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Progress of right ventricular dilatation in adults with repaired tetralogy of Fallot and free pulmonary regurgitation

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ABSTRACT

Background: The time course of progressive dilatation of the right ventricle (RV) in adults with pulmonary regurgitation (PR) late after repair of tetralogy of Fallot (TOF) is poorly characterized.
Methods: We analysed cardiac MRI data (1.5 T) from 14 adult repaired TOF patients (26 ± 11 years of age) with dilated RVs and known significant PR, on 2 separate visits with a between MRI period of 2.1 ± 1.0 years.
Results: Indexed RV end diastolic volume (RVEDVi) increased over 2 years (142 ± 19 to 151 ± 20 mL/m^2, $p = 0.005$; change = 8.4 ± 9.3 mL/m^2, range = −6 to 26 mL/m^2; annual mL/m^2 increase = 4.3 ± 4.6; annual percentage increase = 3.1 ± 3.3%), whilst RV ejection fraction decreased (53 ± 8 to 49 ± 7 %, $p = 0.039$). RV muscular corpus (RVMC) EDVi significantly increased (130 ± 19 to 138 ± 20 mL/m^2, $p = 0.014$), whereas RV outflow tract (RVOT) EDVi did not (12 ± 7 vs 13 ± 6 mL/m^2, $p = 0.390$). No other RV or LV measures significantly changed during the inter-MRI period. The change in RVEDVi correlated significantly with LV end diastolic volume ($r = -0.582$, $p = 0.029$), RVEDVi:LVEDVi ($r = 0.6$, $p = 0.023$) and RVMC EDVi ($r = 0.9$, $p < 0.001$) but not RVOT EDVi ($r = 0.225$, $p = 0.459$).
Conclusions: Adult repaired TOF patients with free PR experienced a mean 3.1%, or 4.3 mL/m^2, annual increase in RVEDVi, unrelated to the initial RVEDVi or PR fraction. The increase in RVEDVi was due to RVMC rather than RVOT dilatation. This provides a guide to the frequency of MR surveillance and insights into the natural history of progressive RV dilatation in this setting.

1. Introduction

Long standing pulmonary regurgitation (PR) is a common occurrence after the repair of tetralogy of Fallot (TOF) due to pulmonary valve excision and/or the frequent use of transannular patch during initial repair of the right ventricular outflow tract. Exposure of the right ventricle (RV) to a chronic regurgitant load leads to RV dilatation and has been associated with negative consequences such as exercise intolerance, arrhythmia and sudden cardiac death [1–7].

RV dilatation in the moderate to severe range is frequently observed in young adult life in repaired TOF patients, at which point replacement of the pulmonary valve (PVR) is considered. Pulmonary valve replacement has been shown to be safe and effective in reducing PR, RV dilatation and QRS duration [8–15]. However, controversy surrounds the degree to which the RV should be "allowed to dilate" before the need for surgical intervention. Many centres advocate a conservative approach of performing surgery when indexed RV end-diastolic volume (RVEDVi) reaches 150 mL/m^2. However, there is some evidence that the RV can be allowed to dilate to as large as 170 mL/m^2 [10,11] whilst still achieving normalisation of RV volume after PV replacement (RVEDVi ≤108 mL/m^2 [16]). PVR timing is based on these RV volumetric cut-points, yet the progression of RV dilatation towards these milestones is poorly understood. Furthermore, the contributions of RV muscular corpus (RVMC) and RV outflow tract (RVOT) volumes in the temporal changes of global RV dilatation have yet to be investigated. Two recent reports have suggested only slow if any progression of RV volumes in this clinical context [17,18]. We therefore sought to characterize temporal changes in global RV, RVOT and RVMC volumes in TOF patients, in our adult congenital heart disease cohort.

