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Ventricular Fibrosis Suggested by Cardiovascular Magnetic Resonance in Adults With Repaired Tetralogy of Fallot and Its Relationship to Adverse Markers of Clinical Outcome

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Background—Late morbidity and mortality remain problematic after repair of tetralogy of Fallot (TOF). We hypothesized that fibrosis detected by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) would be present in adults with repaired TOF and would be related to adverse markers of outcome.

Method and Results—LGE was scored in the right and left ventricles (RV and LV) of 92 adult patients who had undergone TOF repair. RV LGE was seen in all patients at surgical sites located in the outflow tract (99%) or the site of ventricular septal defect patching (98%) and in the inferior RV insertion point (79%) and trabeculated myocardium (24%). LV LGE (53%) was located at the apex consistent with apical vent insertion (49%), in the inferior or lateral wall consistent with infarction (5%), or in other areas (8%). Patients with supramedian RV LGE score were older (38 versus 27 years, $P<0.001$) and more symptomatic (38% versus 8% in New York Heart Association class II or greater, $P=0.001$), had increased levels of atrial natriuretic peptide (7.3 versus 4.9 pmol/L, $P=0.041$), and had a trend to higher brain natriuretic peptide (12.3 versus 7.2 pmol/L, $P=0.086$), exercise intolerance (maximum $\dot{V}O_2$ 24 versus 28 mL $\cdot$ min^{-1} $\cdot$ kg^{-1}, $P=0.021$), RV dysfunction (RV end-systolic volume 61 versus 55 mL/m^2, $P=0.018$; RV ejection fraction 50% versus 56%, $P=0.007$), and clinical arrhythmia (26% versus 10%, $P=0.039$). Non–apical vent LV LGE also correlated with markers of adverse outcome. In a multivariate model, RV LGE remained a predictor of arrhythmia.

Conclusions—RV and LV LGE were common after TOF repair and were related to adverse clinical markers, including ventricular dysfunction, exercise intolerance, and neurohormonal activation. Furthermore, RV LGE was significantly associated with clinical arrhythmia. **(*Circulation*. 2006;113:405-413.)**

Key Words: arrhythmia ■ magnetic resonance imaging ■ risk factors ■ tetralogy of Fallot ■ fibrosis

Advances in cardiothoracic surgery have greatly improved the prognosis for patients who undergo repair of tetralogy of Fallot (TOF); however, late ventricular dysfunction remains a problem and is related to pulmonary regurgitation, arrhythmia, and sudden cardiac death.[1–4] Autopsy specimens have suggested fibrosis to be causative.[5] Late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) has already contributed to our understanding of the pathophysiology of both ischemic[6–8] and nonischemic[9–11] causes of dysfunction in the left ventricle (LV) and has been validated with histology in these contexts. LGE suggestive of fibrosis has also been demonstrated in the systemic right ventricle.[12] In the present study, we hypothesized that LGE would be present in adults with surgically repaired TOF and that it would relate to ventricular dysfunction and potentially to markers of clinical outcome.

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Methods

Patient Population

Consecutive patients from a dedicated adult congenital heart clinic who had undergone repair of TOF between August 2002 and January 2005 participated. Patients with a permanent pacemaker were excluded. The study was approved by the local research ethics committee, and all patients gave written informed consent. Ninety-two patients (56 males) were studied with LGE CMR. One further patient attended, but the study was excluded owing to a mild, self-limiting reaction to contrast.

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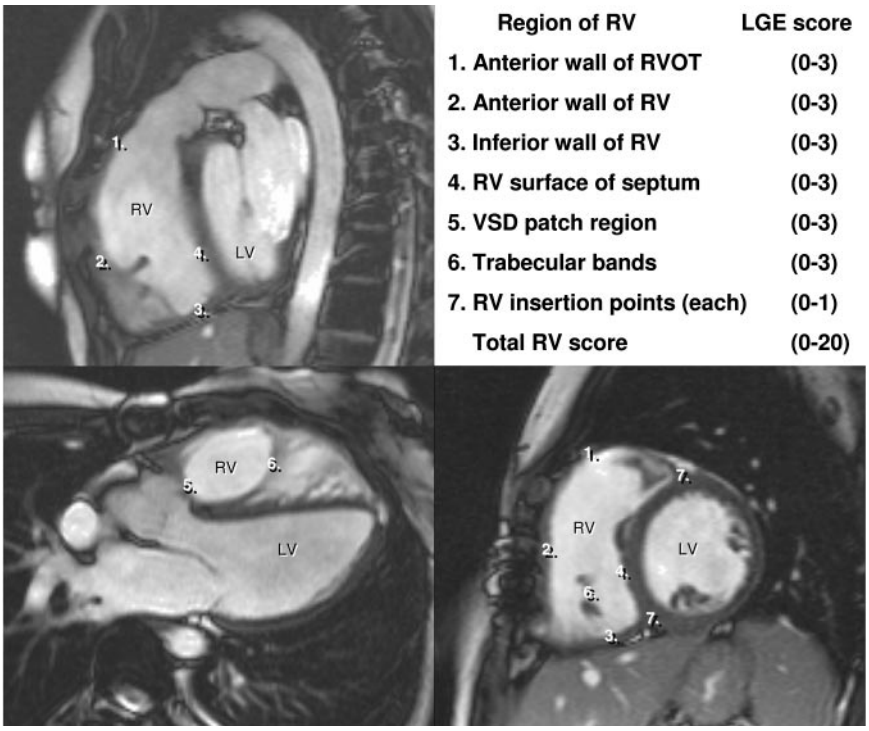

