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Original Article

Evaluation of the relationship between cardiopulmonary exercise test findings and clinical status in children and adolescents with congenital heart disease

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ABSTRACT

Background. The cardiopulmonary exercise test is accepted as a helpful diagnostic tool in risk stratification, evaluation of prognosis, and guiding treatment modality in adults with congenital heart disease. In this study, we present our experience with the use of cardiopulmonary exercise test in children with congenital heart disease in different physiological and anatomical classifications.

Methods. In this retrospective study, 25 children and adolescents who applied to the pediatric cardiology outpatient clinic between 2017 and 2020 with the diagnosis of different types of congenital heart disease were included. Demographic characteristics, electrocardiogram, echocardiogram, cardiopulmonary exercise test, spirometry, pro-BNP values, and in selected 20 patients; cardiac MRI data were examined. The modified Ross classification was used for heart failure grading.

Results. The mean age of the patients was 14.8 ±2.39 years. Fifteen (60%) of the patients were male and 10 (40%) were female. In the modified Ross classification, patients in group I-II had significantly higher maximum exercise time, heart rate reserve %, peak VO2, and VO2/kg values compared to those in group III (p=0.026, p=0.007, p=0.043, p= 0.018, respectively). Cardiopulmonary exercise test and spirometry values obtained from the patients were evaluated in the light of clinical and other laboratory findings, and surgical/interventional treatment was decided for 4 patients with the use of these test results.

Conclusions. Cardiopulmonary exercise test is a useful noninvasive diagnostic tool in guiding the treatment decision and predicting the prognosis of pediatric patients with congenital heart disease, who have borderline symptoms.

Key words: child, congenital heart disease, cardiopulmonary exercise test, Ross classification.

Today, thanks to advances in medicine and surgical techniques, children with congenital heart disease (CHD) can survive into adolescence and adulthood. However, residual lesions may persist after cardiac repair and these lesions may lead to progressive alteration of cardiac function.[1,2] The decision to treat the residual lesion depends on the extent of the lesion and the patient's symptoms of exercise intolerance. The regular bicycle or treadmill exercise tests and six-minute walking tests are used to determine the patient's exercise capacity with some information regarding the myocardial ischemia and occurrence of arrhythmias. The goal has been to detect problems before clinical symptoms are overt. Cardiopulmonary exercise tests (CPET) are performed by monitoring the individual's respiratory gas exchange, oxygen use (VO2: oxygen consumption), carbon dioxide production (VCO2), and minute ventilation (VE) during exercise, in addition to the electrocardiogram (ECG), blood pressure, and oxygen saturation monitoring, and can evaluate the patient's symptom-limited maximum increased exercise tolerance.[3] In studies, the superiority of CPET over other exercise tests

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has been stated for evaluation of the functional cardiovascular capacity of patients as well as the response of the respiratory system, muscular and metabolic systems to exercise.[4] CPET evaluates the cardiac performance using maximum oxygen uptake (VO2max) assessment in the clinical follow-up to evaluate morbidity and mortality.[5] In adults with chronic heart failure, VO2max correlates with both the quality of life and prognosis. Therefore, CPET has become the 'gold standard' for quantifying disease severity in adult cardiology. These results have also been found in adults with CHD, and CPET is now recommended in the follow-up of this particular population.[6-8]

Studies and experience regarding the use of CPET in the evaluation of functional capacity and heart failure in children with CHD, and in the direction of medical treatment of these patients are not sufficient as in adults. To contribute to the literature, we would like to present our experience with the use of CPET in children with CHD in different physiological and anatomical classifications.

Material and Methods

Study Population

In this retrospective study, 25 children and adolescents who were admitted to the pediatric cardiology outpatient clinic with different types of CHD between 2017 and 2020 were included. Patients' data were evaluated retrospectively. Demographic characteristics, electrocardiogram, echocardiogram, cardiopulmonary exercise test, spirometry, pro-BNP values, and in selected 20 patients cardiac MR data were examined. The existing pathologies of the patients were classified according to the anatomical classification in the 2018 American College of Cardiology (ACC)/ Adult congenital heart disease (ACHD) guidelinea.[5] The modified Ross classification was used for heart failure grading.[9] This research was reviewed and approved by the institutional Ethics Committee of our Koç University (approval number: 2020.265.IRB1.088).

