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Serial Cardiopulmonary Exercise Testing in Patients after Extracardiac Conduit Total Cavopulmonary Connection for Single-Ventricle Hearts: An Observational Study

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Objective To analyze the aerobic fitness and evolution of exercise tolerance in patients with single-ventricle physiology after total cavopulmonary connection (TCPC) with an extracardiac conduit (ECC).

Study design This retrospective cohort study included patients with previous ECC–TCPC who underwent cardiopulmonary exercise testing (CPET) between September 2010 and September 2019. Patients who completed at least 2 tests (≥6 months apart) with adequate levels of effort were recruited for the serial CPET evaluation.

Results We identified 70 patients (50% male) with a mean age of 6.45 ± 5.14 years at ECC–TCPC and 15.67 ± 5.03 years at the initial CPET. The peak oxygen consumption (peak VO_2) to predicted value (peak PD) was 55.90 ± 16.81%. Twenty of the 70 identified patients (50% male) were recruited for serial analysis. The average number of CPETs was 2.6 per patient. The average duration from the first CPET to the last CPET was 3.64 years. The peak VO_2 and PD increased slowly, with mean rates of 38.77 ± 129.01 mL/min and 1.66 ± 6.40%, respectively, during the study period.

Conclusions Although the patients had lower exercise tolerance after ECC–TCPC compared with their normal peers, exercise tolerance appears to have been preserved over the adolescent period in those who underwent serial testing after ECC–TCPC. *(J Pediatr 2021;■:1-8)*.

The Fontan procedure has become the preferred surgical strategy for managing patients with functional single ventricles since its introduction in the early 1970s.[1] With the evolution of the Fontan procedure, total cavopulmonary connection (TCPC) has been the preferred procedure for surgical palliation for more than 20 years.[2,3] TCPC uses either an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC) to connect the inferior vena cava to the pulmonary arteries, providing the advantages of stable hemodynamics and reduced atrium-related complications.[4,5] With its characteristics of lower operative mortality, a lower prevalence of early and late arrhythmias, improved hemodynamics, fewer postoperative complications, and applicability to various complex cardiac anatomies (especially those with heterotaxy syndrome with anomalous systemic or pulmonary venous return),[6,7] ECC–TCPC has become more popular than ILT-type reconstruction.

The reported clinical results of ECC–TCPC in patients with functional single-ventricle physiology have been satisfactory.[8] Our previously reported data show estimated event-free survival rates of 90.6% at 1 year, 89.3% at 5 years, and 77.2% at 10 years.[9] Patients after the Fontan procedure now commonly survive into adulthood with longer life expectancy. Over time, they acquire morbidities within and outside the cardiovascular system,[10] and numerous studies have documented significantly impaired exercise function of patients with post-Fontan circulation.[11-13]

BMI	Body mass index
ACSM	American College of Sports Medicine
BSA	Body surface area
CPET	Cardiopulmonary exercise testing
ECC	Extracardiac conduit
FEV1	Forced expiratory volume in 1 second
FEV1P	Percentage of forced expiratory volume in 1 second to predicted value
FVC	Forced vital capacity
FVCP	Percentage of forced vital capacity to predicted value
HR	Heart rate
ILT	Intra-atrial lateral tunnel
MET	Metabolic equivalent
MVV	Maximum voluntary ventilation
MVVP	Percentage of maximum voluntary ventilation to predicted value
OUES	Oxygen uptake efficiency slope
Peak PD	Percentage of peak oxygen consumption to predicted value
RER	Respiratory exchange ratio
TCPC	Total cavopulmonary connection
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption

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Most previous studies on this association were based on cross-sectional data, however; only 1 study performed serial cardiopulmonary exercise testing (CPET) in patients with previous Fontan surgery and concluded that the exercise function of patients with previous Fontan tends to decline, especially during late adolescence.[14] However, that study included data from patients after either ILT-type or ECC-type reconstruction. Therefore, the present study was conducted to better characterize and assess the natural history of the exercise capacity of patients after ECC–TCPC by serial testing.

