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ARTICLE

Chronotropic Response and Pulmonary Function are Associated with Exercise Performance in Children and Adolescents with Repaired Tetralogy of Fallot Independent of Cardiac Function

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ABSTRACT

Objective: The determinants of exercise capacity in repaired tetralogy of Fallot (rTOF) are multifactorial and remain incompletely understood. This study sought to evaluate the association of chronotropic response with exercise parameters and investigate the determinants of heart rate reserve (HRR) in a cohort of children and adolescents with rTOF. **Design:** We retrospectively analyzed patients with rTOF, age 8–18 years, who underwent cardiac magnetic resonance (CMR) and cardiopulmonary exercise test (CPET) for research purposes. Linear regression models were performed to test associations among clinical, CMR and CPET parameters. Outcomes included percent-predicted maximum VO_2 (%mVO_2) and HRR. **Results:** A total of 148 patients were included (mean age 12.3 ± 3.1 years). The majority of patients had TOF with pulmonary stenosis (80%) and underwent transannular patch TOF repair (78%). Median age at surgical repair was 4.2 months (IQR 1.2, 8.4). There was preserved RV ejection fraction (60.4 ± 8.3%) and moderate pulmonary insufficiency (regurgitant fraction 35.2 ± 16.6%). On CPET, %mVO_2 was overall diminished (76.5 ± 17.9%), and % predicted forced vital capacity (FVC) was diminished on spirometry. HRR, FVC and ability to reach maximum effort were independently associated with greater %mVO_2. FVC, net forward flow in the main pulmonary artery/m^2, and reaching maximum effort were associated with greater HRR, independently of RV volume, degree of PI and RV ejection fraction. **Conclusions:** In patients with rTOF, HRR and pulmonary function (FVC) are more important contributors to exercise performance than right ventricular function. Interventions to improve chronotropic health and pulmonary function should be explored.

KEYWORDS

Exercise; pediatrics; congenital heart disease; exercise testing; tetralogy of Fallot

1 Introduction

Although the long-term survival is favorable, patients with repaired tetralogy of Fallot (rTOF) have impaired exercise capacity as measured by diminished percent-predicted maximum oxygen consumption (%mVO_2) even before reaching adulthood, and exercise capacity declines over time [1–3]. Lower %m VO_2 is associated with worse health status and quality of life, and is a predictor of mortality in this population [4–6]. Measures of exercise performance on cardiopulmonary exercise test (CPET) can be variable within each patient and the determinants of exercise performance in rTOF have not been completely elucidated.

The variability in exercise performance in rTOF and incomplete understanding of its determinants are likely in part due to the many contributing factors to exercise performance, including ventricular function, pulmonary insufficiency, pulmonary function, and chronotropic competence [7–12]. Habitual exercise has been associated with better exercise capacity independently of ventricular function [7]. Diminished pulmonary function, indicating restrictive lung physiology, is associated with diminished exercise capacity in patients with single ventricles, and in adults with congenital heart disease, and has been recently demonstrated to be associated with lower exercise capacity in youth with TOF as well [8–10]. We have previously shown that greater HRR and a greater reduction in pulmonary insufficiency at peak exercise are associated with superior exercise capacity, but we did not find an association of pulmonary insufficiency severity and RV systolic function at rest with exercise parameters [11]. Additionally, while we found RV contractile reserve to be impaired in this population, with a decline in RV function at peak exercise, this change in ventricular function itself was not associated with exercise performance. Our prior study prospectively evaluated a smaller cohort of patients with rTOF (n = 32) [12]. The present study sought to validate and augment our prior findings, by evaluating whether HRR is significantly associated with exercise performance in a larger cohort of patients operated for TOF. We also sought to identify additional contributing factors associated with exercise performance in this population, including pulmonary function measured as FVC. Lastly, we aimed to identify factors associated with HRR since chronotropic health might be modifiable in rTOF.