CPET procedures

CPET was performed with a Carefusion (Vyntus® CPX, Germany) device using an automated sphygmomanometer with adapted pediatric cuffs, pediatric face mask, a calibrated gas analyzer, breath-to-breath measurements software, a 12-lead ECG monitor (GE CardioSoft® ECG, USA), a pulse oximeter, and a ramp protocol at 10 watts/minute incremental workload using with a bicycle ergometer. According to the incremental ramp protocol, the test consisted of 3 parts. The first part consisted of a 1-minute rest period, the second part consisted of a warm-up period of 2 minutes (0 Watt and a pedal speed of 60 rpm), and the third part consisted of an exercise period in which the workload was increased by 10 Watts per minute. Maximum heart rate was targeted by increasing the workload according to the patient's tolerance. The test was terminated due to fatigue, leg pain, chest pain, and shortness of breath. ECG, blood pressure and oxygen saturation values were monitored during the test for all the patients. From CPET data, oxygen uptake (VO2; ml/kg/min), carbon dioxide production (VCO2; ml/kg/min), respiratory exchange ratio (RER=VCO2/VO2), minute ventilation (VE; breaths/min), ventilatory equivalent for oxygen (VE/VO2), ventilatory equivalent for carbon dioxide (VE/VCO2), maximum workload (Watts), and oxygen pulse (VO2/HR; ml) were recorded.

Spirometry

Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/ FEVC ratio, predictive FEV1 values were obtained by performing a pulmonary function test with the spirometry mouthpiece of the Carefusion (Vyntus® CPX, Germany) device before and after the exercise test.

Statistical Analysis

SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA) statistical program was used for statistical analysis of the results. Categorical data were analyzed using the Chi-square test. For the

numerical variables, the 'Student-t test' was used for those with a normal distribution, and the Mann-Whitney-U Test for those with non-normal distribution. ANOVA test was used together with a post hoc test for comparisons between groups. Frequency and percentage in categorical data and mean±standard deviation values in numerical data were given as descriptive values. The limit of significance was accepted as $p<0.05$.

Results

Patients

A total of 25 children with CHD were included in this retrospective study. The mean age of the patients was 14.8 ±2.39 years (range 10-18 years,). Fifteen (60%) of the patients were male and 10 (40%) were female. Demographic characteristics, clinical, laboratory, and imaging data of the patients are given in Table I. Surgical/transcatheter procedure was performed in 15 of the patients due to the existing pathology, and 8 of them were under medical follow-up. Eight patients (32%) had marked dyspnea on exertion and palpitations at rest who are in Ross classification group III or IV. The remaining 17 (68%) patients had minimal symptoms.

12 lead ECG revealed right bundle branch block (RBBB) in 11 patients, left bundle branch block (LBBB) in one patient and complete atrioventricular block in one patient. Two patients had permanent pacemaker in dual chamber pacemaker (DDDR) mode. Two patients in group I and III had symptomatic tachycardias who needed antiarrhythmic therapy. One of them was diagnosed as atrioventricular nodal reentry tachycardia and the other was diagnosed as ventricular tachycardia and they were taking flecainide as antiarrhythmic treatment.

Diminished systemic ventricle ejection (EF<55%) was detected in two patients with L-TGA and single ventricular physiology who underwent bilateral Glenn anastomosis. Clinically significant valvular insufficiency was detected in 7 of the patients. Of these, 3 had aortic and 4 had tricuspid and pulmonary valve insufficiency together. Patients with bicuspid aortic valve have no severe aortic stenosis. Regarding the anatomical severity classification, there were 18 patients in group II and 6 patients in group III respectively. There were 17 patients in groups I and II and 8 patients in groups III and IV according to the physiologic severity classification (Ross Classification). In group 4, 1 patient had single ventricular anatomy and the other patient had moderate pulmonary valve stenosis who underwent arterial switch operation.

