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Mechanisms of maintained exercise capacity in adults with repaired tetralogy of Fallot

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ABSTRACT

Background: The mechanisms whereby cardiac output is augmented with exercise in adult repaired tetralogy of Fallot (TOF) are poorly characterised.
Methods: 16 repaired TOF patients (25 ± 7 years of age) and 8 age and sex matched controls (25 ± 4 years of age) underwent cardiopulmonary exercise testing and then real-time cardiac MRI (1.5 T) at rest and whilst exercising within the scanner, aiming for 30% heart rate reserve (Level 1) and 60% heart rate reserve (Level 2), using a custom-built MRI compatible foot pedal device.
Results: At rest, TOF patients had severely dilated RVs (indexed RV end-diastolic volume: 149 ± 37 mL/m^2), moderate-severe PR (regurgitant fraction 35 ± 12%), normal RV fractional area change (FAC) (52 ± 7%) and very mildly impaired exercise capacity (83 ± 15% of predicted maximal work rate). Heart rate and RV FAC increased significantly in TOF patients (75 ± 10 vs 123 ± 17 beats per minute, $p < 0.001$; 44 ± 7 vs 51 ± 10%, $p = 0.025$), and similarly in control subjects (70 ± 11 vs 127 ± 12 beats per minute, $p < 0.001$; 49 ± 7 vs 61 ± 9%, $p = 0.003$), when rest was compared to Level 2. PR fraction decreased significantly but only modestly, from rest to Level 2 in TOF patients (37 ± 15 to 31 ± 15%, $p = 0.002$). Pulmonary artery net forward flow was maintained and did not significantly increase from rest to Level 2 in TOF patients (70 ± 19 vs 69 ± 12 mL/beat, $p = 0.854$) or controls (93 ± 9 vs 95 ± 21 mL/beat, $p = 0.648$).
Conclusions: During exercise in repaired TOF subjects with dilated RV and free PR, increased total RV output per minute was facilitated by an increase in heart rate, an increase in RV FAC and a decrease in PR fraction.

1. Introduction

We have recently demonstrated that patients with repaired tetralogy of Fallot (TOF) have near normal exercise capacity, even in the setting of severe right ventricular (RV) dilatation and severe pulmonary regurgitation (PR) [1]. However, the mechanisms whereby cardiac output is augmented with exercise in this setting are poorly understood.

Recently, real-time magnetic resonance imaging (MRI) techniques have been developed, to allow MRI of cardiac structures and blood flow during exercise [2,3]. A thorough appreciation of the biventricular response to exercise in adult repaired TOF may facilitate a more complete understanding of the onset and underlying causes of exercise-related symptoms. Furthermore, in patients who are asymptomatic and have normal or very mildly impaired exercise capacity the addition of real-time MRI imaging of the exercising heart may provide greater sensitivity in observing altered cardiac function, when compared to resting MRI alone.

We thus studied ventricular function and cardiac flows during exercise in adults with repaired tetralogy of Fallot with moderate to severe pulmonary regurgitation and RV dilatation and correlate these measures with objective assessments of exercise capacity.

2. Material and methods

2.1. Study population

Sixteen adult repaired tetralogy of Fallot patients (25 ± 7 years of age) were prospectively recruited to undergo clinically indicated resting cardiac MRI, cardiac MRI during exercise and a standard cardiopulmonary exercise test (CPET). The exercise cardiac MRI

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and CPET were performed on the same day as the resting cardiac MRI in all but 2 cases, where they returned within a month. Patients were included in the study if they had TOF as a primary diagnosis (TOF variants were excluded), were older than 15 years, had an indexed RV end-diastolic volume (RVEDVi) > 105 mL/m^2 and had a PR fraction > 20%. Eight healthy age and gender matched controls (25 ± 4 years of age) were also recruited for comparison. The control group underwent exercise cardiac MRI and CPET on the same day. Controls were included if they undertook 2 or less structured exercise sessions per week. Ethics approval was obtained from the Royal Prince Alfred Hospital Human Research Ethics Committee, Sydney, and all participants gave informed consent.