Figure 1. The segmental system used for both recording the location and scoring the extent of RV LGE. The division of the RV into 7 segments is shown in slices aligned with the RVOT, the LV outflow tract, and the LV short axis, with maximum LGE score per segment in brackets. Regions of RV wall showing LGE were graded according to the linear extent of enhanced myocardium in a given segment as follows: 0=no enhancement, 1=up to 2 cm, 2=2 to 3 cm, and 3=more than 3 cm in length. Enhancement seen in trabeculations, including the moderator band, was graded as 0=no enhancement, 1=enhancement of 1 trabeculation, 2=enhancement of 2 to 4 trabeculations, and 3=enhancement of more than 4 trabeculations. The inferior and superior RV-LV insertion regions (marked 7) were originally each scored either 0 or 1 for absence or presence of visible LGE, but later, their contribution to the total score was excluded. VSD indicates ventricular septal defect.

CMR Acquisition and Regional Assessment

All scans were acquired with a 1.5-T scanner (Siemens Sonata). After routine assessment of anatomy, a short-axis contiguous stack of steady-state free-precession cine images (7-mm slices) from the atrioventricular ring to the apex was acquired. All patients underwent a standardized full assessment, including quantification of the degree of pulmonary regurgitation by non–breath-hold phase-velocity mapping in a plane transecting the reconstructed pulmonary trunk[13] and measurement of biventricular volumes and function. Both the right ventricle (RV) and LV were also imaged in at least 3 long-axis and the short-axis planes. The maximum linear extent of the akinetic area identified in 1 or more of these planes was measured by 2 observers (PJK and SVB).

CMR Analysis of Volumes and Mass

All scans were rendered anonymous. The short-axis stack was quantified by planimetry by Simpson's method to determine myocardial mass and ventricular function with semiautomated software (CMRtools, Cardiovascular Imaging Solutions). A single observer (SVB) made all measurements. The RV free wall below the pulmonary valve and trabecular ridges and bands on the RV side of the septum were included in RV mass and excluded from blood pool measurements. The reproducibility for this population has been described previously.[14] The following measurements were included: RV and LV end-diastolic volume index (EDVi); RV and LV end-systolic volume index (ESVi); RV and LV ejection fraction (EF); RV and LV mass index.

CMR LGE Acquisition

Late gadolinium imaging was performed as described previously [12] by a single operator (SVB) with the use of a 2D segmented fast low-angle shot inversion recovery sequence, with the acquisition optimized for imaging nonischemic myocardial fibrosis and the RV.[12] Briefly, imaging was performed from 5 minutes after injection of gadolinium-DTPA 0.1 mmol/kg IV. Great care was taken to exclude or recognize artifacts during acquisition, including off-null effects. The inversion time was adjusted meticulously to maintain nulling of healthy myocardium, typically increasing from 310 to 420 ms. Imaging parameters were optimized to individual patient heart rate and breath-hold ability, and scanning proceeded quickly, typically with 30 views taken in less than 10 minutes, with phase swapping, systolic images, and crosscuts to define sometimes subtle RV LGE. Both ventricles were covered by imaging all short-axis views from base to apex with inversion recovery after gadolinium. In addition, standard LV long-axis planes, RV long-axis planes including a sagittal RV outflow tract, RV outflow tract (RVOT), and RV oblique and 4-chamber views, as well as crosscuts of suspected enhanced regions, were acquired. Any crosscuts were also compared with a further cine image acquired in the corresponding plane.

LGE Analysis

For the LV, a standard 17-segment model was used, with segments scored on a 5-point scale (0=no LGE and 1=1% to 24%, 2=25% to 49%, 3=50% to 74%, and 4=75% to 100% of the myocardium in the segment that showed LGE).[15] For the RV, segments have been described,[16] but no universally accepted segmentation system exists, particularly with respect to the heart after repair of TOF. Therefore, we designed a segmentation system to account for the anatomy and geometry of the RV after repair of TOF and the types of LGE found (Figure 1). LGE was considered present if there was bright signal within the myocardium (not blood pool), in good-quality late enhancement images in locations that either did not alter when reimaged in the same plane with a phase swap or that were also visible in another plane that cut the area in question. Locations were not double-counted. The maximum score was 20. We confirmed the interstudy reproducibility of this semiquantitative scoring system by repeating scans and analysis on 20 patients (mean 6-month interval) blind to the previous study (SVB, PJK).