2 Methods

2.1 Study Population

We included in this analyses patients with rTOF who participated in a cross-sectional study with prospective data collection, ages 8–18 years, at our center from January 2005 to February 2009, in which they underwent concurrent research-based cardiac magnetic resonance imaging (CMR) and CPET within a three-month period. Subjects for the study were identified from existing research studies and clinical databases at our institution. Inclusion required the confirmed diagnosis of TOF by review of medical records, a history of complete surgical TOF repair, and age 8 to 18 years on study enrollment. Preoperative echocardiographic reports, cardiac catheterization studies, and operative notes were reviewed to confirm the diagnosis. A complete TOF repair was defined as closure of the ventricular septal defect and relief of right ventricular outflow tract obstruction, if necessary. Complete repairs were either staged (patients with complex TOF anatomy that first undergo a unifocalization procedure to an right ventricular to pulmonary artery conduit or aortopulmonary shunt for completion of closure of ventricular septal defect at a later stage. Palliative procedures include, for example Blalock Taussig shunts placed prior to complete TOF repair. The cohort description and study results were previously published [13]. A written questionnaire assessing habitual exercise and exercise restriction was retrospectively administered to patients who completed CPET with metabolic measurements, as previously described [7]. Patients with metabolic exercise data available were included in this analysis. The presence of a genetic syndrome and deletion status was recorded. Patients with a pacemaker or documented arrhythmia were excluded from the analysis.

2.2 Study Procedures

2.2.1 Cardiopulmonary Exercise Testing

Patients underwent CPET on a treadmill or electronically braked cycle ergometer as previously published [7]. Metabolic data were obtained on a breath-by-breath basis using a metabolic cart (SensorMedics Encore, Yorba Linda, CA), which included maximum oxygen consumption (VO_2 max), maximum work rate in Watts (physical working capacity) and ventilatory equivalents of carbon dioxide (VE/VCO_2) measured at the anaerobic threshold. Percent-predicted maximum oxygen consumption (%mVO_2) and percent-predicted maximum work was calculated for each patient according to normative values for age, gender and body weight [14,15]. Percent-predicted maximum oxygen consumption was used to define exercise performance and was considered abnormal if below 85% of the predicted value [14–16]. Oxygen pulse (O_2 pulse) was

calculated as the VO_2 max divided by the peak heart rate, and was used as a surrogate of stroke volume. A respiratory exchange ratio of 1.1 or greater was used to define maximum aerobic effort on CPET [15,17]. HRR was calculated as the difference between peak and resting heart rate. A normal chronotropic response was defined as a heart rate greater than 185 beats per minute at peak exercise [17,18]. Resting indices of pulmonary function were obtained immediately prior to exercise testing using standard methods of spirometry [19]. Forced vital capacity (FVC) and forced expiratory volume within one second (FEV_1) were measured. Percent predicted FVC was calculated for each patient according to reference values for healthy age and gender matched children and adolescents [20]. Breathing reserve at peak exercise was estimated using FEV_1 and calculated using the calculation, breathing reserve = [1 - (FEV1 × 40)]/100] [21].

2.2.2 Cardiac Magnetic Resonance

Using a standard imaging protocol, CMR studies were performed with a 1.5-T Avanto Whole-Body Magnetic Resonance System (Siemens Medical Solutions, Erlangen, Germany as previously published [13,7]. The CMR studies were read by an experienced physician blinded to the patients' clinical information. CMR variables included pulmonary regurgitant fraction (RF), RV end-systolic (RVESV) and end-diastolic RV volumes (RVEDV) and RV ejection fraction (RVEF). RV volumes were indexed to body surface area (m^2) and RVEF greater than 50% was considered normal [22,23].

2.2.3 Habitual Exercise Questionnaire

As previously described, the exercise questionnaire recorded the types of physical activities in which the subjects participated and the number of hours per week for each activity for each subject [24,7]. Based on the calories and metabolic equivalents per hour of activity, the activities were divided into classes by their aerobic intensity and the class of maximum intensity activity for each subject was noted. In total, there were 4 categories of exercise activity based on intensity ranging from no activity to three increasing classes [25].

2.3 Statistical Analysis

Categorical variables are described using frequency and percentages. Continuous variables are presented as mean and standard deviation (SD) or as median with the first and third quartile values, as appropriate. Univariable and multivariable linear regression was used to examine the relationship between the clinical variables and the outcomes of interest, $\%mVO_2$ and HRR, which were utilized as continuous variables. All analyses were adjusted for the Respiratory Exchange Ratio (RER) to account for subjects that achieved maximal tests, as well as for presence of genetic syndrome. Variables with a *P*-value <0.2 on univariable analysis were considered for the multivariable model, and retained in the model if the P value was <0.05, or if they were determined pre hoc to be clinically important. We tested for collinearity between predictors, which were considered collinear if correlation coefficient greater than 0.50, and did not include collinear predictors in the same model. In order to account for significant differences that can be potentially ascribed to reaching a maximal effort on CPET, we conducted regression models restricting the group to those that achieved a maximal effort.

