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Right Ventricular Contractile Reserve is Impaired in Children and Adolescents with Repaired Tetralogy of Fallot-an Exercise Strain Imaging Study

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Abstract

Background: Pulmonary insufficiency (PI) and right ventricular (RV) dysfunction are long-term complications in rTOF. We sought to investigate RV contractile reserve and changes in PI that occur during exercise in patients with repaired tetralogy of Fallot (rTOF) and the association of these changes with exercise performance using stress echocardiography.

Methods: Subjects with rTOF (n = 32) and healthy controls (n=10) were prospectively enrolled and underwent rest and peak exercise echocardiograms during standard CPET protocol on cycle ergometer or treadmill. RV contractile reserve was defined as the change in RV global longitudinal strain (RVGLS) from rest to peak exercise. PI was assessed with the diastolic systolic time velocity integral ratio (DSTVI) and diastolic/systolic velocity ratio (D/S Ratio) from pulmonary artery Doppler interrogation. Exercise measures included heart rate reserve, percent-predicted maximum oxygen consumption (%mVO₂), percent-predicted maximum work (%mWork) and oxygen pulse.

Results: Right ventricular contractile reserve was impaired in rTOF compared to controls with a significant drop in the absolute value of RVGLS from 17% (range 8-27) at rest to 13% (range 5-28) at peak exercise. Similarly, PI decreased at peak exercise, with a drop in DSTVI and D/S ratios. Reduction in PI was directly associated with %mVO₂, %mWork, and greater oxygen pulse. Heart rate reserve was directly associated with %mVO₂ and %mWork. RV contractile reserve was not associated with any exercise parameters.

Conclusions: Patients with rTOF have an abnormal myocardial response to exercise with impaired RV contractile reserve compared to control subjects. Heart rate reserve and reduction in

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Conflicts of interest: None

PI at peak exercise are associated with better exercise performance and appear to be significant contributors to exercise performance in rTOF. Measures to improve chronotropic health in rTOF should be explored.

Keywords

Tetralogy of Fallot; Contractile Reserve; Strain; Exercise Stress Echocardiography; Congenital Heart Disease

Introduction:

Residual pulmonary insufficiency (PI) in surgically repaired tetralogy of Fallot (rTOF) results in right ventricular (RV) dilation and potentially in RV dysfunction. RV dysfunction can be progressive and is associated with diminished exercise capacity and other morbidities, including diminished quality of life.^{1-3,45} The normal RV has the ability to augment systolic function during exercise, an adaptive phenomenon referred to as contractile reserve.⁶ With increasing exercise intensity, there is progressive increase in RV systolic pressure with resultant increase in wall stress, coronary perfusion and oxygen extraction such that the RV work requirement is proportionally greater than that of the left ventricle.^{7, 8} Therefore, evaluation of the RV during stress (such as exercise) when work requirement is greatest, may unmask subclinical RV dysfunction that might not be evident at rest. Contractile reserve has been shown to have prognostic significance in other forms of right sided heart disease such as pulmonary arterial hypertension, valvular disease, and in primarily left ventricular pathology in the adult population.⁹⁻¹¹

Exercise stress echocardiography in children with congenital heart disease has not had widespread use, and in rTOF, in particular, data on the RV response to exercise is scarce.¹² Patients with rTOF are known to have diminished RV global longitudinal strain (RVGLS) at rest and have been shown to have reduced left ventricular contractile reserve.¹³⁻¹⁵ However, no studies have investigated the RV myocardial deformational response to peak exercise along with changes in PI, and how these changes correlate with exercise performance.

In this study, we sought to prospectively investigate the RV contractile reserve in rTOF using exercise stress 2D speckle-tracking strain imaging, a relatively less load-dependent measure than conventional indices of cardiac function.¹⁶ We also sought to investigate the association of RV contractile reserve and PI with aerobic capacity as these associations may inform patient monitoring, timing of therapeutic interventions and exercise recommendations in rTOF.

We hypothesized that patients with rTOF would have normal RV contractile reserve with an increase in RV strain at peak exercise as compared to rest.