2.2. Resting cardiac MRI protocol

MRI was performed using a 1.5T MR scanner (Philips Acheiva; Philips, Best, The Netherlands).

2.3. Assessment of resting ventricular volumes and function using standard cine MRI.

Short axis, vertical long axis and 4-chamber views of both ventricles were acquired over 9–12 slices utilising retrospectively gated steady-state free precession (b-FFE) cine MRI images. Imaging parameters acquired during a single breath hold were: 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. Assessment of ventricular volumes and function using short axis cine images was manually traced along the endocardial border at end-diastole and end-systole using OSIRIX open source medical imaging software (32Bit v3.9.x). Simpson's rule was used to calculate end-diastolic and end-systolic volumes for both ventricles; fractional area change was calculated from these volumes.

2.3.1. Resting MR flow calculation

Pulmonary artery and aortic flow data were acquired during a breath-hold using a phase-sensitive (Venc set at 200 cm/s and adjusted to avoid aliasing), 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). Imaging planes were standardised as the main pulmonary artery midpoint and aortic sino-tubular junction. Through plane flow data was acquired utilising retrospective cardiac gating. Phase contrast images were used to obtain arterial blood flow via semiautomatic vessel edge-detection algorithm (View Forum, Phillips system) with manual operator correction. Pulmonary artery net forward flow (mL) and PR fraction (%) were calculated as total forward pulmonary flow minus retrograde pulmonary flow, and percent retrograde pulmonary flow over total pulmonary flow, respectively. Similar calculations were used to determine aortic forward flow and regurgitant fraction. Total RV and LV output per minute was calculated as pulmonary artery net forward flow and aortic net forward flow multiplied by heart rate, respectively.

2.4. Exercise cardiac MRI protocol

Cardiac function and flows were assessed using real-time free breathing MR imaging at rest, 30% heart rate reserve (Level 1) and 60% heart rate reserve (Level 2). Target exercising heart rates were determined using the following calculation: target heart rate = resting heart rate + ([maximum heart rate − resting heart rate] × either 0.3 or 0.6). Maximal heart rate was obtained at peak exercise during the cardiopulmonary exercise test described below.

Increase in heart rate was achieved using a custom built, MRI compatible step-style ergometer. Study participants were placed in the supine position with an approximately 45° bend at their knees to allow stepping exercise without contacting the MR tunnel. A 5 channel cardiac receive coil and VCG were placed on the subject's chest. During exercise, participants were verbally instructed to either increase or decrease their cadence to reach and then maintain the desired heart rate. Once the heart rate had reached a plateau (typically after 1 to 2 min of exercise) at the target rate, imaging commenced.

Localiser and calibration scans were performed at the outset before the following real-time MR images were captured at rest, Level 1 and Level 2: 4-chamber cine; short-axis cine stack (4 slices); aortic flow; and pulmonary artery flow. Real-time imaging parameters were: TR = 4 ms; TE = 1.4 ms; flip angle = 60°; slice thickness = 8 mm; matrix = 192 × 192; field of view 380 mm; and temporal resolution corresponding to 92 ms. 100 temporal dynamics were obtained at each slice with corresponding velocity encoding (Venc 150–300 cm/s, adjusted to avoid aliasing). Imaging planes were selected and flow calculations were performed as described above. Fractional area change at rest and during exercise was obtained from real-time 4-chamber cine images utilising OSIRIX software (32Bit v3.9.x) to trace the endocardial border during end-diastole and end-systole, as described above and previously validated [4]. All real-time data was collected in less than 60 s from commencement of imaging protocol.

2.5. Bicycle cardiopulmonary exercise testing protocol

An electronically braked bicycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands) was used to perform progressive, maximal exercise tests. Ramped protocols were individually determined, as described by Jones et al. (1985) [5]. A period of at least 2 minute low resistance pedalling followed maximal exertion whilst heart rate, blood pressure and ECG morphology were monitored. Breath by breath expiratory gas analysis (VMax229; SensorMedics; Yorba Linda, California) and ECG monitoring (Cardiosoft, version 6.51, GE Healthcare, Waukesha, Wisconsin) were performed. Blood pressure was periodically measured and oxygen saturation measurements (Radical, Massimo Corp, Irvine, USA) were also obtained continuously. Work rate, heart rate, blood pressure, oxygen consumption, carbon dioxide production, ventilation, oxygen saturation and ECG morphology were continuously collected during the testing period.