Secondary analyses were restricted to subjects in which habitual exercise data were available with the goal of determining whether measured associations persisted after adjusting for habitual exercise. We also conducted secondary analysis restricting to those that achieved or did not achieve maximal tests. No other sensitivity analyses were performed. A *p*-value of 0.05 or less was considered statistically significant. Analyses were conducted using Stata version 14.1 (StataCorp, College Station, TX).

3 Results

3.1 Study Cohort

Complete data from a total of 148 subjects were available for analysis. The majority were male (65%) and white (85%). Most subjects had a preoperative anatomy of TOF with presenting anatomy of pulmonary stenosis (80%) and underwent operative correction with a transannular patch (77%). The average age at time

of testing was 12.3 ± 3.14 years. Median age at repair was 4.2 months (IQR 1.2, 8.4). Genetic syndromes were present in 28 patients (19%) of subjects, and included DiGeorge Syndrome, Alagille Syndrome, Goldenhar Syndrome, Duane Syndrome and VATER Association (Tab. 1). Of the 28 patients with a genetic syndrome, 24 (86%) had DiGeorge Syndrome.

Table 1: Demographics and cardiac history in subjects with repaired TOF

	Repaired TOF (n = 148)
Gender, Male, n (%)	104 (65)
Race, White, n (%)	136 (85)
Age at testing, years	12.3 ± 3.14
Weight, kg	42.7 ± 15.2
Height, cm	147 ± 16.8
Body Surface Area, m^2	1.31 ± 0.29
Genetic Syndrome n (%)	No genetic syndrome 120 (81)
Cardiac Diagnosis n (%)	
Pulmonary stenosis	116 (78.4)
Pulmonary atresia	24 (16.2)
Absent pulmonary valve leaflets	8 (5.4)
Age at repair (months)	4.2 (0–36)
Type of TOF repair, n (%)	
Palliative	17 (11.5)
Complete	125 (84.4)
Staged	4 (2.7)
Other/Unknown	2 (1.4)
Type of repair if complete or staged	N (%)
Transannular patch	99 (76.7)
Non-transannular patch	13 (10.0)
Right ventricle to pulmonary artery conduit	10 (7.8)
Unknown/not available	7 (5.5)

3.2 Clinical Status

The majority of CPETs were performed on the cycle ergometer (87%). The majority of patients (n = 92/148 or 62.2%) achieved a maximum test defined as RER >1.10. Aerobic capacity was diminished in the cohort as measured by mean percent predicted maximum VO_2 (%mVO2) of 76.5 ± 17.9% and mean percent predicted maximum work (%mWork) of 83.2 ± 23. There was no significant difference in %mVO2 based on treadmill *vs*. cycle ergometer mode of testing, 68.9 ± 17.6% *vs*. 77.5 ± 17.8% respectively (P = 0.06).

On CMR, there was moderate residual pulmonary insufficiency with average pulmonary regurgitation (%) of 35.2 ± 16.6. The RV and LV ejection fractions were normal. There was overall mild RV dilation with indexed RV end diastolic volume of 116.3 ± 35.4 ml/m2 (Tab. 2).

Table 2: Exercise and cardiac MRI parameters

	Repaired TOF (n = 148)
Exercise Parameters	
Mode of cardiopulmonary exercise test (CPET)	
Treadmill, n (%)	20 (13%)
Cycle ergometer, n (%)	133 (87%)
Respiratory Exchange Ratio (RER)*	1.13 ± 0.12
Maximal CPET (RER >1.1)	92 (62.2%)
Submaximal CPET (RER <1.1)	56 (37.8%)
Heart rate, bpm	
Rest	79 (53–116)
Peak	181 (138–210)
Heart rate reserve	101 (37–140)
Maximum oxygen consumption (ml/kg/min)	31.7 ± 8.3
Maximum work (watts)^	112 ± 48
Percent predicted maximum VO_2, %	76.5 ± 17.9
Percent predicted maximum Work, %^	83.2 ± 23
Oxygen Pulse, ml/beat/m^2	5.53 ± 7.0
VE/VCO_2 Slope	36.8 ± 1.37
VE/VCO_2 at anaerobic threshold	39.4 ± 7.2
Oxygen saturation at rest (%)	97.6 ± 1.66
Oxygen saturation at peak (%)	96.6 ± 0.92
Forced vital capacity (L)	2.25 ± 0.92
Forced vital capacity (%)	77 ± 16.4
FEV1	1.99 ± 0.8
FEV1 to FVC Ratio	0.88 ± 0.08
Habitual exercise (hours per week) n = 69	0.9 ± 0.8
Cardiac MRI	
RV ejection fraction (%)	60.4 ± 8.3
LV ejection fraction (%)	68.8 ± 7.4
Indexed RV end diastolic volume (ml/m2)	116.3 ± 35.4
Indexed RV end systolic volume (ml/m2)	47.5 ± 20.4
Indexed LV end diastolic volume (ml/m2)	66.9 ± 13.6
Indexed LV end systolic volume (ml/m2)	21.3 ± 8.5
Pulmonary regurgitant fraction (%)	35.2 ± 16.6
Indexed LV stroke volume (ml/m2)	45.7 ± 8.5
Indexed RV stroke volume (ml/m2)	69.9 ± 18.9
Indexed main pulmonary artery net forward flow (ml/m2)	43 ± 9.2