Methods:

Study Population

A cross sectional study with prospective enrollment of patients with rTOF and control subjects presenting for clinically indicated CPET at our center was conducted from May

2015-June 2016. Eligible subjects were identified from the outpatient exercise laboratory schedule and invited to participate in the study. We included subjects ages eight years and older with history of surgically rTOF. The choice of age was based upon the youngest age at which subjects are generally able to complete a CPET. All anatomic sub-types of rTOF were included, including those patients with history of pulmonary valve replacement. Subjects with pacemakers were excluded. Healthy control subjects were patients referred for exercise stress test who had normal cardiac structure and function on echocardiogram and no history of significant arrhythmia. The study was approved by the Institutional Review Board for the Protection of Human Subjects at the Children's Hospital of Philadelphia and participants gave written informed consent.

Rest and Stress Echocardiography:

A focused protocol-based echocardiogram was performed immediately prior to CPET (rest), and the same protocol was repeated immediately after completion of the CPET (peak exercise). Standard pediatric transthoracic echocardiographic views were obtained on a Phillips IE33 machine (Phillips, Andover, MA, USA) using appropriate sized transducers. Images were obtained by one of three sonographers trained on the study's protocol. Images were digitally stored and measurements were performed offline using Syngo Dynamics software (Siemens, Ann Arbor, MI, USA) and Cardiac Performance Analysis Software (TomTec, Germany) by a single observer.

Imaging Protocol

An apical four-chamber view fully profiling the RV was obtained to perform off-line RV longitudinal strain measurements at rest and at peak exercise, adjusting the frame rate accordingly (average > 50 Hz) to provide adequate strain tracings. Thereafter, the parasternal short axis view was used to interrogate the main pulmonary artery (MPA) and branch pulmonary arteries. Interrogation of the MPA with color, pulsed and continuous-wave Doppler was performed. The pulsed wave Doppler tracing was used to obtain time-velocity integrals of diastolic and systolic flows in the MPA. At peak exercise, priority was given to first obtaining the 2D apical four-chamber view for offline strain measurements immediately followed by the interrogation of the main pulmonary artery while the subject's heart rate was still elevated.

To quantify PI, we obtained offline measurements of the regurgitant (diastolic) and antegrade (systolic) time velocity integrals and a ratio of those was calculated (diastolic to systolic time-velocity integral ratio, or DSTVI) (Figure 1). We used the DSTVI as we have previously shown that the DSTVI ratio correlates with pulmonary regurgitant fraction measured by cardiac magnetic resonance imaging.^{17, 18}

Using speckle-tracking analysis software (Cardiac Performance Analysis Software, TomTec, Germany) the endocardial and epicardial borders of the RV were manually traced in end-systole and end-diastole on the four-chamber apical view offline by a single observer. The tracings were manually adjusted to RV wall thickness and the pericardium was excluded. RV global longitudinal strain (RVGLS) curves which included the RV free wall and septum were derived from the tracings (Figure 2). RV free wall strain (RVFWS) was also calculated

as the mean peak longitudinal strain of the 3 segments (basal, mid, apical) of the RV free wall. Intra-observer variability was assessed a priori in 10 samples from non-study subjects with rTOF.

RV contractile reserve was defined as the change in the absolute value of RVGLS or RVFWS from rest to peak exercise and absolute values of RV strain were reported. Longitudinal strain is generally reported as a negative number as it is a measure of myocardial fiber longitudinal shortening during systole. Therefore, while more negative strain values reflect greater myocardial deformation when expressed as an absolute value the higher numbers reflect greater myocardial deformation. Based on normative data from the control group, RVGLS and RVFWS values were considered abnormal if the absolute value was less than the lower bound of the 95% Confidence Interval, at rest.

Cardiopulmonary Exercise Testing:

Patients underwent standard cardiopulmonary exercise test using an electronically braked cycle ergometer or 1-min incremental treadmill protocol, changing both speed and grade based on the subject's weight and designed to achieve maximal volition in 10-12 minutes. Maximal volition was defined as achieving a respiratory exchange ratio of greater than 1.10 (VCO_2/VO_2).¹⁹ Ventilatory and metabolic data were obtained using breath-by-breath expired gas analysis on a metabolic cart (SensorMedics, Yorba Linda, CA). The percent of predicted maximum VO_2 (%m VO_2) was calculated for each patient, according to normative values for age, gender and body size. Exercise performance was defined by percent m VO_2 and defined as abnormal if less than 85% of the predicted value.²⁰⁻²² Oxygen pulse was calculated as the maximum VO_2 divided by the peak heart rate and indexed for body surface area ($ml/O_2/beat/m^2$), and used as a surrogate of stroke volume. A normal heart rate response was defined as heart rate greater than 185 beats per minute at peak exercise.²³ Heart rate reserve was calculated as the difference between maximum heart rate at peak exercise and resting heart rate.²³