2.6. Statistical methods

All data are presented as mean ± SD. Statistical comparisons were performed with 2-tailed paired Student t tests; paired samples t test for within group comparisons and independent samples t test for between group comparisons. Pearson's correlation coefficient was used to assess relations between resting cardiac MRI, exercise cardiac MRI and CPET variables. A two-tailed p-value of <0.05 was used to infer statistical significance. Statistical analyses were performed with SPSS V.21 for Windows (SPSS).

3. Results

3.1. Participant characteristics

All TOF patients ($n = 16$) had a transannular patch repair at a mean age of 2.2 ± 1.3. In TOF patients, height was 173 ± 9 cm, weight was 69 ± 15 kg and there were 10 (63%) males. In the controls, group height was 180 ± 6 cm, weight was 77 ± 13 kg and there were 5 (63%) males. There were no statistically significant differences between the TOF and control groups in the above mentioned patient characteristics.

3.2. Resting cardiac MRI results

Resting cardiac MRI results are shown in Table 1. Overall, the group had severely dilated RVs, moderate–severe PR fraction and lower-normal RVEF.

3.3. Exercise cardiac MRI results

3.3.1. TOF patients vs controls

There were no significant differences in biventricular fractional area change between TOF patients and controls, other than lower RV FAC during Level 2 exercise in TOF patients (51 ± 10% vs 61 ± 9%, $p = 0.045$). Aortic and pulmonary artery net forward flow as well as total LV output per minute was significantly lower in TOF patients than controls at rest (aortic net forward flow: 72 ± 14 vs 98 ± 12 mL/beat, $p < 0.001$; pulmonary artery net forward flow: 72 ± 20 vs 93 ± 9 mL/beat, $p = 0.009$; total LV output per minute: 5.6 ± 1.4 vs 6.9 ± 1.5 L/min, $p = 0.042$) and both levels of exercise ([Level 1: aortic net forward flow: 76 ± 14 vs 100 ± 14 mL/beat, $p = 0.001$; pulmonary artery net forward flow: 74 ± 20 vs 96 ± 15 mL/beat, $p = 0.014$; LV output: 7.7 ± 1.7 vs 10.1 ± 1.5 L/min, $p = 0.003$; total RV output per minute: 7.5 ± 2.2 vs 9.6 ± 1.7 L/min, $p = 0.028$] [Level 2: aortic net forward flow: 75 ± 11 vs 102 ± 19 mL/beat, $p < 0.001$; pulmonary artery net forward flow: 69 ± 12 vs 95 ± 21 mL/beat, $p = 0.01$; total LV output per minute: 9.3 ± 1.9 vs 13.1 ± 1.9 L/min, $p < 0.001$]), despite no difference in heart rate (Rest: 76 ± 10 vs 70 ± 10 beats per minute, $p = 0.22$, Level 1: 100 ± 10 vs 100 ± 5, $p = 0.735$, Level 2: 123 ± 17 vs 127 ± 12, $p = 0.50$) (see Figs. 1 and 2).

Table 1
Resting cardiac MRI results in TOF patients.

Indexed left ventricular end-diastolic volume (mL/m^2)	78 ± 11
Indexed left ventricular end-systolic volume (mL/m^2)	32 ± 9
Left ventricular stroke volume (mL/beat)	83 ± 13
Left ventricular ejection fraction (%)	59 ± 6
Left ventricular cardiac output (L/min)	6.2 ± 1.0
Indexed right ventricular end-diastolic volume (mL/m^2)	149 ± 37
Indexed right ventricular end-systolic volume (mL/m^2)	73 ± 25
Right ventricular stroke volume (mL/beat)	139 ± 40
Right ventricular ejection fraction (%)	52 ± 7
Right ventricular cardiac output (L/min)	10.4 ± 3.3
Pulmonary regurgitant fraction (%)	35 ± 12
Regurgitant volume (mL/beat)	46 ± 27