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Original Article

Effect of ventricular function and volumes on exercise capacity in adults with repaired Tetralogy of Fallot

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ABSTRACT

Objectives: Investigate the effects of left and right ventricular function and severity of pulmonary valve regurgitation, quantified by cardiac magnetic resonance (CMR), on exercise tolerance in adult patients who underwent ToF repair at a young age.
Methods: This is a retrospective cohort study of 52 patients after ToF surgery and 33 age- and sex-matched healthy volunteers. CMR and cardiopulmonary exercise testing (CPET) were performed on all patients; CPET was performed on control subjects.
Results: The main finding of CPET was a severe decrease in oxygen uptake at peak exercise VO_{2peak} in TOF patients. The patients were characterized also by lower pulse O_{2peak} and heart rate at peak exercise. Ejection fraction of the right and left ventricles was correlated (r = 0,32; p = 0,03). Left ventricle ejection fraction was negatively correlated with right ventricular volumes (r = −0,34; p = 0,01) and right ventricular mass (r = −046; p < 0,00). Right ventricular mass was positively correlated with left ventricular variables (left ventricle end diastolic volume, r = 0,43; p = 0,002; left ventricle end systolic volume, r = 0,54; p < 0,00) as was $VO_{2peak:}$ LVEDV (r = 0,38; p = 0,01); LVESV (r = 0,33; p = 0,03) and LV mass (r = 0,42; p = 0,006).
Conclusion: Exercise intolerance in adults with repaired ToF is markedly depressed. The decreased exercise capacity is correlated with impaired RV function and may be associated also with LV dysfunction, which suggests right-to-left ventricular interaction.

1. Introduction

Tetralogy of Fallot (ToF) is one of the most prevalent cyanotic congenital heart diseases requiring surgery early in life.[1] The common consequence of the primary surgery is pulmonary regurgitation, which may be well tolerated for decades. However, the presence of residual lesion can lead to progressive enlargement and dysfunction of the right ventricle (RV), exercise intolerance, ventricular and atrial arrhythmias, heart failure and sudden cardiac death.[2] RV dysfunction may also affect left ventricular (LV) function.[3] Implantation of the pulmonary valve may be performed to avoid these consequences[2]. Bedside clinical criteria, ventricular volume and function are factors in determining whether pulmonary valve replacement (PVR) is feasible.[4]

Cardiac magnetic resonance (CMR) is the current gold standard for evaluating RV performance and pulmonary valve regurgitation in patients after ToF operation. Cardiopulmonary exercise testing (CPET) provides objective information about the function of the

Abbreviations: TOF, Tetralogy of Fallot; RV, right ventricle; CPET, cardiopulmonary exercise testing; CMR, cardiac magnetic resonance; PVR, pulmonary valve replacement; PR, pulmonary regurgitation; EDV, end diastolic volume; ESV, end systolic volume; LV, left ventricle; RV, right ventricle EF ejection fraction; NYHA, New York Heart Association; VO2, oxygen uptake.

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heart, lungs and muscles and has been proposed as a useful tool for optimal timing of PVR.[5] Previous studies have reported on exercise intolerance in adults with repaired ToF.[2,6] Babu-Narayan SV et al.[2] showed that in ToF patients undergoing PVR, preoperative oxygen uptake was predictive of early postoperative mortality. However, the relationship between right-side cardiac abnormalities and exercise capacity in this patient group is poorly understood.[7]

The goal of the present study was to determine the effect of the left and right ventricular function and severity of pulmonary valve regurgitation, quantified by CMR, and to determine the relationship of the ventricular function to exercise tolerance in adult patients who had undergone ToF repair at an early age.

