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Research Article

Mid Term Evaluation of Patients Undergoing Surgery for Tetralogy of Fallot with 24 Hour Rhythm Holter and Cardiopulmonary Exercise Testing

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Objective: This study aimed to obtain mid-term evaluation of exercise capacity and arrhythmias with cardiopulmonary exercise testing (CPET) and 24-hour rhythm Holter in Tetralogy of Fallot (TOF) patients who underwent surgery.

Materials and Methods: The study group consisted of patients over 6 years of age who had undergone complete correction surgery for TOF, while the control group consisted of healthy children of a similar age group who did not have any heart disease. Echocardiography, 24-hour Holter monitoring and CPET were applied to both groups.

Results: Study group included 14 patients who were operated on due to TOF and 9 healthy children as the control group. During echocardiographic examination; aortic diameter, pulmonary annulus, right ventricular (RV) systolic and diastolic areas were found to be significantly larger in the patient group (p=0.044, p=0.017, p=0.05, p=0.012 respectively). Myocardial performance index (Tei index-MPI) calculated from mitral and tricuspid valve annulus was found to be significantly higher in the patient group (p=0.05 for both). During CPET, stroke volume and VO2max levels were significantly smaller in patients (p=0.004, p=0.044 respectively).

Conclusion: Although operated TOF patients are asymptomatic in the mid-term, the exercise capacity in these patients is lower than in healthy individuals and this decrease is related to right ventricular size and dysfunction.

Keywords: Tetralogy of Fallot, Exercise Capacity, Arrhythmia

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1. INTRODUCTION

Tetralogy of Fallot is the most common cyanotic congenital heart disease in adults. Native disease consists of four different anatomical features: 1) Obstruction of the right ventricular outflow tract, 2) Non-restrictive large ventricular septal defect, 3) Dextroposition of the aorta, 4) Right ventricular hypertrophy. Initial corrective surgery for TOF using cardiopulmonary by-pass was performed in 1955.[1] Nowadays, corrective operation is performed with a mortality rate less than 5% in many centers throughout the world.[2] However during long term follow-up of operated patients there is still increased morbidity and mortality risks. Pulmonary insufficiency and stenosis are the most common hemodynamic problems in patients, which develop due to patches and muscle resections in the right ventricular outflow tract, leading to enlargement and dysfunction of the right ventricle. These structural and functional changes of the right ventricle may also cause electrocardiographic changes, arrhythmia and even sudden death.[3]

CPET is widely used in the diagnosis and monitoring of the patients with heart disease. CPET evaluates exercise capacity, visible response to exercise, helpful in determination of life expectancy and prognosis. CPET also define the risks of arrhythmia and sudden death in postoperative patients with TOF. The commonly used stimulation modes in exercise testing include bicycle ergometers, treadmills, total body workout equipment, etc., among which the first two are the most frequently used ones.[4]

Pulmonary regurgitation (PR), which is seen especially in those with transannular patch repair and leads to progressive right ventricular dilatation, is the most common residual lesion after TOF repair. The degree of PR and exercise tolerance tests show a negative correlation. Therefore, in asymptomatic patients, CPET could give objective information about the

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function of the heart and can be a useful tool for deciding the optimal time for pulmonary valve replacement (PVR) in the presence of significant RV dilation with or without dysfunction.[5]

The aim of the study was mid-term evaluation of exercise capacity and arrhythmias with 24-hour rhythm Holter and CPET in TOF patients who underwent surgery. In addition, it was aimed to reveal the relationship between CPET results and echocardiographic findings.

2. MATERIAL AND METHODS

In this observational cohort study; between July 2016 - December 2016 we enrolled 14 patients with TOF who underwent total correction and followed up by Marmara University Pediatric Cardiology Department. Control group consisted of 9 healthy children with similar age and gender characteristics, without any cardiac or systemic illness. The ages of the patient and control groups participating in the study were between 5 and 20 years.

Patient files were retrospectively analyzed. Chest x-ray, 12-lead ECG, 24-h Holter monitoring, echocardiography were performed. Plasma Pro-BNP values of the patients were recorded. In echocardiographic studies; M-Mode, two-dimensional (2D) echocardiography and tissue Doppler imaging (TDI) techniques were used. All patients underwent CPETwith using Cortex ML3B device. Modified Bruce protocol was used with an individualized ramp protocol exercise stress testing. The following parameters were recorded constantly throughout the exercise test: Peak oxygen uptake $VO_{2max,}$ predicted VO_2 (%), as well as CO_2 elimination VCO_2, peak heart rate (PHR), respiratory exchange ratio ($RER = VCO_2/VO_2$), VE/VCO_2, VE/VO_2. The PHR reached was calculated as the percentage of expected HR at maximum exercise according to age. Stroke volume was calculated indirectly by dividing the VO_{2max} value by PHR.