Other Investigations

Standard 12-lead ECGs were acquired for all patients. QRS duration, QTc, and QT and JT dispersions were measured manually (OG).[17,18] RV restrictive physiology was assessed by a single echocardiographer (WL) looking for laminar anterograde flow in the pulmonary artery in late diastole present throughout the respiratory cycle (the *a* wave).[19,20] Echocardiographic data were available for 81 of 92 patients. Venous blood was taken from 70 patients after 20 minutes of supine rest and immediately centrifuged at 3000 rpm for 15 minutes at 4°C. Aprotinin plasma aliquots were stored at −75°C until subsequent batch analysis (immunoradiometric assay) for A-

and B-type natriuretic peptides (ANP and BNP). Cardiopulmonary exercise testing was performed with graded treadmill exercise. After we obtained resting measurements, all patients were encouraged to exercise to exhaustion. Resting and peak heart rate and blood pressure, duration of exercise, maximum $\dot{V}O_2$, $\dot{V}O_2$ expressed as a percentage of predicted, $\dot{V}E/\dot{V}CO_2$ slope, anaerobic threshold, and R value were recorded. Maximum $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, and anaerobic threshold were excluded from analysis if the R value was <1 (n=7). Clinical arrhythmia was defined as sustained arrhythmia associated with symptoms or syncope with ECG confirmation. Arrhythmia included both atrial and ventricular arrhythmias but not nonsustained Holter ventricular tachycardia.[4,21]

Statistical Analysis

All continuous variables were expressed as mean±SD or median (quartile 1–quartile 3) according to distribution. Continuous variables were analyzed by either 2-sample independent *t* test or Mann-Whitney test where appropriate. Correlations were assessed by Spearman rank correlation coefficient. Categorical data were analyzed by χ^2 test. A nonparametric Kruskal-Wallis test was used to compare different variables in the lower, middle, and upper quartiles of RV LGE score. A binary logistic regression model was constructed to test whether RV LGE was statistically a "predictor" of clinical arrhythmia after adjustment for age and exercise duration. Intraclass correlation coefficient was used to assess reproducibility of the RV LGE score. A probability value less than 0.05 was considered statistically significant. All data were analyzed with SPSS version 11 (SPSS Inc).

Results

Patient Demographics

Patient characteristics are summarized in Table 1.

TABLE 1. Patient Characteristics

	Mean±SD or Median (Quartile 1–3), Range (n=92)
Age, y	32.2±11, 13–60
Age at repair, y	5 (2–8), 0.75–36
Palliative surgery before repair*	36/92
Shunt-to-repair time, y	6.3±4.9
RVOT reconstruction†	33/55
Follow-up since repair, y	27 (19–33), 4–41
Redo surgery	16/92
Redo transcatheter intervention	17/92
New York Heart Association class I‡	72/92
Clinical arrhythmia/syncope§	16/92
ANP above upper limit of normal (>11 pmol/L), n (%)	6/70 (9)
BNP above upper limit of normal (>4 pmol/L), n (%)	58/70 (83)
Echo evidence of RV restrictive physiology, %	31
QRS duration, ms	152 (132–164), 91–212
QRS dispersion, ms	89±41, 18–68
QT dispersion, ms	87±84, 24–160
JT dispersion, ms	79±29, 24–148
Maximum $\dot{V}O_2$, mL·min^{-1}·kg^{-1}	26.6±7.4, 14–50
Predicted $\dot{V}O_2$, % predicted	80±20, 43–200
$\dot{V}E/\dot{V}CO_2$ slope	29.7±8.0, 19–64
Non–breath-hold pulmonary regurgitant fraction,%	34 (28–41), 0–65

*A total of 31 shunts were used: 4 Waterston, 27 Blalock-Taussig.

†Operative notes were available for 55 patients. Nineteen underwent transannular patch, 14 RVOT patch, and 10 conduit insertion. The remaining 12 underwent subpulmonary resection only.

‡New York Heart Association class 1=72, class II=18, and class III=2.

§There were 11 cases of atrial tachycardia (3 atrial reentry, 5 classic atrial flutter, and 3 atrial fibrillation), 3 cases of documented sustained ventricular tachycardia, and 2 cases of syncope.

RV LGE: Locations and Types

All patients had RV LGE; 3 basic types were observed. First, RV LGE occurred at surgical sites in all patients in the RVOT (99%) and/or the site of ventricular septal defect patching (98%; Figure 2). Second, RV LGE occurred in the RV trabeculations including the moderator band (22/92, or 24%; Figure 3); these patients were older, had later repair, and had higher RV ESVi (age 36.9±10 versus 30.6±11 years; repair at 6.0 [4.5 to 13.0] versus 4.0 [2.0 to 8.0] years; and ESVi 61.2 (52.6 to 84.3) versus 54.4 (41.4 to 71.1) mL/m^2; P=0.025, 0.034, and 0.046, respectively). Third, RV LGE occurred frequently at the RV insertion points (inferior 74/92, or 79%; superior 13/92, or 14%; Figure 2). No significant clinical or functional correlates were found with this pattern, so RV insertion point enhancement was excluded from all subsequent analysis.

RV LGE: Clinical Correlates

The extent of RV LGE varied widely (mean score 4.0±2.4, median 3; interquartile range 3 to 5; Figures 2 and 3). The group of patients with above-median scores was older and had longer follow-up, later repair, and adverse clinical markers, including decreased exercise tolerance, increased neurohormones, increased RV ESVi, decreased RV EF, higher LV LGE scores, and more documented clinical arrhythmia (Table 2), but there were no significant ECG differences between the 2 groups. Patients were divided into lower-quartile, middle-quartiles, and upper-quartile RV LGE groups. Age, age at repair, longer follow-up, ANP, BNP, RV ESVi, and LV LGE were significantly different in different RV LGE groups (Kruskall-Wallis $P<0.05$; Figure 4). Patients with extensive RV LGE (≥75th centile; n=23) were more likely to have restrictive RV physiology (11/23 [43%] versus 12/58 [24%], P=0.037).

