

# High Variability of Right Ventricular Volumes and Function in Adults with Severe Pulmonary Regurgitation Late After Tetralogy of Fallot Repair



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**Our aim was to assess changes of right ventricular end-diastolic volumes (RVEDVi) and right ventricular ejection fraction (RVEF) in asymptomatic adults with repaired tetralogy of Fallot, with native right ventricular outflow tract and severe pulmonary regurgitation by serial cardiac magnetic resonance imaging (CMR). The study included 23 asymptomatic adults who underwent  $\geq 3$  CMR studies (total of 88 CMR studies). We compared changes in RVEDVi and RVEF between first and last study (median follow-up: 8.8 years, interquartile range: 6.3 to 13.1 years) and between all study pairs. Variability of measurements between study pairs (65 consecutive and 139 nonconsecutive CMR study pairs) were assessed using Bland–Altman analysis and intraclass correlation coefficients. On average, there were no significant changes of RVEDVi or RVEF over the study period (change in RVEDVi:  $+0.4 \pm 17.8$  ml/m<sup>2</sup>, change in RVEF:  $-1.0 \pm 5.5\%$ ). Assessment of variability of measurements between study pairs demonstrated no systematic change in RVEDVi and RVEF between study pairs with limits of agreement within the range of previously published studies (RVEDVi  $-29.1$  to  $+27.2$  ml/m<sup>2</sup>; RVEF  $-11.5\%$  to  $10.2\%$ ). High intraclass correlation coefficients for RVEDVi (0.943, 95% CI 0.906 to 0.965,  $p < 0.001$ ) and RVEF (0.815, 95% CI 0.697 to 0.887,  $p < 0.0001$ ) indicate high reliability of reported measurements. In conclusion, in asymptomatic adults with repaired tetralogy of Fallot with native right ventricular outflow tracts and severe pulmonary regurgitation, CMR measurements of RV volumes and RVEF remain stable during follow-up with variability between CMR studies in individual patients, as expected for interobserver and interstudy variability. Measurements derived from a single CMR study or changes occurring between 2 CMR studies should be used with caution for clinical decision-making. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2022;166:88–96)**

Severe pulmonary regurgitation is the most prevalent residual lesion after childhood repair of tetralogy of Fallot.<sup>1–3</sup> In some retrospective studies, an association between the presence of residual pulmonary regurgitation with adverse outcomes was observed.<sup>1</sup> Cardiac magnetic resonance

imaging (CMR) has emerged as the reference method for measurements of right ventricular volumes and function. Based on CMR studies, European and North American guidelines for the management of adults with congenital heart disease recommend specific thresholds of right ventricular volumes and function (right ventricular end-diastolic volumes [RVEDVi] of  $\geq 160$  ml/m<sup>2</sup>, right ventricular end-systolic volume [RVESVi]  $\geq 80$  ml/m<sup>2</sup>, right ventricular ejection fraction [RVEF]  $< 45\%$ ) for prosthetic pulmonary valve replacement in asymptomatic adults with repaired tetralogy of Fallot.<sup>4,5</sup> Although there is a general belief that right ventricular dilatation and dysfunction are progressive in nature, only a few studies have actually analyzed its evolution using cardiac magnetic resonance imaging.<sup>6–11</sup> The aim of this study was to analyze changes in right ventricular volumes and function in clinically stable, asymptomatic adults with repaired tetralogy of Fallot with native right ventricular outflow tracts and residual severe pulmonary regurgitation using serial CMR imaging.

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## Methods

From the Swiss SACHER-registry (*ClinicalTrials.gov* Identifier NCT 2,258,724), we identified asymptomatic adults with repaired tetralogy of Fallot; severe residual pulmonary regurgitation and a native right ventricular outflow tract; followed at the university hospitals of Basel, Berne, and Zurich (CMRs performed at the University Children's hospital); who had undergone  $\geq 3$  CMR studies during adulthood; without any interventions, endocarditis, or arrhythmias between studies. Only patients with pure pulmonary regurgitation without concomitant right ventricular outflow tract obstruction were included. The registry was approved by the local ethics committee (BASEC: 2019-01935) and all patients had given written informed consent for analysis of clinical data at the time of enrollment into the registry. The study complies with the Declaration of Helsinki. Baseline patient characteristics and results from cardiac magnetic resonance imaging were derived from chart review. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

All CMR studies had been performed on clinical indication as part of routine follow-up as recommended in guidelines.<sup>12,13</sup> All CMR studies followed previously published protocols and were performed and analyzed at each center by the same dedicated specialist teams with extensive experience in the field.<sup>14</sup> Severe pulmonary regurgitation was defined as pulmonary regurgitation fraction  $>30\%$  on cardiac magnetic resonance imaging as suggested by guidelines.<sup>4</sup> Impaired right ventricular systolic function was defined as an RVEF  $<45\%$ .<sup>15,16</sup>

Clinical decision making in asymptomatic adults with repaired tetralogy of Fallot is based on ventricular dimensions indexed to body surface area. For the purpose of this study, measurements of RVEDVi, indexed to body surface area; RVESVi, indexed to body surface area; RVEF; and pulmonary regurgitant fraction were abstracted from clinical CMR reports. Interobserver variability was tested with blinded re-analysis of 30 CMR studies (15 study pairs) by a CMR specialist of a different study center.