This study was conducted with the approval of local Clinical Research and Ethics Committee (Date: 01.04.2016, Decision No: 09.2016.216) of our instutition. The study complied with the principles of the Declaration of Helsinki.

2.1. Statistical analysis

The statistical analysis of the collected patient data was carried out using IBM Statistical Package for the Social Sciences (SPSS) version 17.0. The Mann-Whitney U test, Kruskal-Wallis test, one-way analysis of variance was applied for comparing the means of continuous variables between two groups. Chi square test was used to compare nominal variables. A statistical significance was accepted when $p<0.05$.

3. RESULTS

14 operated TOF patients and 9 normal controls were included. In patient group; Pro-BNP levels and the duration of QRS interval measured on ECG were found to be significantly higher (p=0.014, p=0.001). A higher cardiothoracic ratio (CTR) was shown in patient group with x-Ray (p=0.010). Demographic and clinical data are tabulated and compared in Table 1.

Table 1.

Demographic, clinical and electrocardiographic findings of TOF patients and controls

	Patients(n=14)	Controls (n=9)	P value
Sex (M/F)	9/5 (%64.2)	6/3 (%66.6)	0.643
Age	13.86±4.44	14.0±2.87	0.727
BMI (kg/m^2)	20.4±4.8	19.5±5.2	0.361
Systolic Blood Pressure (mmHg)	113.7±9.9	108.4±9.6	0.219
Diastolic Blood Pressure (mmHg)	66.2±8.6	64.2±7.0	0.590
Follow-up Period(year)	11.86± 4.72		
Pro-BNP(pg/mL)	**126.2±157.3**	**27.2±19.6**	**0.014**
CTR	**0.5±0.044**	**0.39±0.05**	**0.010**
PHR	79.7±13.2	80.6±12.7	0.824
PR (ms)	152.9±27.9	155.6±38.4	0.974

Table 1. (Continued)

QTc	0.4±0.038	0.37±0.035	0.100
QRS (ms)	**141.43±42.58**	**80.00±16.67**	**0.001**

(BMI: Body mass index; Pro-BNP: Brain natriuretic peptide)

The average Ao diameter and the PA diameter of the patient group were increased significantly (p = 0.044, p=0.017). It was observed that the RV end-diastolic and end-systolic area measurements of the patient group were larger than the control group (p=0.012, p=0.05). Mitral and tricuspid valve IRT measured by TDI echocardiography in the patient group was increased compared to the control group (p= 0.021, p=0.025). ICT was determined from the mitral and tricuspid valves were found to be similar. Likewise, in the mitral and tricuspid valve; MPI was found to be significantly higher in the patient group (p= 0.05 for both). Echocardiographic measurements are demonstrated in table 2, table 3 and table 4.

Table 2.

M-Mod Echocardiographic measurements in TOF patients and controls

Controls(n=9)	Patients(n=14)	Controls(n=9)	P value
IVSd (cm)	0.83±0.15	0.78±0.11	0.570
LVEDD (cm)	4.31±0.59	4.38±0.37	0.550
LVESD(cm)	2.56±0.74	2.74±0.26	0.950
LVPWD (cm)	1.01±0.9	0.7±0.11	0.700
SF (%)	38.3±5.4	37.4±3.3	0.330
EF (%)	70 ±7.3	67.1±4.5	0.270
LA (cm)	3.1±0.71	2.8±0.56	0.610
AO(cm)	**2.8±0.61**	**2.2±0.33**	**0.044**
TAPSE(mm)	21.9±4.47	24.5±5	0.220

(IVSd: Interventricular septum thickness; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LVPWd=left ventricular posterior wall thickness at diastole; SF: Shortening fraction; EF: Ejection fraction; LA: Left atrium; AO: Aorta; TAPSE: Tricuspid Annular Plane Systolic Excursion)

Table 3.

