

Late Gadolinium Enhancement Cardiovascular Magnetic Resonance of the Systemic Right Ventricle in Adults With Previous Atrial Redirection Surgery for Transposition of the Great Arteries

Sonya V. Babu-Narayan, BSc, MRCP; Omer Goktekin, MD; James C. Moon, MRCP;
Craig S. Broberg, MD; George A. Pantely, MD; Dudley J. Pennell, MD, FRCP;
Michael A. Gatzoulis, MD, PhD; Philip J. Kilner, MD, PhD

Background—Patients treated for transposition of the great arteries by atrial redirection surgery have a right ventricle (RV) that sustains systemic pressures long term. Late RV dysfunction occurs in these patients; the reasons for this are unclear, but myocardial fibrosis may be important. Myocardial fibrosis can be visualized by late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR). We hypothesized that LGE would be present in the systemic RV and relate to adverse clinical features.

Methods and Results—We performed CMR on 36 consecutive adult patients (mean age, 27 years) after atrial redirection surgery for transposition of the great arteries. Late gadolinium RV enhancement was seen in 22 patients (61%) with various patterns. Patients with RV LGE were older (30 versus 22 years; $P<0.001$) and had increased RV end-systolic volume index (43 versus 35 mL/m²; $P=0.03$), decreased RV ejection fraction (57% versus 62%; $P=0.02$), increased QRS duration (108 versus 97 ms; $P=0.01$), and increased QT dispersion (93 versus 71 ms; $P=0.002$). The extent of LGE correlated with age ($r=0.59$, $P<0.001$) and QRS duration ($r=0.67$, $P<0.001$) and inversely with RV ejection fraction ($r=-0.76$, $P<0.001$). The incidence of documented arrhythmia and/or syncope (10 of 36) was significantly higher in the late gadolinium–positive group (9/22 versus 1/14; $P=0.03$).

Conclusions—LGE CMR suggestive of myocardial fibrosis occurs in the systemic RV of patients after atrial redirection surgery. The extent of LGE correlates with age, ventricular dysfunction, electrophysiological parameters, and clinical events, suggesting prognostic importance that merits further investigation. (*Circulation*. 2005;111:2091-2098.)

Key Words: heart ventricles ■ magnetic resonance imaging ■ heart defects, congenital
■ transposition of great vessels ■ fibrosis

Before use of the arterial switch operation, patients with transposition of the great arteries were palliated by redirection of blood at the atrial level with the Senning¹ or Mustard operation.² There is a contemporary adult population in whom the right ventricle (RV) must sustain systemic pressure long term. Late RV dysfunction is common in these patients³ and may be related to myocardial fibrosis. In patients with a systemic left ventricle (LV), cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) can detect myocardial fibrosis in both ischemic and nonischemic cardiomyopathies.^{4,5} We hypothesized that LGE would be present in the systemic RV and that it would be associated with markers of adverse clinical outcome.⁴

Methods

Patient Population

Consecutive patients with transposition of the great arteries who had undergone either the Mustard or Senning procedure were invited to participate. Patients with a permanent pacemaker in situ were excluded. The local research ethics committee approved the study, and all patients gave written informed consent.

Cardiovascular Magnetic Resonance

A 1.5-T scanner was used (Siemens Sonata). After routine assessment of anatomy, the patency of atrial pathways and function of valves were assessed by steady-state free precession (SSFP) cine imaging in a sequence of specified oblique planes. They were aligned with each atrial pathway, the inflow valves in long-axis planes, and the outflow tracts. Peak velocity was measured at the

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From the Adult Congenital Heart Unit, Royal Brompton Hospital (S.V.B., O.G., C.S.B., G.A.P., M.A.G.); Centre for Advanced Magnetic Resonance in Cardiology, Royal Brompton Hospital (S.V.B., J.C.M., D.J.P., P.J.K.); and National Heart and Lung Institute, Imperial College (S.V.B., D.J.P., M.A.G., P.J.K.), London, UK.