LV LGE: Locations and Types

Three basic types of LV LGE were observed. First, LV LGE occurred at the apex, segment 17 (42/87; 48%), consistent with insertion of an apical vent at surgery (Figure 2). This did not correlate with any adverse markers apart from age (34±9.3 versus 28±12 years, $P<0.001$). Second, LV LGE typical of myocardial infarction was found in 5 (5%) of 92 cases (Figure 5). This was located inferiorly or laterally in all cases and also involved the apex, but a greater extent of LGE distinguished these cases from the first group. Third, discrete foci of LV LGE occurred in other locations in 7 patients. In 3 of these patients, noncontrast imaging showed that the LGE was associated with focal myocardial fatty infiltration.

LV LGE: Clinical Correlates

Total LV LGE score correlated weakly with RV LGE score (r=0.39, $P<0.001$). Patients with LV LGE not consistent with an apical vent (non–apical vent LV LGE) had higher RV LGE score (4.0 [4.0 to 7.0] versus 3.0 [2.0 to 5.0], P=0.004)

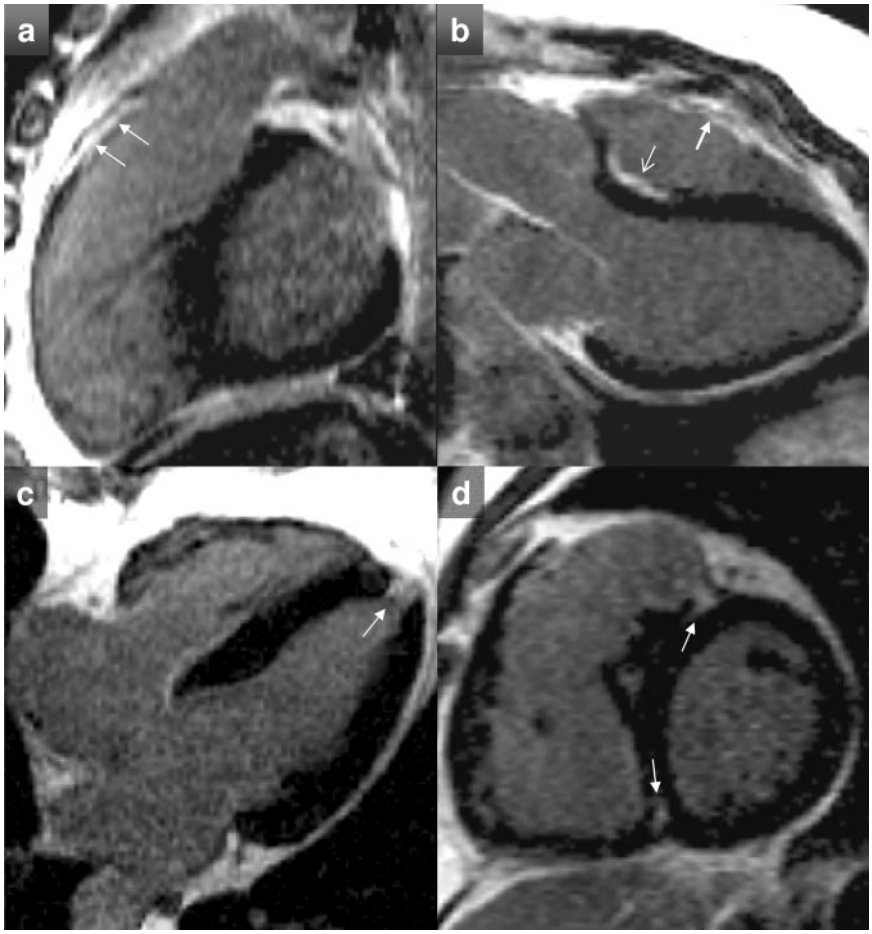

Figure 2. Typical LGE patterns late after TOF repair. Regions affected appear white with LGE CMR in contrast to the black appearance of normal myocardium. Typical sites of LGE included the following: a, anterior wall of RVOT (91/92, 98.9%; arrows); b, region of surgical patching of the ventricular septal defect (90/92, 97.8%; arrow); c, site of apical vent insertion in the LV (42/87, 48.3%; arrow); and d, inferior (74/92, 80.4%; lower arrow) and superior (13/92; 14.1%; upper arrow) insertion points.

and more arrhythmia (5/16 versus 7/76, $P=0.017$) and were older (39±11 versus 31±11 years, $P=0.018$), with later repair (8.0 [4.0 to 34.0] versus 4.0 [2.0 to 7.0] years, $P=0.017$), although there was no difference in the length of follow-up (33 [15–34] versus 26 [18–32] years, $P=$NS). They had lower peak heart rate and shorter exercise duration (162 [126–171] versus 173 [162–190] bpm, 558 [459–775] versus 824 [658–920] s, $P=0.006$ and 0.025, respectively) and higher ANP (10.4 [7.4 to 16.8] versus 5.3 [3.2 to 7.8) pmol/L, $P=0.009$). LV volume was increased (LV EDVi 83.9 [76.8 to 88.6] versus 68.7 [60.8 to 80.8] and LV ESVi 40±20 versus 25±11 mL/m^2, $P=0.012$ and 0.017, respectively), and LV EF decreased (55±14% versus 66±7%, $P=0.027$). Similarly, the LV infarction patients (n=5) were older, with later repair (age 45±6 versus 32±11, repair at 11±3 versus 7±6 years; $P=0.007$ and 0.015, respectively) but also had a greater incidence of previous palliative shunt (4/5 versus 27/87, $P=0.04$), more redo surgery to the pulmonary valve (4/5 versus 17/87, $P=0.009$), and increased BNP (30.4±16.5 versus 10.3±7.5 pmol/L, $P=0.021$).