2D and Doppler Echocardiographic measurements in TOF patients and controls

	Patients(n=14)	Controls(n=9)	P value
RV Area (dia) (cm^2)	**26.4±7.5**	**17.5±6.1**	**0.012**
RV Area (sis) (cm^2)	**16.3±7.5**	**10.2±3.6**	**0.050**
PA (cm)	**2.26±0.73**	**1.47±0.65**	**0.017**
RVESV (ml)	33.8±19.7	29.4±6.1	0.680
RVEDV(ml)	80.5±32.4	75±24.3	0.700
RVEF(%)	58.2±10.8	62.4±6.1	0.700
RVFAC (%)	48 ±28.5	43.6±7.1	0.980
Mitral E (cm/sec)	1 ±0.15	0.95 ±0.11	0.390
Mitral A (cm/sec)	0.6±0.11	0.58±0.13	0.570
DT(sec)	132.5±44.6	146.6±29	0.310
IVRT(sec)	65.4±14.4	61.9±14	0.610

(RV: Right ventricular; PA: Pulmonary annulus; RVESV: Right ventricular end-systolic volumes; RVEDV: Right ventricular end -diastolic volumes; RVEF: Right ventricular ejection fraction; RVFAC: Right ventricular fractional area change; DT: Decelaration time; IVRT: Isovolumic relaxation time)

Table 4.

TDI echocardiography measurements of mitral and tricuspid valves in TOF patients and controls

	Patients(n=14)	Controls(n=9)	P value
ET (mitral) (sec)	287.5±25.7	286.2±30.8	0.256
ET (tricuspid) (sec)	272.5±16.1	263.6±17.9	0.200
IRT (mitral) (sec)	**79.4±12.8**	**66.4±1.6**	**0.021**
IRT (tricuspid) (sec)	**76 ±13.4**	**63 ±9.5**	**0.025**
ICT(mitral) (sec)	61.6±9.7	70.7±12.9	0.072
ICT (tricuspid) (sec)	80.7±12.6	74.7±12.2	0.550
MPI (mitral) (sec)	**0.53±0.06**	**0.45±0.12**	**0.050**
MPI (tricuspid) (sec)	**0.58±0.056**	**0.53±0.1**	**0.050**

(ET: Ejection time; IRT: Isovolumic relaxation time; ICT: Isovolumic contraction time; MPI: Myocardial performance index)

Seven patients (50%) could complete the 15-minute period for CPET. Eight of the patients (57.1%) were able to run to the level 5, two (14.2%) to the level 4, three (21.4%) to the level 3, and one (7.1%) to the end of the level 1. The calculated stroke volume in the patient group was lower than the control group (p = 0.004). The baseline oxygen saturation and VO_{2max} level observed in the patient group were significantly lower than the control group (p = 0.017, p=0.044). Respiratory rate, PHR, VE/VO_2, VE/VCO_2, RER values were similar in groups. 24 hour Holter monitoring revealed ventricular premature beats in 10 (71.4%) of the patients. Table 5 shows the CPET results.

Table 5.

CPET variables of TOF patients and controls

	Patients(n=14)	Controls(n=9)	P value
PHR (bpm)	164.2±24.1	168.7±12.9	0.825
Stroke Volume (ml)	**135.3±36.9**	**184.7±32.4**	**0.004**
MinO_2 saturation(%)	**90.6±9.6**	**97.2±1.5**	**0.017**
VO_2 (max)(ml/kg/min)	**29.2±10.37**	**31.44±7.43**	**0.044**
VO2(%)	41.4±15.5	46.1±10.7	0.470
VE/VO_2slope	28.8±3.8	29.3±4.0	0.975
$VE/VC0_2$slope	25.9±1.8	26.8±2.4	0.256
RER	1.12±0.09	1.18±0.17	0.613

Supraventricular premature beats were detected in six patients (42.3%) which were clinically insignificant and did not need medical treatment.

4. DISCUSSION

PR is the most important complication in operated TOF patients. Although variable degrees of PR related to operated TOF can be tolerated for many years, PR in some patients becomes severe and is associated with dilatation and dysfunction of the RV and subsequently the left ventricle, therefore contributes to long-term morbidities, including exercise intolerance, arrhythmia and possibly sudden death.[6] PVR is performed in patients with operated TOF to protect the RV from the adverse effects of chronic volume overload, and there is no consensus on the optimal timing of PVR in operated asymptomatic patients.