Correspondence to Dr Michael A. Gatzoulis, Adult Congenital Heart Unit, Royal Brompton Hospital, Sydney St, London SW3 6NP, UK. E-mail M.Gatzoulis@rbh.nthames.nhs.uk

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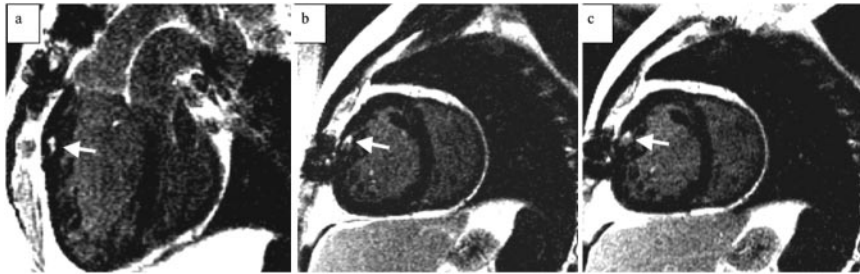


Figure 1. a, Inversion recovery CMR image showing focal LGE in the trabeculated free wall of the RV (arrow). b, The same region is seen in the short-axis view (arrow) and is still present (c) when the phase encoding has been swapped (arrow). There is also subtle enhancement at the junction between RV and LV.

narrowest point of each caval pathway and in the pulmonary venous atrial compartment if narrowed. Then a short-axis contiguous stack of 7-mm SSFP cine images (3-mm gap) was acquired from the atrioventricular ring to the apex. Late gadolinium imaging was performed with the use of a segmented fast low-angle shot inversion recovery sequence from at least 5 minutes after injection of 0.1 mmol/kg IV gadolinium-DTPA. Multiple long- and short-axis slices were acquired, duplicating those of the SSFP cines. Typical parameters were repetition time/echo time/flip angle/voxel size/segments as follows: R-R minus $\geq 10\%$ /4.3 ms/20°/2.2×1.3×8 mm/23. Great care was taken to exclude or recognize artifacts. A 90° presaturation pulse was applied to mask cerebrospinal fluid and prevent ghosting. The inversion time was adjusted to maintain nulling of healthy myocardium, typically increasing from 310 to 420 ms as blood gadolinium levels declined. The acquisition window was placed in the most static part of the cardiac cycle. Imaging parameters were optimized to individual patient heart rate and breath-hold ability. Typically, readout was every second heart beat or third beat in patients with rapid or irregular rhythms. Any image showing suspected LGE was repeated after swapping of the phase encode direction. In addition, to help define subtle endocardial LGE, a systolic image was sometimes acquired. An average of 22 late gadolinium images per patient were acquired in planes identical to pregadolinium cine views to allow side-by-side comparison. The image set was reviewed by 2 observers for the presence or absence of LGE. LGE was considered present if there was bright signal within the myocardium on at least 2 views (phase-swap or cross-cut) in the presence of good nulling and no artifact (Figure 1).

Analysis of Volumes, Function, and Mass

Dedicated software (CMRtools, Cardiovascular Imaging Solutions) was used for manual tracing of endocardial and epicardial borders in each slice. Simpson's method was applied to determine myocardial mass, end-diastolic volume, end-systolic volume, and ejection fraction of each ventricle. RV free wall below the aortic valve and trabecular ridges and bands on the RV side of the septum were included in RV mass measurements. A single observer (S.V.B.) made the ventricular measurements in all patients, each requiring ≥ 60 minutes. Twelve patients were remeasured by the same observer (minimum 6-month interval) as well as a second observer (P.J.K.), both blind to previous measurements for calculation of intraobserver and interobserver variability.

Any LGE present was quantified by a single operator using manual planimetry, applying Simpson's method to express the resultant measurement as a percentage of total RV mass. Height and weight were measured on the day of scanning, and values for volumes and mass were indexed to body surface area.

ECG Analysis

Standard 12-lead ECGs were obtained and recorded at 25 mm/s. The QRS duration and corrected QT interval (QTc) were documented. Subsequent ECG measurement was done by a single observer (O.G.) who was blinded to clinical data. QT interval and JT interval were measured manually with the use of a digital caliper and magnifying glass at each lead as previously described.⁶ Whenever possible, 3 consecutive cycles were measured in each of 12 leads to calculate the mean R-R interval.