2. Methods

2.1. Patient population

This is a retrospective cohort study. The echocardiography, CMR and CPET data for all patients with repaired ToF were reviewed retrospectively. Patients were referred for exercise testing as part of routine clinical follow-up at the Department of Cardiac and Vascular Diseases, Institute of Cardiology Jagiellonian University College of Medicine in the John Paul II Hospital in Krakow. A main diagnosis was determined for every patient from hospital records, and patients were included in the study if they had ToF as primary diagnosis (ToF variants were excluded). In addition, age- and sex-matched healthy controls for comparison were voluntarily recruited via an advertisement. The control subjects were healthy at clinical examination, and had no medical history, medication or current symptoms suggesting cardiovascular disease.

2.2. Study protocol

From the patients' medical records, we extracted all clinical and demographic variables. The New York Heart Association functional class was recorded, and selected vital signs were measured, i.e. weight and height, from which we computed the body mass index (weight/height^2 expressed in kg/m^2).[8] Information on cardiac malformation, type of previous cardiac operations, age at surgical repair, and current medications were recorded. CMR and CPET were performed on every patient; CPET only was performed on controls.

2.3. CMR: imaging protocol

Breath-hold, ECG-gated imaging was performed using cardiac phased-array coil on 1.5T whole-body scanner (Magnetom Sonata Maestro Class, Siemens, Erlangen, Germany) in LV and RV short-axis and axial views. After scout imaging, cine biventricular imaging, with breath-hold steady-state free precision gradient echo technique, and flow-sensitive imaging at the pulmonary valve level, with free-breathing phase-contrast technique, were acquired. The imaging plane for a flow sequence was oriented perpendicularly to the main pulmonary artery at the level of the pulmonary valve. The velocity encoding was set at 100–550 cm/s to avoid an aliasing artifact.

2.4. CMR: image analysis

Cine and flow images were assessed off-line by use of a dedicated software package (MASS Medis, Leiden, the Netherlands). For cine images, endocardial and epicardial borders were outlined on short-axis images as described.[9] If the basal slice contained both ventricular and atrial myocardium, contours were drawn up to their junction and joined by a straight line through the blood pool. In the basal slice, if the pulmonary valve was visible, only the volume below the pulmonary valve level was included. For calculation of RV inflow portion, blood volume was excluded from RV volume if the surrounding wall was thin and not trabeculated, as it was considered to be in right the atrium. LV and RV end-diastolic volume (LVEDV, RVEDV), end-systolic volume (LVESV, RVESV), myocardial mass and ejection fraction (LVEF, RVEF) were computed. EDV, ESV and myocardial mass were indexed to body surface area.

For flow images, vessel contours were drawn and propagated throughout the cardiac cycle. The forward flow and backward flow were calculated; backward flow was considered to represent the volume of pulmonary regurgitation. Based on the forward and backward flow volumes, the fraction of pulmonary regurgitation (PRF) was calculated and classified as mild ($<$20%), moderate (20% to 39%), or severe ($\geq$40%). Based on Myerson et al.,[10] we decided to accept $\geq$40% regurgitation fraction as severe, and accordingly divided patients into those with severe or non-severe PR with respect to CPET and CMR imaging study variables.

2.5. Cardiopulmonary exercise testing

CPET was performed on a treadmill with a modified Bruce protocol (Reynolds Medical System, ZAN-600) as described.[11] To avoid pharmacologic influence, beta blockers were discontinued before CPET was done. Oxygen saturation and 12-lead electrocardiogram were continually monitored during the test, and blood pressure was measured manually every two minutes. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (V_e) were measure with computerized breath-by-breath analyzer. Peak oxygen uptake (VO_2 peak) was defined as the highest value at peak workload and was expressed in ml/kg/min and as% of predicted value. Oxygen pulse (pulse O_2) was defined as the amount of oxygen consumed per heart beat. The ventilator equivalent for oxygen (V_e/VCO_2) was the amount of ventilation needed for the uptake of a given amount of oxygen; the ventilatory equivalent for carbon dioxide (V_e/VCO_2) was the amount of ventilation needed for the elimination of a given amount of carbon dioxide. The respiratory exchange ratio (RER) was calculated by dividing the VO_2 by VCO_2.