Statistical Analysis:

Descriptive statistics are presented as mean $\pm$ standard deviation or median (minimum-maximum) for continuous variables and frequency counts (percentages) for categorical variables. Mixed-effects linear regression models with identity link were used to examine the changes in echocardiographic parameters from rest to peak exercise. Mixed-effects models implemented via maximum likelihood account for correlations arising from the repeated measures obtained at rest and at peak exercise and allow using all measurements obtained from each subject. The models for RVGLS/RVFWS were adjusted for DSTVI ratio. The model for DSTVI was adjusted for change in heart rate. This approach enabled us to verify whether faster heart rate resulted in shorter diastolic period (and hence, diminished PI), for example. Linear regression models were used to assess the association of changes in echocardiographic parameters and heart rate reserve with measures of exercise capacity (%m VO_2 , work, and oxygen pulse). Because RVGLS and RVFWS were interchangeable, we present models using RVGLS as it is a more inclusive parameter of RV function. Sensitivity analyses were performed to examine the potential outliers and influential points. These measurements were assessed by visual examination of histograms and normal

probability plots of residuals from each model. Intra-observer reproducibility was assessed with intraclass correlation coefficients and considered adequate if greater than 0.80. Statistical analyses were conducted using Stata 14.1 (StataCorp, College Station, TX) and the significance level was set at 0.05 for all tests.

Results:

Thirty-two subjects with rTOF and ten control subjects were prospectively enrolled and baseline characteristics of both groups are summarized in Table 1. The mean age at testing in patients was 16.4 ± 4.9 years with average time from complete TOF repair of 15.8 ± 5.2 years. The majority was male (66%) and Caucasian (63%) in the rTOF group. Most patients had a history of pulmonary stenosis (81%) and underwent transannular patch repair (72%). Age at TOF complete surgical repair was 3.7 months (range 0.1-60.5). Five patients had pulmonary valve replacement (16%) (Table 1). In the control group, there were 60% females, age range 10 to 15 years. In controls, RVGLS and RVFWS at rest was 26% [95% CI (23, 29)] and 27% [CI (24, 31)], respectively. At peak exercise, RVGLS was 34% [CI (31, 37)] and RVFWS was 35% [CI (32, 39)].

Exercise Characteristics in rTOF:

Most CPET were performed on a cycle ergometer (94%). Complete exercise data was available for 29 of 32 patients (91%). Ventilatory and metabolic data were not available for three patients due to inability to wear the mouthpiece (n=2) or by request of the primary cardiologist (n=1). A maximum test was achieved by the majority of participants (90%) and no tests were terminated for arrhythmias or symptoms. During image acquisition at peak exercise, all patients were in normal sinus rhythm. Normal heart rate response was documented in 41% of patients (n=13). The average heart rate reserve was 108 ± 20.2 bpm. The %mVO₂ and the percentpredicted maximum work (%mWork) were diminished in the overall cohort (median 76%, range 42-118, and median 72%, range 34-115, respectively). (Table 2)

Contractile reserve and changes in PI from rest to peak exercise:

In comparison to the control group, rTOF patients had diminished RVGLS at rest with significant worsening of RVGLS at peak exercise, even after adjusting for change in PI (DSTVI) (Figures 3 & 4). Results were the same when RVFWS was used (Table 3 & 4). rTOF patients had a significant decrease in RV strain at peak exercise whereas controls demonstrated a significant increase in RV strain at peak exercise (Table 4) (Figure 5). In contrast, the tricuspid S' velocity in the rTOF group increased from baseline to peak exercise. There was no significant change in TAPSE from rest to peak exercise (Table 3). Strain measurements were reproducible with intra-class correlation coefficient of 0.84.

The DSTVI ratio decreased at peak exercise, indicating a decrease in PI. This change occurred in the setting of a decrease in retrograde diastolic time velocity integral (TVI) whereas the antegrade systolic TVI remained unchanged (Table 3). The change in DSTVI from rest to peak exercise was not significant after adjusting for change in heart rate, suggesting that heart rate may drive the change in PI as it results in shorter diastolic time.