We compared changes in RVEDVi and RVEF between the first and the last CMR study for the entire cohort and between all pairs of CMR studies in individual patients.

Interobserver and interstudy variabilities between CMR studies were assessed using the methods described by Bland and Altman and by estimation of intraclass correlation coefficients (ICC).

Statistical analysis was performed using SPSS version 26.0 (SPSS, Inc., Chicago, Illinois). Descriptive data are presented as median (range or interquartile range), mean  $\pm$  standard deviation, and proportions, as appropriate. For comparisons between average measurements of right ventricular dimensions and function, and biometric data, paired *t* tests or related samples Wilcoxon tests were used, as appropriate. For comparison between groups, chi-square or Fischer's exact tests were used, as appropriate. Interobserver variability and interstudy variability were investigated as described by Bland and Altman and by calculating ICC estimated with variance components models.<sup>17</sup> Agreement for each measurement (limits of agreement) was

expressed as 2 standard deviations of the interstudy differences. ICC estimates and their 95% confidence intervals (CI) were calculated using SPSS statistical package version 26 (SPSS Inc, Chicago, Illinois) based on a mean-rating, absolute-agreement, 2-way mixed-effects model. The ICC indicates the proportion of variability explained by real changes of measurements as opposed to interstudy variability, observer differences, or random error. A *p* value  $<0.05$  (2-sided) was considered statistically significant.

## Results

Of all adults with repaired tetralogy of Fallot followed at the participating centers, 235 had undergone at least 1 CMR study. Of these, 77/235 had a native right ventricular outflow tract (33%) (i.e., without previous conduit or bioprosthesis implantation) with severe pulmonary regurgitation (defined as a regurgitation fraction  $\geq 30\%$ ). Of these 77 patients, 41 patients had serial CMR studies and 23 patients had at least 3 complete consecutive CMR studies (range: 3 to 7 studies). These 23 patients were included in the study group. This allowed analysis of a total of 88 CMR studies amounting to 65 pairs of consecutive CMR studies and a total of 139 consecutive and nonconsecutive study pairs (e.g., comparison of first study with third CMR study, second CMR study with fourth CMR study, and so on). Median age at first CMR was 26.1 years (IQR: 19.9 to 38.2 years) and median follow-up duration was 8.8 years (IQR: 6.3 to 13.1 years). Within the study cohort, 15 patients (65%) were women. A total of 9 patients had undergone a palliative procedure (39%) before intracardiac repair. Intracardiac repair had been performed at a median age of 3.8 years (IQR: 2.4 to 49 years). A total of 19 patients (83%) had undergone transannular patch repair. All patients had native pulmonary outflow tracts without previous conduit or bioprosthesis implantation. None of the patients had any degree of right ventricular outflow tract obstruction. All patients were in sinus rhythm. None of the patients had a sustained atrial or ventricular arrhythmia, infective endocarditis, or new onset heart failure over the study period.

For the entire study cohort, illustrated in [Table 1](#), there were no significant changes in right ventricular volumes, right ventricular ejection fraction, and pulmonary regurgitant fraction over the study period. This was also true for all

Table 1

Average changes of right ventricular volumes and ejection fraction between baseline CMR study and last CMR study in the 23 patients of the study cohort

	Baseline CMR	Last CMR	<i>p</i> Value
RVEDVi (ml/m <sup>2</sup> )	158.1 $\pm$ 30.7	158.7 $\pm$ 29.1	0.890
RVESVi (ml/m <sup>2</sup> )	81.4 $\pm$ 24.1	83.6 $\pm$ 24.6	0.457
RVEF (%)	49.1 $\pm$ 7.8	48.1 $\pm$ 8.2	0.394
Pulmonary regurgitant fraction (%)	43.4 $\pm$ 13.6	43.5 $\pm$ 7.4	0.956
Weight (kg)	65.5 $\pm$ 13.9	70.4 $\pm$ 13.5	0.001
Body surface area (m <sup>2</sup> )	1.73 $\pm$ 0.19	1.80 $\pm$ 0.18	0.001
Heart rate (beats / minute)	73 $\pm$ 9	79 $\pm$ 9	0.047

CMR = Cardiac magnetic resonance imaging; RVEDVi = Right ventricular end-diastolic volume indexed to body surface area; RVEF = Right ventricular ejection fraction; RVESVi = Right ventricular systolic volume indexed to body surface area.