2.6. Statistical analysis

All statistical analyses were performed by use of the statistical software package StatSoft STATISTICA 12.5. All data are expressed as mean with 95% confidence interval or median with interquartile range. Continuous variables were tested for normal distribution by use of the Shapiro-Wilk test and compared by use of the two-tailed Student's *t*-test (in case of normal distribution) and Mann–Whitney *U* test (in case of non-normal distribution). Correlations between nominal variables were tested with Spearman's rank correlation coefficient or Pearson rank correlation coefficient test, depending on normal distribution of interval variables. Correlations between ordinal variables data were analyzed by use of Kendall's tau test. All ordinal and interval data were tested with Spearman test. A p value of $<$0.05 was considered statistically significant.

3. Results

3.1. Population characteristics

Table 1 shows the demographics of the 52 patients with ToF repair and 33 control subjects. There were no significant differences between the patients and controls in the variables measured.

Table 2 gives the characteristics of the patients who underwent ToF repair.

Table 1
Demographics of patients with ToF repair and control subjects.

	Patients (n = 52)	Controls (n = 33)	P values
Age	29 ± 8.9	28 ± 4.7	>0.05
Male/female	30/22	24/0	>0.05
Height	168 ± 10.5	179 ± 9.9	>0.05
Weight	65.2 ± 14.5	73.3 ± 11.3	>0.05
BMI	23.2 ± 4.7	22.7 ± 1.6	>0.05
BSA	1.7 ± 0.2	1.9 ± 0.2	>0.05

BMI = body mass index; BSA = body surface area.

Table 2
Characteristics of the patients who underwent ToF repair.

Median age at repair (yr).	5.8 ± 3.0
Number with prior Blalock-Taussig repair	9
Number with pulmonary valve replacement	9
NYHA functional class	NYHA 0–11 (21.2%) NYHA I – 24 (46.2%) NYHA II – 16 (30.8%) NYHA III – 1 (1.8%) NYHA IV – 0
Median age of CEPT (yr)	27.0 ± 10.0
Median age of MRI study (yr)	27.2 ± 9.0

NYHA = New York Heart Association, CEPT = cardiopulmonary exercise testing; MRI = cardiac magnetic resonance.

Table 3
Results of cardiopulmonary test in patients and controls.

CPET parameter	Patients (n = 52)	Controls (n = 33)	P value
VO_2 peak (%N)	67.2 ± 16.7	123 ± 20.5	0.0001
VO_2 peak (ml/kg/min)	25.5 ± 8.0	48.0 ± 7.8	0.0001
Pulse O_2 peak	16.7 ± 4.8	29.4 ± 11.1	0.0001
Heart rate (beat/min)	149.8 ± 38.5	172 ± 37.6	0.004
Total time of exercise (min)	15.2 ± 4.5	16.1 ± 3.2	0.32
RER_{peak}	1.1 ± 0.2	1.0 ± 0.1	0.12
V_e/O_{2peak}	28.2 ± 9.4	30.5 ± 4.0	0.2
V_e/CO_{2peak}	25.8 ± 6.2	27.3 ± 3.5	0.21

3.2. Cardiopulmonary exercise testing

Table 3 illustrates the results of cardiopulmonary tests in the patients and control subjects. Markedly lower VO_{2peak} and O_{2peak} in patients compared with control subject is evident. However, RER $_{peak}$, VE/O_{2peak}, and VE/CO_{2peak} values were not significantly different in the two populations.

Table 4 illustrates that were no differences in CPET variables in ToF patients with severe PR (PRF ≥ 40%) compared with corresponding values in those with the mild or moderate PR (PRF < 40%).

3.3. CMR imaging study

Table 5 shows CMR results in ToF patients with severe PR (PRF ≥ 40%) or moderate (PRF < 40%). LV mass and PRF were significantly different between the two populations, but several other variables were not different.