CPET Data

CPET and spirometry data of the patients are shown in Table II. Patients were compared according to the anatomical and modified Ross classification (Table III a,b). In anatomical severity classification comparison, no statistically significant findings were found between groups II and III in terms of the parameters.

When the CPET and spirometry values between the groups were compared according to the modified Ross classification; Maximum exercise time, heart rate reserve (HRR)%, VO2%, and VO2/kg values were significantly higher in patients in group I-II compared to group III-IV ($p=0.026$, $p=0.007$, $p=0.043$, $p=0.018$, respectively). No correlation was found between pro-BNP levels and exercise parameters.

CPET-spirometry values, clinical and other laboratory findings were used to decide the treatment modality as medical or surgical. Four patients underwent surgical-interventional treatment at a final decision with the substantial impact of the CPET findings (Table IV). 4 patients with tetralogy of Fallot had lower VO2% values (mean±SD:59.75±9.6) and higher VE/VCO2 (mean±SD: 32.6±1.56) and VE/VO2 (mean±SD: 32.95±2.15) values compared to the all the other patients (mean±SD: 72.85±19.9, mean±SD: 28.65±2.99, mean±SD: 27.74±3.63, respectively). The remaining 2 patients with tetralogy of Fallot

Table I. Baseline characteristics of the patients in the study.

Age (year)		14.8 ±2.39 (10-18)
Gender (M/F)		15 (60%)/10 (40%)
Body Mass Index		19.96±3.14 (14-26)
Conduction disorder	None	12
	LBBB	1
	RBBB	11
	CAVB	1
Resting Heart Rate (bpm)		80.48±11.13 (52-108)
Permanent Pacemaker		2
Distribution of the ACHD According to the 2018 ACC/ ACHD Anatomic Classification		
	Anatomic Severity Group 1 (4%)	1
	Congenital complete AV Block	1
	Anatomic Severity Group 2 (72%)	18
	Bicuspid Aortic Valve (balloon valvuloplasty)	2
	Bicuspid Aortic Valve (Medical Follow-up)	5
	VSD (surgical closure)	1
	AVSD (surgically corrected) with moderate/mild MR	2
	Tetralogy of Fallot (total correction)	6
	Mitral Valve Prolapse	1
	Hypertrophic cardiomyopathy	1
	Anatomic Severity Group 3 (24%)	6
	Double outlet RV+ VSD+ASD+ single ventricle (Fontan)	1
	cc-TGA	1
	Pulmonary atresia+ IVS (surgically corrected)+ PR (moderate)	1
	Ebstein	1
	Bilateral Glenn anastomosis+ RV hypoplasia+PS	1
	d-TGA (arterial switch)	1
Physiologic Severity Groups (Ross Classification)		
	I	6(24%)
	II	11(44%)
	III	6 (24%)
	IV	2 (8%)
	Systemic Ventricle EF (%)	70.76 ± 9.22 (52-89)
	Systolic Pulmonary Artery Pressure (mmHg)	35.08 ±12.79 (20-75)
	NT-ProBNP (ng/mL)	98.19±103.56 (8.5-429)
	Cardiac MRI Parameters	
	RV EF (%)	55.79±10.46 (25-73.5)
	LV EF (%)	57.21±6.41 (45-69)

ACHD: adult congenital heart disease, AV: atrioventricular, AVSD: atrioventricular septal defect, BNP: brain natriuretic peptide, CAVB: complete atrioventricular block, cc-TGA: congenitally corrected transposition of great arteries, d-TGA: dextropose transposition of great arteries, EF: ejection fraction, F: female, IVS: intact ventricular septum, LBBB: left bundle branch block, LV: left ventricle, M: Male, MR: mitral regurgitation, MRI: magnetic resonance imaging, PS: pulmonary stenosis, RBBB: right bundle branch block, RV: right ventricle, VSD: ventricular septal defect.