LGE and Arrhythmia

Patients with documented clinical arrhythmia were older and had a more frequent history of redo surgery, reduced exercise capacity, more symptoms, and more RV and LV LGE (Table 3). By multivariate analysis with the 3 most clinically relevant variables (age, exercise duration, and RV LGE score), RV LGE score remained a predictor of arrhythmia, despite adjustment for both age and exercise duration. Exercise duration also remained an inverse predictor, but age did not. Each unit increase in RV LGE score was associated with a 34% greater likelihood of documented clinical arrhythmia (OR 1.34, 95% CI 1.04 to 1.81; $P=0.032$).

Interscan LGE Reproducibility

LGE CMR applied to the RV with this scoring system was highly reproducible (intraclass correlation coefficient 0.97 for RV and 1.0 for LV). The high LV reproducibility was driven by the clear presence or absence of evidence of transmural apical vents.

Discussion

Myocardial LGE was present in both the RV and LV of adults with repaired TOF and was related to increased age, impaired exercise capacity, ventricular dysfunction, and clinical arrhythmia. LGE has become widely regarded as a marker of fibrosed, scarred, or otherwise abnormal myocardium, an assumption that has been validated histologically in selected cases.[10,22] In this setting, we believe that LGE represents fibrosis, in agreement with a previous histological study.[5]

Surgical Scarring, Akinetic RVOT Areas, and RV LGE

LGE was commonly seen in locations that probably reflected surgical resection, incision, patching, suturing, or vent inser-

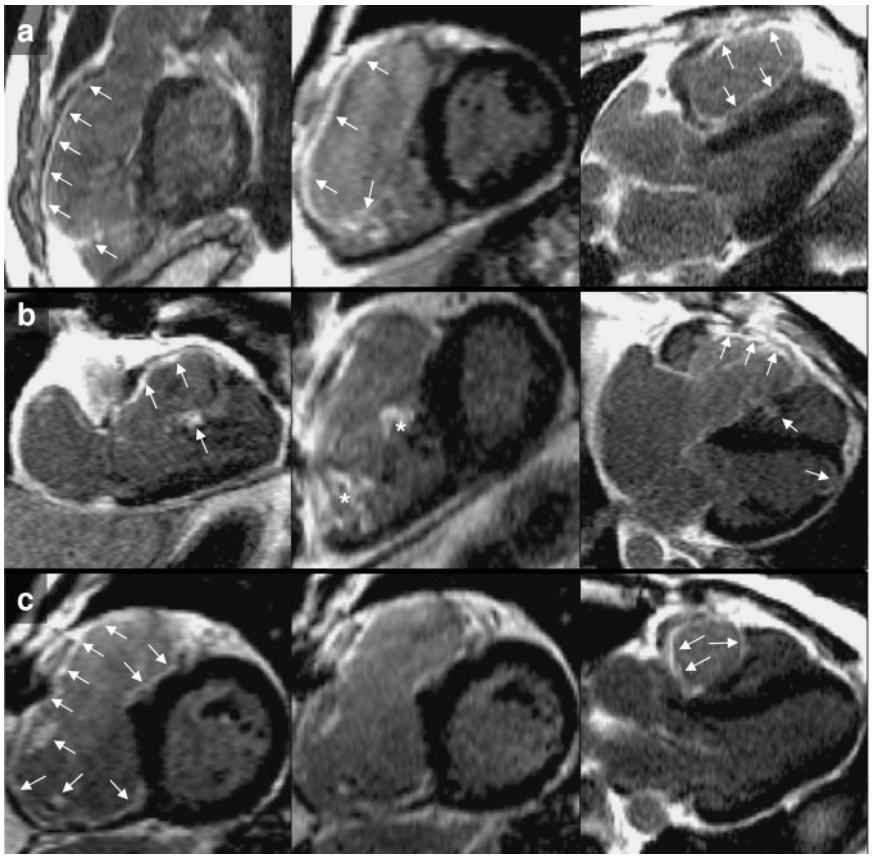

Figure 3. Examples of extensive RV LGE seen in repaired TOF. Rows a, b, and c are selected LGE images from 3 different individuals, from left to right: a, RVOT, short-axis (SA) and LV outflow tract (LVOT) views. The large enhanced area of the RVOT and RV anterior wall corresponded to akinesia on cines. LGE extends to the trabeculated myocardium, including the moderator band. b, RV long-axis view, SA and 4-chamber views: LGE corresponded to akinesia of the anterior wall on cine imaging, extending more inferiorly than is commonly seen. LGE of the trabeculated RV myocardium is present (asterisk). c, Left and middle panels show the same mid-SA slice imaged twice, showing extensive subendocardial LGE. The phase-encode direction has been swapped between the 2 to exclude artifact as a cause. On the right, the LVOT plane shows RVOT LGE (arrows).

tion. All patients had RV LGE in the RVOT free wall, whether or not a patch had been used. Thin, akinetic, sometimes bulging RVOT regions are a frequent finding in patients with repaired TOF, and they have a negative impact on EF[23] and provide a substrate for arrhythmia.[24] The RVOT LGE generally correlated with RVOT wall-motion abnormality, but in some cases, LGE indicated the presence of fibrosis in areas that cannot be detected by cine images alone (for example, in trabeculated and endomyocardial regions).