41 patients with serial CMR studies analyzed (RVEDVi on first versus last CMR study:  $153.4 \pm 32.4$  versus  $153.4 \pm 28$  ml/m<sup>2</sup>,  $p = 0.98$ ; RVEF on first versus last CMR study:  $47.6 \pm 7.7$  versus  $47.7 \pm 7.5\%$ ,  $p = 0.85$ ). Among the 23 patients within the study cohort, there was a small, albeit statistically significant, average increase in body weight over the study period, corresponding to a small increase in body surface area. In addition, there was a small increase of average heart rate. Over the entire study period, 15 patients (65%) fulfilled at least once the indication for pulmonary valve replacement according to the North American guidelines and 16 patients (70%) according to the European guidelines. In 2/15 patients (13%) meeting the North American guidelines criteria for pulmonary valve replacement and in 1/16 patients (6%) meeting the European guidelines criteria, measurements of right ventricular volumes decreased and/or RVEF increased during follow-up to the point that patients no longer met guidelines criteria for intervention.

On average, there were no significant changes of RVEDVi, RVESVi, RVEF, or pulmonary regurgitation fraction over the follow-up duration of more than 8 years. There were, however, large deviations (both increasing and decreasing values) between individual study pairs. This translates into merely absent average absolute changes in RVEDVi ( $+0.4 \pm 17.8$  ml/m<sup>2</sup>), RVESVi ( $+2.1 \pm 13.5$  ml/m<sup>2</sup>), RVEF ( $-1.0 \pm 5.5\%$ ), and pulmonary regurgitation fraction ( $+0.1 \pm 11.3\%$ ) with relatively large standard deviations, reflecting variability of measurements ( $p > 0.1$  for all comparisons).

Although average right ventricular volumes remained stable within the entire study cohort, variability of RVEDVi between study pairs in individual patients were large, as illustrated in Figure 1. Among the 65 consecutive study pairs, an increase in RVEDVi was observed in 33 study pairs (51%), a decrease in 29 study pairs (45%), and no change in 3 study pairs (5%) (Figure 1). A total of 5 patients (22%) with an RVEDVi  $\geq 160$  ml/m<sup>2</sup> at some point during follow-up had regression of RVEDVi to  $< 160$  ml/m<sup>2</sup> on subsequent CMR studies (Figure 1).

Although average right ventricular ejection fraction remained stable within the entire study cohort, variability of RVEF between study pairs in individual patients were large, as illustrated in Figure 2.

Over the entire study period, among the 65 consecutive study pairs, an increase of RVEF was observed in 27 (42%), a decrease in 28 (43%), and no change in 10 (15%) study pairs. When analyzing deviations of RVEF in individual patients, all measurements were within the range of  $\pm 10\%$  of the mean of all measurements of RVEF in individual patients (Figure 2).

Figure 3 shows Bland-Altman plots for interstudy variability. Small differences of mean values for RVEDVi and RVESVi of  $< 1$  ml/m<sup>2</sup> and differences of mean values for RVEF of  $< 1\%$  suggest no systematic changes of measurements between studies. Limits of agreement for RVEDVi were  $-29.1$  to  $+27.2$  ml/m<sup>2</sup>, for RVESVi  $-22.5$  to  $24.0$  ml/m<sup>2</sup>, and for RVEF  $-11.5\%$  to  $10.2\%$ . Intraclass correlation coefficients were 0.913 to 0.943 (95% CI 0.879 to 0.965) for RVEDVi and RVESVi ( $p < 0.001$ ) and 0.812 to 0.815 (95% CI 0.738 to 0.887) for RVEF ( $p < 0.001$ ).

Interobserver variability was studied by re-analysis of 30 CMR studies (15 study pairs) by a second observer at a different institution. The second observer was blinded to results of the first analysis, and the sequence of studies was random. Re-analysis included 5 study pairs with stable RVEDVi on first analysis, and 5 study pairs with a decrease and 5 study pairs with an increase of RVEDVi between CMR studies. Changes of RVEDVi between first analysis, re-analysis, and Bland-Altman plots are displayed in Figure 4. The extent of increase or decrease of RVEDVi on first analysis was attenuated on re-analysis (Table 2). Intraclass correlation coefficients for RVEDVi was 0.969 (95% CI 0.932 to 0.985,  $p < 0.0001$ ) for RVESVi 0.963 (95% CI 0.901 to 0.984,  $p < 0.0001$ ) and for RVEF 0.911 (95% CI: 0.808 to 0.957,  $p < 0.0001$ ).

## Discussion

Our data, analyzing measurements of serial CMR studies, demonstrate stable right ventricular dimensions and function over a median follow-up period of more than 8 years in asymptomatic adults with repaired tetralogy of Fallot without previous conduit implantation and severe pulmonary regurgitation. The analysis of serial CMR studies allows us to demonstrate that changes in right ventricular volumes and ejection fraction between CMR study pairs can be attributed to interobserver and interstudy variability and must not reflect a real change. Limits of agreement for all measurements are within the range of previously published studies investigating variability of CMR measurements in patients with repaired tetralogy of Fallot.<sup>18,19</sup>

Timing of pulmonary valve replacement for asymptomatic patients with native right ventricular outflow tracts and severe residual pulmonary regurgitation after childhood repair of tetralogy of Fallot is currently a debated topic in congenital heart disease.<sup>20</sup> Contemporary guidelines recommend pulmonary valve replacement in asymptomatic patients with RVEDVi of  $\geq 160$  ml/m<sup>2</sup>, RVESVi  $\geq 80$  ml/m<sup>2</sup>, and/or impaired right ventricular systolic dysfunction.<sup>4, 5, 14, 21, 22</sup>