Methods

In this retrospective cohort study, the data were obtained from a single medical center in southern Taiwan. We recruited all patients undergoing ECC–TCPC for single-ventricle physiology referred from the Pediatric Cardiovascular Surgery Department to the Rehabilitation Department between September 2010 and September 2019 for CPET, with the following additional inclusion criteria: subjects who underwent a complete transthoracic echocardiographic examination, a standard 12-lead electrocardiography, and a symptom-limited treadmill exercise test. The indications for ECC–TCPC in our institution are as follows: age >1 year, body weight >9 kg, mean pulmonary artery pressure <20 mmHg, ejection fraction >30%, and Nakata index >150 mm^2/m^2. Basic clinical characteristics, including sex, age, body weight, height, and dates of ECC–TCPC and CPET, were recorded. Complications, such as arrhythmias, protein-losing enteropathy, atrioventricular regurgitation, pulmonary artery stenosis, and late failure (ie, severe sequelae after ECC-TCPC necessitating reoperation), number of hospitalizations, and medications between the time of ECC–TCPC and CPET, were also recorded.

For serial analysis, all post-ECC–TCPC patients who had undergone at least 2 CPETs, separated by >6 months, between September 2010 and September 2019 were identified and selected. Only patients who achieved a respiratory exchange ratio (RER) at peak exercise of >1.05 were included in the serial analysis to ensure that they could expend good exercise efforts.[14] We also performed a subgroup analysis between patients whose heart rate (HR) at peak exercise (peak HR) was >85% or <85% of the age-predicted value to evaluate whether sinus node dysfunction after surgery would be a factor that limits peak exercise capacity over time. This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS17-CT11-11).

Each patient underwent a symptom-limited progressive exercise test, which included a treadmill, a flow module, a gas analyzer, and an electrocardiographic monitor (Metamax 3B; Cortex Biophysik). Before treadmill exercise testing, each patient was familiarized with the procedures and equipment used in the test. All patients underwent the exercise testing according to the ramped Bruce protocol suggested by the American College of Sports Medicine (ACSM). We terminated the test when the patients demonstrated subjective unbearable symptoms, when they could no longer continue, or when they attained maximal effort as indicated by the ACSM.[15] Exercise tests with a peak RER of >1.05 or peak HR of >85% of the predicted value during the test phase were considered maximally performed tests.[16]

Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured using the breath-by-breath method during the testing. In addition, blood pressure, HR, HR reserve (defined as peak HR minus baseline HR), and RER were measured throughout the exercise test. The anaerobic threshold (AT) was determined by the VE/VO_2 and VE/VCO_2 methods.[17] Peak VO_2 was the maximum oxygen uptake measured at peak exercise, and the measured VO_2 was divided by a constant, 3.5 mL $\times$ kg $-$ 1 $\times$ min—1, to derive metabolic equivalents (METs). The percent of peak VO_2 to predicted value (peak PD) was the percentage of the measured peak METs to the predicted peak METs after comparison with the normal standards for cardiopulmonary response to exercise in Taiwan.[18] The slope of ventilation vs CO_2 elimination (VE/VCO_2 slope) was measured from the second minute of the test phase until the respiratory compensation point was reached.[19] The equation $VO_2 = a \log(VE) + b$ was used, and the graphic slope of this equation was determined as oxygen uptake efficiency slope (OUES).[20] We calculated the OUES using the entire duration of exercise. Given the variable anthropometric changes in adolescents caused by their development, the OUES was normalized by the body surface area (BSA) as suggested.[21] The BSA was calculated as BSA (m^2) = 0.024265 $\times$ $Ht^{0.3964} \times Wt^{0.5378}$, where Ht is height in centimeters and Wt is weight in kilograms.[22]

