Effect of ventricular size and function on exercise performance and the electrocardiogram in repaired tetralogy of Fallot with pure pulmonary regurgitation

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ABSTRACT

Background : **In repaired tetralogy of Fallot (TOF), exercise test parameters like peak oxygen uptake and ventilatory efficiency predict mortality. Studies have also suggested cardiac magnetic resonance (CMR)-derived right ventricular (RV) size threshold values for pulmonary valve replacement in repaired TOF. However, effects of proposed RV size on exercise capacity and morbidity are not known.**

Methods : **The relationship between CMR-derived ventricular size, function, and pulmonary regurgitation (PR) and NYHA class, exercise performance, and electrocardiogram (ECG) was studied in patients of repaired TOF with pure PR in a retrospective review of records.**

Results : **46 patients (22 females), mean age 14 years (8–30.8), were studied. There was no relationship between CMR-derived ventricular size, function, or PR and exercise test parameters, or NYHA class. RV end systolic and end diastolic volume correlated positively with the degree of PR. QRS duration on ECG correlated positively with RV end-diastolic volume ($P < 0.01$, $r^2 = 0.34$) and PR ($P < 0.01$, $r^2 = 0.52$).**

Conclusions : **In repaired TOF and pure PR, there is no correlation between ventricular size or function and exercise performance. RV size increases with increasing PR. Timing of pulmonary valve replacement in TOF with pure PR needs further prospective evaluation for its effect on morbidity and mortality.**

Keywords : Cardiac magnetic resonance imaging, exercise performance, right ventricle, tetralogy of Fallot

INTRODUCTION

Tetralogy of Fallot (TOF) is the most common congenital cyanotic heart disease and accounts for 6–10% of all congenital heart disease. There has been a significant decline in the early surgical mortality (<2%) so that patients with repaired TOF now constitute a large and growing population.[1-6] In patients with repaired TOF, residual hemodynamic and structural abnormalities are common.[7] Right ventricular (RV) dilation resulting primarily from pulmonary regurgitation (PR) is responsible for arrhythmias, exercise intolerance, heart failure, and death.[7]

In patients with repaired TOF, cardiovascular magnetic resonance (CMR) has emerged as the "gold standard" in evaluation of the RV and quantification of PR. Traditionally, pulmonary valve replacement in repaired TOF with severe regurgitation is performed when there are overt symptoms of progressive exercise intolerance or heart failure, syncope, or ventricular tachycardia.[8-11] Recent studies have advocated early replacement of the pulmonary valve in this group of patients based on failure of postoperative normalization of RV size if the surgery is delayed.[12-16] However, these reports have failed to show any beneficial effect of early replacement of the pulmonary valve on patient's morbidity or mortality.

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In patients with repaired TOF, exercise test parameters like peak oxygen uptake and ventilatory efficiency (VE/VCO_2 slope) have been shown to predict cardiac death on follow-up.[17] In this study, we evaluate the effects of CMR-derived ventricular size and function and PR on patient's symptoms (NYHA class), functional capacity (exercise performance), and electrocardiogram (ECG) findings in repaired TOF with pure PR and no significant stenosis.

MATERIALS AND METHODS

Congenital CMR database at our institution was reviewed to identify all patients with repaired TOF and significant pulmonary valve regurgitation between 1/2006 and 1/2010. Patients with a pure regurgitant lesion (patients with moderate or more PR and less than 20 mmHg peak instantaneous RV outflow tract gradients on echocardiogram) who underwent exercise stress test and CMR within 4 weeks of each other were included in the study. Patients with mixed stenotic and regurgitant lesions were excluded from the study. The study was approved by University Institutional Review Board.

CMR imaging was performed on 1.5 T scanners (GE Medical System, Milwaukee, WI, or Siemens, Erlangen, Germany). Retrospective gated steady-state free-precession (SSFP) cine images were used for the assessment of the RV and left ventricular (LV) volumes as well as systolic function. The cine SSFP sequence parameters were as follows: repetition time 2.8 ms, echo time 1.4 ms, flip angle 51°, slice thickness 8–10 mm, matrix 192 × 256, field of view 300–380 mm, and temporal resolution 25-40 phases. RV and LV volume and systolic function were calculated using Simpson's rule by manually tracing the endocardial outline at end-diastole and end-systole in each of the short-axis cine images (QMass MR, Medis, Leiden, The Netherlands).