Although progressive right ventricular dilatation and dysfunction are often quoted as a fact in studies about patients with tetralogy of Fallot and severe pulmonary regurgitation, only a few studies have addressed the evolution of right ventricular volumes and function over time.<sup>6-11</sup> In alignment with our findings, these studies demonstrated stable right ventricular volumes and function or only small changes over variable follow-up times. Limitations of these studies include the enrollment of heterogeneous patient populations, including patients with and without severe pulmonary regurgitation and the combined analysis of pediatric and adult patients. An important limitation is that all but 1 of these studies compared study pairs of 2 consecutive CMR studies only.

Wald and colleagues reported an increase in right ventricular volumes ( $\geq 30$  ml/m<sup>2</sup>), a decrease in RVEF ( $\geq 10\%$ ), or a decrease in LVEF ( $\geq 10\%$ ) in 15% of their entire population of 339 patients. Hoelscher and colleagues reported an increase in RVEDVi ( $\geq 20$  ml/m<sup>2</sup>) in their study cohort in 24% of 85 patients over a median follow-up of 3.4 years. For their entire study population, Wald and colleagues

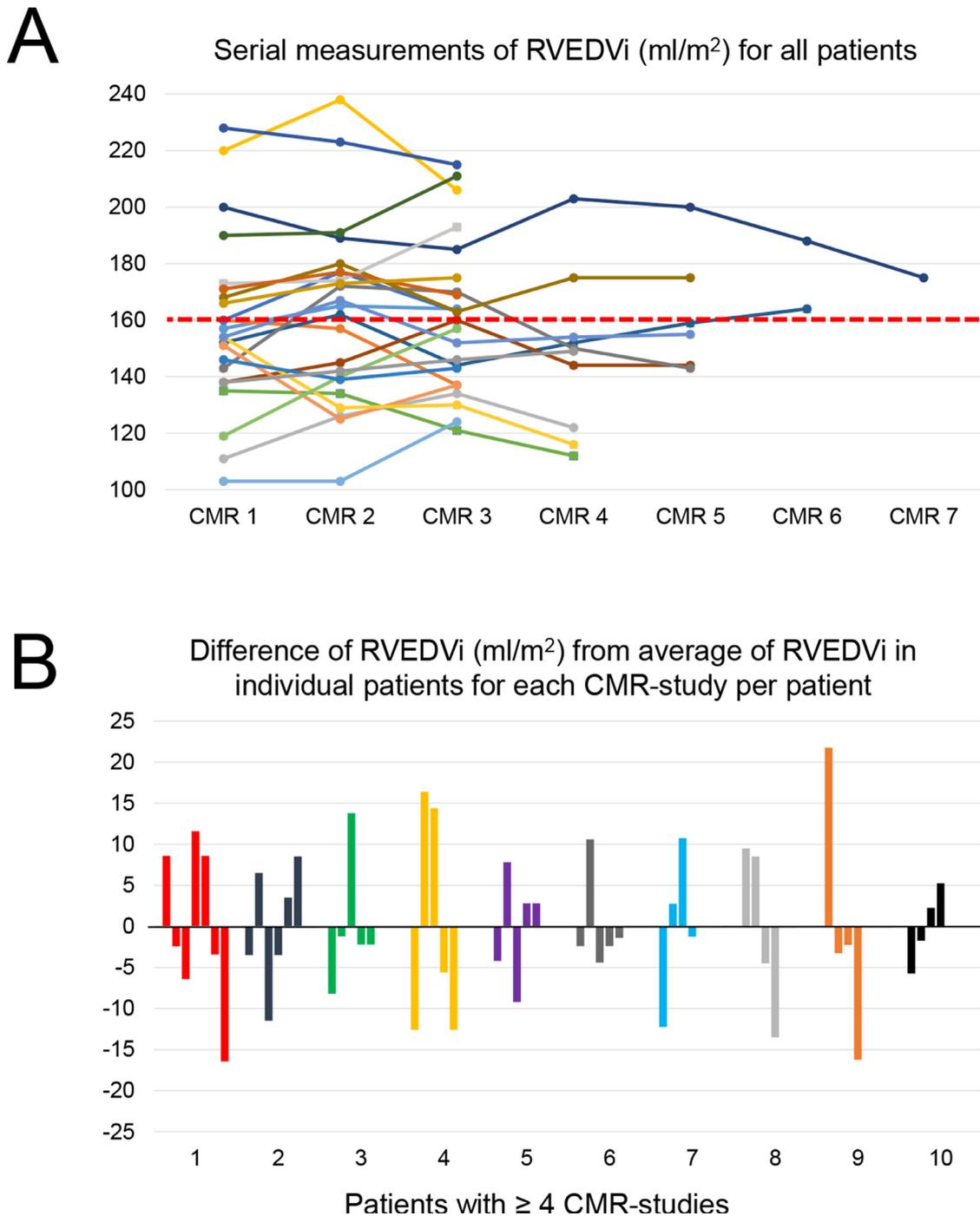


Figure 1. Serial CMR measurements of RVEDVi. (A) Serial measurements in all 23 individual patients; the dotted red line marks threshold for severe right ventricular dilatation, used for indication of pulmonary valve replacement in current guidelines. (B) Serial measurements in patients with  $\geq 4$  CMR studies. The figure plots the difference of RVEDVi (ml/m<sup>2</sup>) from average of RVEDVi in individual patients for each CMR study. The baseline of the figure represents the average of RVEDVi of CMR studies in individual patients.

