Longitudinal right ventricular function is a better predictor of right ventricular contribution to exercise performance than global or outflow tract ejection fraction in tetralogy of Fallot: A combined echocardiography and Magnetic Resonance Study

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Aims
The contribution of the systolic function of the right ventricular (RV) outflow tract (RVOT) and of longitudinal shortening of the body of the right ventricle to global RV systolic function and exercise capacity in patients after tetralogy of Fallot (TOF) repair is unclear. Our aim was to characterize the functional role of the RVOT and to identify the most suitable method of assessing RV systolic function in clinical practice.

Methods
The cardiac magnetic resonance (CMR) studies, echocardiograms, and medical records of 50 consecutive patients with repaired TOF who underwent CMR were reviewed. The volumes of the RVOT and of the remainder of the RV were measured separately. Echocardiographic RV strain measurements based on ultrasound speckle tracking were collected.

Results
After excluding the akinetic RVOT, RVEF was statistically higher (47.1 vs. 45.0%, P < 0.0001) but the average increase in EF was small. The correlations of fractional area change and global longitudinal strain, both by echocardiography, with global RVEF were moderate (r = 0.59, P = 0.0001 and r = 0.56, P = 0.0004, respectively). The correlation between RVEF and predicted maximal oxygen consumption (VO₂max-predicted) was weak, regardless of whether the akinetic RVOT was included or not (r = 0.33, P = 0.049 and r = 0.36, P = 0.03, respectively). Of all imaging parameters, echocardiographic RV longitudinal strain correlated best with VO₂max-predicted (r = 0.66, P = 0.0001).

Conclusions
In patients following TOF repair, echocardiographic and CMR descriptors of global RV systolic function are, at best, weak predictors of exercise tolerance. Longitudinal function of the RV, measured remotely from the RVOT, may be a more important determinant of exercise performance than global RVEF in patients with aneurismal RVOTs.

Keywords
Tetralogy of Fallot • Right ventricle • Magnetic resonance imaging • Echocardiography • Ventricular function
Introduction

Long-term complications after tetralogy of Fallot (TOF) repair are mainly related to dilation and dysfunction of the right ventricle. Cardiac magnetic resonance (CMR) is the reference technique for assessing right ventricular (RV) volume and ejection fraction (EF). When measuring RV end-diastolic and end-systolic volumes for the calculation of RVEF by CMR, it is common practice to include the RV outflow tract (RVOT) in the RV endocardial contours. In patients with large RVOT patches and aneurismal outflow tracts, the systolic function of the RVOT is markedly lower than that of the rest of the ventricle. Consequently, a very large, dyskinetic RVOT patch will lead to reduction in global EF, even in the presence of preserved function of the inflow and trabecular components of the right ventricle. With this study, we sought to assess the effect of RVOT function on global RVEF in a contemporary cohort of children and adolescents after TOF repair. Furthermore, we aimed at identifying the method of RV systolic function assessment that best predicts the patients’ functional capacity. Specifically, we hypothesized that longitudinal RV shortening would be a better predictor of exercise tolerance than overall EF.

Methods

Following approval by our institution’s research ethics board, we retrospectively reviewed the results of clinical CMR studies in 50 consecutive patients with repaired TOF between August 2007 and January 2009, and collected their demographic and clinical information. These CMR studies were previously analysed under a different objective. We excluded multiple studies in the same patient as well as patients with RV to pulmonary artery conduits. The results of a clinical cardiopulmonary exercise test (CPET) and echocardiography (echo) were recorded, as long as these tests were performed within 12 months of the CMR. CPETs were performed using a standard cardiopulmonary cycle ergometry exercise testing with continuous monitoring by 12-lead electrocardiogram, ventilation and blood pressure measured every 2 min, as previously described. The predicted maximal oxygen consumption (VO₂ max-predicted) was used as a surrogate parameter for clinical status. Patients who underwent either surgical or catheter interventions in between CMR, echo or CPET were excluded from the study.