RV Fibrosis: Early Insult, Perioperative Damage, or Progressive Change?

RV LGE likely reflects previous myocardial insult. Patients with more fibrosis had later repair, which suggests that preoperative cyanosis and pressure overload may have predisposed to myocardial damage. In older TOF patients, fibrosis may also reflect an earlier surgical era of repair via ventriculotomy and perhaps more aggressive RVOT reconstruction, with more transannular patch use. Unintended perioperative adverse effects, such as damage to the right coronary artery or its branches or the negative effect of cardiopulmonary bypass, could also play a role. Younger patients, in contrast, may have benefited from improvements in surgical and bypass techniques, including myocardial protection, and so have lower fibrosis scores despite having LGE in similar locations. LGE was also seen in sites remote from surgical instrumentation, in trabecular and endocardial sites, which may be more vulnerable to ischemic insult. Such patients had decreased RV function, increased age, and later repair, with a trend to longer follow-up since surgery, but whether the ischemic insult was preoperative, perioperative, or postoperative remains unknown. We postulate that at least 1 of the mechanisms for progressive fibrosis is ventricular dilatation and hypertrophy resulting from pulmonary regurgitation or stenosis, which leads to stretching, arrhythmia generation, and adverse RV remodeling, particularly in vulnerable border zones between normal and fibrotic myocardium.

LV Fibrosis

LV LGE relating to apical vent insertion was expected,[25] but other locations require further explanation. Small, localized, discrete LV LGE may be due to perioperative, embolic microinfarction. Indeed, 5 patients had a pattern consistent with infarction and wall-motion abnormalities. Potential mechanisms include perioperative damage to anomalous or normal coronary arteries; adverse, progressive ventricular-ventricular interaction[23]; and silent myocardial infarction due to acquired ischemic heart disease. LV dysfunction is known to relate to adverse outcomes,[26,27] and our findings lend support to fibrosis as a potentially relevant cause.

Clinical Relevance

The extent of RV fibrosis was related not only to adverse markers of RV systolic function, particularly RV ESVi and RV EF, but also to restrictive physiology, neurohormonal activation, and exercise intolerance, which supports the clinical relevance of the RV LGE seen in the present study. The burden of pulmonary regurgitation was substantial in the present study cohort. Pulmonary valve replacement is re-

TABLE 2. Relationship of RV LGE to Clinical and Neurohormonal Markers, Cardiopulmonary Exercise Testing and Ventricular Volumes and Function

	Low RV Score (≤Median), n=50	High RV Score (>Median), n=42	*P*	Correlation (Spearman) *r* (*P*)
Age, y	27.3±10.1	38.0±9.2	<0.001	0.47 (≤0.001)
Age at repair, y	3.0 (1.6–5.8)	7.0 (4.0–10.3)	<0.001	0.45 (≤0.001)
Follow-up since repair, y	20.5 (15.6–27.0)	32.0 (27.0–34.5)	<0.001	0.36 (≤0.001)
Symptoms (NYHA ≥2), n (%)*	4/50 (8)	16/42 (38)	0.001	...
Documented arrhythmia, n (%)†	5/50 (10)	11/42 (26)	0.039	...
ANP, pmol/L	4.9 (2.9–6.9)	7.3 (4.6–10.0)	0.041	0.29 (≤0.014)
BNP, pmol/L‡	7.2 (5.3–10.0)	12.3 (6.4–17.0)	0.086	0.22 (≤0.074)
Restrictive RV physiology, n (%)	12/44 (27)	13/37 (35)	NS	...
Peak exercise heart rate, bpm	170 (162–189)	172 (154–185)	0.083	−0.24 (≤0.025)
Duration of exercise, s	840 (742–927)	768 (578–855)	0.001	−0.24 (≤0.023)
Maximum $\dot{V}_{O_2}$, mL·min^{-1}·kg^{-1}	28.4±7.8	24.2±6.0	0.021	−0.21 (≤0.058)
$\dot{V}_{O_2}$, % predicted	81±24	77±21.9	NS	−0.13 (≤0.26)
RV EDVi, mL/m^2	126 (110–142)	134 (114–160)	0.085	0.23 (≤0.025)
RV ESVi, mL/m^2	55 (48–68)	61 (52–87)	0.018	0.32 (≤0.002)
RV EF, %	56±9	50±11	0.007	−0.30 (≤0.004)
Akinetic area, length in mm	3.0 (2.1–3.0)	3.8 (2.9–5.0)	<0.001	0.48 (≤0.001)
LV ESVi, mL/m^2	26±12	28±14	NS	0.06 (≤0.60)
LV EF, %	66±7	63±11	NS	−0.10 (≤0.34)
LV LGE score	0.0 (0.0–2.0)	2.0 (0.0–3.0)	<0.001	0.39 (≤0.001)
QRS duration, ms	156 (147–165)	155 (141–163)	NS	0.03 (≤0.81)
QRS dispersion, ms	40±9	42±11	NS	0.02 (≤0.83)
QT dispersion, ms	84±32	84±28	NS	0.12 (≤0.27)
JT dispersion, ms	80±32	78±27	NS	0.11 (≤0.30)

*Symptoms were primarily shortness of breath on exertion and fatigue.

