Background—We hypothesized that fibrosis detected by late gadolinium enhancement (LGE) cardiovascular magnetic resonance predicts outcomes in patients with transposition of the great arteries post atrial redirection surgery. These patients have a systemic right ventricle (RV) and are at risk of arrhythmia, premature RV failure, and sudden death.

Methods and Results—Fifty-five patients (aged 27±7 years) underwent LGE cardiovascular magnetic resonance and were followed for a median 7.8 (interquartile range, 3.8–9.6) years in a prospective single-center cohort study. RV LGE was present in 31 (56%) patients. The prespecified composite clinical end point comprised new-onset sustained tachyarrhythmia (atrial/ventricular) or decompensated heart failure admission/transplantation/death. Univariate predictors of the composite end point (n=22 patients; 19 atrial/2 ventricular tachyarrhythmia, 1 death) included RV LGE presence and extent, RV volumes/mass/ejection fraction, right atrial area, peak VO₂, and age at repair. In bivariate analysis, RV LGE presence was independently associated with the composite end point (hazard ratio, 4.95 [95% confidence interval, 1.60–15.28]; P=0.005), and only percent predicted peak VO₂ remained significantly associated with cardiac events after controlling for RV LGE (hazard ratio, 0.80 [95% confidence interval, 0.68–0.95]; P=0.009/5%). In 8 of 9 patients with >1 event, atrial tachyarrhythmia, itself a known risk factor for mortality, occurred first. There was agreement between location and extent of RV LGE at in vivo cardiovascular magnetic resonance and histologically documented focal RV fibrosis in an explanted heart. There was RV LGE progression in a different case restudied for clinical indications.

Conclusions—Systemic RV LGE is strongly associated with adverse clinical outcome especially arrhythmia in transposition of the great arteries, thus LGE cardiovascular magnetic resonance should be incorporated in risk stratification of these patients. (Circ Cardiovasc Imaging. 2015;8:e002628. DOI: 10.1161/CIRCIMAGING.114.002628.)

Key Words: arrhythmias, cardiac fibrosis, magnetic resonance imaging, prognosis, transposition of great vessels

Myocardial fibrosis is implicated in late right ventricular dysfunction in patients who have undergone atrial redirection surgery (Mustard/Senning operation) for transposition of the great arteries.1,2 The RV in these patients functions as the systemic ventricle which predisposes to arrhythmia, premature systemic RV failure, and sudden death.3–13 Atrial tachyarrhythmia has been reported as the most common early clinical complication,5,7,11,13,14 is associated with significant clinical morbidity, has been suggested to reflect systemic RV dysfunction, and is a recognized marker of elevated atrial pressure and increased mortality.5,7,13,15 Thereafter, RV dysfunction precedes the onset of symptoms, clinical heart failure, and death.16,17 RV dysfunction is associated with mortality in some series18,19 and is a well-recognized limitation of the Mustard/Senning operation,20 with recent studies appearing to indicate that this outcome can be improved, with longer-term follow-up reporting favorable outcomes.21,22 The role of late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) in detecting fibrosis and predicting clinical outcome in these patients is unknown.

In our study of 55 patients undergoing LGE CMR and followed prospectively for a median of 7.8 years, we found a strong association between RV LGE and adverse clinical outcomes, mainly new-onset atrial arrhythmia and health care use (such as hospitalization, transplantation, or death) compared with patients without LGE in the RV. In this study, LGE CMR predicted adverse clinical outcome better than other clinical and CMR markers (such as RV volumes and mass and peak VO₂). RV LGE was present in 56% of patients, with only 15% LGE in other ventricles. The RV was the only chamber with a significant association with adverse clinical outcomes. RV LGE was present in patients with new-onset atrial arrhythmia (atrial or ventricular), decompensated heart failure, hospitalization, or transplant or death, but not in patients with isolated ventricular arrhythmia. RV LGE location was in the RV outflow tract, midventricle, and RV apex. The RV LGE extent was associated with adverse clinical outcomes, and RV LGE area was associated with peak VO₂ suggesting that the presence of LGE predicts RV dysfunction. RV LGE was present in patients who underwent cardiac transplantation, with LGE extent being independently associated with transplantation. Atrial tachyarrhythmia was the most common reason for hospitalization and was associated with RV LGE. There was agreement between RV LGE by CMR and histologically documented focal RV fibrosis in an explanted heart, suggesting that RV LGE can detect fibrosis detected by histology.