A pulmonary function test was performed using spirometry at rest. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximal voluntary ventilation (MVV) were measured. We divided the measured FVC by the predicted FVC (FVCP), the measured FEV1 by the predicted FEV1 (FEV1P), and the measured MVV by the predicted MVV (MVVP). The predicted value of each variables by spirometry was calculated based on the spirometric reference equations for healthy adolescents in Taiwan.[23]

SPSS for Windows, version 19.0 (IBM) was used for all analyses. Continuous data were expressed as mean ± SD, and categorical variables were presented as absolute number and/or percentage. Normality and homoscedasticity were examined before each analysis. To compare the outcomes between the sexes, between different echocardiographic groups, and for the subgroup analysis between patients whose peak HR was >85% and <85% of the age-predicted value, the independent *t* test was used for normally distributed variables, and the Mann–Whitney *U* test was used for nonnormally distributed variables. For the differences between initial and final values for each exercise test variable, we used the paired Student *t* test to compare the data. Correlations of variables of CPET, echocardiographic findings, and clinical outcomes were examined using Pearson correlation analysis for normally distributed variables and Spearman correlation analysis for nonnormally distributed variables. A *P* value <.05 was considered to indicate statistical significance.

Results

Seventy-five patients who underwent ECC–TCPC during the inclusion period were identified and included. Five of them died, from ventricular dysfunction in 4 patients and pneumonia with sepsis in 1 patient. The medical records of the remaining 70 patients between the time of ECC–TCPC and the first CPET were reviewed. Follow-up was 100% complete, with a mean duration of 9.25 ± 6.10 years. Nine patients (12.9%) had atrial tachyarrhythmia, and 2 patients had complete atrioventricular block that necessitated permanent pacemaker implantation after ECC–TCPC. Seven patients (10%) required late reoperation, including atrioventricular valve surgery in 4 patients, pulmonary arteriovenous fistula exclusion in 1 patient, refenestration in 1 patient, and resection of a late left ventricular outflow tract obstruction in 1 patient.

Two antiplatelet drugs, aspirin and dipyridamole, were prescribed exclusively for thromboembolic prevention. Warfarin was added in 9 patients with supraventricular arrhythmia and 1 patient with previous mechanical atrioventricular valve replacement. The warfarin dose was titrated to maintain an international normalized ratio of 2.0-3.0. During the follow-up period, 1 conduit thrombosis was observed.

Among the 70 analyzed patients, the 3 most common diagnoses were heterotaxy (41.4%), tricuspid atresia (20.0%), and double-inlet single ventricle (12.9%) (**Table I**). On average, 2.1 palliative procedures were performed for each patient before ECC–TCPC completion. All patients underwent a bidirectional Glenn procedure before ECC–TCPC, which was performed at a mean age of 2.86 ± 3.02 years. The mean interval between the bidirectional Glenn procedure and ECC–TCPC completion was 3.59 ± 4.86 years. Regarding the echocardiographic features of the cohort before the first CPET, the mean fractional shortening was 39.91% ± 8.96%. Seven patients (10%) presented with moderate or severe atrioventricular regurgitation, 41 (58.6%) presented with pulmonary artery stenosis, and 12 (16.1%) still had Fontan fenestration before the first CPET.