reported a small but significant average increase in RVEDVi ( $+4 \pm 18$  ml/m<sup>2</sup>) and an average decrease of RVEF ( $-1 \pm 6\%$ ) over a median follow-up duration of 2.2 years. Changes showed large standard deviations, almost identical to standard deviations found in our study. Hoelscher and colleagues reported no change in average RVEDVi and RVEF for the entire study cohort. In

summary, both studies reported an increase in RVEDVi and/or decrease of RVEF in a substantial proportion of patients; whereas no or only small changes were found for the entire study populations. Although not explicitly reported, this observation means that in both studies, there must have been a subgroup of patients with a significant decrease of right ventricular dilatation and an increase in

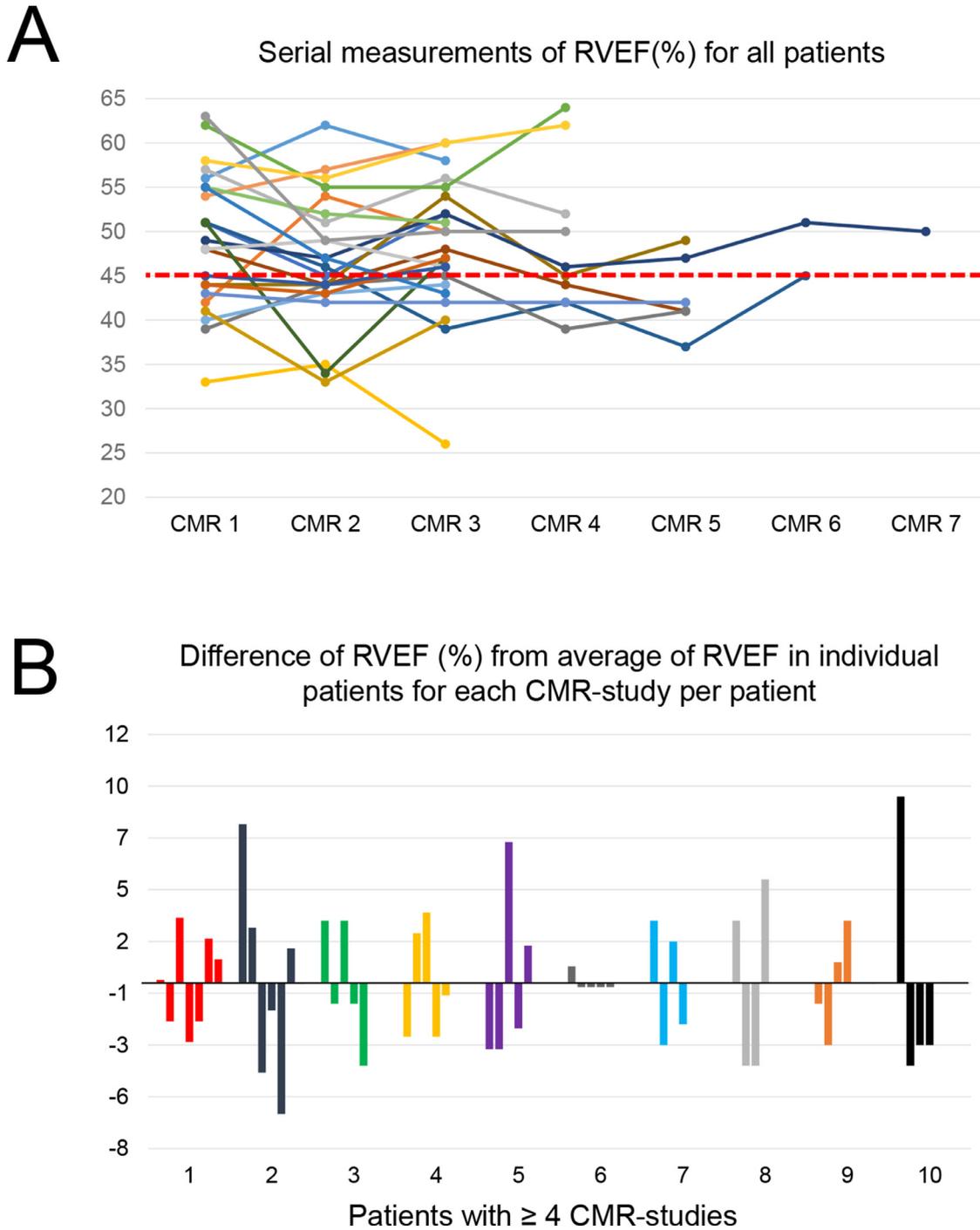


Figure 2. Serial CMR measurements of RVEF. (A) Serial measurements in all 23 individual patients; the dotted red line marks threshold for impaired systolic ventricular function, used for indication of pulmonary valve replacement in current guidelines. (B) Serial measurements in patients with  $\geq 4$  CMR studies. The figure plots the difference of RVEF (%) from average of RVEF in individual patients for each CMR study. The baseline of the figure represents the average of RVEF of CMR studies in individual patients.