The benefits of CMR in identifying myocardial fibrosis is well established, with LGE CMR being the current standard imaging technique.23 LGE CMR has been used in a variety of cardiovascular diseases to predict cardiovascular outcome in patients with myocardial infarction,24 heart failure,25,26 and long-QT syndrome,27 and has also been used in patients undergoing interventional procedures (such as percutaneous mitral valve repair) to identify patients at risk of adverse outcomes on the basis of myocardial fibrosis28 and in predicting the success of mitral valve repair.29 While there has been interest in using LGE CMR to identify myocardial fibrosis and its association with clinical outcomes, the role of LGE CMR in patients with transposition of the great arteries is unclear. Our study indicates that RV LGE is strongly associated with adverse clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries. Furthermore, RV LGE is associated with adverse clinical outcomes in patients with transposition of the great arteries, suggesting that RV LGE should be incorporated in risk stratification of these patients.

See Clinical Perspective

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failure, and sudden death. Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) can be used for detecting myocardial fibrosis. In the systemic left ventricle (LV), LGE has prognostic significance in ischemic heart disease and cardiomyopathies. Previous studies of RV LGE in patients with a systemic RV showed that its presence and extent relate to impaired RV function, exercise intolerance, and arrhythmia. These early studies, however, were purely cross-sectional and lacked histological validation. We hypothesized that fibrosis detected by RV LGE would predict adverse outcome in a prospective study of these patients.

**Methods**

**Patients and Study Design**

Consecutive patients post Mustard/Senning repair referred for clinical CMR scan were invited to participate in this prospective study and gave written informed consent. The study was conducted according to the Declaration of Helsinki. The local research ethics committee approved the study.

The prespecified composite clinical end point consisted of new-onset clinically documented sustained tachycardia or heart failure hospital admission/transplantation/death. Tachycardia was defined as sustained atrial tachycardia fibrillation or ventricular tachycardia (≥30 s) or ventricular fibrillation. Heart failure admission was defined as admission for diuresis of fluid overload not secondary to acute arrhythmia presentation. CMR attendance was the start of follow-up which was continued until the first outcome event or to the last clinical visit. All events during follow-up, including nonsustained ventricular tachycardia, were recorded for all patients (censored or not for the composite end point) for separate analysis. Mortality data from the Office for National Statistics, which registers all UK deaths, were complete for all patients. Baseline data included demographics, previous surgical intervention, New York Heart Association (NYHA) class, electrocardiography, and cardiovascular magnetic resonance imaging exercise testing.

**CMR Acquisition and Analysis**

LGE CMR at 1.5-Tesla (Siemens) was performed using a segmented fast low-angle shot inversion recovery sequence from at least 5 minutes after injection of 0.1 mmol/kg IV gadolinium as previously reported. LGE was considered present if bright signal was detectable in at least 2 views (phase swap or cross-cut), in the presence of good nulling and no artifact, and agreed by 2 independent readers (>10 years of experience in CMR). LGE was quantified by manual planimetry in short-axis planes with 8-mm slice thickness, including compact myocardium, trabeculations, and papillary muscles, and not RV–LV insertion regions. The septum was treated as part of the RV. To derive %RV LGE, the volume of LGE was divided by RV mass. A standardized CMR protocol for assessment status post Mustard/Senning was performed. A short-axis contiguous stack of 7-mm cine images (3-mm gap) was acquired for quantification of ventricular function and mass using Simpson's method. Manual planimetry was performed by a single observer with RV trabeculations excluded from the blood pool and included in RV mass measurements (CMRtools, Cardiovascular Imaging Solutions, London). Post atrial redirection surgery, part of the pulmonary venous atrial compartment remains anatomically right atrial. The maximum contoured anatomic right atrial area, just before atrioventricular valve opening excluding the part of the pulmonary venous compartment composed of left atrial and pulmonary venous tissue, was chosen to quantify the right atrial maximal area indexed to body surface area. Twelve random patients were remeasured by the same observer (minimum 6-month interval), as well as a second blinded experienced observer, for intraobserver and interobserver variability.