Statistical Analysis

Kolmogorov-Smirnov analysis was performed to assess data distribution. Data are expressed as mean and SD or median and interquartile range as appropriate. Unpaired *t* test was performed for normally distributed data, and Mann-Whitney test was performed when this was not appropriate. The χ^2 or Fisher exact test was performed on noncontinuous variables, as appropriate. Correlation was tested with Pearson's coefficient. The null hypothesis was rejected if the probability value was ≤ 0.05 . Mass, volumes, and ejection fractions were compared both between observer 1 and 2 (interobserver) and between the first and second measurements from observer 1 (intraobserver). For each variable, the SD of the difference between the measurements was divided by the mean and expressed as a percentage (coefficient of variability), as reported elsewhere.⁷

Results

The population characteristics are summarized in Table 1. Thirty-six patients (mean age, 27 ± 7 years) (21 male [mean age, 28 ± 8 years] and 15 female [mean age, 27 ± 7 years]) were studied. Thirty-four patients had undergone Mustard and 2 Senning atrial redirection surgery. Mean follow-up after atrial redirection was 24 ± 6 years. Thirty-three were in New York Heart Association class I, and 3 patients (all with positive LGE) were in New York Heart Association class II. All studies were performed uneventfully. Myocardial LGE was present in 22 patients (61%).

Functional and Clinical Correlates of Late LGE

Results are shown in Table 1. Patients with LGE were older, had longer time since surgery, higher RV end-systolic volume index, and lower RV ejection fraction (RVEF).

There was no significant difference between the LGE group and the non-LGE group with respect to gender, presence or absence of junctional rhythm, RV end-diastolic volume index, RV mass index, parameters of LV size and function, incidence of previous baffle reintervention, or associated ventricular septal defect (VSD). A trend toward later repair (2.8 ± 7 versus 1 ± 1 years; $P=0.07$) was seen in the LGE group. Of the 10 patients with documented arrhythmia or syncope, 9 were in the LGE group ($P=0.03$). Patients with arrhythmia had more extensive fibrosis, were older, and had higher RV mass index. Detailed characteristics for this group are shown in Table 2.

Location and Patterns of LGE

LGE was visible in 4 patterns (Figures 2 and 3). First, localized full-thickness RV anterior wall enhancement was seen in 16 patients (44%), generally 1 to 4 cm in length but 8 cm in 1 patient, with this type being associated with obvious wall thinning and akinesia on corresponding cine images. Second, small foci of enhancement were seen in the walls or

TABLE 1. LGE and Clinical Correlates

	All Patients (n=36)	Fibrosis Present (n=22)	Fibrosis Absent (n=14)	<i>P</i> *	Correlation With Extent of Fibrosis (% RV Mass), <i>r/P</i> ≤0.02
Age, y	27±7	30±8	22±4	0.001	0.59
RVEDVi, mL/m ²	93 (80–110)	101 (83–120)	90 (74–102)	NS	0.39
RVESVi, mL/m ²	38 (32–45)	43 (33–54)	35 (29–39)	0.03	0.70
RVEF, %	59 (53–64)	57 (50–61)	62 (57–67)	0.02	–0.76
RVMi, g/m ²	83 (71–94)	88 (68–99)	77 (74–86)	NS	0.55
LVEDVi, mL/m ²	78±20	75±22	82±16	NS	–0.62
LVESVi, mL/m ²	29±11	27±12	31±9	NS	–0.48
LVEF, %	62±10	62±11	63±7	NS	–0.37
LVMi, g/m ²	31 (24–36)	34 (22–37)	30 (27–33)	NS	NS
QRS, ms	104±16	108±8	97±8	0.01	0.67
QRS dispersion	40 (35–48)	40 (36–48)	40 (31–53)	NS	NS
QTc	437±43	443±45	427±40	NS	0.52
QT dispersion, ms	80 (68–107)	93 (76–135)	71 (60–86)	0.002	0.38
JT dispersion, ms	90±31	100±33	76±20	0.01	NS
Syncope/arrhythmia	10	9	1	0.03	...
Baffle reintervention†	8	6	2	NS	...
Prior VSD	11	8	3	NS	...

Values in first 3 columns are mean±SD or median (interquartile range). RVEDVi indicates RV end-diastolic volume index; RVESVi, RV end-systolic volume index; RVMi, RV mass index; LVEDVi, LV end-diastolic volume index; LVESVi, LV end-systolic volume index; LVMi, LV mass index; and QRS, QRS complex duration.

*Mann-Whitney/*t* test/ χ^2 .