right ventricular ejection fraction. As there is no plausible physiologic explanation for these observations, the only rational explanation is variability of the measurement itself.

There are several reasons for the observed variability of CMR measurement. (1) Studies on intra- and interobserver variability of CMR measurements of right ventricular volumes and function in patients with repaired tetralogy of Fallot have been published.<sup>18,19</sup> Limits of agreement for

intraobserver variability has been shown to be about  $\pm 10\%$  to  $15\%$  for right ventricular volumes and ejection fraction with larger limits of agreement for interobserver and inter-study variability accounting for around  $\pm 15\%$  to  $20\%$ , depending on study settings and studied cohorts. (2) Many known and unknown biomechanic factors may have an impact on right ventricular volumes and function. Changes in body surface area due to weight changes may affect

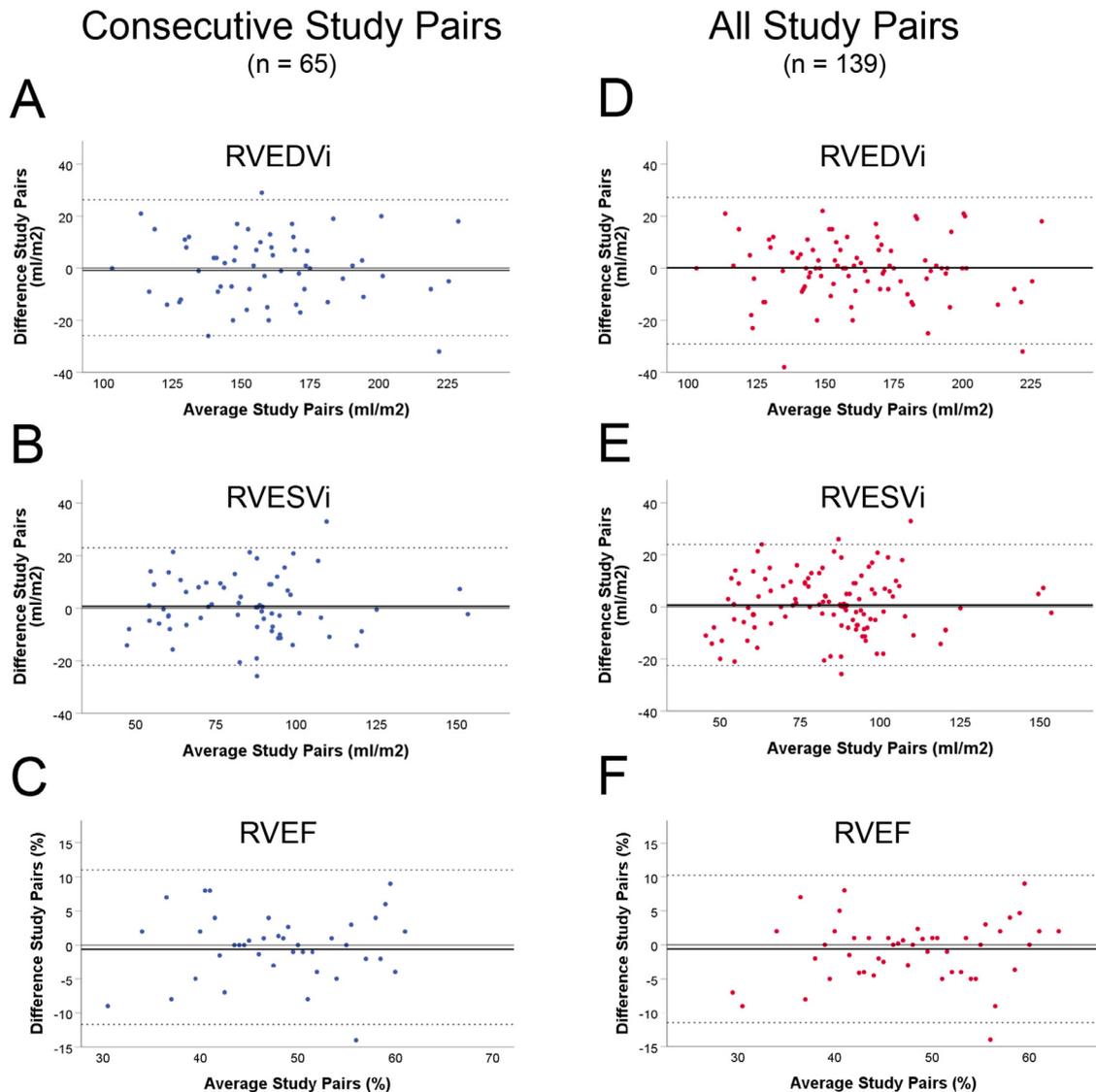


Figure 3. Interstudy variability (Bland Altman plots). (A to C): consecutive CMR studies; (D to E): all CMR studies.