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2. Methods

2.1. Patient population

140 adult repaired TOF patients had undergone cardiac MRI in our imaging facility; 69 subsequently underwent PVR or percutaneous pulmonary valve implantation (PPVI). Of the remaining 71 patients who had not undergone surgical or percutaneous procedure to implant a pulmonary valve, 14 had 1 or more follow up cardiac MRIs. Data was used in these 14 patients referred for 2 clinically indicated cardiac MRIs, and if more than 2 scans had been undertaken, the greatest inter-MRI period was chosen. Overall, the inter-cardiac MRI period was 2.1 ± 1.0 years. Ethics approval was obtained from the Royal Prince Alfred Hospital Human Research Ethics Committee, Sydney, and all participants gave informed consent.

2.2. Cardiovascular MRI protocol

MRI was performed using a 1.5 T MR scanner (GE medical system).

2.2.1. Assessment of ventricular volumes and function using cine MRI

4 chamber and short axis views covering both ventricles (9–12 slices) were acquired in the vertical long-axis using retrospectively gated steady-state free precession (FIESTA) cine MR images. Image parameters: TR = 3.2 ms; TE = 1.6 ms; flip angle = 78°; slice thickness = 8 mm; matrix = 192 × 256; field of view-300–380 mm; and temporal resolution = 40 ms, acquired during a breath-hold. Assessments of RV and LV volumes were performed by manual segmentation of short-axis cine images with endocardial outline at end diastole and end systole (performed in Osirix software, version 4.0 32 bit). Regional analysis of the RV volumes in systole and diastole was then performed, where the RV was divided in the fibrous RVOT and RVMC components. The delineation of these segments was based on the following criteria. The fibrous RVOT was contoured from the pulmonary valve leaflets superiorly, to the fibrous to muscular transition zone with in the RVOT anteriorly based on delayed enhancement studies. Posteriorly the fibrous RVOT was contoured to include volume until the superior aspect of the interventrcular septum. An arbitrary line was contoured between the lower anterior and posterior landmarks to define the lower border zone of the fibrous RVOT. Fibrous RVOT measurements were independently analysed in all subjects by two observers with an intraclass correlation coefficient of 0.977 for end-systolic measurements and 0.923 for end diastolic measurements. Simpson's rule was used to calculate end-diastolic and end-systolic volumes for both ventricles and the RVOT; ejection fractions (EF) were calculated from these volumes.

2.2.2. MR flow calculation

A phase sensitive (VENC 200) gradient-echo sequence (TR, <5 ms; TE, <3 ms; flip angle, 15°; slice thickness, 7 mm; field of view = 300–380 mm matrix, 256 × 240, temporal resolution = 30 ms) during breath hold was used to acquire pulmonary artery (PA) and aortic flow data. The midpoint of the main PA and ascending aorta (sinotubular junction) were used as imaging planes. Through-plane flow data was acquired by use of retrospective cardiac gating. Phase contrast images were used to calculate arterial blood flow by use of a semiautomatic vessel edge-detection algorithm (Reportcard, 4.0, GE, Milwaukee) with manual operator correction. Net forward flow within the main PA (mL) and PR fraction (%) were calculated as total PA flow minus backward PA flow, and percent backward PA flow over total PA flow, respectively. These calculations were similarly made for the aortic flow.

2.2.3. Late gadolinium enhancement: scar/fibrosis imaging

Segmented phase-sensitive inversion recovery sequences (Image parameters: TR = 2 × RR interval; TE = 3.4 ms; flip angle = 25°; slice thickness = 10 mm; matrix = 144 × 256; field of view = 300–380 mm, acquired during a single breath-hold) were used to identify myocardial scar 10 min post-administration of intravenous contrast (0.2 mmol/kg of gadolinium pentatate, Magnevist). There entire short and long-axis of the LV and RV.

2.3. Statistical methods

All data are presented as mean ± SD. Statistical comparison of initial and follow up MRI data was performed with a 2-tailed paired Student *t* tests. The pre-specified primary study endpoint was change in RVEDVi. As other endpoints were inter-related and the study was exploratory in nature, *p*-values were not adjusted for multiple comparisons. Pearson's correlation coefficient was used to assess relations between change in RVEDVi and other MRI variables. Inter-observer variability in RVOT volume analysis was assessed via interclass correlation. Statistical significance was inferred at a two-tailed *p*-value <0.05. Statistical analyses were performed with SPSS V.21 for Windows (SPSS).