^ Maximum Work and Predicted Maximum Work were measured on patients who underwent CPET on cycle ergometer (n = 133).

3.3 Habitual Exercise

Of the 69 subjects with available habitual exercise information, 3 were in class 1 (4.4%), 11 in class 2 (15.9%), 21 in class 3 (30.4%) and 34 in class 4 (49.3%). The average hours of exercise per week were 0.9 ± 0.8 hours.

3.4 Factors Associated with Exercise Performance (%mVO$_2$)

On univariable analysis, the following predictors were directly associated with higher %mVO$_2$: HRR, oxygen saturation at peak exercise, number of hours per week of habitual exercise, FVC, breathing reserve, respiratory exchange ratio and main pulmonary artery net forward flow (indexed). Presence of a genetic syndrome was associated with lower %mVO$_2$. On multivariable analysis, factors independently associated with greater %mVO$_2$ included HRR, FVC and absence of genetic syndrome. (Tab. 3).

Table 3: Analysis of predictors of exercise performance

Outcome	Predictor	Coefficient (95% CI)	P
Percent Predicted Maximum VO$_2$ (%)	Heart Rate Reserve	0.38 (0.23, 0.53)	**<0.001**
	Indexed RV end diastolic Volume	0.09 (–0.004, 0.18)	0.06
	RV stroke volume	0.03 (–0.06, 0.12)	0.471
	LV stroke volume	0.04 (–0.13, 0.21)	0.621
	BSA at CPET	–8.044 (–17.8, 1.71)	0.105
	Age at CPET	0.15 (–0.77, 1.08)	0.749
	Genetic syndrome	–19.2 (–26, –12.4)	**<0.001**
	RV ejection fraction	–0.006 (–0.39, 0.38)	0.977
	LV ejection fraction	0.19 (–0.25, 0.63)	0.4022
	Pulmonary valve regurgitant fraction	0.06 (–0.12, 0.26)	0.484
	Indexed RV end systolic volume	0.10 (–0.05, 0.26)	0.195
	Rest O2 saturation	0.94 (–0.822, 2.71)	0.293
	Peak O2 saturation	1.59 (0.36, 2.83)	**0.012**
	Habitual exercise	11.56 (6.29, 16.82)	**<0.001**
	Forced vital capacity	0.46 (0.29, 0.63)	**<0.001**
	Breathing reserve	0.03 (–0.06, 0.12)	**0.002**
	RER	10.5 (4.76, 16.3)	**<0.001**
	Main pulmonary artery net forward flow	0.33 (–0.005, 0.67)	**0.053**
Multivariable Model R^2 = 30.5 (n = 140)			
Percent Predicted Maximum VO$_2$ (%)	Heart rate reserve	0.232 (0.08, 0.38)	**0.003**
	Forced vital capacity	0.25 (0.068, 0.43)	**0.008**
	Maximum test reached	4.07 (–1.71, 9.78)	0.167
	Genetic Syndrome	–10.5 (–17.9, –3.03)	**<0.006**
	Number of sternotomies	–1.48 (–5.22, 2.26)	**0.44**

Table 3 (continued).