We observed positive correlation between RVEF and LVEF (r = 0.32; p = 0.03). LVEF was negatively correlated with RV volumes (RVEDV r = −0.29; p = 0.04; RVESV r = −0.34; p = 0.01) and RV mass (r = −0.46; p < 0.001). RV mass was positively correlated with parameters of LV (LVEDV r = 0.43; p = 0.002; LVESV r = 0.54; p < 0.001).

VO_2 peak was positively correlated with LV parameters: LVEDV (r = 0.38; p = 0.01); LVESV (r = 0.33; p = 0.03) and LV mass (r = 0.42; p < 0.001). In patients with severe PRF (>40%), we found positive correlations between maximal time of exercise and LV diastolic diameter (r = 0.63; p = 0.02), LV systolic diameter (r = 0.56; p = 0.04), LVEDV (r = 0.50; p = 0.05), LVESV (r = 0.52; p = 0.04). Peak oxygen uptake per kg was positively correlated with LV systolic diameter (r = 0.56; p = 0.04), RV mass (r = 0.53; p = 0.04), and LVEDV (r = 0.63; p < 0.001), LVESV (r = 0.57; p = 0.02). VO_2 peak was positively correlated with RVEDV (r = 0.53; p = 0.04), LVEDV (r = 0.73; p < 0.001), LVESV (r = 0.70; p < 0.001), and LV mass (r = 0.69; p < 0.001). Scatter plots depicting these correlations are shown in Fig. 1.

In patients with non-severe PRF (<40%) we found negative correlations between LVEDV (r = −0.68; p = 0.03), LVESV (r = −0.73; p = 0.02) and LV mass (r = −0.7; p = 0.03) and maximal time of exercise. Also, in these patients, maximal oxygen uptake was negatively correlated with PRF (r = −0.77; p = 0.01).

4. Discussion

Impaired exercise capacity has been widely reported in adults after repair of ToF.[2,5,6] Our study also shows that exercise tolerance in these patients is reduced, and they had lower heart rate at peak exercise and lower pulse O_{2peak} compared to corresponding values in controls. Similar findings have been found in the *meta*-analysis of Roetes et al.[12,13]

We found that peak oxygen uptake, which is the conventional expression of exercise capacity, was significantly lower in repaired

Table 4
Results of patients' cardiopulmonary exercise testing.

CPET variable	Mean value ± SD whole group	PRF < 40%	PRF ≥ 40%	p-value
T, (min)	15.2 ± 4.5	16.3 ± 2.6	16.7 ± 2.8	0.78
HR_{peak} (beat/min)	149.8 ± 28.5	151.7 ± 29.2	156.9 ± 23.9	0.62
Pulse O_{2peak}	16.7 ± 4.8	18,22 ± 4,52	18.1 ± 3.6	0.94
VO_{2peak}	1.7 ± 0.6	1.8 ± 0.5	1.8 ± 0.6	0.88
$VO2_{peak}$ (%N)	67.2 ± 16.7	71.4 ± 11.9	73.6 ± 15.8	0.71
$VO_{2/}kg_{peak}$(ml/kg/min)	25.5 ± 8.0	26.9 ± 5.9	28.2 ± 6.5	0.61
$VO_{2/}kg_{peak}$(%N)	73.1 ± 18.4	75.0 ± 12.0	81,75 ± 15.8	0.26
$VCO2_{peak}$	1.8 ± 0.7	1.9 ± 0.5	2.0 ± 0.7	0.66
RER_{peak}	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	0.64
VE/O_{2peak}	28.2 ± 9.4	30.0 ± 10.1	29.7 ± 7.1	0.93
VE/VCO_{2peak}	25.8 ± 6.2	27.8 ± 5.7	27.2 ± 4.8	0.78
VE_{peak}	52.9 ± 22.1	56.9 ± 17.8	59.8 ± 22.0	0.73
BR_{peak}	72.6 ± 27.3	72.3 ± 27.4	67.5 ± 27.4	0.66
Bf_{peak}	36.1 ± 10.6	36.4 ± 12.2	37.2 ± 8.3	0.85