Cardiac magnetic resonance

Studies were performed in a 1.5 T unit (‘Avanto’, Siemens Medical Solutions, Erlangen, Germany), using a standardized protocol. The imaging acquisition settings are detailed elsewhere. In summary, RV volumes and function were measured from a stack of short-axis cine images, using commercially available software (‘QMass’, Version 7.2, Medis Medical Imaging Systems, Leiden, The Netherlands). All ventricular volume studies were contoured de novo by an experienced reader (L.G.W.) who was blinded to the patients’ clinical status and echo findings. Corrected (sometimes called ‘effective’) RV stroke volume was calculated by substracting the regurgitant volume per heart beat (measured by phase contrast velocity mapping) from the stroke volume. Corrected EF was calculated by dividing corrected stroke volume by RV end-diastolic volume. RV end-systolic and end-diastolic volumes were measured twice. Once, including the non-contractile RVOT and a second time excluding this portion of the right ventricle (Figures 1 and 2). The endocardial contours including the complete RVOT were drawn up to the pulmonary valve level.

This was identified by the presence of pulmonary valve remnants and/or dephasing artefact from turbulent antegrade flow during systole. The non-contractile RVOT was defined by drawing a line connecting the proximal limit of the akinetic free wall of the RVOT and the superior insertion point the RVOT to the ventricular septum on the respective short-axis images.

Phase contrast flow velocity mapping of the main pulmonary artery was performed and analysed using commercially available software (‘QFlow’, Version 5.2, Medis Medical Imaging Systems).
Echocardiography
Echocardiographic exams were performed following standardized clinical protocols on one of the following machines: IE-33 (Philips, Andover, USA) or Vivid-7 (General Electric, Milwaukee, USA). All data were digitally stored and measurements were performed offline using the Syngo analysis software (Siemens).

RV areas at end-diastole and end-systole from apical four chamber images were used to calculate RV fractional area change (%FAC). To account for significant intraventricular conduction delay which was present in all patients, RV end-diastole and end-systole were defined not by electrocardiographic criteria, but by the time point at which the RV was the largest and smallest, respectively, similar to what is common practice in CMR.

Speckle tracking derived RV walls longitudinal strain was measured off-line on the apical four chamber images, using ‘Cardiac Performance Analysis’ (TomTec, Munich, Germany). Strain of the basal, mid and apical segments of the RV septal and lateral walls was calculated separately followed by averaging the values of each wall. All values were averaged to calculate global RV longitudinal strain.

Lastly, the echocardiographic studies were reviewed for the presence of restrictive physiology, as evidenced by the consistent end-diastolic (following the P-wave on the electrocardiogram) forward flow in the branch pulmonary artery by pulsed-wave Doppler.

Statistical analysis
Statistical analysis was performed using InStat (Graphpad Software, La Jolla, USA). The descriptive data for continuous variables are presented as means (± standard deviations) or medians and ranges if applicable. Measurements of RV volumes and ejection fractions before and after exclusion of the RVOT were compared using two-tailed, paired Student’s t-tests. For categorical variables including gender, use of a TAP, and presence of restrictive RV physiology, we compared groups using a two-tailed un-paired Student’s t-test. Pearson correlation coefficients were used for correlation analyses in normally distributed data sets. P-values of <0.05 were considered significant.

Results
The patients’ mean age was 13 ± 2.8 years (range 7–18 years), with a male to female ratio of 26:24. The mean age at complete repair had been 1.5 ± 0.9 years (range 0.8–2.1 years). A transannular patch had been used in 37 out of the 50 patients (74%).
Cardiopulmonary exercise testing results were available in 34 patients (68%) with a mean time interval of 3.8 ± 4.2 months (range 0–12 months) between CPET and CMR. ECGs were available in 45/50 patients (90%) with a mean time interval of 2.2 ± 2.8 months (range 0–12 months) from CMR. All patients had a right bundle branch block. The mean QRS duration was 137 ± 23 ms (range 92–184 ms).