Outcome	Predictor	Coefficient (95% CI)	P
Multivariable Model 2 R^2 = 29.3 (n = 140)			
Percent Predicted Maximum VO_2 (%)	Heart Rate Reserve	0.11 (–0.09, 0.31)	0.265
	Forced Vital Capacity	0.23 (0.04, 0.41)	**0.015**
	Maximum test reached	–29.10 (–59.7, 1.34)	0.061
	Genetic Syndrome	–10.6 (–18.0, –3.28)	**0.005**
	Interaction between RER and HRR	0.26 (–0.05, 0.56)	0.10
Multivariable Model 3: subjects that achieved a maximal test R^2 = 0.063 (n = 87)			
Percent Predicted Maximum VO_2 (%)	Forced Vital Capacity	0.27 (0.0003, 0.53)	**0.05**
	Genetic Syndrome	6.21 (–51.2, 63.7)	0.83
	Interaction between forced Vital capacity and genetic syndrome	–0.22 (–1.03, 0.60)	0.60

Presence of genetic syndrome was interchangeable with presence of 22q11.2 deletion (DiGeorge) syndrome in the model. Number of prior sternotomies was not directly associated with %mVO_2 and was not a confounder of these associations. On secondary analysis restricted to the subjects that achieved a maximal exercise test, we found that FVC was associated with %mVO_2. When we added genetic syndrome to the model with an interaction term for genetic syndrome and FVC, FVC was associated with %mVO_2 with a *P*-value of 0.05, and genetic syndrome or the interaction term were not significant. In a similar model restricting subjects to those that achieved a sub-maximal test including an interaction term for deletion status and FVC, HRR is the only factor associated with %mVO_2 (P = 0.003). (Tab. 3).

In secondary analysis restricted to subjects with available habitual exercise data (n = 69), the association between HRR and mVO_2% was of similar magnitude to the overall cohort but with a broader confidence interval (P = 0.09), while duration of habitual exercise and FVC were both directly associated with higher mVO_2% independently of the ability to achieve a maximum test and of HRR (Tab. 4).

Table 4: Predictors of exercise performance in subjects with habitual exercise data (n = 65)

Outcome	Predictor	Coefficient (95% CI)	R^2	P
Percent-Predicted Maximum VO_2 (%)	Heart rate reserve	0.184 (–0.035, 0.402)	34.9	0.098
	Forced vital capacity	0.271 (0.002, 0.54)		**0.048**
	RER	6.76 (–2.67, 16.2)		0.157
	Habitual exercise	8.25 (2.67, 13.82)		**0.004**

3.5 Factors Associated with Heart Rate Reserve

On univariable analysis, the following factors were directly associated with increased HRR: RV and LV end diastolic volume (indexed), RV and LV stroke volume, LV and RV cardiac output and net forward flow in the main pulmonary artery/m^2, duration of habitual exercise, older age at testing, body surface area, oxygen saturation at peak exercise, FVC, and lower VE/VCO_2 at anaerobic threshold (Tab. 5).

Table 5: Analysis of predictors of heart rate reserve

Outcome	Predictor	n	Coefficient (95% CI)	P
Univariable Analysis				
Heart Rate Reserve	Habitual Exercise	71	6.41 (0.39, 12.4)	**0.037**
	RVEDV indexed	126	0.099 (0.10, 0.187)	**0.029**
	RVESV indexed	126		0.349
	Age at surgery (months)	122		0.132
	Age at testing	153	1.03 (0.12, 1.93)	**0.026**
	Body surface area	153	12.15 (2.56, 21.7)	**0.013**
	Resting O_2 sat	150		0.66
	Peak O_2 sat	128	1.44 (0.15, 2.74)	**0.029**
	RV stroke volume	128	0.161 (0.081, 0.241)	**<0.001**
	LV stroke volume	128	0.347 (0.196, 0.499)	**<0.001**
	RV ejection fraction	128	0.212 (0.164, 0.589)	0.266
	LV ejection fraction	128	0.154 (–0.274, 0.584)	0.476
	LVEDV indexed	126	0.33 (0.107, 0.554)	**0.004**
	LVESV indexed	126		0.222
	PV regurgitant fraction	124		0.481
	RV mass (indexed)	122	0.116 (–0.015, 0.248)	0.082
	LV cardiac output	128	4.57 (2.28, 6.86)	**<0.001**
	RV cardiac output	128	2.06 (0.887, 3.23)	**0.001**
	VE/VCO_2 at anaerobic threshold	104	–0.533 (–0.974, –0.09)	**0.017**
	Forced vital capacity	142	0.366 (0.191, 0.540)	**<0.001**
	Breathing reserve	91		0.74
	Pulmonary valve anatomy	122		
	Pulmonary stenosis	99		
	Pulmonary atresia	19	–9.29 (–18, –0.565)	0.037
	Absent pulmonary valve	7	–9.6 (–22.9, 3.7)	0.156
	MPA net forward flow (indexed)	124	0.596 (0.283, 0.91)	**<0.001**
	Presence of genetic syndrome	151	–13.3 (–20.4, –6.24)	**<0.001**
	Deletion status	151	–12.8 (–20.4, –5.23)	**0.001**
Multivariable Model R^2 = 22.3				
Heart Rate Reserve	RER	114	9.49 (3.48, 15.5)	**0.002**
	MPA net forward flow (indexed)	114	0.53 (0.21, 0.842)	**0.001**
	Forced vital capacity	114	0.207 (0.029, 0.38)	**0.023***
	Number of sternotomies	140	–3.07 (–6.95, 0.81)	**0.12**

*The coefficient for FVC was 0.16 (–0.028, 0.34) p = 0.095 when number of sternotomies were added. Other coefficients were not affected by number of sternotomies.