**Other Methods**

Cardiopulmonary exercise testing was performed using symptom-limited treadmill exercise and assumed valid within 6 months from the CMR study. Peak oxygen uptake (peak VO₂), the percent of predicted peak VO₂ (peak VO₂%), and ratio of minute ventilation to carbon dioxide production (VE/VECO₂) were recorded, and data were excluded from analysis if the respiratory quotient value was <1 (n=2). Heart rate reserve was calculated as peak pulse rate on exercise minus resting pulse rate. Standard 12-lead electrocardiograms were recorded at 25 mm/s and QRS duration and QT dispersion recorded. The explanted heart from the patient who underwent transplantation was examined macroscopically, and histological sections were stained for fibrous tissue.

**Statistical Methods**

Continuous data are summarized as mean (±SD) or median (interquartile range), as appropriate. Comparisons between groups were made using a t test, Mann–Whitney test, or Fisher exact test as appropriate. Correlation was tested with Pearson's coefficient or Spearman's ρ. Receiver-operating characteristics analysis was used to determine the optimal cutoff whereby fibrosis extent detects end points. The association between variables and event-free survival was tested using a Cox proportional hazards model. Because of the relatively small number of outcome events, it was not appropriate to perform a full multivariable analysis and we focused on univariate and bivariate analyses. Presence of LGE was tested alongside other predictive univariate parameters in a series of pairwise comparisons. The Cox model was also used to predict the 5-year event rate of patients using peak VO₂% alone, and then in combination with LGE status. Kaplan–Meier survival curves were used to estimate the survival distributions of patients with and without fibrosis (log–rank test). Variability was expressed as the mean percent error, derived as the absolute difference between the 2 sets of observations, and divided by the mean of the 2 sets of observations. All tests were 2-sided and a P value of <0.05 was considered significant.

**Results**

**Patient Characteristics**

Fifty-five systemic RV patients, 50 post Mustard, and 5 post Senning (mean age, 27±7 years) underwent LGE CMR and were prospectively followed for median 7.8 (interquartile range, 3.8–9.6) years (patient characteristics summarized in Table 1). Forty-two (76%) were in New York Heart Association class I, the remainder in class II. RV LGE was present in 31 patients (56%). No patient had LV LGE. RV LGE extent ranged from 100 to 2002 mg (0.06%–5.7% of RV mass). Clinical correlations of RV LGE presence and extent are summarized in Table 1. RV LGE extent related to QRS duration (r=0.61; P=0.001); QRS duration related to increased RV volumes (RV end-diastolic and end-systolic volume index: r=0.33; P=0.038 and r=0.52; P<0.001) and decreased RV ejection fraction (r=−0.57; P<0.001).

**LGE and Clinical Outcome**

The presence of RV LGE was associated with an increased risk of reaching the prespecified composite clinical end point (median time to event of 3.5 years). There were 21 tachyarrhythmias (16 atrial tachycardia, 3 atrial fibrillation, and 2 ventricular tachycardia) and 1 death contributing to the composite end point. Kaplan–Meier curves for the composite end point showed a significant difference between patients with and without fibrosis (log–rank P=0.001; Figure 1A). Univariate predictors of adverse outcome are summarized in Table 2. None of the LV parameters were predictive of outcome. In a bivariate model
after controlling for RV LGE, only peak \( V_o \) of 0.8% remained significantly associated to cardiac events (Table 3). Figure 1B shows the contribution of patient LGE status for the prediction of 5-year event rate compared with using the peak \( V_o \) alone. For example, for peak \( V_o \) of 70%, the 5-year risk of an event is 23%, but increases to 35% or decreases to 8% depending on whether LGE is present or absent at CMR. By receiver-operating characteristics analysis, a fibrosis extent cutoff value of 2800 mg provided the best sensitivity (71%) and specificity (65%) for the composite end point (area under the curve=0.758; \( P=0.010; 95\% \text{ CI}, 0.60–0.92\)).

At study end, there were 32 events in total (Figure 2). In 8 of the 9 patients (89%) with >1 event, atrial tachyarrhythmia preceded the other events (2 deaths, 1 transplantation, 3 heart failure admissions, and 4 nonsustained ventricular tachycardia). Death was because of sudden death in 1 and was non-cardiac in the other. Ventricular tachyarrhythmia (sustained/ nonsustained) during follow-up was related to positive RV LGE at CMR (\( P=0.030; \text{ Table 4} \)).