Table I. Diagnosis and previous operative characteristics before ECC–TCPC

Characteristics	Value
Diagnosis, n (%)	
Heterotaxy, double-outlet right ventricle, complete atrioventricular septal defect	29 (41.4)
Tricuspid atresia	14 (20.0)
Double-inlet single ventricle	9 (12.9)
Pulmonary atresia with intact ventricular septum	6 (8.6)
Mitral atresia	3 (4.2)
Ebstein anomaly	3 (4.2)
Complete atrioventricular septal defect	2 (2.9)
Hypoplastic left heart syndrome	2 (2.9)
L-transposition of great arteries	2 (2.9)
Total	70 (100.0)
Previous procedures before ECC–TCPC, n	
Bidirectional Glenn shunt	70
Systemic pulmonary arterial shunt	37
Pulmonary artery banding	13
Pulmonary artery angioplasty	10
Atrial septectomy	8
Damus–Kaye–Stansel procedure	2
Repair coarctation	2
Atrioventricular valve repair	2
Bulboventricular resection	1
Atrioventricular valve replacement	1
Pulmonary vein angioplasty	1
Atriopulmonary anastomosis	1
Total (average n of procedures/patient)	148 (2.1)
Echocardiographic features before the first CPET	
Ventricular fractional shortening, %, mean ± SD	39.91 ± 8.96
Qualitative assessment of atrioventricular regurgitation, n (%)	
None or trivial	40 (57.1)
Mild	23 (32.9)
Moderate or severe	7 (10.0)
Pulmonary artery stenosis, n (%)	
No	29 (41.4)
Yes	41 (58.6)
Presence of a Fontan fenestration, n (%)	
No	58 (83.9)
Yes	12 (16.1)

The final analysis of cardiopulmonary function after ECC–TCPC for single ventricle was performed from the initial CPET of the 70 patients. The study cohort included 35 male (50.0%) and 35 female (50.0%) patients, with an average age of 6.45 ± 5.14 years at the time of ECC–TCPC and 15.67 ± 5.03 years at the first CPET. Male patients had a higher weight (*P* = .01) and body mass index (BMI) (*P* = .004) than female patients (**Tables II** and **III**). Considering aerobic fitness, both male and female patients after ECC–TCPC had significantly lower FVC, FEV1, MVV, and peak VO_2 than the norm predicted values. The overall mean peak HR was 153.49 ± 24.56 bpm, the mean VE/VCO_2 slope was 32.15 ± 7.54, the mean peak MET was 6.74 ± 1.88, and the mean peak PD was 55.90 ± 16.81%. The male patients had higher FVC (*P* = .001), FEV1 (*P* = .001), and MVV (*P* = .034) values compared with the female patients, whereas the female patients had a higher peak PD (*P* < .001) and peak RER (*P* = .024) (**Table IV**). Comparisons of findings of the initial CPET between different echocardiographic variables and the correlation analysis between variables of the initial CPET and ventricular fractional shortening by echocardiography are provided in **Table V** (available at www.jpeds.com). No significant differences or correlations were found.

Serial CPET data were available for 35 patients; of these, 5 patients were excluded from the analysis owing to suboptimal effort, with an RER of <1.05. Therefore, the study population for serial analysis comprised 30 patients. Among these 30 patients, 20 (subgroup 1) had a peak HR of >85% of the age-predicted value, whereas the remaining 10 patients did not (subgroup 2). The average number of exercise tests was 2.8 per patient. The demographic and clinical features

Table II. Demographic characteristics of patients with single-ventricle physiology after ECC–TCPC

Characteristics	Fontan total (N = 70)	Fontan males (N = 35)	Fontan females (N = 35)	*P* value*
Age at CPET, y	15.67 ± 5.03	15.11 ± 4.68	16.23 ± 5.38	.358
Age at Fontan, y	6.45 ± 5.14	6.13 ± 5.46	7.09 ± 4.44	.211
Time from Fontan to first CPET, y	9.25 ± 6.10	9.08 ± 5.02	9.42 ± 5.12	.390
Height, cm	152.83 ± 21.62	153.07 ± 27.99	152.60 ± 12.85	.929
Weight, kg	50.43 ± 17.79	55.85 ± 20.71	45.02 ± 12.36	**.01**
BMI, kg/m^2	19.44 ± 4.07	22.53 ± 5.78	19.07 ± 3.32	**.004**
Resting HR, bpm	86.19 ± 15.96	86.66 ± 18.73	85.71 ± 12.87	.807

Data are mean ± SD. Significant *P* values are in bold type.
*Mann–Whitney *U* test (continuous variables) or χ^2 test (categorical variables) between the sexes.

of the study cohort did not differ significantly from those of the 5 patients with serial studies who did not meet the inclusion criteria. The average age at receipt of ECC–TCPC was 6.52 ± 4.44 years, and that at the first CPET was 14.38 ± 5.47 years. The average interval from the first CPET to the last CPET was 3.63 years. No significant differences in demographic and clinical features were observed between subgroups 1 and 2 (**Table III**).