normalized ventricular volumes. Different loading conditions and heart rate may add to interstudy variability.<sup>23,24</sup> Whether “correction” of CMR measurements for hemodynamic variables, such as heart rate, blood pressure, or more standardized imaging protocols (e.g., defining a period of fasting before imaging) are feasible and have an impact on outcomes may be explored; however, such studies will pose substantial logistic challenges. (3) An important flaw of many studies is that they focused on analysis of single CMR study pairs with 2 consecutive studies only. In our study with serial measurements, there was a very high chance that an increase in right ventricular volumes or ejection fraction between the first and second study was followed by a decrease in the next CMR study and vice versa. This observation is explained by an important statistical phenomenon called regression to the mean.<sup>25</sup> This statistical phenomenon applies to all serial measurements of non-independent samples and may explain parts of the individual variability of serial measurements of patients in our study.<sup>25</sup> This effect may particularly explain most of

the discrepancies between the findings in our study compared with the studies by Wald and Hoelscher.

Given the priority of the topic, there are surprisingly few actual data on ventricular remodeling in children and adults with significant pulmonary regurgitation after childhood repair of tetralogy of Fallot. The scarce data available suggest that remodeling occurs within the first few years after surgery, followed by more stable findings in long-term follow-up.<sup>26</sup> Individual differences of right ventricular remodeling, both in terms of right ventricular dilatation and dysfunction are poorly understood. In our patient cohort with relatively uniform cardiac physiology, huge differences in right ventricular dimensions and function (the range of RVEDVi on the first CMR study was 103 to 228 ml/m<sup>2</sup>) were found.

Our data challenge the general notion or dogma that pulmonary regurgitation inevitably leads to progressive dilatation and dysfunction in adulthood. At least rapid progression in asymptomatic patients with native right ventricular outflow tracts seems unlikely. As for all other