Cardiac magnetic resonance and echocardiography
Imaging results are summarized in Table 1. Echocardiograms with adequate image quality within 12 months of the CMR studies were available for 39/50 patients (78%). The mean time interval between the echo and CMR was 3.5 ± 4.6 months (range 0–12 months). Of the total of 39 patients, 38 (97%) had only trace to mild tricuspid regurgitation (TR). No patient had severe TR. We found evidence of restrictive RV physiology in 8/37 (22%) patients.

Information on restrictive physiology was not obtainable in 2/39 (5%) of our study group.

Table 1 Magnetic resonance and echocardiographic imaging results

<table>
<thead>
<tr>
<th>Cardiac magnetic resonance</th>
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<tr>
<td>LV ejection fraction (%)</td>
<td>60 ± 7 (40–75)</td>
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<tr>
<td>RV ejection fraction (%)</td>
<td>47.1 ± 8.3 (21.5–68.4)</td>
</tr>
<tr>
<td>Corrective ‘effective’ RV ejection fraction (%)</td>
<td>27 ± 8.6 (13–30)</td>
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<tr>
<td>Pulmonary regurgitation fraction (%)</td>
<td>37 ± 13 (0–58)</td>
</tr>
<tr>
<td>Pulmonary regurgitation volume (L/min/m²)</td>
<td>2.17 ± 0.99 (0–4.19)</td>
</tr>
<tr>
<td>RVOT EDV indexed (mL/m²)</td>
<td>10.5 ± 6.4 (2–36)</td>
</tr>
<tr>
<td>RVOT ESV indexed (mL/m²)</td>
<td>9.4 ± 6.8 (1–37)</td>
</tr>
<tr>
<td>RVOT ejection fraction (%)</td>
<td>10.5 ± 3.9 (–83–70)*</td>
</tr>
<tr>
<td>Echocardiography (n = 39)</td>
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</tr>
<tr>
<td>RV fractional area change (%)</td>
<td>36.3 ± 8.1 (5.2–48.8)</td>
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<tr>
<td>Longitudinal strain: global RV</td>
<td>16.0 ± 3.4 (7.4–22.2)</td>
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<tr>
<td>Longitudinal strain: average RV septal wall</td>
<td>14.4 ± 3.2 (6.2–20)</td>
</tr>
<tr>
<td>Longitudinal strain: average RV lateral wall</td>
<td>17.7 ± 4.1 (7.8–26.6)</td>
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</table>

Table 1 shows the CMR volumetric measurements before and after excluding the akinetic RVOT. RV end-diastolic, end-systolic, and stroke volumes were significantly higher, and RVEF was significantly lower when the akinetic RVOT was included. The absolute gain in RVEF by excluding the RVOT was 2.1 ± 1.4% (range −1.0 to 4.8%), representing 5.1 ± 4.4% (range −2.6 to 24.7%) relative gain of RVEF when compared with the conventional contouring method. The indexed diastolic and systolic RVOT volumes which were excluded by the second contouring method were 10.5 ± 6.4 mL/m² (range 2.0–35.8 mL/m²) and 9.4 ± 6.8 mL/m² (range 1.1–37.5 mL/m²) respectively, representing 6.0 ± 2.5% (range 2.0–15%) and 14 ± 6.7% (range 3.0–37%) of the total RV end diastolic volume and RV end systolic volume, respectively.

The indexed diastolic RVOT volumes correlated inversely with global RVEF (r = −0.50, P = 0.0002). Patients with decreased RVEF (<45%, 28 subjects) had a significantly higher indexed diastolic RVOT volume than patients with an RVEF >45% (16.8 vs. 11.3 mL/m², P = 0.005).