On multivariable analysis, FVC, net forward flow in the main pulmonary artery/m^2 and ability to reach maximum effort were independently associated with HRR. When the model was adjusted for deletion status, net forward flow in the main pulmonary artery/m^2 and ability to reach maximum effort remained independently associated with heart reserve. This model explains 24% the HRR. (Tab. 5). When the model was adjusted for number of prior sternotomies, FVC was not significantly associated with HRR (P = 0.095), indicating that sternotomies confound the association of FVC with HRR. Net forward flow in the main pulmonary artery/m^2 and ability to reach maximum effort were associated with HRR independently of prior sternotomies. On secondary analysis restricting the group to those that achieved a maximum test, we found that net forward flow in the main pulmonary artery/m^2 and deletion status were associated with HRR. When we examined the group that achieved a sub-maximal test, we found that the only factor associated with HRR was the net forward flow in the main pulmonary artery/m^2 (Tab. 3).

In the subset of subjects with habitual exercise data, net forward flow in the main pulmonary artery/m^2 was associated with HRR independently of ability to reach a maximum test, FVC and habitual exercise (Tab. 6).

Table 6: Predictors of heart rate reserve in subjects with habitual exercise data (n = 54)

Outcome	Predictor	Coefficient (95% CI)	R^2	P
Heart Rate Reserve	RER	6.62 (–4.8, 18)	26.8	0.25
	MPA net forward flow (indexed)	0.67 (0.137, 1.2)		**0.015**
	Forced vital capacity	0.256 (–0.048, 0.562)		0.097
	Habitual exercise	3.39 (–2.61, 9.41)		0.261

4 Discussion

In this study, we retrospectively analyzed factors associated with mVO_2% and HRR in a large cohort of patients with TOF that underwent CPET, CMR and habitual exercise survey as part of a research study. Our prior prospective study of TOF undergoing exercise testing showed greater HRR was associated with superior exercise capacity and therefore in this study we sought to validate and augment our prior findings in a large well phenotyped cohort. Our main findings were: 1) FVC was independently associated with %mVO_2, and 2) FVC, net forward flow in the main pulmonary artery, and the ability to reach maximum effort were independently associated with HRR.

Chronotropic incompetence with depressed maximal heart rate during exercise has been shown in patients with congenital heart disease after surgical repair including those with rTOF [26–29]. Importantly, chronotropic incompetence is a predictor of morbidity and mortality in adults with rTOF [30–32]. In normal hearts, stroke volume increases to certain degree during exercise and further increase in cardiac output (defined as stroke volume X heart rate) is accomplished by augmentation of the heart rate. Therefore, an adequate chronotropic response to exercise is necessary to achieve a normal maximal oxygen consumption. In patients with CHD, increases in stroke volume maybe impaired due to myocardial dysfunction and/or valvular abnormalities, therefore if these patients also have inadequate chronotropic response, they can have significantly impaired cardiac output during exercise [18]. We found that chronotropic response as measured by HRR was independently associated with exercise performance, after accounting for RV ejection fraction and degree of pulmonary insufficiency, however, this association did not persist when we restricted the analysis to the group of patients that achieved a maximal effort on CPET, likely because this group of patients has better chronotropic response. We have previously demonstrated a relationship between HRR and aerobic capacity in a smaller group of rTOF undergoing stress echocardiography [17,18]. In particular, we previously reported that HRR was

associated with better exercise performance as measured by %mVO_2 [18]. Other studies have also shown that chronotropic impairment is a significant contributor to aerobic capacity in rTOF [11,12,29,33,34]. Similarly to our finding of no association between HRR and %mVO_2 in those that achieve a maximal exercise test, a study by Mulla and colleagues demonstrated no correlation between chronotropic impairment and exercise performance in a small groups of patients with rTOF after transannular patch repair [27]. Thus, one's effort during exercise testing is important and needs to be taken into account. After we analyzed the effect of chronotropic response on %mVO_2, we pursued more analyses to investigate mechanisms underlying impaired chronotropic response in the same rTOF group. Proposed causes of chronotropic incompetence after repair of CHD include sinus node dysfunction, abnormal autonomic function, neurohormonal activation and cardiac arrhythmias [28,31,32,35,36]. Patients with documented cardiac arrhythmia or pacemaker were not included in our analysis. We were unable to assess autonomic function or neurohormonal activation in our study cohort. However, there was no evidence of arrhythmia or sinus node dysfunction as only seven patients (4.7%) had a baseline heart rate less than 60 bpm with a normal peak exercise heart rate.