T = time; HR = heart rate; VO_{2peak} = peak oxygen uptake; VCO_{2peak} = peak carbon dioxide uptake; RER = respiratory exchange ratio; V_e/VO_{2peak} = peak ventilatory equivalent for oxygen; V_e/VCO_{2peak} = peak ventilatory equivalent for carbone dioxide; V_e = minute ventilation; BR = breathing reserve; Bf = breathing frequency.

Table 5
CMR data of patients with ToF.

CMR variables	Mean value and SD range	PRF < 40%	PRF ≥ 40%	p-value
Indexed RVEDV, mL/m^2	127.8 ± 40.5	118.5 ± 31.2	130.2 ± 42.6	0.42
Indexed RVESV, mL/m^2	63.7 ± 30.3	56.7 ± 21.4	65.5 ± 32.2	0.42
RVEF, %	50.2 ± 9.3	52.9 ± 7.8	49.6 ± 9.6	0.32
RV mass, g	52.2 ± 20.9	52.3 ± 31.0	52.1 ± 18.0	0.98
LVEF, %	57.2 ± 6.6	58.2 ± 5.3	57.0 ± 6.9	0.61
Indexed LVEDV, mL/	77.4 ± 21.8	82.4 ± 19.5	76.1 ± 22.3	0.42
Indexed LVESV, mL/m^2	33.1 ± 10.7	35.0 ± 11.8	32.6 ± 10.5	0.53
LV mass, g	108.8 ± 31.0	124.8 ± 44.8	104.8 ± 25.7	0.07
PRF, %	42.0 ± 9.4	32.0 ± 6.6	47.9 ± 4.3	<0.001

CMR = cardiacmagnetic resonance; ToF = Tetralogy of Fallot; RVEDV = right ventricle end-diastolic volume; RVESV = right ventricle end-systolic volume; RVEF = right ventricle ejection fraction; RV mass = right ventricle mass; LVEF = left ventricle ejection fraction; LVEDV = left ventricle end-diastolic volume; LVESV = left ventricle end-systolic volume; LV mass = left ventricle mass; PRF = pulmonary regurgitation fraction.

