Assessment of Diffuse Ventricular Myocardial Fibrosis Using Native T1 in Children With Repaired Tetralogy of Fallot

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Background—Myocardial fibrosis is linked with adverse clinical outcomes in adults after tetralogy of Fallot repair (rTOF). Native T1 times (T1) by cardiac magnetic resonance have been shown to be a surrogate marker of diffuse myocardial fibrosis. The objective was to quantify native T1 in children post-rTOF and to evaluate their relationship with surgical, imaging, and clinical factors.

Methods and Results—A retrospective cross-sectional study was performed. Midventricular native T1 were obtained in 100 children post-rTOF using a modified look-locker inversion recovery cardiac magnetic resonance sequence and compared with 35 pediatric controls. rTOF patients, aged 13.0±2.9 years, had higher indexed right ventricular (RV) end-diastolic (range 85–326 mL/m^2, mean 148 mL/m^2) volumes, and lower RV and left ventricular (LV) ejection fractions compared with controls. RV, but not LV, T1 were higher in patients than in controls (1031±74 versus 954±32 ms, P<0.001) and female patients had higher RV T1 compared with males (1051±79 versus 1017±68 ms, P=0.02). LV T1 correlated with RV T1 (r=0.45, P<0.001), cardiopulmonary bypass (r=0.30, P=0.007), and aortic cross-clamp times (r=0.32, P=0.004). RV T1 correlated inversely with RV outflow tract gradient (r=-0.28, P=0.02). Longer aortic cross-clamp times were independently associated with LV and RV T1 on multivariable analysis. There was no association between exercise intolerance, arrhythmia, and native T1 or LV extracellular volume.

Conclusions—Children after rTOF do not have elevated LV native T1 or LV extracellular volume, but show evidence of increased RV native T1 suggestive of diffuse RV fibrosis, for which volume loading seems to be a risk factor. Surgical bypass and cross-clamp times are associated with fibrotic remodeling over a decade later. **(*Circ Cardiovasc Imaging*. 2017;10:e005695. DOI: 10.1161/CIRCIMAGING.116.005695.)**

Key Words: children ■ fibrosis ■ magnetic resonance imaging ■ myocardial ■ tetralogy of Fallot

Despite excellent early and intermediate results, patients with repaired tetralogy of Fallot (rTOF) are at risk of significant long-term morbidity, including heart failure, exercise intolerance, arrhythmias, and sudden death.[1–3] Right ventricular (RV) and left ventricular (LV) dysfunction are associated with these adverse outcomes.[4,5] Fibrotic remodeling is thought to play an important role in the pathophysiology of ventricular dysfunction.[6] The extent of localized myocardial scarring on cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) imaging is associated with ventricular dysfunction and adverse outcomes in adults after rTOF.[6,7] More recently, CMR T1 relaxometry has emerged as a valid and reproducible technique for quantifying diffuse myocardial fibrosis.[8–10] Extracellular volume (ECV) fraction, based on pre- and postcontrast T1 times, is elevated in a mixed cohort of adolescents and adults late after rTOF and is found to be associated with unfavorable ventricular remodeling and adverse clinical outcomes.[11,12] The presence and potential significance of imaging markers of diffuse myocardial fibrosis in young patients after rTOF are emerging, with the study of RV ECV in a mixed cohort[12] and pilot data from postcontrast T1 measurements[13] suggesting that myocardial fibrosis is increased in this population. The primary objective of this study was to determine if children after rTOF have evidence of diffuse myocardial fibrosis using noncontrast T1. The secondary objective was to explore possible pathogeneses and the clinical significance of diffuse fibrosis in these patients.

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Methods

The Hospital for Sick Children research ethics board approved this single-center retrospective cross-sectional study and waived the requirement for informed consent. The hospital database was screened for patients after rTOF who had undergone a CMR examination including T1 relaxometry between October 2013 and May 2016. Patients with a primary diagnosis of an atrioventricular septal defect with TOF, absent pulmonary valve syndrome, and major aortopulmonary collaterals or who underwent pulmonary valve replacement after the initial repair or subsequent cardiac surgeries were excluded.

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Patients with a significant residual ventricular septal defect as well as CMR studies with poor modified look-locker inversion (MOLLI) recovery image quality were excluded. If patients had multiple CMR examinations during the studied time period, only the first test was analyzed. Clinical and demographic information were obtained from the patients' medical records.

The control group consisted of children and adolescents with normal baseline cardiac investigations who were referred for a screening CMR (eg, likely noncardiac chest pain for coronary artery assessment with subsequently normal coronaries on CMR or asymptomatic family members of patients with arrhythmogenic RV cardiomyopathy with normal electrophysiology and imaging examinations).

Cardiac Magnetic Resonance

All CMR examinations were performed on a 1.5-Tesla scanner ("Avanto"; Siemens Medical Systems, Erlangen, Germany). The protocol included a cine short-axis stack for quantification of ventricular volumes, mass and ejection fraction, and main pulmonary artery phase contrast flow velocity mapping. In patients who underwent CMR for the first time, scar imaging with LGE in short-axis and axial planes were obtained. Native T1 were derived using a MOLLI sequence at a single mid short-axis level with 2 inversion pulses followed by 5 and 3 single-shot image acquisitions during diastole. The interval between the inversion pulses was adapted to the patients' heart rates, to allow for recovery of longitudinal relaxation before next inversion experiments. Images were acquired during breatholds when possible to minimize respiratory motion artifact. An in-line motion correction algorithm was used to improve coregistration of the 8 individual images before analysis. The other sequence parameters included repetition and echo times of 2.68 and 1.13 ms, respectively, 8 mm slice thickness, 1.4×1.4 mm in-plane resolution and flip angle of 35°.