3. Results

3.1. Patient population (n = 14)

Cardiac MRI data was included from 14 patients (age at evaluation 26 ± 11 years; mean age at repair 3.2 ± 2.9 years; 7 males). Patient demographics and surgical details are outlined in Table 1. TOF was the primary diagnosis and a trans-annular patch repair had been performed in all 14 patients.

3.2. MRI results (n = 14)

MRI results are displayed in Table 2. Initially, the cohort had moderate RV dilatation (indexed RV end-diastolic volume [RVEDVi]; 142 ± 19 mL/m^2, indexed RV end-systolic volume [RVESVi]; 68 ± 17 mL/m^2), moderate to severe PR (PR fraction; 33 ± 11%) and normal RV ejection fraction (RVEF; 53 ± 8%). Indexed LV end-diastolic volume (LVEDVi; 76 ± 10 mL/m^2) and LV ejection fraction (LVEF; 61 ± 5%) were within normal ranges, however, LV end-systolic volume was mildly elevated (LVESVi; 30 ± 7 mL/m^2). LV and RV stroke volumes (SV) were maintained (LVSV; 82 ± 15 mL, RVSV; 132 ± 21 mL). RVOT volume was 8.6 ± 4.6% of RV volume (indexed RVOT end-diastolic volume [RVOT EDVi]; 12 ± 7 mL/m^2).

After 2.1 ± 1.0 years, RVEDVi had increased significantly (to 151 ± 20 mL/m^2, $p = 0.005$; change = 8.4 ± 9.3 mL/m^2, range = −6 to 26 mL/m^2; annual mL/m^2 increase = 4.3 ± 4.6; annual percentage increase = 3.1 ± 3.3%). RVESVi (77 ± 19 mL/m^2, $p = 0.009$) and RVMC indexed end-diastolic volume (RVMC EDVi; 138 ± 20 mL/m^2, $p = 0.014$) also increased, and RVEF decreased (49 ± 7%, $p = 0.039$). RVEDVi increased from below to above an RVEDVi of 150 mL/m^2 in 3 patients (see Fig. 1). No other RV or LV structural or functional measures significantly changed in the period between MRIs.

Change in RVEDVi was significantly correlated with initial LVEDVi ($r = -0.582$, $p = 0.029$), initial RVEDVi:LVEDVi ($r = 0.6$, $p = 0.023$) and change in RVMC EDVi ($r = 0.919$, $p < 0.001$) but not change in RVOT EDVi ($r = 0.182$, $p = 0.552$) (see Fig. 2).

Table 1
Cohort characteristics.

Participants (*n*)	14
Age (years)	26 ± 11
Males (*n*)	7
Age at TOF repair (years)	3.2 ± 2.9
Years between TOF repair and 1st MRI	23 ± 8

TOF indicates tetralogy of Fallot.

Table 2
Cardiac MRI values at initial and follow up MRI.

	MRI 1	MRI 2	Change
RVEDVi (mL/m^2)	142 ± 19	151 ± 20*	8.4 ± 9.3
RVESVi (mL/m^2)	68 ± 17	77 ± 19*	9.2 ± 11.3
RVMC EDVi (mL/m^2)	130 ± 19	138 ± 20*	7.6 ± 9.5
RVOT EDVi (mL/m^2)	12 ± 7	13 ± 6	0.4 ± 1.7
RVSV (mL)	132 ± 21	132 ± 23	0.1 ± 13.8
RVEF (%)	53 ± 8	49 ± 7*	−3.6 ± 5.8
RVCO (L)	9.0 ± 1.3	9.0 ± 1.6	0.0 ± 1.4
PRF (%)	33 ± 11	33 ± 12	0.3 ± 4.4
RV:LV ratio	1.9 ± 0.3	1.9 ± 0.3	0.0 ± 0.2
LVEDVi (mL/m^2)	76 ± 10	79 ± 11	3.0 ± 7.2
LVESVi (mL/m^2)	30 ± 7	31 ± 7	1.1 ± 5.7
LVSV (mL)	82 ± 15	85 ± 15	3.3 ± 11.2
LVEF (%)	61 ± 5	60 ± 5	−1.1 ± 4.4
LVCO (L)	5.6 ± 0.6	5.8 ± 1.1	0.2 ± 1.1

* indicates $p < 0.05$; EDVi indicates indexed end-diastolic volume; ESVi, end-systolic volume; RVMC, RV muscular corpus; RVOT, RV outflow tract; SV, stroke volume; EF, ejection fraction; CO, cardiac output; PRF, pulmonary regurgitant fraction.