The higher frequency of right bundle branch block characterized by long QRS duration in TOF patients who underwent surgery has been attributed to the effect of cardiac surgery. Right ventricular enlargement and QRS prolongation greatly increase the risk of symptomatic arrhythmia. The most sensitive predictor of life-threatening ventricular arrhythmia is a QRS duration of ≥180 msec on the resting ECG.[7] In our

study, the QRS duration was longer in the patient group. Additionally, four patients had an increased QRS duration over 180 ms and two of these patients underwent PVR surgery. In our study, Pro-BNP levels of the patient group were found to be higher than the control group. In the study of Çetin et al showed that Pro-BNP levels were higher in adult operated TOF patients who underwent CPET; it was stated that PHR and VO_{2max} levels were lower and exercise durations were shorter.[8] In our study no correlation was found between PHR and Pro-BNP levels. But there was a correlation between higher Pro-BNP levels and lower $VO_{2max,}$ levels in patient group.

Cardoso et al. showed that there was a positive correlation between follow-up time and diastolic dysfunction.[9] In our study patient group tricuspid valve MPI which was measured to evaluate right ventricular function, was found to be significantly higher. Abd El Rahman et al stated that restrictive state in RV leads to decreased RV compliance and decrease in ICT, which results in underestimation of MPI.[10] In our study, patient group had longer IRT in both tricuspid and mitral valves; while ICT was similar in both groups.

In the postulate developed by French physiologist Bernheim, it was revealed that the left ventricle functionally affects the right ventricle. Later studies showed that the right ventricle also affected the left ventricle, this was called the 'reverse Bernheimeffect.'[11] It has been shown that in operated TOF patients, left ventricular functions deteriorate as the follow-up period increases. Left ventricular dysfunction is more common as the age at surgery is delayed. Exposure of the myocardium to long term hypoxia is also one of the factors causing this condition.[12] Therefore, multipl studies indicated that the total correction operation must be performed before the age of one.[13] In our study, left ventricular EF and SF measurements were found to be similar in both groups, however MPI measured from the lateral annulus of the mitral valve was higher in the patient group and higher BNP levels were found in patient group.This finding indicate the presence of left ventricular dysfunction in operated TOF patients.

Studies showed that, nearly one third of adults with operated TOF have an aortic root diameter≥40 mm.[14] Patients in our study have larger Ao and PA diameters than the control group. Previous studies indicated that there is a direct association between pulmonary regurgitation and PA diameter.[15]

CPET is an important tool used in the management of adults with operated TOF. In patients with TOF, assessment of exercise capacity at any given time and its changes over time are important in determining the impact of residual hemodynamic lesions and the need for intervention. Giardiani and colleagues showed that adult TOF patients with predicted VO_2 39% were at greater risk for cardiac-related death.[16] We demonstrated that the achievable VO_{2max} values of the patient group were lower than the control group. But there was no difference VO_2(%) levels between groups. Carvalho et al have suggested a significant relation between the degree of pulmonary regurgitation and stroke volume or PHR.[17] We found that the stroke volume of the patient group was lower than the control group.

Shafer et al. demonstrated that VO_2 (%) values, baseline O_2 saturation and VE/VCO_2 slope were worse in adult TOF cases than healthy controls.[18] In our study, while the baseline O_2 saturation of the patient group were lower than the control group, no difference was detected in terms of $VE/VCO_2$and VO_2 (%) values.

Diller et al. showed that adults with congenital heart disease VO_{2max} ≤15.5 ml/kg/min are at an increased risk of major adverse cardiovascular events.[19] In our study, we detected lower VO_{2max} levels in TOF patients. There isn't any threshold VO_{2max} level spesific for TOF patients yet.

In one multicentre study showed that 43% of adults with operated TOF had experienced at least 1 sustained arrhythmia or arrhythmia intervention and prevalence of atrial tachyarrhythmias was 20.1%.[20] Harrison et al identified monomorphic ventricular tachycardia in 18 of 254 operated TOF patients.[21] None of our patients had clinically significant rhythm abnormalities.

In conclusion, even after successful surgery; the patients with TOF have decreased exercise capacity in objective assessment and this is

related to hemodynamic problems and ventricular functions. Further studies are needed for determining the optimal timing for re-intervention.

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The Declaration of Conflict of Interest/ Common Interest
No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval
University of Marmara Ethics Committee approved the study with decision number 09.2016.216 dated 01.04.2016.

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