Table II. Cardiopulmonary exercise testing and spirometry parameters.

Parameters	mean±SD (range)
Exercise Duration (minutes)	12.3±5.14 (4.5-25)
Maximal Heart Rate (bpm)	159.68±25.95 (95-189)
Maximal Heart Rate %	83.88±13.98 (47-101)
HRR %	83.88±13.98 (47-101)
Peak respiratory exchange ratio	0.99±0.66 (0.83-1.13)
SaO2 at peak exercise %	98.44±1.47 (95-100)
VO2max (ml/min)	1558.04±490.50 (867-2673)
VO2max/kg (ml/min/kg)	30.05±7.63 (16-46.9)
VO2 %	71.72±18.98 (40-115)
VE/VCO2	28.57±3.31 (21.6-33.9)
VE/VO2	28.58±3.92 (21.6-36)
Peak O2 Pulse	10.15±2.76 (6.4-16.2)
FEV1/FVC (%)	91.18±10.76 (68-116)
FEV1 (% pred)	91.25±17.10 (56-137)
FVC (% pred)	88.04±15.84 (58.5-130.6)

FEV1/FVC (%): forced expiratory volume in 1 second/ forced vital capacity, HRR: heart rate reserve, pred: predicted, SaO2: oxygen saturation, VE/VO2: ventilatory equivalent for oxygen, VE/VCO2: ventilatory equivalent for carbon dioxide, VO2max: maximum oxygen uptake.

had similar values as the rest of the group and there were clinical and laboratory differences between the 4 patients with tetralogy of Fallot who had low VO2max values. Two patients with tetralogy of Fallot were in group II according to the Ross classification, and cardiac MRI RVEF values were higher and RVEDV indices were lower than the other 4 patients with tetralogy of Fallot.

In two patients who were operated on, CPET parameters improvement was observed in the follow-up (Table IV).

Discussion

Children with CHD account for 0.8 to 1% of all live births in developed countries.[10,11] Almost all pediatric patients reach adulthood with advances in surgery and percutaneous procedures. However, many of the patients are at risk of premature death from heart

Table III. a. Comparison of CPET variables between anatomic severity group II and group III.

	Group II (n=18)	Group III (n=6)	p
Maximal exercise duration	12.3±5.00	10.94±5.24	0.566
Maximal Heart Rate	163.88±21.97	150.66±36.57	0.673
Max. Heart Rate %	86.22±12.13	78.50±19.07	0.293
HRR %	86.22±12.13	78.50±19.07	0.255
Maximal RER	0.99±0.05	1.00±0.09	0.829
SaO2 at max. exercise	98.7±1.26	97.6±1.26	0.330
Peak VO2max%	73.55±17.55	60.50±16.84	0.237
VO2/kg	31.24±6.79	25.40±9.12	0.106
VE/VCO2	28.77±3.77	28.46±1.54	0.420
VE/VO2	27.88±3.91	28.73±3.21	0.310
Peak O2 Pulse	10.4±2.97	9.36±1.97	0.210
FEV1/FVC (%)	89.88±11.56	91.45±6.57	0.370
FEV1 (% pred)	91.98±19.79	88.46±7.63	0.330
FVC (% pred)	89.8±18.09	82.76±6.95	0.180

b. Comparison of CPET variables between Ross classifications group I-II and group III-IV.