Table 1. Systemic RV LGE and Clinical Characteristics

<table>
<thead>
<tr>
<th>Correlation With Fibrosis Extent, %</th>
<th>LGE+ ( n=31 )</th>
<th>LGE− ( n=24 )</th>
<th>( P ) Value*</th>
<th>( r_{r_s} ) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, y</td>
<td>0.9 (0.5–1.9)</td>
<td>1.2 (0.6–3.1)</td>
<td>0.7 (0.5–1.2)</td>
<td>0.048†</td>
</tr>
<tr>
<td>Age at scan, y</td>
<td>27±7</td>
<td>30±7</td>
<td>23±5</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Prior atrial arrhythmia, n</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>0.033†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69±16</td>
<td>73±17</td>
<td>62±12</td>
<td>0.011†</td>
</tr>
</tbody>
</table>
| Male sex, n | 33 | 15 | 18 | 0.166 | ...
| NYHA class ≥1 | 13 | 11 | 2 | 0.026† | ... |
| RVEDVi, mL/m² | 106±34 | 115±38 | 95±23 | 0.045† | \( r_2=0.12; P=0.502 \) |
| RVESVi, mL/m² | 39 (32–52) | 48 (34–76) | 35 (31–41) | 0.010† | \( r_2=0.13; P=0.458 \) |
| RVEF, % | 59 (52–64) | 58 (47–61) | 60 (58–66) | 0.019† | \( r_2=0.25; P=0.160 \) |
| LVEF, % | 71±17 | 69±15 | 74±31 | 0.122 | \( r_2=0.08; P=0.965 \) |
| LVMi, g/m² | 32±16 | 34±18 | 30±12 | 0.329 | ... |
| LA, cm²/m² | 67±33 | 75±40 | 56±14 | 0.040† | \( r_2=0.10; P=0.588 \) |
| RVEDVi/LVEDVi | 1.2 (1.1–1.5) | 1.4 (1.2–1.7) | 1.2 (1.0–1.4) | 0.001† | \( r_2=0.31; P=0.072 \) |
| RAA, cm²/m² | 10±3 | 11±3 | 9±2 | <0.001† | \( r_2=0.32; P=0.066 \) |
| LVEDVi, mL/m² | 79±21 | 76±24 | 83±15 | 0.149 | ... |
| LVESVi, mL/m² | 28±11 | 26±12 | 31±8 | 0.107 | \( r_2=0.34; P=0.046 \) |
| LVEF, % | 65±9 | 66±10 | 64±7 | 0.481 | ... |
| LVMI, g/m² | 32±16 | 34±18 | 30±12 | 0.329 | ... |
| QRS duration, ms | 105±21 | 111±23 | 95±15 | 0.006† | \( r_2=0.61; P=0.001 \) |
| QT dispersion, ms | 128±64 | 131±72 | 123±53 | 0.947 | ... |
| Peak \( V_o \), mL/kg/min | 25±6 | 24±5 | 28±7 | 0.025† | \( r_2=0.27; P=0.157 \) |
| Percent predicted \( V_o \), % | 71±17 | 69±15 | 74±21 | 0.313 | ... |
| VE/Vco₂ slope | 34±8 | 34±8 | 33±9 | 0.528 | ... |
| Heart rate reserve, bpm | 92±23 | 84±24 | 101±18 | 0.032† | \( r_2=0.46; P=0.011 \) |
| Baffle reintervention§, n | 24 | 15 | 9 | 0.584 | ...
| Operated VSD||VSD | 13 | 12 | 1 | 0.003† | ... |
| Tricuspid regurgitation≥1¶ | 19 | 18 | 1 | <0.001† | ... |

EDVi indicates end-diastolic volume indexed to body surface area; EF, ejection fraction; ESVi, end-systolic volume indexed to body surface area; LGE, late gadolinium enhancement; LV, left ventricular; Mi, mass indexed to body surface area; NYHA, New York Heart Association; \( r_{r_s} \), Pearson/Spearman; RAAi, right atrial maximal area indexed to body surface area; RV, right ventricular; VE/Vco₂ slope, ratio of minute ventilation to carbon dioxide production; \( V_o \), oxygen uptake; and VSD, ventricular septal defect.