†Please see footnote (§) in Table 1.

‡Significant if upper-quartile LGE patients are compared with remainder; 14.4 (12.5–29.4) vs 7.4 (5.3–11.7) pmol/L, $P<0.001$; see Figure 4.

ported to be beneficial,[28] although optimal timing is unclear. Assessment of RV LGE may contribute to this challenging decision-making process. In multivariate analysis, RV LGE score was a predictor of documented clinical arrhythmia, despite adjustment for age and exercise duration. Islands of fibrosis represent potential foci of ventricular reentry. Arrhythmia documented in patients in the present study included sustained ventricular tachycardia and syncope but also atrial tachycardia, which was more common. In patients with evidence of extensive RV (and LV) fibrosis, the latter may be a marker of ventricular dysfunction.[29,30] RV LGE and its extent may therefore contribute to risk stratification for arrhythmia and sudden cardiac death and thus assist in decision making with regard to arrhythmia intervention, including automated internal cardiac defibrillator implantation.

Study Limitations

In this evaluation of RV LGE patterns in TOF, we have grouped different patterns and assumed that they related to fibrosis, although no histological validation has been performed. In the longer term, documentation of in vivo changes and correlation with postmortem histological appearances may be possible. The cross-sectional nature of this study limits its ability to determine the precise mechanisms or rate of progression of fibrosis, because cause-and-effect cannot be disentangled. In terms of multivariate analysis, this is a population with relatively few clinical events to predict; however, only 3 variables were put into the multivariate model, and therefore, in our opinion, the data have not been overfitted. A larger, prospectively followed-up cohort may give further information on additional causes of fibrosis, its precise prognostic value, and its potential response to different interventions.

Conclusions

RV and LV LGE suggestive of fibrosis are common after TOF repair. The findings described here give new in vivo insights into late pathophysiological mechanisms. The presence of fibrosis was related to adverse clinical markers, including ventricular dysfunction, exercise intolerance, and neurohormonal activation. In particular, RV LGE was a predictor of arrhythmia, which has potential prognostic implications with respect to morbidity and mortality. Further

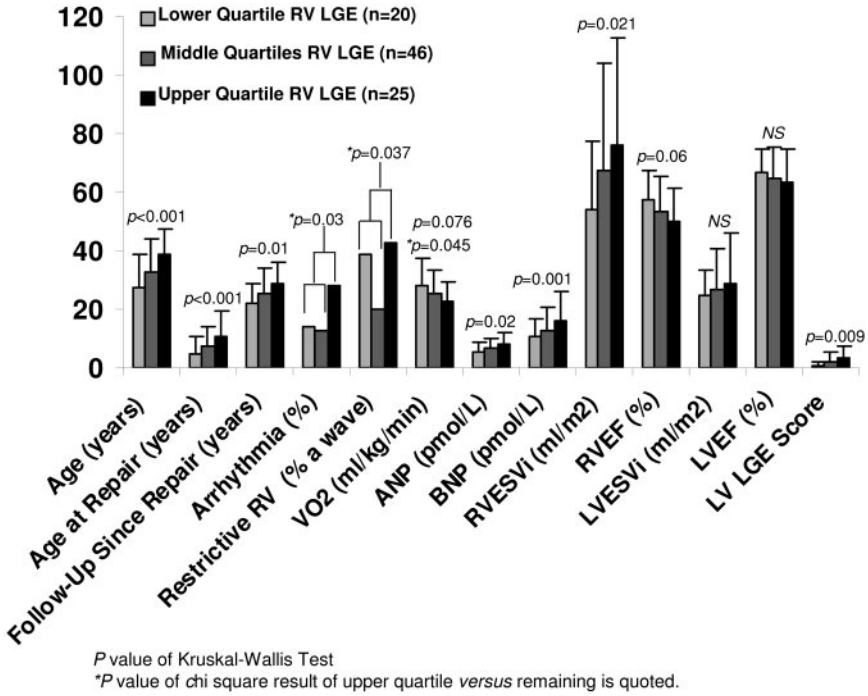

Figure 4. RV LGE and markers of outcome. Differences in clinical, neurohormonal, and CMR variables between patients classified according to lower-quartile, middle-quartiles, and upper-quartile RV LGE score are illustrated in the bar chart. P values are for Kruskal-Wallis test. *P values are for χ^2 result of upper-quartile vs remaining quartiles.

studies may validate the role of LGE CMR in risk stratification and optimal timing of hemodynamic surgery or arrhythmia intervention.

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Disclosure

None.