†Either surgical or transcatheter reintervention to any of the atrial pathways.

trabeculations of the RV in 16 patients (44%). Third, enhancement was seen in the basal septum in 7 patients (19%). This was consistent with a previously known VSD in 6 of these patients, 4 of whom had known previous VSD patching and 2 of whom had a VSD that had closed spontaneously. Fourth, localized enhancement was frequently faintly visible at the insertion between the RV and LV inferiorly (32/36; 89%) and superiorly (13/36; 36%). We did not include this almost ubiquitous finding in our analysis of the extent of LGE. The incidence of this type of enhancement was not different between the 2 groups (17/22 LGE patients and 12/14 non-LGE patients; *P*=NS). The few patients (*n*=4) in whom there was no enhancement of this type were found to have no difference in ventricular volumes or function but had lower RV mass index (66±13 versus 90±30 g/m²; *P*=0.04).

LGE and ECG Associations

QRS duration, QT dispersion, and JT dispersion were significantly increased in the LGE group (*P*=0.01, *P*=0.002, *P*=0.02), although there was no significant difference in QRS dispersion, PR interval, QT interval, or QTc. The extent of LGE correlated positively with QRS duration and QTc and less strongly with QT dispersion (Table 1). Within the LGE-positive group itself, patients with documented arrhythmia (*n*=9) had more enhancement than those without arrhythmia (*n*=13) (2.1±1.7% versus 0.6±0.6%; *P*=0.03).

Extent of LGE and Ventricular Function

The amount of LGE expressed as a percentage of indexed RV mass was quantified and ranged from 0% to 6%. There was a negative correlation between percentage of LGE and RVEF and a positive correlation between percentage of LGE and both RV end-systolic volume index and age (Figure 4). Although the trend toward higher RV mass index in the LGE group versus the non-LGE group was not significant, there was a positive correlation between percentage of LGE and RV mass index (*r*=0.55, *P*=0.001) (Table 1). There were inverse correlations between RV mass index and RVEF (*r*=–0.59, *P*<0.001), LV ejection fraction (LVEF) and RV end-systolic volume index (*r*=–0.53, *P*=0.001), and LVEF and RV mass index (*r*=–0.45, *P*=0.006). There was a correlation between RVEF and LVEF (*r*=0.47, *P*=0.004).

Reproducibility of Ventricular Volumes and Mass

The coefficients of variability for intraobserver/interobserver reproducibility were as follows, respectively: RV mass index 5.6%/4.9%, RV end-diastolic volume index 2.7%/3.8%, RV end-systolic volume index 4.9%/8.3%, RV stroke volume index 3.3%/12.0%, RVEF 3.0%/7.8%, LV mass index 6.5%/17.3%, LV end-diastolic volume index 3.5%/5.2%, LV end-systolic volume index 9.1%/7.0%, LV stroke volume index 6.1%/8.8%, LVEF 5.7%/5.3%. Intraobserver variability was less than interobserver variability for almost all variables. There was higher variability for LV mass, which was not

TABLE 2. Clinical Characteristics and CMR Findings With Regard to Documented Arrhythmia or Episodes of Syncope

	Arrhythmia/Syncope		<i>P</i> *
	Present (n=10)	Absent (n=26)	
Fibrosis, %	1.6 (0.7–2.4)	0.3 (0–0.28)	0.001
Clinical characteristics			
Age, y	31±8	25±6	0.04
Prior VSD	3/10	5/26	NS
Reintervention	2/10	10/26	NS
Simple surgery	4/10	7/26	NS
Mild/moderate baffle obstruction	7/10	10/26	NS
>NYHA class I	3/10	0/26	0.02
CMR findings			
RVEDVi, mL/m ²	96 (83–120)	93 (78–108)	NS
RVESVi, mL/m ²	43 (36–54)	36 (31–43)	NS
RVEF, %	53 (34–61)	60 (55–65)	0.08
RVMi, g/m ²	98 (87–104)	77 (68–87)	0.03
LVEDVi, mL/m ²	68±21	82±19	0.06
LVESVi, mL/m ²	24±8	31±11	NS
LVEF, %	65±10	63±8	NS
LVMi, g/m ²	36 (24–41)	30 (24–35)	NS
ECG parameters			
QRS, ms	124±13	110±10	0.007
QRS dispersion	40 (33–47)	42 (33–46)	NS
QTc	464±52	426±35	0.03
QT dispersion, ms	78 (73–127)	80 (62–105)	NS
JT dispersion, ms	98±37	87±28	NS

Values are mean±SD or median (interquartile range). NYHA indicates New York Heart Association; RVEDVi, RV end-diastolic volume index; RVESVi, RV end-systolic volume index; RVMi, RV mass index; LVEDVi, LV end-diastolic volume index; LVESVi, LV end-systolic volume index; LVMi, LV mass index; and QRS, QRS complex duration.