*\( \text{Mann–Whitney/U test/Fisher exact test.} \)
†Statistically significant \( P \) value.
‡RV wall stress=systolic blood pressure×RV end-systolic volume/mass.
§Twenty-four patients (44%) underwent ≥1 either surgical (n=10) or transcatheter (n=14) reintervention(s) to any of the atrial pathways.
||VSD varied from small muscular to large inlet. All LGE+ patients with operated VSD had LGE at the patch site but also elsewhere in the RV. One LGE- patient had small unoperated restrictive VSD.
¶Absent, physiological=0 (n=37), mild=1 (n=16), moderate=2 (n=1), and severe=3 (n=1).

RV LGE and Histological Correlation in 1 Patient

One patient underwent heart transplantation 7 years after CMR study because of severely dilated RV with excessive hypertrophy and poor systolic function. He had already presented with atrial arrhythmia before this. The explanted heart showed a markedly fibrotic RV with clear agreement between
location and extent of the fibrosis indicated by the in vivo LGE CMR and macroscopically confirmed fibrosis in the explanted heart (Figures 3A and 3B). Furthermore, milder fibrosis was present in additional areas of the RV beyond those identified by LGE CMR that appeared macroscopically but not microscopically normal. There was no fibrosis present in the subpulmonary LV (Figure 3B).

**RV LGE Progression**

Five years from CMR study, 1 patient presented with exercise intolerance, syncope, and nonsustained ventricular tachycardia corresponding with palpitations. There was prolongation of QRS duration (from 176 to 196 ms), whereas RV ejection fraction remained impaired but stable (29%). CMR repeat study before implantation of automated implantable cardioverter defibrillator showed a clear increase in the amount of RV LGE compared with baseline (Figure 4).

**Reproducibility of CMR Measurements**

The coefficient of variability for intraobserver and interobserver reproducibility was 1.5%/1.7% for the LGE mass. Intraobserver and interobserver reproducibility of indexed systemic RV volumetric measurements were mass, 5.6%/4.9%; end-diastolic volume, 2.7%/3.8%; end-systolic volume, 4.9%/8.3%; stroke volume, 3.3%/12.0%; and ejection fraction, 3.0%/7.8% as previously reported.1

**Discussion**

We have shown that systemic RV fibrosis in patients with transposition of the great arteries post atrial redirection surgery is common and associated independently with clinical outcome. Furthermore, systemic RV LGE by CMR was in accord with histological fibrosis in an explanted heart from a patient undergoing transplantation. Finally, our data from 1 patient suggest that RV fibrosis may progress with time and this progression appeared to coincide with clinical decline.

**RV Fibrosis and Its Independent Association With Clinical Outcome**

Our previous study of LGE in systemic RV patients was cross-sectional.1 In this prospective, larger study, we show that the mere presence of RV LGE at CMR, irrespective of its extent, had the strongest association with the predefined clinical composite end point compared with other univariate predictors. Our findings suggest that even a small amount of fibrosis detected by LGE CMR identifies patients at greater risk of adverse outcome, as previously shown in other cardiac patients.25 Furthermore, there was a relation between risk and the extent of fibrosis, as a 1% increase in RV LGE was associated with 38% greater likelihood of reaching the end point over a median of 6.5 years. By bivariate analysis, LGE presence was more strongly associated with outcome than RV volumes, RV ejection fraction or peak $V_{O2}^\text{peak}$, and retained its predictive value when compared with the only other independent predictor, peak $V_{O2}^\text{peak}$%. Peak $V_{O2}^\text{peak}$% reflects exercise capacity accounting for age and sex and has been shown to predict death or cardiac-related hospital admission in this population.26 When fibrosis status was added to peak $V_{O2}^\text{peak}$%, risk prediction for cardiac events was further refined. Although there is interplay between hemodynamics, scar substrate, and electric instability in these patients, both exercise physiology and fibrosis carry prognostic value. Therefore, our data show that the combination of these 2 noninvasive markers could aid in routine clinical evaluation of patients and risk stratification for arrhythmia and sudden death.