Free breathing cine phase contrast flow measurements were acquired in the main pulmonary artery (40 phases per cardiac cycle) with retrospective cardiac gating (repetition time 5.9 ms, echo time 3.7 ms, flip angle 150°, slice thickness 6 mm, matrix 256 × 256). The velocity-encoded peak velocity was typically 200. Pulmonary flow was calculated from the phase-contrast images with a semiautomatic vessel edge-detection algorithm with operator correction (QFlow MR, Medis, Leiden, The Netherlands). PR fraction was calculated as the percent backward flow over the forward flow. All volume and flow measurements were indexed for body surface area and expressed in ml/m^2.

Cardiopulmonary exercise testing was performed using a bicycle ergometer. The workload was increased by 10–20 W/min and patients exercised until exhaustion. Breath-by-breath respiratory gas exchange measurements and the 12-lead ECG were monitored continuously during the exercise test. Blood pressure was recorded every 2 min. The following data were obtained from the exercise stress test: (1) peak oxygen uptake, (2) anerobic threshold (using modified V-slope method), (3) oxygen pulse (peak oxygen uptake/peak heart rate), (4) respiratory exchange ratio (RER), (5) ventilatory efficiency (slope between minute ventilation and carbon dioxide elimination using linear regression analysis), (6) peak work, and (7) peak heart rate. The tests were considered maximal with a RER of ≥1.09.

Patient's medical records were reviewed to obtain data regarding patient symptoms, and QRS duration on ECG. Based on symptoms, patients were classified according to the New York Heart Association functional class.

Continuous variables are summarized as mean ± SD or median and range. The proportions are expressed as percentages. Pearson's correlation coefficients were used to assess relations between the following parameters: (1) biventricular size and systolic function and various parameters of exercise performance, (2) degree of pulmonary valve regurgitation and various parameters of exercise performance, (3) RV size and QRS duration on ECG, (4) biventricular size and systolic function and NYHA grade, and (5) degree of pulmonary valve regurgitation and NYHA grade. Multiple linear regression analysis was used to evaluate the simultaneous effects of MRI measures on exercise performance parameters. Multivariate linear regression analysis was performed using the independent variables with P values < 0.05 on univariate analysis. All statistical tests were two sided, and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 46 patients were included in this retrospective study. The majority were in NYHA class I or II. The baseline patient characteristics are shown in Table 1.

CMR findings and exercise stress test findings are shown in Tables 2 and 3, respectively. On linear regression analysis, there was no statistically significant relationship between any parameter of exercise performance and CMR-derived parameters of ventricular size, function, or degree of PR. Table 4 depicts the lack of statistical correlation between CMR-derived parameters of RV and LV size, systolic function and degree of PR, and peak oxygen uptake and ventilator efficiency slope (VE/VCO_2). As expected, VE/VCO_2 increased with advancing age. Figure 1 shows the lack of correlation between peak oxygen uptake and RV end-diastolic volume. The findings remained unchanged on subgroup analysis including patients with RV end-diastolic volume of >150 ml/m^2 (n = 13).

There was a statistically significant and positive correlation between degree of PR and RV end-systolic

Table 1: Baseline characteristics

Characteristics (N = 45)	Number (%) or Value
Females	22 (48.9)
Previous surgeries; median (range)	1 (1-4)
Mean age in years (range)	14 (8–30.8)
Median age in years	12
New York Heart Association Class	
1	28 (62.3)
2	15 (33.3)
3	2 (4.4)
4	0

Table 2: CMR imaging findings

Right ventricular end-diastolic volume (ml/m^2)	130 ± 46
Right ventricular end-systolic volume (ml/m^2)	69 ± 27
Right ventricular stroke volume (ml/m^2)	61 ± 13
Effective right ventricular stroke volume (ml/m^2)	39 ± 7
Right ventricular ejection fraction (%)	47 ± 7
Pulmonary regurgitation fraction (%)	35 ± 19
Left ventricular end-diastolic volume (ml/m^2)	69 ± 14
Left ventricular end-systolic volume (ml/m^2)	28 ± 8
Left ventricular ejection fraction (%)	56 ± 5