A commercially available software package with a curve-fitting algorithm, CVI42 (Version 5.0, Circle Cardiovascular Imaging, Calgary, AB, Canada), was used to measure native T1. T1 relaxation curves were derived from regions of interest drawn manually within the interventricular septum (IVS), LV free wall, entire LV myocardium, and diaphragmatic wall of the RV (Figure 1). Care was taken to ensure that regions of interests were within myocardial walls thus avoiding partial volumes with blood pool or epicardial fat. Likewise, areas of LGE were excluded from regions of interest. A single observer performed analyses for cases and controls. Native T1 were assessed by a second observer in 18 randomly selected cases and 18 controls.

Ventricular volumes and mass were quantified in the usual clinical fashion using commercially available software ("QMass," version 7.6; Medis Medical Imaging Systems, Leiden, The Netherlands). Flow was analyzed using "QFlow" (version 5.6, Medis); pulmonary regurgitant (PR) volume and fraction were quantified in the usual fashion. Late end-diastolic forward flow as a marker of restrictive physiology was defined as a distinct peak of forward flow before the upstroke of systolic forward flow in the main pulmonary artery.[14]

Echocardiography

Clinical transthoracic echocardiography studies within 6 months of CMR were collated. RV end-diastolic dimension *z* score, RV outflow tract (RVOT) peak Doppler gradient, estimated RV systolic pressure, and fractional area change were collected. Chamber dimensions were quantified in accordance with published guidelines.[15]

Electrocardiography, Cardiopulmonary Exercise Testing, and Arrhythmias

The results of cardiopulmonary exercise testing and 24-hour Holter monitoring were recorded if performed within 18 months of the CMR examination. Cardiopulmonary exercise testing was performed using an upright bicycle and a modified Bruce protocol with standard metabolic measurements of expiratory gases. As long as the patient performed to maximal effort, peak oxygen consumption, anaerobic threshold, and workload were recorded as a percentage of predicted results for patient sex and age.[16] A reduction in exercise capacity was defined as 70% or less of predicted peak oxygen consumption. QRS duration on electrocardiograms closest to the CMR date was recorded. Clinically relevant arrhythmias were defined as presence of one or more of the following on Holter or exercise testing: supraventricular tachycardia, ventricular ectopy not suppressed at peak exercise,

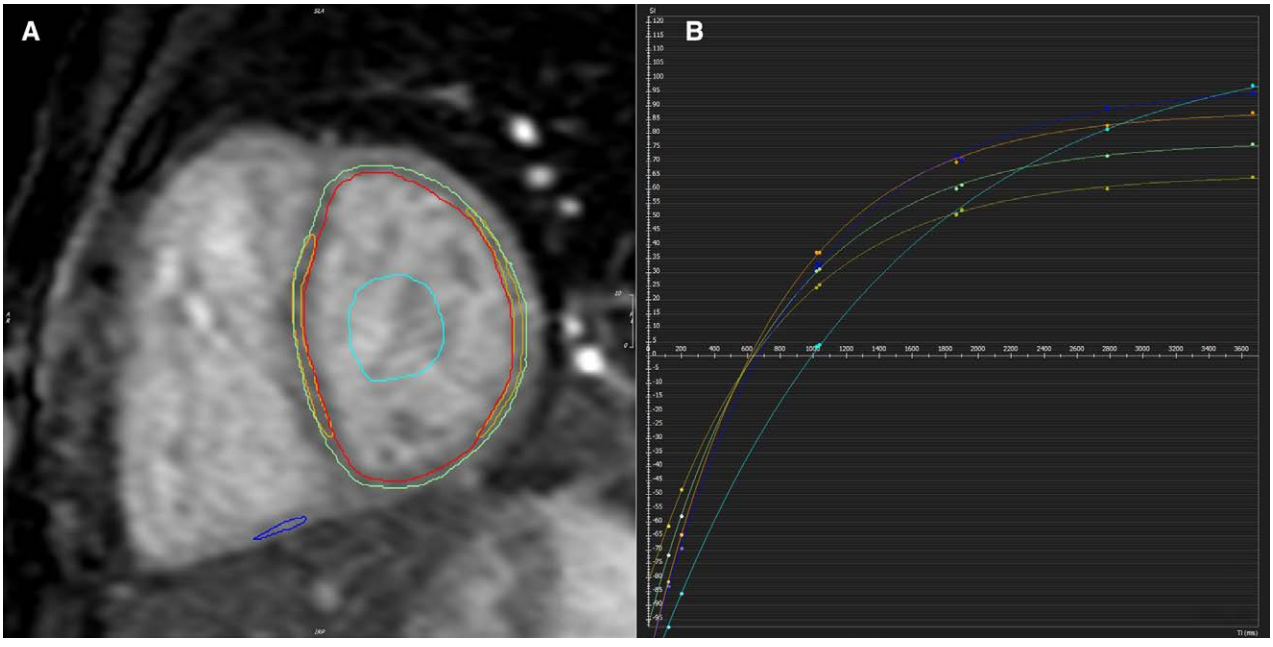

Figure 1. Noncontrast T1 mapping. **A**, Noncontrast T1 maps were acquired from electrocardiogram-gated and motion corrected modified look-locker inversion sequences. Regions of interest (ROI) were drawn within the interventricular septum (orange), left ventricular (LV) free wall (yellow) and right ventricle (blue). The entire LV myocardium T1 was derived by endocardial (red) and epicardial (green) contours. **B**, A curve-fitting algorithm was applied to each ROI, and myocardial T1 were derived using exponential curves of best fit.