Detectable systemic RV LGE in our cohort might represent the tip of the iceberg of true RV fibrosis extent given that a relatively limited extent of RV LGE related to impaired RV function and was associated with outcome. There was excellent agreement between the location and extent of RV LGE areas documented on the in vivo CMR scan and ventricular fibrosis in the explanted heart from 1 patient in our cohort; RV LGE at CMR therefore does represent RV fibrosis and can detect all macroscopically visible areas of fibrosis including small areas of patchy fibrosis. Diffuse RV fibrosis was also present histologically throughout the myocardium in areas that appeared macroscopically normal, and this was undetectable by LGE CMR in keeping with a recent case report.27 Our findings suggest that further CMR research aimed to quantify total fibrosis burden from both focal macroscopic and diffuse microscopic fibrosis is warranted.
Potential Causes of RV LGE and Evidence of Its Possible Progressive Nature

The cause of RV LGE demonstrated may be preoperative,28 peroperative, or related to longstanding pressure load on the systemic RV. RV fibrosis was associated with later surgery in our study. This coupled with previous evidence that RV regional wall abnormalities are already present before atrial redirection surgery29 suggests that preoperative cyanosis may play a role in the development of RV fibrosis. We submit that RV fibrosis is likely to be multifactorial relating to factors, such as later repair, surgical era, and ongoing pathological RV remodeling with age. We have previously suggested that active progression of RV fibrosis during follow-up can occur, as previously suggested22 and evidenced by increased number of affected myocardial regions at the follow-up CMR study in 1 patient in this cohort. As we cannot to date provide systematic follow-up data of the LGE extent for the whole patient cohort, future studies to validate our findings and further explore the potential for RV fibrosis as a therapeutic target are warranted.

Although not the focus of our study, we also have early findings that active progression of RV fibrosis during follow-up can occur, as previously suggested32 and evidenced by increased number of affected myocardial regions at the follow-up CMR study in 1 patient in this cohort. As we cannot to date provide systematic follow-up data of the LGE extent for the whole patient cohort, future studies to validate our findings and further explore the potential for RV fibrosis as a therapeutic target are warranted. Although to date there are few clinical trials,32–36 a recent report that eplerenone resulted in improvement in altered baseline collagen turnover biomarkers compared with placebo36 supports the exploration of the clinical role for current and novel antifibrotic drug therapy.

RV Fibrosis, Mechanoelectric Remodeling, and Atrial Tachyarrhythmia

Our study showed systemic RV fibrosis, yet the tachyarrhythmia events predicted by it were mostly atrial. Atrial tachyarrhythmia in these patients usually precedes clinical
RV failure, ventricular arrhythmia/sudden death and is well understood to be a marker of ventricular disease. Our finding that patients almost always presented with atrial tachyarrhythmia first and that intrinsic ventricular disease evidenced by LGE CMR predicted atrial tachyarrhythmia supports this notion. Fibrosis-related systemic RV diastolic dysfunction with abnormal relaxation, increased myocardial stiffness, and impaired diastolic filling may lead to atrial dilation facilitating atrial arrhythmia. Diastolic dysfunction may then further exacerbate coronary supply. The onset of systemic ventricular dysfunction imposes additional hemodynamic load on the pulmonary venous atria. Arrhythmia is likely triggered by ongoing adverse remodeling and progressive hemodynamic load on a predisposed atrial substrate caused by extensive atrial surgery. RV LGE was related to increased right atrial area and the presence of mild or more TR in our cohort and all 3 were univariate predictors of atrial tachyarrhythmia. As the presence of TR is secondary to RV dilatation even a mild degree of TR in this setting may represent ventricular dysfunction and may further contribute to the development of arrhythmias because of atrial volume loading.

Of note, ventricular tachyarrhythmia is the cause of sudden death after atrial redirection surgery for which RV fibrosis could be an underlying morphological substrate. The fact that nonsustained and sustained ventricular arrhythmia were associated with RV fibrosis in our study supports this. QRS duration (≥140 ms) has been reported to be a predictor of sudden death or sustained ventricular tachycardia. Of the 4 patients from our cohort with a QRS duration ≥140 ms, 3 had evidence of both RV LGE and atrial tachyarrhythmia. In keeping with previous reports, the extent of systemic RV LGE correlated with QRS duration which in turn related to RV volumes and ejection fraction suggesting a ventricular mechanoelectric interplay.