Table 3: Findings of cardiopulmonary exercise stress test

Peak oxygen uptake (ml/kg/min)	35 ± 10
Predicted peak oxygen uptake (%)	83 ± 27
Oxygen uptake at anerobic threshold (ml/kg/min)	22 ± 8
Peak work (Watts)	110 ± 49
Peak oxygen pulse (ml/beat)	9 ± 4
Ventilatory efficiency slope (VE/VCO_2)	36 ± 6
Heart rate at rest (beats/min)	84 ± 13
Heart rate at peak exercise (beats/min)	170 ± 17
Predicted heart rate at peak exercise (%)	84 ± 9
Respiratory exchange ratio at peak exercise	1.1 ± 0.07

Table 4: Univariate regression analysis of potential predictors of peak oxygen uptake and ventilator efficiency [minute ventilation (VE)/carbon dioxide elimination (VCO_2)] slope

Variable	Peak VO_2		VE/VCO_2	
	R^2	*P*	R^2	*P*
Age	0.07	0.07	0.2	0.002
RVEDVi (ml/m^2)	0.03	0.23	0.08	0.08
RVESVi (ml/m^2)	0.02	0.4	0.04	0.2
PR fraction (%)	0.05	0.14	0.04	0.2
RVEF (%)	0.007	0.6	0.04	0.2
LVEDVi (ml/m^2)	0.02	0.4	0.17	0.06
LVESVi (ml/m^2)	0.06	0.1	0.17	0.06
LVEF (%)	0.07	0.3	0.14	0.2

RVEDVi: Right ventricular end-diastolic volume indexed; RVESVi: Right ventricular end-systolic volume indexed; PR fraction: Pulmonary regurgitation fraction; RVEF: Right ventricular ejection fraction; LVEDVi : Left ventricular end-diastolic volume indexed; LVESVi: Left ventricular end-systolic volume indexed; LVEF: Left ventricular ejection fraction

(P = 0.0003, r^2 = 0.3) and RV end-diastolic volume (P < 0.0001, r^2 = 0.4) indicating an increase in ventricular volume with worsening PR [Figure 2]. There was no relationship between RV and LV size, RV and LV function, or degree of PR and NYHA class. QRS duration on ECG correlated positively with RV end-diastolic volume (P < 0.01, r = 0.34) and degree of PR (P < 0.01, r = 0.52).

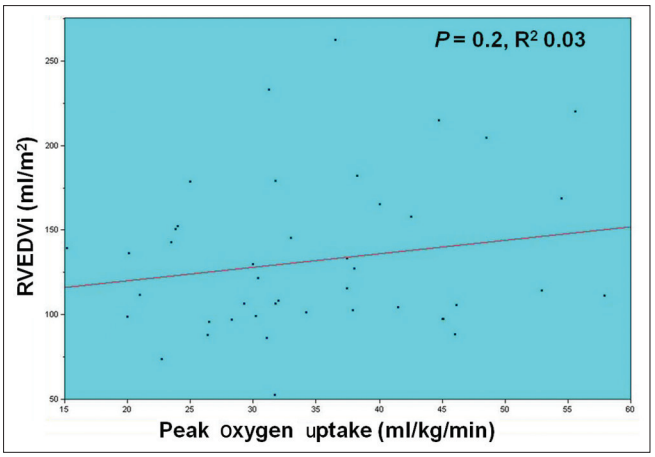

Figure 1: Scatter plot showing the relationship between CMR-derived RV end-diastolic volume indexed to body surface area (RVEDVi) and exercise stress test-derived peak oxygen uptake (VO_2 max)

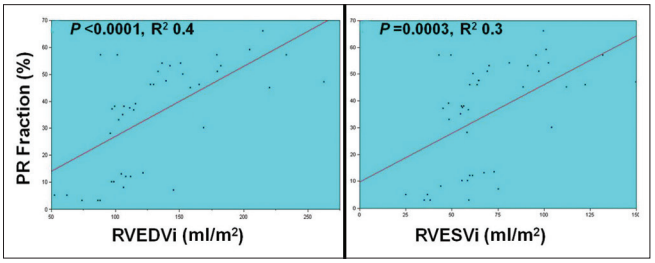

Figure 2: Scatter plot showing the relationship between CMR-derived RV end-diastolic volume indexed to body surface area (RVEDVi) (panel A) and right ventricular end-systolic volume indexed to body surface area (RVESVi) (panel B) and PR fraction