frequent premature ventricular ectopics defined as >100 isolated or ≥20 couplets over 24 hours,[5] nonsustained or sustained ventricular tachycardia.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk, NY). Measurements were expressed in mean values with SD or absolute numbers with percentages where appropriate. A χ^2 test was used to compare the binary variable of sex between the cases and controls and 2-tailed independent samples *t* test was used to compare continuous variables between the groups when data were normally distributed. The Mann–Whitney *U* test was used to compare non-normally distributed continuous data between the smaller subgroups. Pearson bivariate correlation determined correlations between continuous variables and point biserial correlation was used to correlate native T1 to dichotomous variables. Variables that correlated with native T1 with a *P* value of <0.1 were entered into a multivariable stepwise linear regression model and the R^2 value was reported for the final model. For the latter and all other analyses, $P<0.05$ were considered statistically significant. Interobserver variability was assessed using Bland–Altman analysis and calculation of the intraclass correlation coefficient to detect proportional bias and determine the level of agreement.

Results

Demographics and Surgical Data

After exclusion of 5 patients with poor quality data sets, 100 cases and 35 control patients were included in the study analysis. Patient demographics are summarized in Table 1. Seventy-eight patients had TOF, 7 were classified as double outlet RV-TOF, and 15 patients had pulmonary atresia-TOF. Genetic syndromes were present in 9 patients, including 22q11.2 chromosomal deletion in four, VACTERL association in 3, and Trisomy 21 in 2 patients.

Seven patients had undergone a Blalock–Taussig or central shunt as a primary procedure. A transannular patch had been performed in 47 patients, valve-sparing surgery in 43, and an RV-pulmonary artery conduit in 9 patients. Information on the type of repair was not available in 1 case. The median age at the time of repair was 5.8 (3.7–8.6) months.

Baseline CMR Parameters

CMR results of the study cohort compared with controls are summarized in Table 1.

The controls were comparable to cases in sex distribution and heart rate, but were older with a higher weight and body surface area. Cases had higher indexed RV end-diastolic volumes, end-systolic volumes, stroke volumes, and lower LV and RV ejection fractions than controls.

LGE was performed in 74 patients. Of these patients, 4 (5%) had positive LGE outside of the ventricular septal defect or RVOT patch. This included focal scarring at RV insertion points into the IVS (2 patients), RVOT adjacent to the outflow patch (1 patient), and anterosuperior RV free wall (1 patient).

LV Native T1

The average native T1 for the entire LV, IVS, and LV free wall were 979±57 ms, 991±61 ms, and 967±72 ms, respectively. There were no statistically significant differences between LV IVS, free wall, or global LV native T1 between cases and controls. There were no statistically significant differences in LV T1 between males and females in either group. A previous aortopulmonary shunt was not associated with increased native T1.

LV ECV was calculated in 60 patients and 26 controls with available hematocrit and postcontrast T1 values. Similar to native T1, LV ECV was not statistically significant between cases and controls (25±4% versus 23±4%, $P=0.18$).

Correlations of LV myocardial native T1 with clinical parameters are summarized in Tables 2 and 3. By univariate analysis, LV native T1 correlated inversely with LV mass-index and LV mass/volume ratio and positively with

Table 1. Patient and Control Characteristics

Variable	Cases (n=100)	Controls (n=35)	*P* Value
Age at CMR, y	13.0±2.9	14.1±2.5	0.04
Male:female, %	59:41	16:19	0.17
Weight, kg	47.2±19.0	62.7±20.0	<0.001
BSA, m^2	1.4±0.3	1.7±0.3	<0.001
QRS duration, ms	129±24	89±10	<0.001
Average HR, bpm	78±13	75±11	0.29
Bypass time, min*	126±46	…	…
Aortic cross-clamp time, min*	70±21	…	…
CMR parameters			
LV mass-index, g/m^2	47.3±10.8	49.8±10.7	0.25
LV mass/volume ratio	0.52±0.10	0.56±0.11	0.08
LVEDVi, mL/m^2	91.5±15.9	89.5±11.7	0.51
LVESVi, mL/m^2	42.4±11.8	36.6±6.7	0.01
LVEF, %	54±6	59±5	<0.001
RV mass-index, g/m^2	42.8±11.3	28.6±4.2	<0.001
RV mass/volume ratio	0.29±0.5	0.30±0.04	0.31
RVEDVi, mL/m^2	148.0±42.3	95.1±14.5	<0.001
RVESVi, mL/m^2	77.1±28.9	45.2±7.6	<0.001
RVEF, %	49±6	52±4	0.001
PR fraction, %	33±14	…	…
PR volume L/min per m^2	1.9±1.1	…	…
Native T1 parameters			
Entire LV, ms	988±57	967±28	0.24
IVS, ms	991±61	971±29	0.08
LV free wall, ms	967±72	954±36	0.31
RV, ms	1031±74	954±32	<0.001
LV ECV, %	25±4	23±4	0.18

Data are expressed as mean±SD or % where appropriate. BSA indicates body surface area; CMR, cardiovascular magnetic resonance; ECV, extracellular volume; EDVi, end-diastolic volume index; EF, ejection fraction; ESVi, end-systolic volume index; HR, heart rate; IVS, interventricular septum; LV, left ventricular; PR, pulmonary regurgitant; RV, right ventricular; and SVi, stroke volume index.