Correlation between CMR and echocardiographic measurements
The RV systolic and diastolic areas by echo correlated well with systolic and diastolic volumes by CMR (r = 0.85, P = 0.0001 and r = 0.68, P = 0.0001, respectively). Global RV longitudinal strain by echo correlated with CMR RVEF, both when including and excluding the RVOT in the EF calculation (r = 0.56, P = 0.0004 and r = 0.58, P = 0.0003, respectively).
Correlations with exercise performance

There was a weak correlation of RVEF with VO2max-predicted, both before and after excluding the akinetic RVOT ($r = 0.33$, $P = 0.049$ and $r = 0.36$, $P = 0.03$, respectively). The other CMR measurements, including indexed RV end-diastolic volume, indexed RV end-systolic volume, RVOT EF, indexed RVOT end-diastolic volume, indexed RVOT end-systolic volume, corrected RV stroke volume, corrected RV ejection fraction, and left ventricular EF did not correlate with exercise tolerance. The correlation of pulmonary regurgitant volume and fraction with VO2max-predicted was weak ($r = 0.38$, $P = 0.04$ and $r = 0.36$, $P = 0.04$, respectively). VO2max-predicted did not differ between male and female patients (66.9 vs. 63.2%; $P = 0.4$), between patients with or without restrictive RV physiology (68.4 vs. 63.4%; $P = 0.4$), and between patients with or without placement of a TAP at the time of complete repair (64.5 vs. 65.8%; $P = 0.8$). Further, VO2max-predicted did not correlate with age at the time of complete repair or duration of the follow-up.

Global RV longitudinal strain by echocardiography showed the best correlation with VO2max-predicted ($r = 0.66$, $P = 0.0001$), slightly better than that of lateral and septal RV wall strain ($r = 0.65$, $P = 0.0001$ and $r = 0.55$, $P = 0.0015$, respectively). Other echo measures, including %FAC, left ventricular EF, as well as the QRS duration showed no correlations with exercise performance. In a bivariate regression model including RVEF (including the QRS duration showed no correlations with exercise performance.

As expected, we found an increase in RVEF after we excluded the aneurismal RVOT. We were surprised, however, by the relatively modest average gain in EF after excluding the akinetic RVOT from the calculation of EF. In most patients, the ‘gain’ in RVEF was thought to be clinically insignificant. In selected individuals, however, the absolute increase in RVEF was as high as 5%, representing a 25% increase over the previous measurement including the RVOT.

The size of the akinetic RVOT was larger in patients who had a lower overall EF by CMR and the RVOT volume was inversely correlated with RVEF. This is in keeping with the results by Davlouros et al.\(^\text{11}\) who found that patients with aneurismal RVOTs had lower RVEFs than patients without outflow tract aneurysms. The inverse correlation of RVOT size and global EF is intuitive as the RVOT dysfunction contributes to a lower global RVEF.

Consistent with the literature, our study showed only a weak correlation between global RVEF and exercise performance.\(^\text{12,13}\) This relationship did not become stronger after excluding the RVOT. In the patients studied here, the regional EF of the RVOT did not predict VO2max-predicted. This is in contrast to a report by Wald et al.\(^\text{6}\) who showed that the systolic function of the RVOT is a more important determinant of exercise tolerance than the remainder of the right ventricle. In their study, lower RVOT EF, but not global RVEF, was associated with the occurrence of sustained ventricular tachycardia.\(^\text{5}\) The reasons for these discrepancies between the study by Wald et al. and the data presented here with regard to the clinical significance of RVOT systolic function are likely related to differences in surgical era and the applied technique, patient age, and imaging approach: less than half of the patients in Wald’s study had undergone a trans-annular patch, when compared with three-fourths in our study. We suspect that this resulted in a higher rate of patients in our study when compared with Wald’s in whom the RVOT did not contribute positively to RV ejection. This is reflected by an average RVOT EF of 11% in our cohort when compared with 41% in the Boston study. (Body et al.\(^\text{14}\) previously reported an EF of 28.5% of the ‘outlet’ portion of the right ventricle). Whereas the mean age of our cohort was 13 years at the time of CMR, Wald’s cohort consisted mainly of adult patients, allowing more time for RV remodelling after complete repair. In contrast to the study by Body et al., both the current report and that by Wald et al. is based on short-axis stacks for volumetry, which might have also contributed to the differences in results.