Similarly, the D/S ratio decreased significantly from rest to peak exercise. Pulmonary valve peak systolic velocity and RV pressure estimate increased from rest to peak exercise (Table 3).

Baseline characteristics such as age at testing, age at surgery, type of surgical repair, RV pressure estimate at rest, or QRS duration did not predict change in RVGLS from rest to peak exercise. Our findings of a significant decrease in RVGLS and PI at peak exercise in patients were unchanged in a sub-group analysis excluding the five patients with history of pulmonary valve replacement.

Associations with exercise performance in rTOF:

There was a modest association between the decrease in PI (measured by the DSTVI ratio) and greater %mWork and oxygen pulse (Figures 6 and 7). Furthermore, a drop in the D/S ratio also correlated with greater %mVO₂ as well as with greater %mWork (Figures 8 and 9).

There was no significant association between RV strain contractile reserve and %mVO₂, %mWork, or oxygen pulse. Heart rate reserve was directly associated with %mVO₂ and %mWork, but not with oxygen pulse (P=0.523). (Table 5, Figures 10 and 11)

Discussion:

In this study, we sought to investigate RV contractile reserve and changes in PI from rest to peak exercise in patients with rTOF. To our knowledge, the use of exercise strain echocardiography to assess the RV is novel in this patient population. The main findings were that at peak exercise, there was impaired RV contractile reserve, but a decrease in PI. The reduction in PI was in turn associated with improved parameters of exercise performance. Changes in heart rate affected changes in PI and heart rate reserve was directly associated with better exercise performance.

The RV contractile response to the physiologic challenge of maximal exercise was reduced in a cohort of children and adolescents with rTOF independently of the change in PI, contrary to the normal expected response to exercise. This finding was regardless of whether RVGLS or RVFWS was used. In healthy children and adults, normal RV contractile reserve is represented by an increase in RV strain with exercise and a strong linear correlation of RV strain with exercise intensity and increase in heart rate^{6,7,24,25} Our findings support the hypothesis that in rTOF, exercise may unmask RV dysfunction shown as an abnormal response in RV strain to peak exercise. These findings are similar to other studies that demonstrate that both echocardiographic and invasive measures of RV function in rTOF, such as RV ejection fraction and cardiac index, do not increase in response to Dobutamine infusion or supine exercise.^{26,27} In adults with rTOF, RV contractile response measured as fractional area change can be impaired even when the ejection fraction by cardiac magnetic resonance is normal. In addition, there is evidence that worse LV ejection fraction and higher LV end systolic volume are associated with RV impaired contractile response.²⁸ Exercise strain imaging has been shown to identify abnormal RV myocardial response to exercise in pulmonary hypertension secondary to systemic sclerosis, where RV contractile response is

blunted even in the presence of normal resting RV strain and normal pulmonary artery pressure.²⁹

Despite the reduced RV strain contractile reserve, we found that the tricuspid S' velocity increased significantly at peak exercise, suggesting an element of normal longitudinal contraction response to exercise. A similar response has been described in healthy adults and children, as well as in children and adolescents with repaired TOF undergoing stress with Dobutamine, even though the magnitude of the response can be lower in rTOF as compared to controls.^{6, 24, 30-32} The discrepancy of the changes in RV strain, both global longitudinal and free wall, with S' velocity in our study has been described in patients with hypertrophic cardiomyopathy where RVGLS was lower than S' at peak exercise.³³ We attribute this discrepancy to the fact that S' velocity solely measures the longitudinal myocardial velocity, while strain provides a more comprehensive functional assessment of the RV, including the contribution of the ventricular septum. In addition, strain as a measure of myocardial deformation is less load and angle dependent compared to DTI and less affected by cardiac translation, which may be significantly increased during exercise^{14, 34, 35} Furthermore, there was no significant change in TAPSE at peak exercise which we have previously shown is not associated with RV ejection fraction on CMR or exercise performance in rTOF.³⁶ We found that the decrease in RVGLS and RVFWS at peak exercise remained significant after adjusting for a decrease in PI, lending support to the relative load independency of this measure of myocardial deformation compared to conventional measures of RV ventricular performance, as has been shown in other studies.^{16, 37} In addition, the finding of impaired RV contractile reserve was unchanged in a sub-group analysis excluding patients with history of pulmonary valve replacement (n = 5), suggesting patients requiring intervention for presumably more significant RV dilation and PI did not drive our results.