*Perfusion records were unavailable in 21 cases.

Table 2. Correlation of Significant Variables With Left Ventricle Global and Regional T1 Parameters and Right Ventricle T1 Parameters Using Univariate Analysis

	Entire LV		RV	
	Correlation coefficient (r)	*P* Value	Correlation coefficient (r)	*P* Value
QRS duration	0.13	0.17	0.22	0.02
Bypass time	0.30	0.007	0.11	0.35
Cross-clamp time	0.32	0.004	0.25	0.02
LV mass-index	−0.28	0.001	−0.29	0.001
LV mass/volume ratio	−0.28	0.002	−0.29	0.048
LVEDVi	−0.05	0.57	−0.20	0.04
RVEDVi	0.14	0.11	0.22	0.01
RVESVi	0.17	0.06	0.22	0.02
PR volume	0.23	0.02	0.24	0.02
RVOT gradient	−0.17	0.12	−0.24	0.02

CMR indicates cardiac magnetic resonance; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LV, left ventricle; PR, pulmonary regurgitation; RV, right ventricle; RVEDVi, indexed RV end-diastolic volume; RVESVi, indexed RV end-systolic volume; and RVOT, right ventricular outflow tract.

cardiopulmonary bypass and aortic cross-clamp times. PR volume, but not PR fraction, correlated with LV T1. Other CMR volumetric parameters and RVOT gradient did not correlate with LV T1. Using multivariable analysis, LV T1 was associated with aortic cross-clamp times.

When comparing patients with elevated LV T1 (defined as 2 SDs above the mean LV T1 for controls) to patients with LV T1 in the normal range, the group with elevated T1 had longer cross-clamp times at primary repair, lower RV fractional area change and RVOT gradient by echocardiography, and lower RV mass/volume ratio by CMR (Tables 4 and 5). Non-LGE myocardium in patients with positive LGE had higher LV T1 (1068±76 ms versus 979±52 ms, P=0.002) and a trend toward increased RV T1 (1093±152 ms versus 1026±70 ms, P=0.09) compared with those without LGE.

RV Native T1

Patients after rTOF had higher native T1 times in the RV inferior wall than controls (1031±74 ms versus 954±32 ms, P<0.001). RV T1 were higher in female rTOF patients compared with males (1051±79 ms versus 1017±68 ms, P=0.02). There was no statistically significant sex difference within the control group. RV native T1 correlated with LV T1, with the strongest association seen between RV and IVS T1 (r=0.55, P<0.001, Figure 2). On univariate analysis, weak negative correlations were noted between RV T1 and RVOT gradient, indexed end-diastolic volume LV, LV mass-index, and mass/volume ratio. Positive correlations were found between RV T1 and PR volumes, aortic cross-clamp times, QRS duration, indexed RV end-diastolic volume, and indexed RV end-systolic volume. RV mass, mass/volume ratio, presence of late end-diastolic forward flow in the main pulmonary artery, or echocardiographic markers of systolic function were not associated with RV T1. During multivariable analysis, RV T1 was associated with aortic cross-clamp time (P<0.001) and female sex (P=0.01, R^2=0.22 for the model).

Table 3. Multivariable Analysis of Factors Associated With Left and Right Ventricular Native T1

Variable	Std β-Coefficient	SE	*P* Value	Model R^2
Left ventricular T1				
Cross-clamp time	0.39	0.29	0.001	0.16
Right ventricular T1				
Cross-clamp time	0.44	0.36	<0.001	0.22
Female sex	0.28	15.73	0.01	

rTOF patients with RV T1 above the mean+2 SD in controls had a lower RVOT gradient, RV systolic pressure, and fractional area change by echocardiography as well as a lower RV mass/volume ratio by CMR (Tables 4 and 5). The quality of the postcontrast MOLLI images in the RV in most patients was insufficient to quantify postcontrast T1.

Native T1 and Clinical Significance

Holter monitoring and exercise testing had been performed in 27 and 51 cases within 18 months of the CMR examination, respectively. Six patients were identified to have arrhythmias on Holter or exercise testing. Five patients had exercise intolerance on exercise testing. There was no association between LV or RV native T1 and exercise intolerance or arrhythmias. In keeping with LV T1, LV ECV was not associated with clinical outcomes in our patient cohort.

Volume Loading Versus Pressure Loading of the RV

Patients had, on average, moderate PR with a fraction of 33%. Patients after transannular patch repair had higher indexed RV end-diastolic volume (160.1±45.4 mL/m^2 versus 137.0±36.3 mL/m^2, P=0.006) and RV-indexed stroke volume (77.8±17.9 mL/m^2 versus 64.5±14.7 mL/m^2, P<0.001) on CMR, and higher RV end-diastolic dimension z score (3.5±1.4 versus 2.6±1.5, P=0.003) on echocardiography compared with non-transannular patch repair patients. T1 did not differ between valve sparing, valved conduit, and transannular patch repairs.