*Mann-Whitney/*t* test/ χ^2 .

surprising given that this subpulmonary ventricle is thin walled.

Discussion

We have shown that regions of abnormal myocardium can be visualized in the systemic RV late after atrial switch with the use of LGE CMR. Such regions are likely to represent focal fibrosis. We also found that the presence and extent of LGE correlate with known markers of adverse outcome, including RV dilatation, impaired systolic function, QRS duration, and QT dispersion.

Background

In the long-term care of patients after atrial redirection surgery, clinicians are eager to understand the pathophysiology of reported late RV dysfunction,^{8,9} reduced exercise capacity,¹⁰ arrhythmia, and mortality from sudden cardiac death.^{11–13} Multiple mechanisms for RV dysfunction late after atrial switch have been postulated. Previously published nuclear medicine data have demonstrated both fixed and

reversible perfusion defects in patients up to 25 years after atrial redirection surgery.^{9,14} In the study by Lubiszewska et al,⁹ stress-induced perfusion abnormalities correlated with increased age, later repair, and lower RVEF and LVEF. This agrees with our evidence of fibrosis correlating with increased age, increased time since repair, and decreased RVEF. Our study allows measurement of RV mass and quantification of the LGE with respect to RV mass, which is not possible by nuclear medicine imaging techniques. Furthermore, CMR allows accurate measurement of biventricular function¹⁵ and the patency of the intra-atrial baffle pathways. We previously demonstrated that excessive RV hypertrophic response is associated with RV systolic dysfunction.¹⁶ In this present larger cohort, we confirmed the inverse correlation between RV mass index and RVEF ($r=-0.59$, $P<0.001$). We also found a correlation between RVEF and LVEF ($r=0.47$, $P=0.004$) and in addition found inverse correlations between LVEF and RV end-systolic volume index and RV mass index ($r=-0.53$, $P=0.001$; $r=-0.45$, $P=0.006$, respectively), suggesting a “ventricular-ventricular interaction.” The present study suggests that hypertrophy is associated with fibrosis in some patients, which in turn correlates with reduced RVEF.

Pathophysiological Mechanisms of Late RV Failure

A number of potential mechanisms might explain the late failure of the systemic RV and the presence of scarring demonstrated by CMR. First, failure may be due to the fact that the morphological RV in this context is challenged with extra workload lifelong and may not have sufficient adaptive capacity with which to respond to this.

Second, preoperative hypoxemia leading to myocardial injury has been suggested as an underlying mechanism. Mean age at surgery was 47±111 months (median, 16; interquartile range, 2 to 530) in the LGE group but 13±13 months (median, 9.75; interquartile range, 2 to 52) in the non-LGE group ($P=NS$). Less LGE in younger patients might also be explained by progressive refinement of cardiothoracic surgery, including the advent of cold cardioplegia and cardiopulmonary bypass. The exposed anterior wall of the RV may be at particular risk of damage from inadequate hypothermia. Cardiopulmonary bypass itself may cause a myocardial insult, especially if prolonged. Other perioperative complications could contribute. However, operative notes (available for 24 of 36 patients) and surgical discharge summaries do not suggest that this is the primary pathogenic mechanism in our patients.

Another possibility is that the hypertrophied and dilated RV, which maintains systemic pressure, may have a coronary artery supply that is inadequate to meet the needs of the increased RV myocardial mass seen late after Mustard or Senning palliation.¹⁶ Our group has previously postulated that excessive RV hypertrophy and an increase in total myocardial mass may result over time in demand-supply mismatch despite patent coronary arteries.¹⁶ Our present data suggest that RV fibrosis is an associated factor contributing to RV dysfunction. It may be that when a