We report a significant decrease in PI at peak exercise. This finding was primarily driven by a drop in the diastolic or regurgitant flow, which in turn was likely a result of faster heart rates and therefore shorter diastolic filling time at peak exercise. Adjusting for heart rate, the change in PI from rest to peak exercise was no longer significant suggesting that increasing heart rate may drive the change in PI in the setting of shortened diastolic period. The concept of the effect of increasing heart rate on pulmonary regurgitation was demonstrated in adults with rTOF using exercise Cardiac MRI (CMR). Similar to our findings, PI regurgitant fraction (RF) decreased as exercise intensity and heart rate increased with resultant augmentation in net pulmonary artery forward flow.³⁸

Data on changes in PI from rest to peak exercise in patients with rTOF are scarce, perhaps given the difficulty in quantifying PI on echocardiography. We used the DSTVI ratio to quantify PI as we have previously shown that this ratio correlates with RF on CMR.^{17, 18} Contrary to our findings, a study in children with rTOF using Dobutamine stress echocardiography and semi-quantitative measures of PI, such as PI velocity, found impaired RV functional reserve and worse PI with pharmacologic stress.²⁶

To our knowledge, the assessment of RV contractile reserve using 2D strain exercise stress echocardiography and its association with simultaneously acquired metabolic exercise parameters has not been previously described in rTOF. We found no correlation between RV

strain contractile reserve and exercise performance. Previous studies have shown that the RV longitudinal peak systolic strain rate at rest is associated with decreased exercise %mVO₂ in rTOF.¹⁴ Using exercise strain echocardiography in healthy children, a linear relationship between LV longitudinal strain reserve and measures of exercise performance including peak VO₂, maximum work and oxygen pulse have been demonstrated.²⁵ We, however, found that the ability to augment RV systolic function during exercise did not correlate with aerobic capacity, possibly due to the fact that RV contractile reserve is but one factor in determining overall exercise performance in rTOF. In addition, it is possible that such correlations are not present in the setting of impaired RV contractile reserve.

We found an association between reduction in PI with better exercise performance. Since the decrease in PI at peak exercise was likely due to shorter diastolic time in the setting of increased heart rate, we postulated that PI is associated with exercise via heart rate reserve. As such, we found that heart rate reserve was directly associated exercise parameters as measured by %mVO₂ and %mWork. This suggests that the ability to increase heart rate at peak exercise (and consequently reduce PI) is an important contributor to exercise performance in rTOF. A possible mechanistic explanation for our finding is that greater heart rate reserve leads to shorter diastolic time resulting in greater drop in PI, increased cardiac output at peak exercise and better parameters of exercise performance.

Given there was no significant association of RV contractile reserve with measures of exercise performance, our findings suggest the ability to increase heart rate during exercise may be a significant contributor to augmentation of cardiac output and aerobic capacity rather than an increase in contractility. It is possible patients with rTOF may have impaired force-frequency relationship, which is the intrinsic property of the cardiac muscle to progressively enhance contractile force with increase in heart rate related to changes in calcium cycling within the cardiomyocyte.^{39, 40} In the early postoperative period, there is evidence of blunted force frequency relationship in rTOF, as evidenced by an impaired myocardial contractile response to pacing.³⁹ Children with rTOF have been shown to have an abnormal chronotropic response during exercise as compared to healthy peers, however its exact contribution to exercise performance is not entirely understood.⁴¹ Chronotropic incompetence may lead to a loss of amplification of the force-frequency response during exercise in rTOF, as has been shown in other disease states such as chronic heart failure, cardiomyopathies and ventricular hypertrophy.^{42, 43, 44} Heart rate reserve has been shown to be a powerful predictor of mortality in adults with CHD, and therefore its contribution to exercise should not be disregarded.^{45, 46} As such, interventions to improve chronotropic health early on in childhood may improve exercise performance and possibly prognosis in rTOF.