A predominantly volume-loaded RV was defined as an RVOT gradient <25 mm Hg and PR fraction of >20%, whereas a pressure-loaded ventricle was defined as RVOT gradient >40 mm Hg and a PR fraction of <20%. Using these definitions, there were 34 patients with volume-loaded RVs and six with pressure-loaded RVs; the remaining 60 patients with mixed volume and pressure-loaded ventricles.

Compared with pressure-loaded ventricles, volume-loaded RVs had higher RV T1, RV end-diastolic dimension z score, indexed RV end-diastolic volume, and indexed RV end-systolic volume, whereas RV mass/volume ratio and RV systolic pressure were lower (Table 6).

Interobserver Variability

A blinded reanalysis of T1 was performed in 18 randomly selected rTOF cases and controls by a second observer. There was no significant interobserver bias with acceptable

Table 4. Sub-Analysis Stratified by Elevated Versus Normal Left Ventricular T1

Variable	Native T1 (Normal Range) Entire LV<1023 ms (n=82)	Elevated Native T1 Entire LV>1023 ms (n=18)	*P* Value
LV T1			
Cross-clamp time, min	65 (52–76)	78 (60–90)	0.04
RVOTO, mm Hg	27 (20–49)	22 (17–31)	0.04
FAC, %	45 (40–49)	38 (28–42)	0.002
RV mass/volume ratio	0.31 (0.26–0.32)	0.27 (0.25–0.29)	0.03

Values expressed as median (interquartile range).FAC indicates fractional area change; LV, left ventricle; RV, right ventricle; and RVOTO, right ventricular outflow tract obstruction.

reproducibility for both LV and RV native T1 measurements (Table 7, Bland–Altman plots in Figure 3). Reproducibility was best for the IVS. Interobserver agreement for RV T1 measurements was comparable to that in the LV free wall.

Discussion

Myocardial fibrosis in adults late after rTOF is associated with impaired ventricular function and adverse clinical outcomes.[11,12] Whether the hearts of young patients after rTOF also suffer from accelerated fibrotic remodeling has been unclear, as are its potential pathogeneses and clinical implications. To the best of our knowledge, this is the largest study on the extent and impact of CMR markers of diffuse myocardial fibrosis in congenital heart disease. Our study adds the following information to our understanding about cardiovascular health in children after rTOF:

1. RV native T1 as a surrogate for diffuse myocardial fibrosis is significantly increased, especially with volume overload and in females;
2. RV native T1 correlates with LV T1, consistent with the concept of ventriculo–ventricular interactions at a tissue level; and
3. Surgical insults to the myocardium at the time of primary repair are risk factors for the development of diffuse myocardial fibrosis.

Table 5. Sub-Analysis Stratified by Elevated Versus Normal Left Ventricular T1

Variable	Native T1 (Normal Range) RV<1018 ms (n=43)	Elevated Native T1 RV>1018 ms (n=56)	*P* Value
RV T1			
RV systolic pressure, mm Hg	42 (35–55)	36 (30–42)	0.02
FAC, %	46 (42–50)	42 (36–46)	0.04
RVOTO, mm Hg	38 (21–51)	24 (19–33)	0.03
RV mass/volume ratio	0.31 (0.26–0.33)	0.28 (0.25–0.31)	0.04

Values expressed as median (interquartile range). FAC indicates fractional area change; RV, right ventricle; and RVOTO, right ventricular outflow tract obstruction.

LV and RV T1

Our findings of increased native RV T1 are congruent with the pediatric post-rTOF T1 mapping study by Kozak et al,[13] who found significantly shorter postcontrast RV T1 than in controls suggesting an increased fibrosis burden in this population. Fibrosis may be attributed to a combination of factors including chronic preoperative hypoxemia, genetic predisposing factors, a proinflammatory response to cardiopulmonary bypass, ventriculotomy, and abnormal loading conditions.[13,17,18] A pilot report by Broberg et al[11] and a more recent prospective study in 52 subjects[19] reported higher LV ECV in adult cases and a more recent publication by Chen et al[12] found that RV ECV was increased in a mixed cohort of adults and children post-rTOF. Although some argue that native T1 is less sensitive toward fibrotic remodeling than ECV, the evidence is conflicting.[20,21] LV septal T1 correlate with myocardial fibrosis on biopsy in adults with aortic stenosis.[22] It is conceivable that children exhibit less LV myocardial fibrosis than adults. This is supported by our findings of a lack of a statistically significant difference between both LV native T1 and LV ECV between cases and controls. As compared to patients studied by Broberg et al,[11] children and adolescents in this study were not only younger with shorter exposure to abnormal loading conditions but also, at least in part, represent a more contemporary surgical era where limitation of postoperative PR as much as possible has become the preferred strategy.[11,23,24] Compared with the 1980s and early 1990s when most of Broberg's patients were operated, intraoperative cardioprotection has improved.[24] Likely as a result of surgical strategy, only 5% of our patients were positive for LGE outside of the ventricular septal defect patch and the distal RVOT, in contrast to 53% reported in adult rTOF patients a decade ago.[6]

The investigators of the German Competence Network[25] found worse RV, but not LV, systolic function and inferior exercise tolerance in female rTOF patients when compared with males. Our finding of higher RV, but not LV, T1 in females is further evidence that girls and women after rTOF may be at higher risk of adverse RV remodeling than boys and men.[25]

We did not find an association between arrhythmia with native T1 or LV ECV, although our study may have been underpowered to detect associations between exercise intolerance or arrhythmias and T1 because of the low incidence of arrhythmias and exercise intolerance in children. In contrast, Chen et al[12] demonstrated an association of LV ECV with arrhythmias in older patients after rTOF. Focal fibrosis on LGE was also associated with exercise intolerance in adults.[6,7]