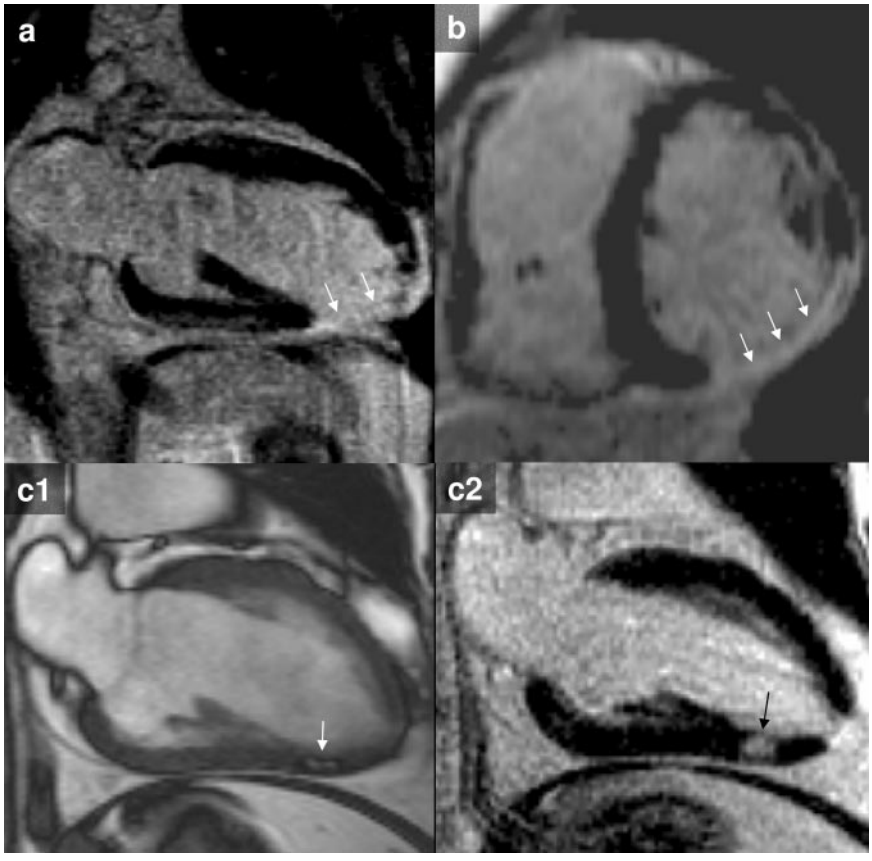

Figure 5. Examples of LV LGE late after TOF repair. Images illustrating unexpected LV infarction (arrows) in 2 different patients (a and b). A further example of localized LV LGE in another patient is shown. The cine frame in c1 and corresponding LGE image in c2 suggest fibrofatty change in this region.

TABLE 3. Relationship of Documented Clinical Arrhythmia After Repaired TOF to Symptoms, Exercise Capacity, and RV LGE Score

	No Arrhythmia (n=76)	Arrhythmia* (n=16)	*P*
Age, y†	31.2±10.6	36.9±12.3	0.043
New York Heart Association class ≥2	12/76	8/16	0.006
Redo surgery, n (%)	8/76 (11)	8/16 (50)	0.004
Peak heart rate, bpm	171 (162–186)	151 (114–171)	0.07
Exercise duration, s†	781±22	622±194	0.002
Maximum $\dot{V}o_2$, mL·min^{-1}·kg^{-1}	27.1±7.6	23.4±4.4	0.079
QRS duration, ms	158 (148–167)	155 (143–164)	NS
QRS dispersion, ms	41±11	40±5	NS
QT dispersion, ms	85±30	78±32	NS
JT dispersion, ms	80±30	73±28	NS
Anterior RV LGE‡	19/76	9/16	0.017
RV LGE score†	3.0 (3.0–5.0)	5.5 (3.8–12.0)	0.032
Non–apical vent LV LGE	7/76	5/16	0.017

*Please see footnote (§) in Table 1.

†Clinically important variables entered into multivariate model.

‡Anterior RV LGE refers to the free wall of the RV below the RVOT.

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CLINICAL PERSPECTIVE

The population of adults with repaired tetralogy of Fallot (TOF) is growing thanks to advances in cardiac surgery and longer-term care; however, right ventricular dysfunction, arrhythmia, and sudden cardiac death remain problematic in the long term. To refine risk stratification, we sought to identify whether fibrosis involving the right ventricle was a substrate that may predispose to adverse late outcomes. Using cardiovascular MRI with late gadolinium enhancement to detect fibrosis, we report the ubiquitous occurrence but varying locations and extent of right ventricular myocardial fibrosis in adults late after TOF repair. Commonly, evidence of perioperative apical vent insertion site fibrosis was seen even decades later, underlining the sensitivity of the technique, but other unexpected left ventricular areas of fibrosis were also seen in a smaller number of patients. Fibrosis in the thin-walled, akinetic regions, commonly found in the right ventricular outflow tract, has potential relevance to the modern surgical technique, for example, with regard to the extent and depth of myocardial resection in this region at the time of surgery. We found the extent of right ventricular fibrosis related was associated with adverse clinical markers, including right ventricular dysfunction, objective exercise intolerance, and neurohormonal activation, and with the incidence of clinical arrhythmias. These data may therefore shed light on the pathophysiological substrate of arrhythmia and ventricular dysfunction in patients with repaired TOF. This in vivo demonstration of fibrosis, whether reflecting a single early insult or progressive change with time, could in the future contribute to risk stratification and decision making on the timing of arrhythmia intervention or hemodynamic surgery such as pulmonary valve replacement. Longitudinal follow-up is needed to substantiate this concept.