In addition to the primary findings, we also found that FVC was directly associated with mVO_2% and HRR independently of RV ejection fraction and pulmonary regurgitation. Prior studies have shown that patients with rTOF have abnormally low FVC, consistent with restrictive lung physiology [27,29,37,38]. There are multiple possible underlying factors for impaired pulmonary function at rest and during exercise in rTOF such as chest wall or rib cage abnormalities after sternotomies and thoracotomies, abnormal development and growth of the lung and pulmonary vasculature, as well as residual hemodynamic issues related to underlying CHD [30]. Patients with TOF have abnormalities in the pulmonary vasculature even before birth and into adulthood, with evidence of altered alveolar development [39,40]. Furthermore, lung growth in rTOF may not accompany somatic growth as seen in healthy children, given evidence of lower resting spirometry measures seen with increases in height [27]. In a recent publication, Akam-Venkata et al demonstrated that restrictive lung physiology is associated with exercise capacity independently of height and age at TOF repair. Height was considered a surrogate for spinal deformities, which were prevalent in the study, and could contribute to diminished FVC [8]. In our study, FVC was associated with the outcomes mVO_2% and HRR, however, its association with HRR was confounded by the number of sternotomies, although the direction of the association was maintained in the model. Thus, there seems to be common pathway between restrictive lung physiology, prior sternotomies, and rib cage abnormalities (as suggested by Akam-Venkata), which influences exercise performance. Contrary to our findings, other studies have not shown a correlation between aerobic capacity and resting spirometry measures despite abnormal resting spirometry [27,29,38]. Interestingly, the subset of patients that reached a maximal effort have a higher HRR than the sub-maximal group, therefore, FVC was the only factor associated with mVO_2%, and HRR does not affect mVO_2 in this group, but it does affect mVO_2 in the sub-maximal effort group.

In adults with rTOF, pulmonary artery vascular function is abnormal and is associated with worse exercise performance [41]. During exercise, there is a normal physiologic vasodilation of the pulmonary vascular bed to allow for increased pulmonary blood flow and a consequent relative decrease in pulmonary vascular resistance and RV afterload [42]. Therefore, the characteristics of the pulmonary vascular bed in rTOF could play an important role during exercise. We propose that better FVC in rTOF may indicate a larger pulmonary bed and therefore greater potential for vasodilation, decreased pulmonary vascular resistance and better alveolar recruitment during exercise. While this hypothesis requires validation, it is possible that RV afterload falls further in individuals with better FVC with consequent increase in net RV forward flow during exercise and improved LV preload leading to superior exercise performance. In our study, VE/VCO_2 at anaerobic threshold was not associated with %mVO_2 indicating that gas exchange efficiency is not a significant contributor to exercise performance in this cohort. Thus, our findings suggest that pulmonary function, as measured by FVC, in addition to routine cardiac functional assessment, is an important variable to follow in rTOF.

There is increased risk for impaired lung function and restrictive lung physiology with earlier surgical interventions, multiple cardiac surgeries and multiple thoracotomies independent of CHD complexity and other risk factors [43–45]. As we have shown, the limitation of FVC is associated in part with the number of prior surgical interventions, and contributes significantly to impaired exercise capacity in these patients. We found that FVC, forward flow in the main pulmonary artery (indexed to body surface area) and ability to reach maximum effort were independently directly associated with HRR. FVC was associated with HRR prior to adjusting for number of sternotomies suggesting that while this association exists, there may be a link between restrictive lung physiology and prior sternotomies which influences exercise performance. A possible explanation for the association of FVC and HRR is that patients with reduced FVC may be limited by a small pulmonary vascular bed and during exercise, have greater RV afterload resulting in a drop in stroke volume and inability to reach a higher maximal heart rate, possibly due to abnormal autonomic function and neurohormonal activation, as suggested by other studies in congenital heart defects [35,36,46]. We found no association between RV ejection fraction or RV size with HRR suggesting that pulmonary function, rather than cardiac function, is associated with chronotropic reserve in rTOF. Contrary to our findings, a study by Meadows et al in young adults with TOF demonstrated that the only factor on cardiac magnetic resonance imaging associated with percent predicted oxygen consumption was right ventricular ejection fraction. This discrepancy in findings is likely due to important differences in the TOF populations studied regarding age and range of ejection fraction [47].