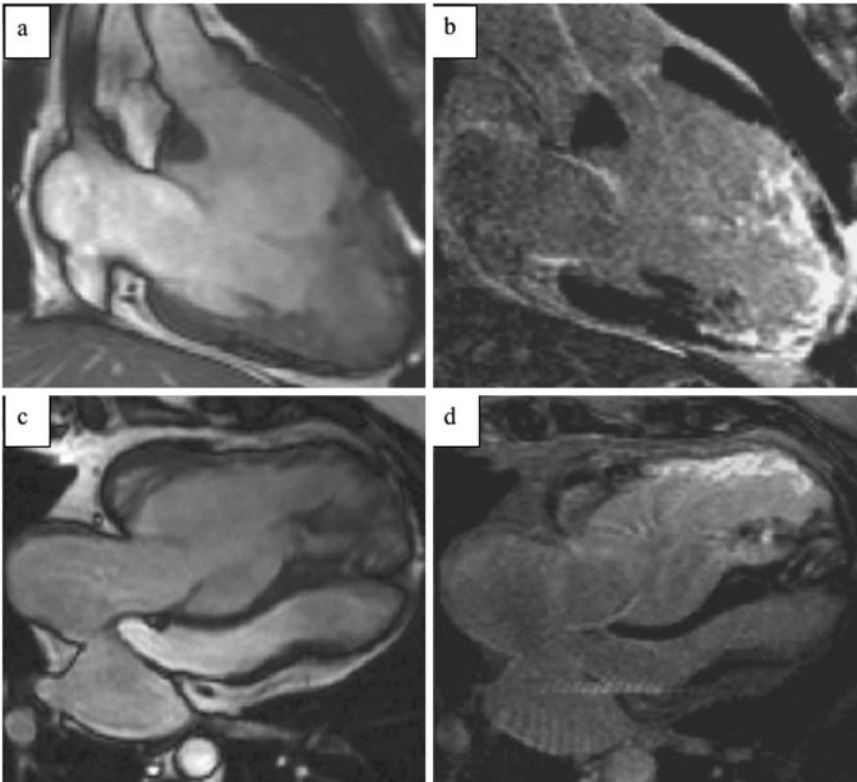


Figure 2. a and c, Diastolic cine frames showing thin, dyskinetic myocardium 8 cm in length in the RV anterior wall, which corresponds to LGE (arrows, b and d).

certain threshold of RV mass is reached, patchy fibrosis ensues, possibly in a manner not dissimilar to that in hypertrophic cardiomyopathy.

Reduction of myocardial flow reserve may also be a potential cause of ischemia. Hyperemic myocardial blood flow to the systolic RV has been shown to be 38% lower in Mustard patients than in controls.¹⁷ Studies of systemic RV patients suggest an abnormal response to dobutamine stress with the use of both echocardiography and CMR^{18–20} and impaired response to exercise, which may support the hypothesis that poor myocardial flow reserve may contribute to the dysfunction observed.

Link Between LGE and Risk Factors for Arrhythmia

Prolonged QRS duration and QT dispersion have previously been shown to be markers of adverse outcome.^{21,22} Sudden cardiac death is the most common cause of late mortality in patients after Mustard or Senning operation.^{11,23} Kammeraad et al²⁴ recently reported that 8 such patients who had died suddenly with documentation of cardiac rhythm at the time, and 10 of 13 who had suffered near-miss sudden death, had either ventricular tachycardia or ventricular fibrillation. Experimental studies suggest that nonuniform recovery of ventricular excitability plays a role in the mechanism of ventricular arrhythmias.²⁵ The interlead variability in QT-interval duration on the standard 12-lead ECG, the so-called QT dispersion, reflects dispersion of recovery time. Increased QT dispersion is a marker of inhomogeneity of ventricular repolarization that favors the development of malignant ventricular arrhythmias. Recently, Sun et al²⁶ found a signif-

icant relationship between increased QT dispersion and sudden cardiac death in patients after Mustard or Senning operation, but mechanisms remained unclear. We have found significant relations between both QT and JT dispersion and the presence of LGE suggestive of systemic ventricular fibrosis. Such fibrosis may predispose to inhomogeneous ventricular repolarization, as expressed by the QT dispersion. Myocardial fibrosis is therefore likely to increase the risk of sudden cardiac death in these patients and have prognostic implications.

Furthermore, our data showed a high prevalence of atrial arrhythmia in patients with LGE. This is in agreement with the concept of atrial arrhythmias being a marker of RV systolic dysfunction when assessed with nuclear imaging, as previously reported, and suggests that atrial arrhythmia in these patients is both a surrogate marker of ventricular dysfunction²² and a predictor of death, as shown by Gewillig et al in 1991.¹² Our present data and the recent report by Kammeraad et al²⁴ imply that although these patients have the potential for fast 1:1 atrioventricular conduction, they probably die from ventricular tachycardia or ventricular fibrillation.