Although RVOT systolic function is important and is more compromised than that of other parts of the right ventricle,\(^\text{14}\) in

### Table 2  CMR RV volume and function with and without akinetic RVOT

<table>
<thead>
<tr>
<th>Measurements including akinetic RVOT</th>
<th>Measurements excluding akinetic RVOT</th>
<th>Student’s t-test</th>
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<tbody>
<tr>
<td>RV end-diastolic volume index (mL/m²)</td>
<td>170 ± 50 (103–341)</td>
<td>160 ± 46 (96–312)</td>
</tr>
<tr>
<td>RV end-systolic volume index (mL/m²)</td>
<td>96 ± 41 (36–282)</td>
<td>86 ± 36 (32–245)</td>
</tr>
<tr>
<td>RV stroke volume index (mL/m²)</td>
<td>75 ± 19 (42–137)</td>
<td>73 ± 19 (44–136)</td>
</tr>
<tr>
<td>RV ejection fraction (%)</td>
<td>45 ± 8.6 (17.3–66.4)</td>
<td>47.1 ± 8.3 (21.5–68.4)</td>
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</table>

CMR, cardiac magnetic resonance; RV, right ventricle; RVOT, right ventricular outflow tract.

Values reported as mean ± standard deviation and ranges.

Discussion

Ejection fraction, measured by CMR, is the most widely accepted descriptor of RV systolic function.\(^\text{4}\) In patients without regional differences in contractile function, global EF is a good representation of all myocardial segments of the right ventricle.\(^\text{10}\) In contrast, in patients after TOF repair, many of whom have very localized systolic dysfunction, the parameter of EF is inherently insensitive to the differences in contractile function between patients with large outflow tract aneurysms but otherwise preserved function and those without RVOT dyskinesia but overall reduced myocardial shortening.

As expected, we found an increase in RVEF after we excluded the aneurismal RVOT. We were surprised, however, by the
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repaired TOF, longitudinal function describes the contractility of the majority of the RV myocardium. The RV systolic function is highly dependent on longitudinal fibre shortening,15 which has been shown to be reduced in post-operative TOF patients.16

The strain assessment by ultrasound speckle tracking is a promising tool which measures directly myocardial shortening free of geometric assumptions,17 and isonotation angle (which affects tissue Doppler derived indices).3 With this in mind, it is not surprising to find this parameter to be a better predictor of exercise tolerance than other markers of RV function. In fact, when compared with other RV indices, RV strain correlated best with VO2max-predicted.

Limitations

Although echo and CMR studies at our institution are obtained according to a standardized protocol, this was retrospective study and the imaging studies were performed on different dates, leaving time for RV remodelling to progress during the interval. Similarly, CPET was not available in all patients within the targeted 12 month-time interval. We attempted to minimize the influence of interval changes by excluding patients with detectable changes in their clinical status and/or an intervention between echocardiography, CMR, and CPET. It is safe to assume that parameters other than descriptors of RV systolic function also influence exercise tolerance after TOF repair. The limited number of patients and retrospective nature of this study dictated a focus on the role of the right ventricle in this cohort.

Conclusions

In patients following TOF repair, echocardiographic and CMR descriptors of global RV systolic function show at best weak associations with exercise tolerance. The longitudinal function of the right ventricle, measured remotely from the RVOT, may be a more important determinant of exercise performance than global RVEF in patients with aneurismatic RVOTs.

Conflict of interest: none declared.

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