Volume Versus Pressure Loading

Children and adolescents with volume-loaded RVs had lower RV mass/volume ratios and higher RV T1 compared with pressure-loaded RVs. A higher RVOT gradient, however, was associated with less fibrosis as indicated by T1. Both findings are in keeping with the results by Chen et al[12] who found that subjects with volume-loaded RVs had higher RV (and LV) ECV compared with patients with pressure-loaded ventricles. They and others speculate that the mode of ECV increase is cardiomyocyte atrophy, which leads to a proportional increase of the extracellular space rather than a primary profibrotic process infiltrating "normal" myocardium, as

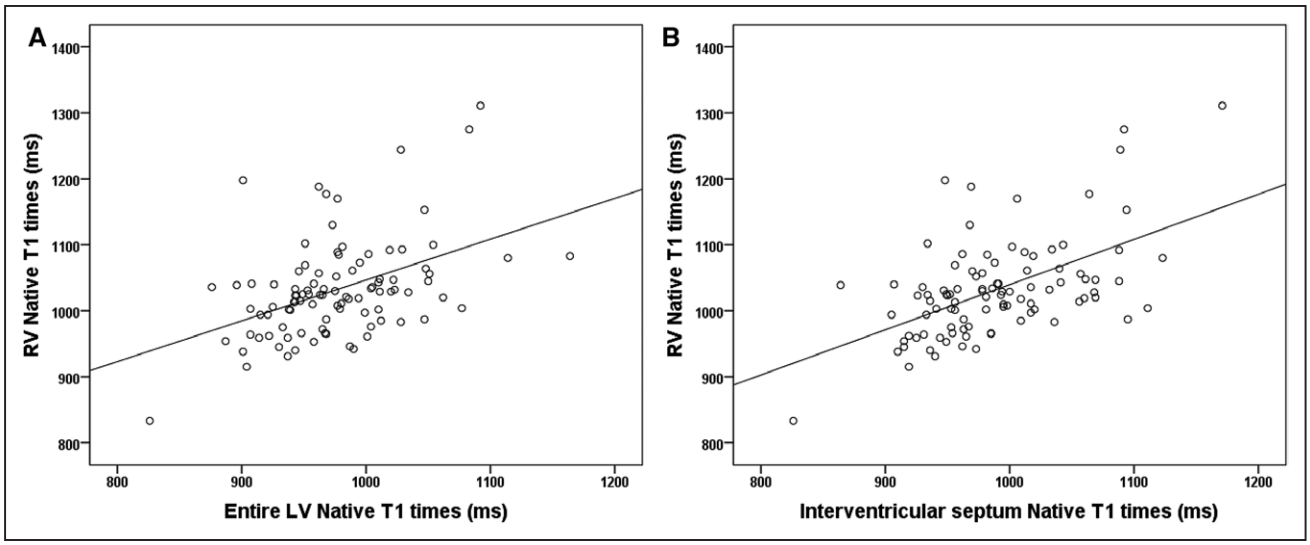

Figure 2. Correlation between right ventricular with global left ventricular (**A**) and interventricular septum (**B**) native T1 parameters. LV indicates left ventricle; and RV, right ventricle.

proposed by others.[26,27] Regardless of the pathophysiological mechanism of extracellular matrix expansion and whether it is absolute or relative to healthy myocyte volume, the results from the current and Chen et al's[12] study support the current surgical strategy of limiting the amount of PR during RVOT reconstruction.[28]

Table 6. Sub-Analysis of Volume Versus Pressure-Loaded Ventricles

Variable	Volume Loading RVOTO<25 mm Hg and PR>20% (n=34)	Pressure Loading RVOTO>40 mm Hg and PR<20% (n=6)	*P* Value
Native T1 parameters			
Entire LV, ms	982 (947 to 1028)	967 (946 to 1003)	0.47
IVS, ms	993 (957 to 1041)	964 (936 to 994)	0.16
LV free wall, ms	960 (930 to 1017)	1014 (940 to 1024)	0.50
RV, ms	1041 (1004 to 1081)	976 (956 to 1005)	0.005
Echocardiography parameters			
RVEDD *z* score	3.7 (2.7 to 4.3)	0.3 (–0.5 to 2.8)	0.001
RVSP, mm Hg	34 (30 to 39)	55 (41 to 58)	0.01
TAPSE	16 (14 to 19)	16 (15 to 17)	0.74
FAC, %	43 (39 to 47)	47 (45 to 49)	0.57
CMR parameters			
LV mass-index	42 (38 to 51)	42 (36 to 49)	0.67
LV mass/volume ratio	0.48 (0.41 to 0.54)	0.5 (0.5 to 0.6)	0.54
LVEDVi, mL/m^2	95 (85 to 100)	79 (78 to 90)	0.03
LVESVi, mL/m^2	45 (38 to 53)	33 (30 to 43)	0.04
LVEF, %	52 (49 to 57)	57 (53 to 61)	0.18
RV mass-index	44 (39 to 48)	43 (32 to 51)	0.78
RV mass/volume ratio	0.28 (0.25 to 0.31)	0.38 (0.32 to 0.41)	<0.001
RVEDVi, mL/m^2	161 (144 to 180)	113 (92 to 130)	<0.001
RVESVi, mL/m^2	85 (72 to 94)	59 (41 to 75)	0.01
RVEF, %	48 (46 to 50)	50 (43 to 54)	0.52

Values expressed as median (interquartile range). EDD indicates end-diastolic dimension; EDVi, end-diastolic volume indexed; EF, ejection fraction; ESVi, end-systolic volume indexed; FAC, fractional area change; IVS, interventricular septum; LV, left ventricular; PR, pulmonary regurgitation; RV, right ventricular; RVOTO, right ventricular outflow tract obstruction; RVSP, right ventricular systolic pressure; and TAPSE, tricuspid annular planar systolic excursion.