4. Discussion

In our cohort of adult repaired TOF patients with free PR, RV volumes significantly increased over 2 years, from 5% below the commonly used RVEDVi indicator for PVR of 150 mL/m^2 to marginally above this cut-point. The observed RV dilatation was related to RVMC volume enlargement but not change in RVOT size, initial RVEDVi or initial PR fraction. In addition to RV dilatation, RVEF significantly decreased during the inter-MRI period.

The natural history of RV dilatation in repaired TOF has not been thoroughly studied. Our results are in contrast to previous reports which did not show a significant increase in RV size or deterioration of RV function over a similar period of time [17,18]. There was some variation in the degree of change in RV size, with 3 patients experiencing approximately up to 25 mL/m^2 increase in RVEDVi and 3 patients exhibiting minimal change in serial RV volumes. The RV dilated moderately in the remaining 8 patients. This variation can, to some extent, be explained by the degree to which the RVMC dilated. We showed that those patients with greater RVMC dilatation experienced greater increase in global RV size.

Progression of RV size is important in this setting, as it has significant implications for the timing of PVR and imaging follow up periods. Specifically, rapid RV dilatation may warrant early surgical intervention and short follow up periods. Early PVR may have the advantage of preventing the potentially damaging effects of an enlarged RV [9,19]. However, reintervention due to limited valve lifespan [20,21] requires consideration, particularly in asymptomatic patients.

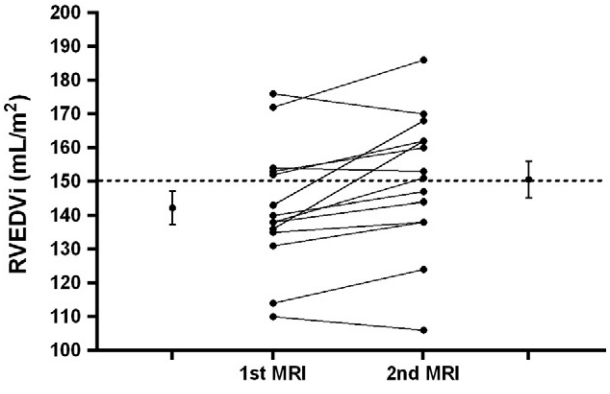

Fig. 1. Right ventricular volume at first and second MRI.

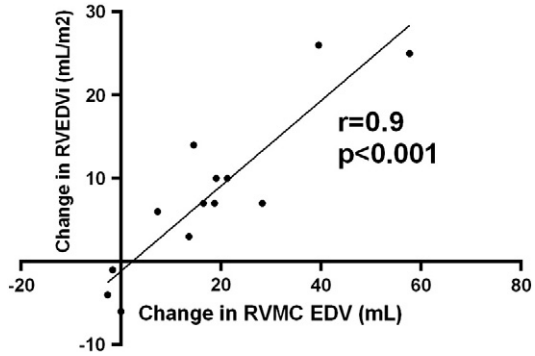

Fig. 2. Correlation of change in RVEDVi with change in RVMC EDV.

4.1. Study limitations

This study was limited by the small number of patients and the relatively short time frame over which they were followed. There is also the possibility of selection bias from patients with echocardiographic evidence of a dilating RV being referred for cardiac MRI. Larger, long-term prospective studies are required to better understand progression of RV dilatation and its determinants throughout the lifespan of TOF patients.

5. Conclusions

The RV continues to dilate in many patients with PR late after TOF repair, approximately 5–10% over 2 years. These data might inform a reasonable interval for serial MRI scanning, especially given the inaccuracy of cardiac ultrasound for precise measurements of RV volumes.

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