the decades. This observation seems relevant because reduced EF (<55% for LV and <45% for RV) in conjunction with severe RV dilatation (>172 mL/m² in female patients and >185 mL/m² in male patients) have been suggested as independent predictors of adverse outcome, such as death, sustained ventricular tachycardia, and an increase in New York Heart Association functional class from III to IV. The gradual increase in end-systolic volumes of both ventricles seen both in male and in female patients contributes to the decrease in EF. Increased RV end-systolic volumes have been associated with reduced end-systolic elastance by conductance catheter, which is believed to represent the gold standard measure for load-independent myocardial contractility.

LMS Method
Variability of surgical techniques and performances in the 14 centers alongside with major improvements in anesthesia, perfusion equipment, and pediatric intensive care have certainly had their impact on observed CMR parameters of cardiac function. For this reason, we used the LMS method, which is known to be appropriate for potential data skewness and heteroscedasticity. For example, the presented reference percentiles for CMR-derived biventricular volumes and mass may have been influenced by a trend toward earlier primary repair in the past 2 decades. The LMS method partly compensates for this effect by applying smoothing techniques that include results of neighboring age regions and by its efficient use of data, allowing percentile computation even for the limited sample sizes at higher ages. Moreover, LMS-derived percentiles can display results with different distributions at various time points and, hence, represent the evolution of function parameters over time that are much more accurate than regression analyses, which generally assume constant ranges of distribution. The LMS method also does not depend on linear relationships among cardiovascular parameters, age, and body size; all these described properties make the LMS-method the method of choice to generate reference data for parameters influenced by multiple factors, including known or suspected sex influence.

Limitations
We used accepted modern statistical methods to establish reference data in repaired TOF. However, a certain grade of parameterization (e.g., by the application of a Box-Cox power transformation to achieve normal approximation of target parameters) is inevitable to enable interpolations. Regular readjustment of such reference data seems important because improved techniques of repair may result in improved ventricular function data in the future. The age range needs to be expanded beyond age 40 years because the majority of patients analyzed in the present study were adolescents or young adults. The presented reference centiles of postoperative CMR parameters in repaired TOF are certainly no substitutes for longitudinal studies, which are highly desirable to compare different reintervention strategies in terms of outcome. The Competence Network’s focus on noninvasive imaging may have introduced a small selection bias, although much effort, including study monitoring, was placed on strict successive patient inclusion without preselection from the participating centers. There were missing data in some categories, as is inevitable in a multicenter investigation, but these were considered unlikely to affect the overall results as they were evenly distributed.

Conclusions
The strictly standardized and prospective multicenter setting of the study allowed the inclusion of a large contemporary sample of patients late after TOF repair. There are significant gender differences of biventricular volumes, function, and mass by CMR late after repair of TOF, suggesting that age and gender cannot be ignored when discussing thresholds because female patients are likely to experience a relatively more severe RV dilatation than male patients when only unisex thresholds are considered. The presented gender-specific percentiles allow for a more realistic framework of reference for an individual male or female patient at a given age than reference values from a normal population. They suggest different long-term trends of ventricular function in repaired TOF compared with reported data from healthy reference populations, with (1) increase of end-diastolic and end-systolic LV volumes, particularly in female patients; (2) increase of end-systolic RV volumes in both sexes; and (3) decrease of biventricular EF in male patients, whereas in female patients, only RVEF decreased. The latter finding seems of particular importance because decreased RVEF and LVEF are increasingly recognized to be associated with adverse outcome, such as death, ventricular sustained tachycardia, and increase in New York Heart Association functional class. This underscores the need for larger longitudinal follow-up studies in repaired TOF to extend these observations to define predictors of adverse outcome to reduce mortality late after repair.

Acknowledgments
We thank all participating centers and investigators for their efforts during the trial (online-only Data Supplement). We also thank Peter Lange, PhD, and Hans Meyer, PhD, for their contributions during the initiation of the trial.

Sources of Funding
This study of the Competence Network for Congenital Heart Defects was funded by the German Federal Ministry of Education and Research (BMBF), FKZ 01GI0210, 01GI0601.
Disclosures

Dr Dubowy served as an expert witness to a social welfare court. Dr Beerbaum has received research grant support from Medical Research Connaught, UK Aortic Stiffness.

References


CLINICAL PERSPECTIVE

Knowledge of range and distribution of biventricular size, function, and mass is crucial for individual assessment by cardiac magnetic resonance after repair of tetralogy of Fallot. This study demonstrated significant gender differences in a large, contemporary cohort of children and adults aged 8 to 59 years. Biventricular volumes and mass were significantly larger in male patients, whereas biventricular ejection fraction was higher in female patients; timing and mode of repair and postrepair pulmonary regurgitation fraction was not different between genders. Sex-specific reference percentiles, established for the age range from 8 to 40 years, suggest that the time course of changes in ventricular function and mass may significantly differ from those seen in healthy subjects, certainly for the right ventricle, but also for the less-affected left ventricle. These data suggest that ignoring gender may result in female patients experiencing relatively more severe ventricular dilatation (e.g., when planning pulmonary valve replacement). Gender- and age-specific volumetric cardiac magnetic resonance reference data are needed to plan individual follow-up and to design future longitudinal outcome studies.
Impact of Gender and Age on Cardiovascular Function Late After Repair of Tetralogy of Fallot: Percentiles Based on Cardiac Magnetic Resonance
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_Circ Cardiovasc Imaging_. 2011;4:703-711; originally published online September 9, 2011; doi: 10.1161/CIRCIMAGING.111.963637

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/4/6/703

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2011/09/09/CIRCIMAGING.111.963637.DC1

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Clinical Trial Registration Information- “Follow up of Post-Repair Tetralogy of Fallot”, ClinicalTrials.gov - NCT00266188

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