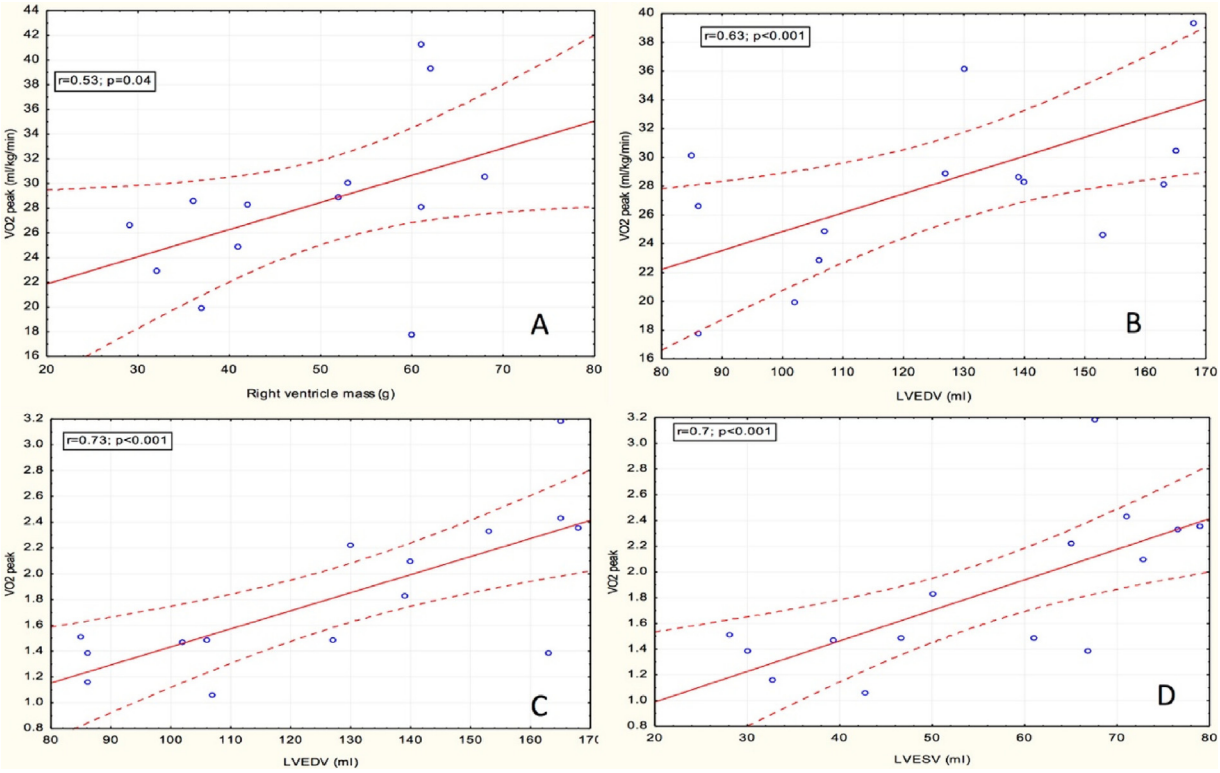

Fig. 1. Scatter plots showing the correlation between different parameters of exercise capacity and cardiac magnetic resonance: A. Correlation of peak oxygen uptake per kg versus right ventricle mass. B. Correlation of peak oxygen uptake per kg versus left ventricle end diastolic volume. C. Correlation of peak oxygen uptake versus left ventricle end diastolic volume. D. Correlation of peak oxygen uptake versus left ventricle end systolic volume.

ToF patients than in normal healthy volunteers. These findings correspond to those of Carvalho et al.,[6] who also noted lower maximal oxygen uptake, but, in contrast with our results, statistical significance was not achieved. In several studies in ToF patients, an average peak oxygen consumption, expressed as a percentage of predicted value, was 51% to 95%.[5,14] We found that exercise function, measured by% VO_{2peak}, was decreased (67.2 ± 16.7%) but not as low as that in the study of Fredriksen et al.,[14] who reported% VO_2 peak of 51% predicted.[14] Our data are also similar to those in a recent study by O'Meagher et al.,[15] which, together with our data, suggest that ToF patients have sufficient exercise cardiac response to maintain nearly normal exercise tolerance, despite a high prevalence of residual right sided-lesions.[15]

Significantly depressed peak VO_2 in ToF patients has been associated with abnormal right ventricle adaptation to exercise.[16] This observation might be explained by reported findings, in which patients with repaired ToF had increased RVEDV and RVESV during exercise.[1] Our study confirmed that peak VO_2 correlates positively with RVEDV in patients with significant PR. These results support the notion that right ventricle adaptation to volume overload could be helpful for maintaining functional capacity. The abnormal response of right ventricle dilation during exercise in ToF patients may suggest that compensatory hypertrophy, which is an adaptation of the right ventricle to hemodynamic insults, had positive effects on exercise capacity; this was demonstrated in our study by positive correlation between right ventricle mass and peak VO_2. Thus, there may be a role of RV diastolic dysfunction in limiting exercise capacity.

Impaired exercise capacity is reportedly related to changes in heart muscle and reduced heart rate response to exercise.[5] Carvalho et al. [6] have suggested that exercise capacity is related to the degree of residual pulmonary regurgitation.

Other potential factors responsible for depressed exercise tolerance in ToF patients are pulmonary artery stenosis, impaired lung function, chronotropic impairment, and ventricular dysfunction.[3] Pulmonary regurgitation causes chronic volume overload or the right ventricle and is related to right ventricle dysfunction.[17] In our study, we confirmed these findings; all parameters of right ventricle were abnormal on CMR.