Table 7. Interobserver Variability for LV and RV Native T1 Parameters

T1 Times	% Mean Bias (95% CI)	*P* Value (95% CI)	ICC	*P* Value
Entire LV, ms	−0.04 (−1.69 to 1.61)	0.95	0.90 (0.73 to 0.96)	<0.001
IVS, ms	−0.13 (−0.83 to 0.58)	0.72	0.98 (0.95 to 0.99)	<0.001
LV free wall, ms	0.27 (−1.52 to 2.05)	0.76	0.94 (0.84 to 0.98)	<0.001
RV, ms	−0.81 (−1.90 to 0.29)	0.14	0.96 (0.90 to 0.99)	<0.001

ICC indicates intraclass correlation coefficient with 95% confidence intervals (CIs); IVS, interventricular septum; LV, left ventricle; and RV, right ventricle.

Effect of Surgical Repair on Fibrosis

The association of LV T1 with cardiopulmonary bypass time and both LV and RV T1 with ischemic time during aortic cross-clamping were unexpected findings, albeit their associations were weak and other factors (for example, duration of ischemia and cyanosis, postoperative chronic volume, or pressure loads) are at play. Cardiopulmonary bypass sets in motion a systemic inflammatory response that becomes more pronounced with longer periods of bypass and cross-clamping.[29] We speculate that the proinflammatory cascade, operative stresses as well as myocardial ischemia and reperfusion injury[30,31] may trigger development of abnormal myocardial remodeling and fibrosis that adversely affects long-term myocardial integrity.[6]

Ventriculo–Ventricular Interactions

There was a moderate correlation between RV and LV T1 in our patients, in keeping with the report by Chen et al[12] on ECV in rTOF patients. These correlations support the concept