In our analysis of the extent of LGE, we did not include the relatively faint enhancement that was frequently at the region of insertion between RV and LV myocardium. In these regions, interwoven as opposed to aligned arrangements of myocardial fibers²⁷ are likely to be associated with relatively more extracellular space than elsewhere because of less perfect packing among myocytes, especially when hypertrophied. We do not think that LGE of

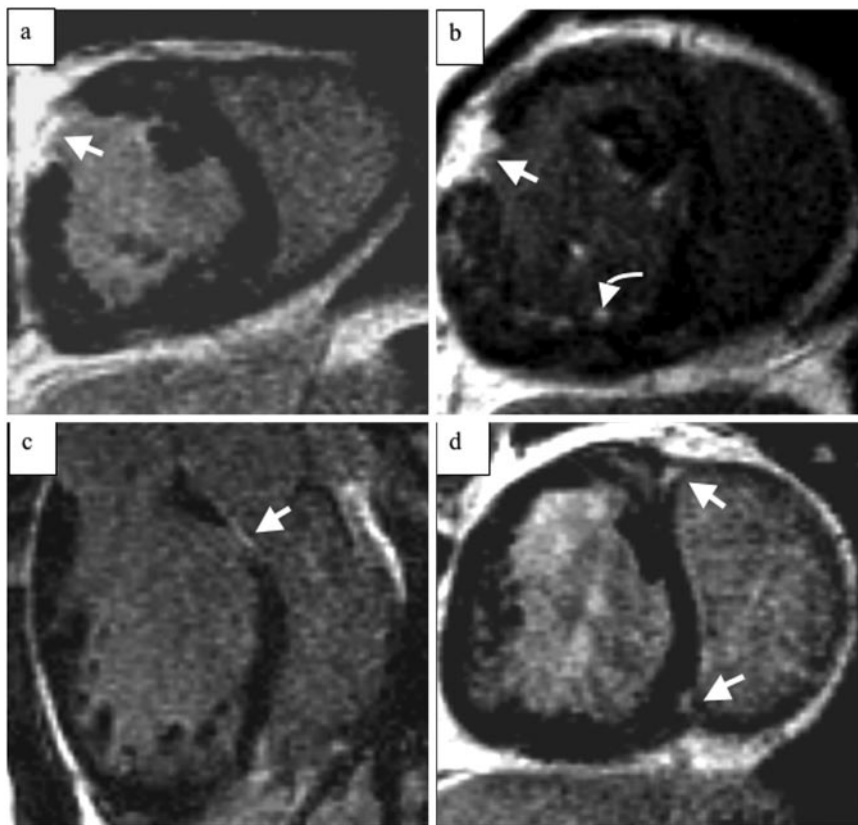


Figure 3. a, Full-thickness LGE of anterior wall of RV. b, RV anterior wall enhancement (arrow) and multiple foci of LGE, suggesting fibrosis of RV trabeculae (curved arrow). c, LGE of a spontaneously closed perimembranous VSD (arrow). d, Superior and inferior LV and RV insertion point enhancement (arrows).

this type, which has been reported in patients with hypertrophic cardiomyopathy,⁴ implies pathological fibrosis.

Implications of LGE

The associations found here between fibrosis, electrophysiological parameters, clinical variables, and RV dysfunction are likely to have prognostic implications with respect to late arrhythmia and sudden cardiac death and thus on late morbidity and mortality for this patient population. Further prospective studies need to examine whether drug therapy may prevent or reverse some of the hypertrophic and fibrotic changes reported here and whether doing so would improve prognosis.

Limitations

The cross-sectional nature of this study limits our ability to make conclusions about the precise mechanisms or rate of progression of fibrosis reported here. In the longer term, documentation of *in vivo* changes and correlation with postmortem histological appearances may be possible. A larger, prospectively followed cohort may reveal further pathogenic mechanisms for fibrosis, its precise prognostic value, and its potential response to therapy.

A number of factors have been found to be associated with fibrosis in this study. The relatively small sample of patients available for study precludes robust multivariate analysis to determine which of these multiple factors is most strongly associated.

Volumetric analysis of the hypertrophied and highly trabeculated systemic RV is challenging. However, in-

traobserver and interobserver variability for the RV in our study were quite acceptable.

There is no consensus on the optimal dose of gadolinium for the detection of fibrosis. Some centers use 0.2 mmol/kg rather than the 0.1 mmol/kg used in the present study. The higher dose requires a longer delay before imaging and costs more but may provide better image quality.