Recent retrospective studies found that a pulmonary regurgitant fraction of approximately $\geq$40% should be considered severe,[10] which is supported by several authors (Jang et al.,[23] Tobler et al.,[18] Ooesternhof et al.,[4] Rosa et. al. [24]) who also identified patients with greater than moderate PR measured in CMR (PRF $>$ 40%).[4,18] In previous studies, the relationship between exercise capacity and right ventricle function measured with CMR has been poorly characterised.[7,16] Other research has reported weak relationship between RVEF and peak exercise capacity[19], although Meadows et al. [16] found positive and independent correlation between RVEF and VO_2 peak and VO_2 at anaerobic threshold. Like Roest et al.,[1] who did not find a correlation between pulmonary regurgitation and right ventricle function and peak oxygen uptake, we found that RVEF in patients with severe PR had no influence on parameters of the cardiopulmonary exercise test. This finding might suggest an adaptive mechanism for preservation of RVEF despite dilatation of the right ventricle due to chronic severe PR. According to O'Meagher, et al.,[7] lack of correlation between RVEF and peak exercise parameters could mean that ejection fraction is of limited value for assessment of exercise tolerance. This opinion is supported by Yap et al.,[20] who did not find significant correlation between exercise capacity and either RVEF or right ventricle stroke volume.

A particularly interesting finding in our analysis is that exercise capacity in ToF patients correlates with both right and left ventricle parameters in CMR. The literature contains little information about right and left ventricular dysfunction in patients with ToF, and only a few studies have identified biventricular dysfunction,[21] although a negative ventricular–ventricular interaction has implied that left heart disease may be a marker of the severity of right heart disease in ToF patient.[17] In our analysis, LVEDV and LVESV correlated positively with peak oxygen uptake, as has been reported by O'Meagher et al.[7] In ToF patients, a major determinant of cardiac output and, thereby, exercise tolerance is left ventricle preload.[19,20] Left ventricle preload is resolved by right ventricle forward flow, taking into account the degree of pulmonary regurgitation.[19] The importance of left ventricle preload in determining exercise tolerance could be explained by our finding of a strong positive relationship between peak oxygen uptake and left ventricle and right ventricle volumes in patients with significant PRF.

Our study demonstrated ventricular interaction by finding significant correlation between ejection fraction of the right and left ventricles. Previously, it was found that relationship between ejection fraction of both ventricles is closely associated with clinical status, although the mechanism of right ventricle dysfunction linked with left ventricle function is incompletely understood.[21] Also, in our analysis, right ventricle mass positively correlated with parameters of left ventricle systolic function, which confirms that excessive right ventricle hypertrophy can impinge on left ventricle filling. This opinion is compatible with the results of studies by Kempny et al.[22] and Geva et al.,[17] recently confirmed by O'Meagher et al.,[7] which described significant ventricular–ventricular interaction. Previous studies have noted that right ventricle size has an impact on left ventricle function[20] and, consequently, exercise tolerance is preserved late after ToF repair despite right ventricle dilatation.[17] Oosterhof et al. [4] documented right-to-left ventricular interaction after PVR, and their findings referred to changes in right ventricle and left ventricle volumes.[4] Because of incomplete data about the impact of right ventricle mass on left ventricle function our findings deserves further investigation.

5. Conclusion

Exercise intolerance in adults with repaired ToF is markedly depressed compared to that in normal healthy control subjects. The decreased exercise capacity is correlated with impaired right ventricle function and may be associated also with left ventricle dysfunction, which suggests abnormal right-to-left ventricular interaction.

Conflicts of interest

The authors have none to declare.

Ethics approval of research

The study protocol was approved by the local Ethics Committee. Each participant provided informed consent to participate in this study (license number 122.6120.88.2016). All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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