In summary, our data would support the concept that reduced pulmonary capacity limits the ability of the RV to maintain adequate stroke volume and cardiac output at higher levels of exercise thus also limiting LV preload under these circumstances. These factors result in limiting exercise performance at lower heart rates resulting in a lower measured HRR.

There are limited data evaluating the relationship between pulmonary function and chronotropic response in CHD. Abnormal pulmonary function as measured by spirometry is associated with increased cardiovascular risk in the adult population with acquired heart disease. It has been proposed that this may reflect the presence of chronic obstructive pulmonary disease (COPD) and a relationship between chronotropic incompetence and reduced exercise performance in patients with COPD, has been described in the adult population [48]. This mechanism has also been proposed in Fontan and TOF patients as well [49]. A blunted heart rate response in COPD has been associated with worse exercise capacity and increased disease severity [50]. Patients with hyperinflation have been shown to have impaired left ventricular diastolic filling and RV dysfunction which may result in effects on stroke volume and cardiac output as well as heart rate [51,52]. It is possible that a similar relationship between pulmonary abnormalities in rTOF and chronotropic incompetence exists.

We also found that net forward flow in the main pulmonary artery was associated with HRR in our study cohort. In a prior study of patients with rTOF undergoing stress echocardiography we found that a decrease in pulmonary insufficiency with increasing heart rate at peak exercise was associated with better exercise performance [11]. The relationship between net forward flow in the main pulmonary artery and HRR suggests a decrease in pulmonary insufficiency during exercise with increasing heart rate and subsequent improved RV output. Similar findings have been demonstrated in adults with rTOF during exercise with increased heart rate and decreased pulmonary insufficiency resulting in increased RV forward flow on CMR [53].

Presence of a genetic syndrome was associated with worse exercise performance in our study, as has been previously shown [54]. In particular, 22q11.2 deletion syndrome and exercise performance have been shown to be mediators of health status and quality of life in rTOF patients [5]. Therefore, understanding the determinants of exercise capacity and potentially intervening to improve exercise performance could also play a role in improving quality of life in patients with rTOF, particularly in those with 22q11.2 deletion syndrome, a prevalent association with TOF. Interestingly, we did not find 22q11.2 deletion syndrome to be independently associated with HRR on multivariable analysis, and thus its effect on exercise performance probably occurs through other mechanisms [55].

In the sub-group of patients with habitual exercise data (n = 69), better FVC and more frequent habitual exercise were independently associated with greater %mVO_2. We found that MPA net forward flow was associated with HRR independently of habitual exercise. It is possible that increased physical activity may play a role in improved pulmonary function resulting in overall better exercise performance regardless of cardiac status. Our findings open potential avenues for intervention, such as exercise rehabilitation programs to improve performance.

5 Limitations

This was a large single center study with prospective data collection including all types of rTOF. Accordingly, these results may not be generalizable to all patients but perhaps to those followed at large tertiary care centers and to patients that undergo TOF surgical repair with a transannular patch. The degree of RV dilation was overall mild in the study group and therefore our findings may not be applicable to patients with rTOF and more significant RV dilation. There was a significant number of patients that achieved a sub-maximal exercise test. Given the overall young age of the study cohort, this could be reflective of incomplete effort rather than reflective of exercise capacity and we are not able to discern between these possibilities in this analysis. The habitual exercise data were obtained retrospectively and in a smaller number of patients. This study was a cross sectional analysis and therefore we were unable to evaluate longitudinal changes in exercise performance, pulmonary function and chronotropic response. In addition, we can only establish associations with our results, but not causality.

6 Conclusions

Our findings suggest that aerobic exercise in patients with rTOF is not limited primarily by cardiac factors such as ventricular function or pulmonary insufficiency but rather by pulmonary function and chronotropic response. Chronotropic response is important in patients that do not reach maximal effort on exercise testing. Evaluation of pulmonary function by spirometry may be an important parameter to assess in rTOF. Interventions such as exercise rehabilitation programs to improve pulmonary health and chronotropic response may potentially improve exercise performance. Interventional studies are needed to establish causality in these relationships and to evaluate results of possible therapies to improve exercise capacity in this population.

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