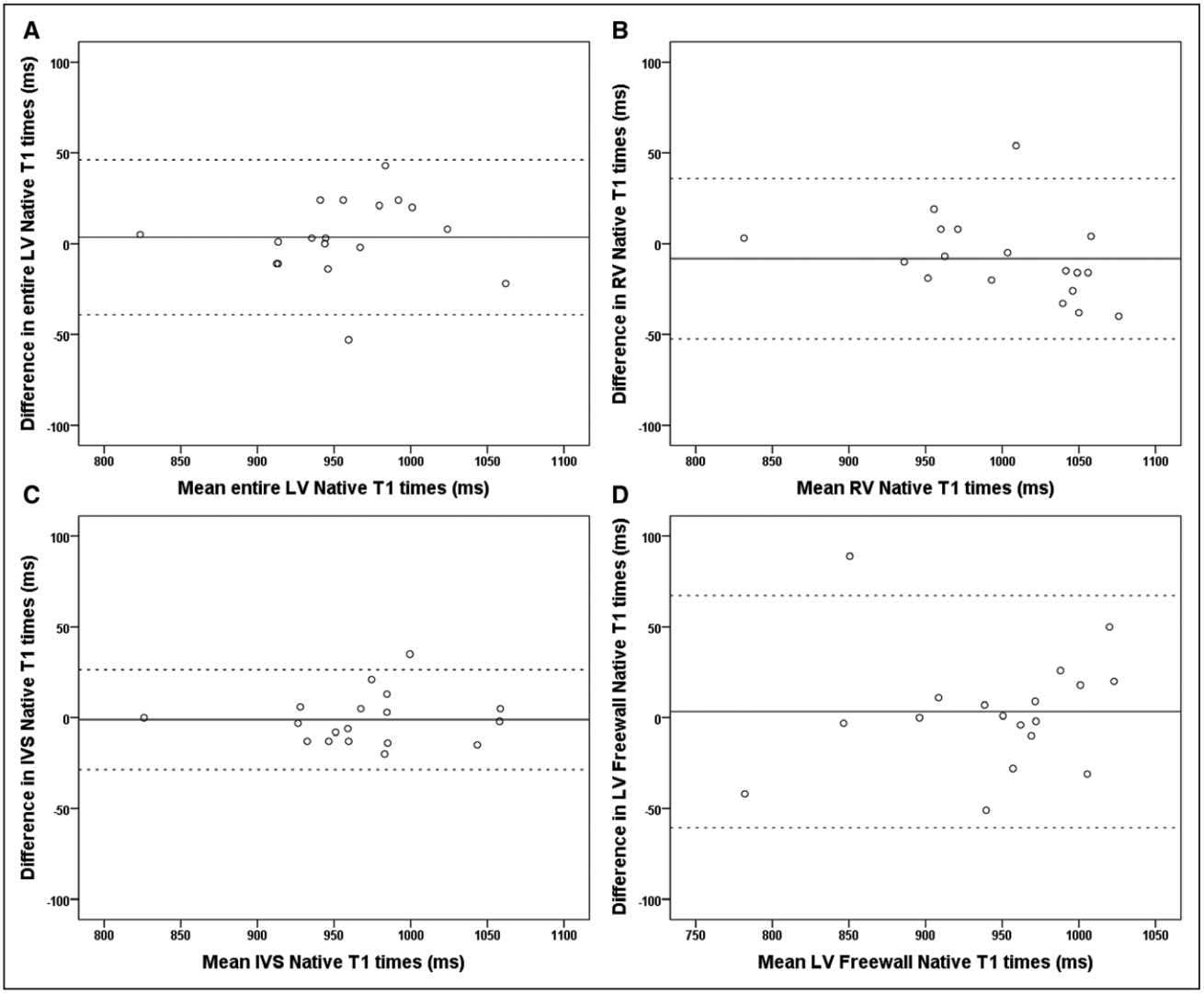

Figure 3. Bland–Altman plots for left and right ventricular native T1 parameters. Bland–Altman scatter plots demonstrate the mean differences between measured T1 values plotted against the average of T1 measurements (in ms) for (**A**) entire left ventricle (LV), (**B**) right ventricle (RV), (**C**) interventricular septum (IVS), and (**D**) LV free wall. Lines for the mean (bold) and +1.96 or −1.96 SDs (dotted) from the mean are shown.

that ventriculo–ventricular interactions also occur at the tissue level, extending beyond the interactions through pulmonary blood flow and septal position.[32]

Native T1 Versus ECV Versus LGE

In comparison with ECV, native T1 relaxometry has the advantage of being a noncontrast technique. As such, it does not depend on an intravenous cannula (which is a concern in children), is not affected by contrast type and does not require acquisition of postcontrast T1 sequences. More importantly, emerging concerns surrounding long-term gadolinium accumulation in brain tissue[33] mandates avoidance of contrast whenever possible, particularly in children. In chronic disease without a significant inflammatory component, as can be assumed to be the case in long-term survivors after rTOF, native T1 relaxometry shows good correlation with collagen amount by histopathology.[21] Although both native T1 and ECV are CMR markers of myocardial fibrosis, they are not interchangeable. Broberg et al[11] found little agreement between LGE and ECV in their study of adults with a variety of congenital heart diseases. In our cohort, patients with LGE demonstrated higher LV T1 (in non-LGE myocardium) and a trend toward higher RV T1, suggesting that focal and diffuse fibrosis development share a common pathway and patients who have evidence of focal myocardial fibrosis are more likely to exhibit diffuse fibrosis.

Study Limitations

We excluded patients who had multiple surgeries from the study cohort to eliminate the confounder of multiple bypass runs. This may have introduced a selection bias; nevertheless, given the impact of cardiopulmonary bypass and aortic cross-clamp times on T1, we feel it was important to control for these variables. The small cohort of patients with pressure-loaded RVs may have affected the comparison between RV loading conditions; however, the statistically significant findings despite the small sample size add weight to the differences observed between pressure and volume-loaded conditions. Measurements of T1 in a single midventricular short-axis slice were used for analysis to limit scan time and breatholds this practice was based on the assumption that interstitial changes are homogenous throughout the myocardium, which may not always be the case. RV T1 can be difficult to measure owing to the thin-walled myocardium, alongside acquisition with MOLLI sequences during diastole using an in-plane resolution of 1.4×1.4 mm. It is possible that partial volume effects may have lead to falsely elevated T1 measurements in volume-loaded ventricles (with potentially thinner myocardium and more partial voluming). However, care was taken to avoid blood pool contamination; the acceptable reproducibility and fact that RV T1 was even lower in controls with presumably thinner myocardium point toward an accurate representation of T1, or at least similar partial volume effects in both groups. Newer sequences have been proposed to overcome potential limitations of MOLLI sequences for RV measurements.[34] RV ECV was not included in our analysis as it remains controversial whether this can be reliably assessed.[11,35] Although Chen et al[12] reported acceptable reproducibility with RV ECV, Plymen et al[36] were less convinced of its feasibility. To date, we have found that measuring postcontrast T1 in the RV to be inherently difficult and not consistently reliable, hence it was not included in our study.

Conclusions

Pediatric survivors after rTOF have elevated RV native T1 times suggestive of diffuse RV myocardial fibrosis, associated with RV volume loading and female sex. In contrast to adults, the LV did not show signs of fibrotic remodeling. However, despite preserved LV myocardial health, at least on average, longer cardiopulmonary bypass and cross-clamp times seem to have a chronic negative effect on ventricular remodeling. Further research into the prognostic significance and progression of RV fibrosis in children is warranted.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Cardiac magnetic resonance markers of myocardial fibrosis late after tetralogy of Fallot repair have been linked with adverse clinical outcomes. The extent and significance of diffuse myocardial fibrosis in children after tetralogy of Fallot repair are unclear. Native T1 relaxometry has emerged as a valid and reproducible technique in quantifying diffuse myocardial fibrosis. The present study shows that children after tetralogy of Fallot repair, especially those with volume-loaded right ventricles, have increased right ventricular T1 suggestive of right ventricular myocardial fibrosis. Contrary to adults, the left ventricle does not show evidence of fibrotic remodeling in children. Surgical insults at the time of primary repair seem to increase the long-term risk of adverse ventricular remodeling. Further research addressing the prognostic significance and progression of right ventricular fibrosis in children is warranted.

Assessment of Diffuse Ventricular Myocardial Fibrosis Using Native T1 in Children With Repaired Tetralogy of Fallot

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