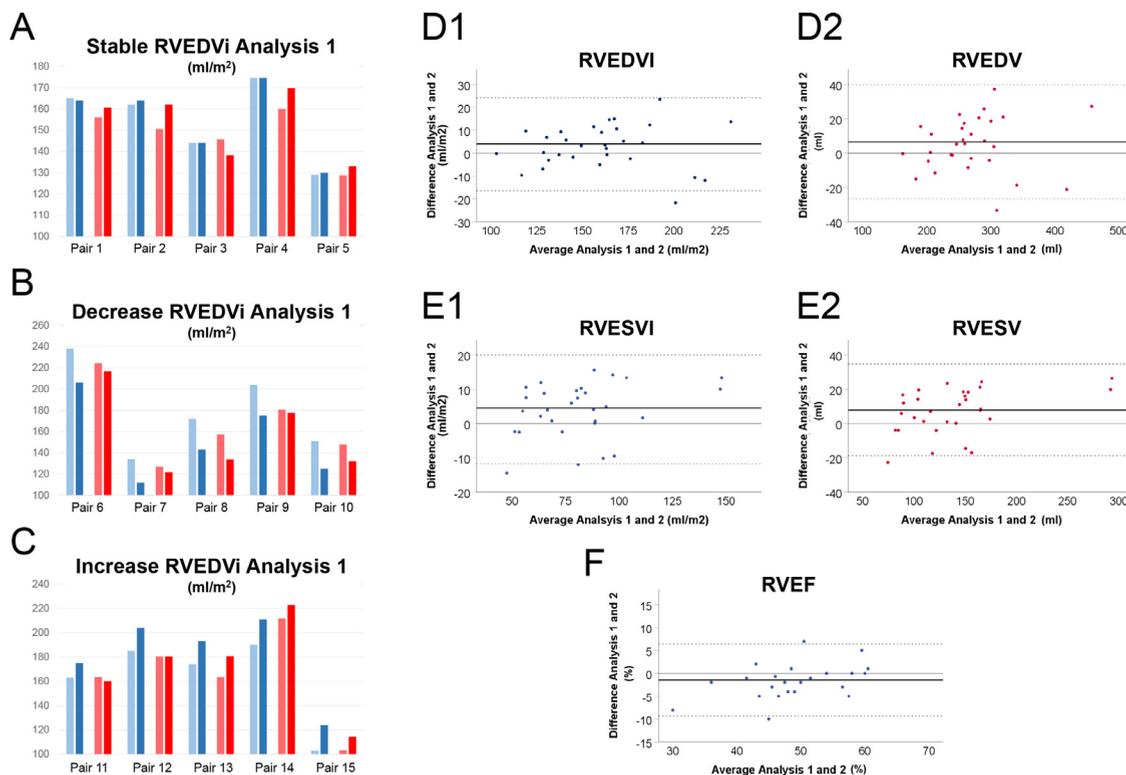


Figure 4. Interobserver variability Panels (A to C): Re-analysis of RVEDVi in 15 study pairs (A). Five study pairs with stable RVEDVi between study pairs on first analysis (B). Five study pairs with decrease of RVEDVi between study pairs on first analysis (C). Five study pairs with increase of RVEDVi between study pairs on first analysis. Bars in shades of blue represent first analysis, bars in shades of red represent blinded re-analysis by second observer; (D to F): Bland Altman plots illustrating interobserver variability. (D1 and D2): plots for RVEDVi and RVEDV. (E1 and E2): plots for RVESVi and RVESV. (F) Plots for RVEF.

measures in our day-to-day clinical work, the importance of careful assessment of serial CMR measurements for a comprehensive evaluation of our complex patients cannot be overemphasized.<sup>4</sup> To minimize interstudy variability, rigorous institutional measures to reduce intra- and interobserver variability are mandatory. Nonetheless, some variability is inevitable. The use of fixed volumetric thresholds for right ventricular dilatation or a certain number of volume changes between 2 CMR studies for indication of pulmonary valve replacement is thus problematic and may be an oversimplification of a complex problem. For example, in patients with a “true” right ventricular end-diastolic volume of 160 ml/m<sup>2</sup>, assuming a variability of ±10% of CMR measurements signify that an increase in RVEDVi from 144 to 176 ml/m<sup>2</sup> (a difference of 32 ml/m<sup>2</sup>) may just reflect the variability of the measurement itself. Following current guidelines, such a patient would qualify for pulmonary valve replacement. In addition to the risk of the intervention

itself and the increasing risk of inevitable subsequent interventions, there is even evidence suggesting that prosthetic pulmonary valve replacement may increase long-term risk of atrial arrhythmias and the risk of infective prosthetic pulmonary valve endocarditis.<sup>27</sup> In other words, premature pulmonary valve replacement can harm patients.

For the time being, we advocate for a careful and individualized approach for the indication of pulmonary valve replacement in adults with repaired tetralogy of Fallot with native right ventricular outflow tract, including serial assessment of right ventricular volumes and function. We recommend to base decisions for pulmonary valve replacement not on a single consecutive pair of measurement, but on serial measurements.

Our study has several limitations. Although we collected patients from 3 centers, given the strict inclusion criteria of patients with at least 3 consecutive CMR studies, the overall number of studied patients is small. Although the study

Table 2  
Re-analysis of CMR studies

	Change of RVEDVi First Analysis(ml/m <sup>2</sup> )	Change of RVEDVi re-Analysis(ml/m <sup>2</sup> )	p Value
Study pairs with stable RVEDVi	0.4±1.1	4.6±7.4	0.225
Study pairs with decrease of RVEDVi	-27.6±3.8	-11.1±8.6	0.043
Study pairs with increase of RVEDVi	18.4±3.7	7.2±8.7	0.043

CMR = Cardiac magnetic resonance imaging; RVEDVi = Right ventricular end-diastolic volume indexed to body surface area.

cohort likely represents a representative proportion of our entire cohort of adults with repaired tetralogy of Fallot and severe pulmonary regurgitation, a selection bias for patients with a favorable clinical disease course cannot be excluded.

The overall results of our study compare well with larger studies on the topic. However, based on our data, a slow progression of right ventricular dilatation or right ventricular dysfunction over decades of follow-up cannot be excluded. Rapid deterioration in a substantial proportion of asymptomatic patients seems very unlikely.

Measurements of CMR studies were derived from clinical CMR reports. Although assessment of interobserver variability in a subset of studies showed limits of agreement comparable with previously published studies, analyses performed in a core lab may have reduced interobserver variability.<sup>19</sup>

In conclusion, in asymptomatic adults with repaired tetralogy of Fallot with native right ventricular outflow tracts and severe pulmonary regurgitation, CMR measurements of right ventricular volumes and right ventricular ejection fraction remain stable during follow-up with important variability between 2 consecutive CMR studies, as expected for interobserver and interstudy variability. Changes in right ventricular volumes or right ventricular ejection fraction crossing established thresholds for pulmonary valve replacement should be used with caution for clinical decision-making in asymptomatic patients.

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## Ethics approval

The registry and the current analysis were approved by the local ethics committee (KEK, BASEC: 2019-01935). All patients had given written informed consent for analysis of clinical data at the time of enrollment into the registry.

## Authors' contributions

M.G. and F.S. conceptualized and designed the study. F. S., J.R., and N.H. collected the data. M.G., J.R., and N.H. analyzed the data. K.W. performed re-analysis of 30 CMR-studies for assessment of inter-observer variability. M.G., J. R., and N.H. drafted the manuscript. E.V., C.K., M.S., and D.T. contributed importantly to methodological issues and analysis of the data. B.S., L.M., D.B., and C.A. and the other authors critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

## Disclosures

The authors have no conflicting interests to declare.

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