Clinical Implications:

In a group of patients with rTOF, the augmentation of RV systolic function at peak exercise does not occur, thus unmasking underlying RV dysfunction in rTOF. This is a relevant finding given that abnormal RV contractile reserve is associated with adverse outcomes in adult patients with pulmonary hypertension and dilated cardiomyopathy.^{10, 47} Contractile reserve may prove a desirable method with which to gauge progression of RV dysfunction in

individuals with rTOF by conducting serial follow-up assessments to evaluate decrement or improvement in RV contractile reserve over time. Worsening contractile reserve could be a marker for sub-clinical RV dysfunction and may prompt further diagnostic work-up and possibly inform decisions about therapeutic interventions, such as pulmonary valve replacement. Furthermore, chronotropic response may prove an important component of exercise performance in rTOF. Chronotropic incompetence in adults with rTOF during exercise has been shown to identify patients with increased mid-term mortality. Therefore, attempts at improving chronotropic health in this population are warranted.^{45, 46}

Limitations:

Our study demonstrates the feasibility of exercise stress strain imaging using a 2D speckle tracking software in a cohort of patients with rTOF. Limitations of this study include: a) small sample size due to the prospective nature of data collection; b) certain parameters could not be accurately evaluated due to suboptimal imaging and limited acoustic windows at peak exercise, such as fractional area change and antegrade end-diastolic flow. We have previously demonstrated that the DSTVI ratio correlates with pulmonary regurgitant fraction measured by cardiac magnetic resonance imaging with evidence of longitudinal validation.^{17, 18} However, quantification of PI using echocardiography is still limited in the rTOF population.

Conclusions:

Exercise stress strain echocardiography is feasible in children and adolescents with rTOF. Patients with rTOF have impaired RV contractile reserve. The significance of this finding warrants future study examining its longitudinal correlation with outcomes. Chronotropic response rather than RV contractile response to exercise is a more significant determinant of aerobic capacity. Future studies aimed at improving the chronotropic response to exercise in rTOF are warranted.

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Abbreviations:

(CPET)	Cardiopulmonary exercise test
(DSTVI)	diastolic systolic time velocity integral ratio
(D/S Ratio)	diastolic/systolic velocity ratio
(MPA)	Main Pulmonary Artery
(PI)	Pulmonary Insufficiency

(rTOF)	repaired Tetralogy of Fallot
(RF)	Regurgitant fraction
(RV)	Right Ventricle/Ventricular
(RVGLS)	Right ventricular global longitudinal strain
(RVFWS)	Right ventricular free wall longitudinal strain
(TAPSE)	Tricuspid Annular Plane Systolic Excursion
(TVI)	Time Velocity Integral
(%mVO2)	percent-predicted maximum oxygen consumption
(%mWork)	percent-predicted maximum work

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Highlights

- Exercise stress echocardiography demonstrates impaired right ventricular contractile reserve (change in RV strain) in TOF compared to normal control subjects.
- PI decreases significantly at peak exercise in TOF. Reduction in PI at peak exercise and heart rate reserve are associated with better exercise performance in TOF
- Measures to improve chronotropic health in TOF may improve exercise performance

Figure 1.

Diastolic to systolic time-velocity integral ratio (DSTVI) obtained from Doppler tracing of the main pulmonary artery. Pulsed-wave Doppler tracing in the main pulmonary artery. Diastolic Time Velocity Integral (blue) was divided by the Systolic Time Velocity Integral (red) to calculate the DSTVI

Figure 2.
Right Ventricular Global Longitudinal strain curves at rest (top) and at peak exercise (bottom)

Figure 3. Right Ventricular Global Longitudinal Strain at rest (blue) and at peak exercise (red) by group, in TOF and Controls. *Circles* represent the mean RVGLS and the *bar* represents 95% CI

Figure 4. Right Ventricular Free Wall Strain at rest (blue) and peak exercise (red) by group, in TOF and Controls. *Circles* represent the mean RVFWS and the *bar* represents 95% CI

Figure 5. Change in Right Ventricular Strain from rest to peak exercise by group, in TOF (red) and Controls (blue). *Circles* represent the mean RV strain and the *bar* represents 95% CI

Figure 6.

Scatterplot of the relationship of change in Diastolic Systolic Time Velocity Integral Ratio and Percent-Predicted Maximum Work in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Percent-Predicted Maximum Work

Figure 7.