	Group 1,2 (n=17)	Group 3,4 (n=8)	p
Max. Heart Rate %	87.23±8.4	85.66±14.44	0.108
HRR %	87.23±8.40	76.75±20.58	**0.007**
Maximal RER	1.00±0.05	0.99±0.07	0.202
SaO2 at max. exercise (%)	98.58±1.32	98.12±1.8	0.506
VO2 max %	79.88±15.66	54.37±13	**0.043**
VO2/kg	32.84±6.66	24.12±6.41	**0.018**
VE/VCO2	28.5±3.19	27.60±2.77	0.871
VE/VO2	28.02±3.1	26.97±3.94	0.103
Peak O2 Pulse	10.39±2.80	9.63±2.77	0.383
FEV1/FVC (%)	89.46±10.77	94.83±10.45	0.193
FEV1 (% pred)	91.77±19.75	90.16±10.48	0.107
FVC (% pred)	89.76±18.37	84.37±8.15	0.266

FEV1/FVC (%): forced expiratory volume in 1 second/ forced vital capacity, HRR %: heart rate reserve, Max: maximum, pred: predicted, RER: respiratory exchange ratio, SaO2: oxygen saturation, VE/VCO2: ventilatory equivalent for carbon dioxide, VE/VO2: ventilatory equivalent for oxygen, VO2max: maximum oxygen uptake.

Table IV. Characteristics of patients for whom surgical/interventional treatment decision was made based on CPET results.

	Patient 1	Patient 2	Patient 3	Patient 4
Age (year)	18	11	18	10
Diagnosis	Operated TOF	Operated TOF+PVR	Operated TOF+PVR	Operated TOF
Anatomic classification	2	2	2	2
Ross classification	3	3	2	2
Valvular pathology	TR+PR (significant)	TR+PR (significant)	TR+PR (significant)	TR+PR (significant)
Echocardiographic systemic ventricular EF value %	60	84	64	69
Cardiac MRI LV-RV EF %	60-58	60.5-67	45-25	55.4-51.4
Cardiac MRI RVEDV index (ml/m^2)	180	108.5	60	154
Pro-BNP (ng/dl)	123	43	198	102
VO2 max. % (pre/post-treatment)	48/61	56/80	66	69
VE/VCO2 (pre/post-treatment)	32.6/28.8	33.5/28.3	33.9	30.4
VE/VO2 (pre/post-treatment)	32.7/29.5	31/27.8	36	32.1
HRR % (pre/post-treatment)	47/67	81/85	86	81
FEV1/FVC (%)	116	82	96	102
FEV1 (% pred)	98	80.1	76	72.7
FVC (% pred)	87	80.1	64.6	70.3

EF: ejection fraction, FEV1/FVC (%): forced expiratory volume in 1 second/ forced vital capacity, LV-RV: left ventricle-right ventricle, MRI: magnetic resonance imaging, pred: predicted, Pro-BNP: pro-brain natriuretic peptide, PR: pulmonary regurgitation, RVEDV: right ventricular end-diastolic volume, TOF: tetralogy of Fallot, TR: tricuspid regurgitation, VE/VCO2: ventilatory equivalent for carbon dioxide, VE/VO2: ventilatory equivalent for oxygen, HRR %: heart rate reserve, VO2max%: maximum oxygen uptake.

failure or arrhythmias.[12-15] In these patients, exercise capacity is the most important factor that endangers their quality of life both preoperatively and postoperatively.[16,17] Impaired exercise capacity may result from prolonged volume or pressure overload, or heart failure resulting from increased myocardial tension or flow. However, all of the pulmonary, vascular, muscular, or metabolic systems may be affected in these patients.[4,11]

CPET is a diagnostic tool that can be used for objective and reproducible assessment of the cardiovascular, respiratory, and muscular systems.[5] In adult studies, CPET has been shown to have prognostic value in patients with a wide variety of CHD conditions.[6,7,18,19] In adult studies, it has been shown that the most valuable parameters in demonstrating the patient's exercise capacity in CPET are peak VO2, VE/VCO2 slope, and HRR.[17,20] However, studies and experience regarding the use of CPET In the evaluation of functional capacity and heart failure in children with CHD and the management of their medical treatment are insufficient. In this study, we aimed to show the contribution of CPET in the management of treatment by evaluating the exercise capacity of children with CHD in different anatomical and functional classes.