DISCUSSION

The key finding of this study is the lack of correlation between measures of exercise performance or symptoms (NYHA class) and CMR-derived RV and LV size, systolic function, or degree of PR in patients with repaired TOF and pure PR. Furthermore, findings remained unchanged on a subgroup analysis including patients with RV end-diastolic volume of >150 ml/m^2 (n = 13). In a previous CMR study on repaired TOF with a similar number of patients (n = 37), RV ejection fraction was the only parameter that had a modest (r = 0.37, P = 0.02) correlation with peak oxygen uptake in patients with repaired TOF and PR.[18] This discrepancy may be secondary to inclusion of patients with mixed lesions (pulmonary stenosis and regurgitation) and better RV hemodynamics.[18] In a recent study evaluating the effects of percuatenous pulmonary valve implantation on exercise performance, parameters of exercise capacity remained unchanged following valve implantation in patients with predominant PR.[19] In the same study, an improvement in exercise capacity was

only seen if some degree of RV outflow tract stenosis was relieved simultaneously with pulmonary valve implantation.[19] Furthermore, exercise capacity reduced if there was any increase in RV outflow tract gradient after pulmonary valve implantation even though PR was cured.[19] In patients with TOF and predominant PR, other studies have shown that peak oxygen uptake remained unchanged even after surgical pulmonary valve replacement.[15,20] On the contrary, in patients with significant pulmonary valve stenosis or RV outflow tract obstruction, exercise performance improves significantly when the obstruction is relieved.[19] It is speculated that the reduced exercise capacity in patients with RV outflow tract obstruction and primarily stenotic lesion is secondary to limitation in cardiac output augmentation during exercise. While in patients with pure PR, during exercise, reduction in diastolic time interval reduces the volume of PR and augmentation in systemic venous return results in preserved exercise capacity.[19]

In recent years, publications have suggested threshold values for replacement of the pulmonary valve in repaired TOF.[7,12-14,16] There has been a shift in clinical practice to replace pulmonary valves based on CMR-derived indices of RV size and degree of PR irrespective of patient symptoms or functional status in repaired TOF. However, it is important to remember that all these studies failed to show a significant advantage of early pulmonary valve replacement based on CMR-derived values of ventricular size, function, and degree of PR with respect to patient morbidity or mortality. This is despite the fact that in patients with repaired TOF, exercise performance parameters like peak oxygen uptake and ventilatory efficiency (VE/VCO_2 slope) have been shown to be a predictor of cardiac death on follow-up.[17] In this study, there was no statistically significant relationship between any parameter of exercise performance and CMR-derived parameters of ventricular size, function, or degree of PR. In Table 4, we selected peak oxygen uptake and ventilatory efficiency (VE/VCO_2 slope) because previous studies have shown these two exercise parameters to be the most important and robust predictors of outcome in repaired TOF and heart failure.[17,21,22]

In this study, QRS duration on ECG correlated positively with RV end-diastolic volume and PR fraction. Previous studies have shown association between QRS prolongation in this cohort and adverse outcome including ventricular tachycardia and sudden death.[23,24] In repaired TOF, severe PR can lead to RV dilation and QRS prolongation which may be a harbinger for future ventricular arrhythmias and sudden death. However, effects of the proposed CMR-derived RV size threshold on future risk of ventricular tachycardia and sudden cardiac death are unknown.

The clinical implications of the present study are that timing of pulmonary valve replacement in TOF with pure PR based on RV size alone fails to address the complexity of the issue and should be reconsidered. There is need for studies evaluating the benefit of early pulmonary valve replacement using proposed threshold values for RV size with regard to patient's functional capacity, symptoms, arrhythmia burden, morbidity, and mortality. Furthermore, exercise CMR imaging and dobutamine stress imaging have been shown to unmask abnormalities in RV response to exercise not appreciated with rest imaging alone.[25] While severe RV dilatation is undoubtedly associated with increased arrhythmia burden and progression to heart failure, consideration of replacement of the pulmonary valve should not just be based on RV size but should be based on a combination of factors such as exercise or stress CMR imaging to unmask overt RV abnormalities, document reduced exercise performance, and expose overt exercise intolerance and arrhythmias.[24]

This study is limited by its retrospective nature and findings of this study are only applicable to patients with repaired TOF and pure PR. This study was not designed to answer the long-term outcome of patients with a dilated RV and PR. The etiology of exercise intolerance in patients with repaired TOF and PR is multifactorial. We speculate that apart from the ventricular size, factors like genetic predilection, abnormal RV hemodynamics, ventricular scarring, autonomic dysfunction, and restrictive pulmonary function may play an important role in determining the exercise capacity in this cohort. The long-term effect of restoration of size on patient morbidity and mortality requires attention in future studies.

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