Scatterplot of the relationship of change in Diastolic Systolic Time Velocity Integral Ratio and Oxygen Pulse in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Oxygen Pulse.

Figure 8.

Scatterplot of the relationship of change in Diastolic-Systolic ratio and Percent-Predicted Maximum VO₂ in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Percent-Predicted Maximum VO₂.

Figure 9. Scatterplot of the relationship of change in Diastolic Systolic ratio and Percent-Predicted Maximum Work in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Percent-Predicted Maximum Work

Figure 10.

Scatterplot of the relationship of Heart Rate Reserve and Percent-Predicted Maximum VO2 in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Percent-Predicted Maximum VO2.

Figure 11.

Scatterplot of the relationship of Heart Rate Reserve and Percent-Predicted Maximum Work in TOF. The red dotted line represents the best-fitting line from the regression with predicted values of Percent-Predicted Maximum Work

Table 1:**Demographics and Clinical Characteristics**

Demographics	TOF (n=32)	Controls (n=10)
Age at testing, Mean $\pm$ SD	16.4 $\pm$ 4.9	12.7 $\pm$ 1.7
Gender, Males	21 (66%)	4 (40%)
Race, White	20 (63%)	7 (70%)
Clinical Characteristics		
Cardiac Diagnosis:		
Pulmonary Stenosis	26 (81%)	
Pulmonary Atresia	5 (16%)	
Absent Pulmonary Valve	1 (3%)	
Age at Complete repair (months), Median (Range)	3.7 (0.1-60.5)	
Time from Complete repair to testing (years), Mean $\pm$ SD	15.8 $\pm$ 5.2	
Type of Repair:		
Transannular patch	23 (72%)	
Right Ventricular Conduit	4 (13%)	
Pulmonary Valvotomy	3 (9%)	
Non-Transannular Patch	2 (6%)	
Pulmonary Valve Replacement	5 (16%)	
Electrocardiographic Findings:		
Normal Sinus Rhythm	32 (100%)	10 (100%)
QRS Duration (msec), mean $\pm$ SD	131.7 $\pm$ 29.7	
Medications:		
Beta blockers	2 (6%)	

SD, Standard deviation.

Data are presented as frequency counts (percentages) unless indicated.

Table 2:

Exercise Parameters in rTOF

	Baseline	Peak
Weight (kg)	58.3 ± 19.1	
Height (cm)	165 (125-185)	
Body Surface Area (m ²)	1.6 (0.94-2.19)	
Heart Rate (bpm)	70 (51-93)	184 (173-190)
Heart Rate Reserve (bpm)		108 ± 20.2
Systolic Blood Pressure (mmHg)	117.7 ± 13.27	166.6 ± 25.56
Diastolic Blood Pressure (mmHg)	68.9 ± 9.51	65.5 ± 10.28
Percent-predicted maximum VO ₂ (%)		76 (42-118)
Percent-predicted maximum work (%)		71.5 (34-115)
Oxygen pulse (ml/beat)		10.2 (4.2-21)

Data are presented as mean ± standard deviation or median (range).

Table 3:**Echocardiographic Parameters in rTOF**

	Baseline	Peak	Coefficients (95% CI)	P
RV Global Longitudinal Strain (%)	16.7 ± 4.88	13.7 ± 5.24	-2.95 (-4.4, -1.5)	0.0001
RV Global Longitudinal Strain (%) *	16.7 ± 4.88	13.7 ± 5.24	-2.5 (-4.3, -0.8)	0.004
RV Free Wall Strain (%)	17.26 ± 5.55	13.98 ± 5.91	-3.28 (-4.93, -1.64)	<0.001
RV Free Wall Strain (%) *	17.26 ± 5.55	13.98 ± 5.91	-2.83 (-4.78, -0.89)	0.004
Diastolic Systolic Time Velocity Integral Ratio (DSTVI)	0.83 ± 0.41	0.60 ± 0.32	-0.22 (-0.29, -0.14)	<0.001
Diastolic Systolic Time Velocity Integral Ratio (DSTVI) #	0.83 ± 0.41	0.60 ± 0.32	0.05 (-0.34, 0.44)	0.7944
Antegrade Systolic TVI (cm)	58.1 (34.3-119)	57.6 (28.8-129)	-2.7 (-6.88, 1.46)	0.202
Retrograde Diastolic TVI (cm)	50.8 (0-79)	33.45 (0-67)	-15.6 (-19.8, -11.3)	<0.001
Diastolic Systolic Velocity Ratio (D/S Ratio)	0.84 ± 0.31	0.66 ± 0.27	-0.17 (-0.23, -0.12)	<0.001
Pulmonary valve peak velocity (m/s)	2.4 (1.8-4.8)	3.8 (1.64-6.20)	1.18 (0.96, 1.4)	<0.001
RV Pressure Estimate (mmHg)	38 (22 - 90)	66 (33 - 136)	29.8 (20.8, 38.8)	<0.001
Tricuspid peak S' velocity (m/s)	0.09 ± 0.02	0.14 ± 0.04	0.05 (0.04, 0.06)	<0.001
Tricuspid peak S' velocity (m/s) *	0.09 ± 0.02	0.14 ± 0.04	0.05 (0.04, 0.07)	<0.001
TAPSE (cm)	1.62 ± 0.43	1.65 ± 0.38	0.03 (-0.09, 0.16)	0.601
TAPSE (cm) *	1.62 ± 0.43	1.65 ± 0.38	0.07 (-0.09, 0.22)	0.400