Peak VO2 is the most important indicator of cardiopulmonary function in CPET in patients with CHD, as it is associated with the cardiac output response.[21] Patients with CHD have impaired maximal VO2 compared to age-matched controls without heart disease.[4,20] In our study, the mean peak VO2 value of the patients was below the normal range, consistent with the literature. It may be useful

to compare peakVO2 with similar forms of CHD to determine whether a patient has an abnormality beyond what would be expected due to existing cardiac pathology.[7,22] Studies have shown that the decreased peak VO2 value has been linked to the severity of the underlying heart disease and patients with Eisenmenger syndrome have been shown to experience the greatest exercise intolerance.[6,7,18,23-25] In our study, the peak VO2 values of children with CHD in different anatomical and physiological classifications were compared. According to the modified Ross classification, the peak VO2 values of the children in the 3rd and 4th groups were statistically significantly lower than the other group (1-2nd), but there was no statistically significant difference between the peak VO2 values according to the anatomical severity.

VE/VCO2 slope, which is one of the other important indicators of CPET, is often called 'ventilation efficienc'' and an increase in this value indicates that a higher VE is required to remove CO2 sufficiently. High VE/VCO2 slope values are well defined in patients with respiratory muscle fatigue, inadequate muscle perfusion, and heart failure.[24,26] In our study, no significant difference was found in VE/VCO2 slope values between anatomical and physiological groups. However, VE/VCO2 slope values were higher than expected in 4 patients with operated tetralogy of Fallot and significant pulmonary valve insufficiency. Shafer et al.[27] found higher VE/VCO2 slope values in patients diagnosed with operative tetralogy of Fallot compared to other patient groups, and this was attributed to incorrect distribution of pulmonary blood flow secondary to pulmonary artery stenosis or insufficiency and as a result, ventilation /perfusion mismatch.

Low heart rate reserve (HRR) is common in adult congenital heart patients with an estimated incidence of 60%.[28] Chronotropic insufficiency may result from intrinsic or iatrogenic dysfunction of the conduction system. Therefore, the cardiac acceleration response to exercise is also low.[19,24] In previous studies, no matter how high the heart rate was, the maximum heart rate and HRR were found to be lower than normal.[29] In our study, although the mean maximum heart rate and HRR of the patients were within the normal range, the HRR values among the physiologically classified groups supported the literature. On the other hand, the fact that 2 patients in Ross classification 3 and 4 had permanent pacemaker may have affected the lower maximum heart rate compared to the other group.

When the spirometry values of the patients were examined, the mean FEV1/FVC (%), FEV1 (% pred), FVC (% pred) values were within the normal range. This result was associated with the younger age of the patients included in our study. Although there are several studies with the same conclusion as ours, they generally worsen with age, impairing exercise tolerance and contributing to respiratory comorbidities.[30-32]

In our study, when the CPET parameters of 4 patients were examined a surgical treatment was decided. The peak VO2 value of the patients is lower than normal and VE/VCO2 and VE/VO2 parameters are higher than normal. These findings were consistent with the results of studies in adult patients.[18,23-25]

There are several limitations to our study. These can be counted as the small number of patients and the absence of different anatomical and physiological groups with similar numbers of patients. We are planning studies with a larger number of patients. The other limitations are the absence of a control group and not having follow-up CPET measurements.

In conclusion, CPET may be a diagnostic method that can be used to evaluate the cardiac, pulmonary; and metabolic response to exercise, cardiopulmonary failure, exercise-related symptoms, and functional capacity of pediatric and adolescent patients with CHD in different anatomical and functional classes to guide their medical treatment. This test should be performed in patients at certain ages to reveal clues of clinical deterioration.

Ethical approval

Ethics/Institutional Review Board approval of institutional Ethics Committee of Koç University, İstanbul, Turkey (ethical approval no: 2020.265.IRB1.088).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NÇ, AÇ; data collection: NÇ, AÇ; analysis and interpretation of results: NÇ, AÇ; draft manuscript preparation: NÇ, AÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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