**Limitations**

Patients with permanent pacemaker/automated cardiac defibrillator were not referred for CMR which may cause a selection bias. No consensus exists on the best method for RV LGE quantification. To date, signal intensity–based thresholds have not been used because of the well-known limitations caused by partial volume effects, the thinner compact RV wall, adjacent retrosternum, sternal wire artifact, and epicardial fat. Therefore, we performed manual planimetry and found reasonable reproducibility. Because of the relatively small number of outcome events, we did not perform multivariable analysis, and therefore cannot determine whether the presence of RV LGE alone could be the main predisposing factor for adverse clinical outcome. Given the low annualized mortality rate, to determine the predictive value of fibrosis imaging for survival, larger multicenter studies would be needed. RV

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**Table 4. Clinical Events at Study End at Median 7.8 (Interquartile Range, 3.8–9.6) Years Follow-Up From CMR**

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients (n=55)</th>
<th>LGE+ (n=31)</th>
<th>LGE− (n=24)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial tachyarrhythmia‡</td>
<td>19</td>
<td>15</td>
<td>4</td>
<td>0.022†</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmia§</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0.030†</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>…</td>
</tr>
<tr>
<td>Heart failure admission</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0.248</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0.248</td>
</tr>
</tbody>
</table>

*Fisher exact test.
†Statistically significant P value.
‡Sixteen patients with atrial tachycardia and 3 patients with atrial fibrillation.
§Two patients with sustained ventricular tachycardia and 4 patients with nonsustained ventricular tachycardia (duration range, 7–22 beats).
Figure 3. A. Macroscopic fibrosis and correlation with in vivo late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) in heart explanted during follow-up. LGE CMR (a and c) and corresponding photographs of macroscopic sections (b and d) showing excellent correlation of CMR LGE with visually fibrotic areas (arrows). The increased signal on balanced steady state free precession (e) and turbo spin echo (f; continuous arrows) is compatible with fat. In (g), the corresponding macroscopic specimen shows epicardial fatty infiltration (continuous arrows) but also right ventricular (RV) endocardial fibrosis. Corresponding histology is shown after staining with Masson’s Trichrome; region (h) shows extensive replacement of the compact myocardium by fatty tissue, whereas the trabeculations lining the cavity contain myocardium (red) and extensive fibrous tissue (green, ×16). Regions (i) and (j) show extensive fatty and fibrous replacement (×100).

B. Microscopic fibrosis and correlation with in vivo LGE CMR. Extensive RV LGE (a; short axis CMR plane) corresponded with macroscopic fibrosis in the explanted heart (b; transverse specimen) with Picrosirius Red staining confirmed collagen in the area of macroscopic fibrosis and corresponding LGE (i inset). Apparently normal looking myocardium at ×25 magnification (ii) shows a lower degree of interstitial/diffuse fibrosis undetected by LGE CMR. No fibrosis was detected in the subpulmonary LV (iii).
LGE status was strongly associated with future clinical events but this does not imply causality because there may be other confounding factors.

Conclusions

LGE in the systemic RV was commonly found in our cohort of adult patients late after atrial redirection surgery for transposition of the great arteries and was strongly and independently associated with adverse clinical outcome. We propose that LGE CMR should be incorporated in risk stratification in these patients.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Patients treated for transposition of the great arteries by atrial redirection surgery with a right ventricle in the systemic position are at risk of arrhythmia, premature systemic right ventricular failure, and sudden death, and improved risk assessment is desirable. We showed that systemic right ventricular late gadolinium enhancement (LGE) detected by cardiovascular magnetic resonance in 56% of our contemporary adult cohort of patients is associated with clinical outcome, mostly sustained, symptomatic atrial arrhythmia. Even a small amount of fibrosis detected by LGE cardiovascular magnetic resonance identified patients with a greater risk of adverse outcome, and the more extensive the LGE the greater the risk of adverse outcome. When we combined the presence of right ventricular LGE with percent of predicted peak oxygen uptake, risk prediction was further refined confirming the additive value of these 2 noninvasive surveillance tools. Future larger studies with mortality as a sole primary end point may define the precise value of systemic right ventricular LGE for predicting survival. Our data suggest that LGE cardiovascular magnetic resonance can aid risk stratification of patients for adverse clinical events allowing prioritization of resources to higher risk patients.
Systemic Right Ventricular Fibrosis Detected by Cardiovascular Magnetic Resonance Is Associated With Clinical Outcome, Mainly New-Onset Atrial Arrhythmia, in Patients After Atrial Redirection Surgery for Transposition of the Great Arteries

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