Data are reported as Mean ± Standard Deviation or Median (Range).

Results are reported as regression coefficients with 95% Confidence Intervals (CI) from the mixed-effects linear regression models.

* Model was adjusted for change in DSTVI ratio from rest to peak

Model was adjusted for change in heart rate from rest to peak

Table 4:

Change in RV strain from rest to peak in rTOF vs. Control Group

Echo Parameters	TOF (n=32)	Coefficients (95% CI)	P1	Controls (n=10)	Coefficients (95% CI)	P2	*Coefficients (95% CI)	P3
RV Global Longitudinal Strain								
Rest	16.6 (8 - 27)	-3 (-4.7, -1.2)	0.001	25.1 (21 - 35)	7.9 (4.8, 11)	<0.001	10.9 (7.3, 14.4)	<0.001
Peak Exercise	13 (5 -28)			34 (27 - 41.1)				
RV Free Wall Strain								
Rest	17 (7 - 29)	-3.3 (-5.1, -1.5)	<0.001	26.1 (22.9 - 37.6)	8.3 (4.8, 11.3)	<0.001	11.3 (7.6, 15.2)	<0.001
Peak Exercise	14.3 (4.5 - 31)			35.5 (25.1 - 42)				

Results are reported as regression coefficients with 95% Confidence Intervals (CIs) from the mixed-effects linear regression models including the group, visit, and interactions of group by visits.

Interactions effects of group by visit for both outcomes were statistically significant (Ps<0.001).

P1 and P2 are p values referring to visit effect (change from Rest to Peak exercise) within the TOF and controls, respectively.

P3 is testing whether change from Rest to Peak exercise is different between the TOF and Controls (Groups by Visit interaction effect).

* Coefficient is the absolute value of the difference in contractile reserve between TOF and controls

Table 5:

Linear Regression Analysis of Exercise Parameters in rTOF

Outcome	Coefficients (95% CI)	r	P
Percent-predicted maximum VO2			
Change in RVGLS (%)	0.18 (−1.64, 2.00)	0.04	0.840
Change in D/S ratio	−55.9 (−102.9, −8.9)	−0.44	0.022
Change in DSTVI	−16.4 (−52.0, 19.2)	−0.18	0.353
Change in heart rate	0.38 (0.03, 0.73)	0.16	0.033
Percent-predicted maximum work			
Change in RVGLS (%)	0.40 (−1.66, 2.45)	0.08	0.694
Change in D/S ratio	−63 (−109, −17.1)	−0.48	0.009
Change in DSTVI	−41.7 (−76.9, −6.6)	−0.43	0.022
Change in heart rate	0.48 (0.12, 0.84)	0.46	0.011
Oxygen pulse			
Change in RVGLS (%)	0.05 (−0.31, 0.42)	0.06	0.772
Change in D/S ratio	−5.6 (−16.0, 4.9)	−0.21	0.283
Change in DSTVI	−9.6 (−15.7, −3.5)	−0.54	0.003
Change in heart rate	0.02 (−0.05, 0.10)	0.12	0.523

Results from the linear regression models are reported as regression coefficients with 95% Confidence Interval (CI) and P values