Finally, diffuse fibrosis may be undetectable by the technique used, and therefore the amount of myocardium seen to be affected (1% to 6%) may represent only a proportion of total fibrosis.

Conclusion

LGE CMR demonstrated that evidence of fibrosis of the systemic RV is common in adult patients after Mustard or Senning procedure for simple transposition of the great arteries. The extent of enhancement correlated with impaired RV systolic function and age, lending support to the notion that with time the systemic RV may deteriorate structurally as well as functionally in time. The interaction between the presence of fibrosis, QRS duration, QT dispersion, and RV dysfunction has prognostic implications with respect to late arrhythmias and sudden cardiac death. Longitudinal studies are required to examine our observations further.

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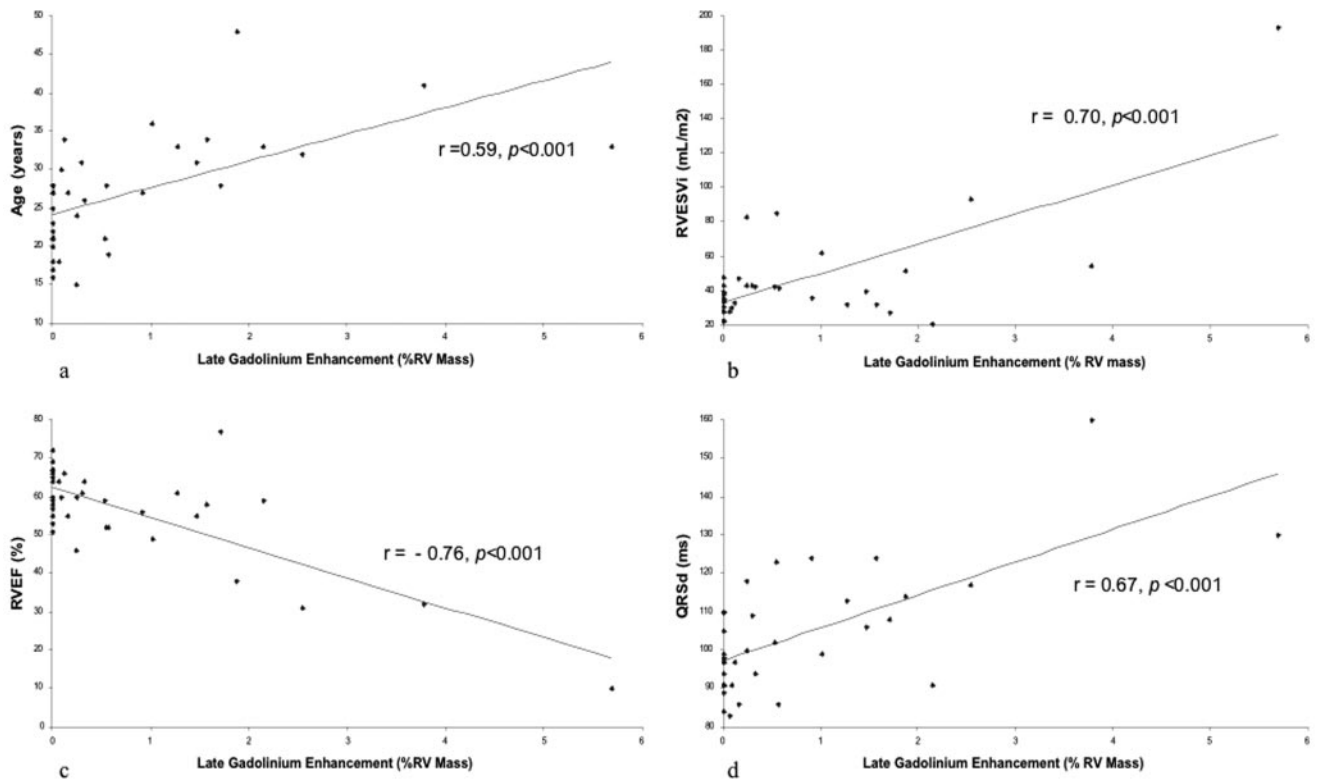


Figure 4. Correlation between extent of late enhancement (percentage of total RV myocardial mass) with age (a); RV end-systolic volume index (RVESVI) (b); RVEF (c); and QRS duration (QRSd) (d).

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