The mean BMI was 20.83 ± 4.71 kg/m^2 (normal range, 18.5-24.9 kg/m^2) at the time of the initial exercise test and 21.86 ± 4.94 kg/m^2 at the final exercise test, showing no significant change (*P* = .116). The peak VO$_2$ and peak MET, although lower than the predicted values, showed no significant change on the final exercise test compared with the earliest exercise test. Peak VO$_2$, peak MET, and peak PD increased slowly during the study period, with mean values of 40.34 ± 140.11 mL/min, 0.12 ± 0.79, and 1.66% ± 6.40% per year, respectively. Significant changes were observed only in the OUES, FVCP, and FEV1P values; all were higher at the final CPET compared with the first CPET (*P* = .007 for OUES, *P* = .001 for FVCP, and *P* < .001 for FEV1P). No significant changes were observed in any of the other exercise variables studied (**Table VI**). Correlations between measures of the initial CPET and clinical variables are provided in **Table VII** (available at www.jpeds.com); no significant correlations were found.

A subgroup comparison between patients with peak HR >85% of the age-predicted value (subgroup 1) and those with peak HR <85% of the age-predicted value (subgroup 2) found no significant differences in CPET variables and pulmonary function at the first and last CPETs, with the exception of a higher peak PD in subgroup 1 at the first CPET (*P* = .004) at the first CPET. Peak VO$_2$ and peak PD increased slowly during the study period in both subgroups. No significant differences in the annual change in CPET variables and pulmonary function values were observed between the subgroups, with the exception of increased FVCP at a rate of 5.69 ± 4.86% per year in subgroup 1 and decreased FVCP at a rate of −4.81 ± 10.79% per year in subgroup 2 (*P* = .029) (**Table VI**).

Discussion

CPET has emerged as a potential tool for risk stratification and prognosis in patients who undergo the Fontan procedure.[24] Various parameters measured during CPET, including peak HR, peak VE/VCO$_2$ slope, VO$_2$ at peak exercise effort, and anaerobic threshold, have been correlated with mortality, morbidity, cardiac adverse events, and risk of heart transplantation in these patients. Patients post-Fontan procedure had significantly lower peak HR compared with controls.[25] A peak HR of <111.5 bpm was significantly associated with an increased risk of mortality or new morbidity.[26] The overall mean peak HR in our study cohort was 153.49 ± 24.56 bpm. We did not observe a significant decline in mean peak HR at the final CPET compared with that at the first CPET (150.67 ± 30.12 bpm vs 156.33 ± 21.12 bpm; *P* = .416).

The VE/VCO$_2$ slope, which indicate the efficiency of gas exchange during exercise, correlates strongly with exercise capacity and can serve as a sensitive predictor of mortality in patients with congenital heart disease or congestive heart failure.[27] It has been noted to be increased in patients post-Fontan procedure.[28] Fernandes et al found that a VE/VCO$_2$ slope of >31.5 is significantly associated with an increased risk of mortality, hospitalization, chronic heart failure, thrombosis, and protein-losing enteropathy in patients post-Fontan procedure.[26] The overall mean VE/VCO$_2$ slope

Table III. Demographic characteristics of the subgroup with serial CPET

Characteristics	Fontan total (N = 30)	HR >85% of predicted (N = 20)	HR <85% of predicted (N = 10)	*P* value*
Age at CPET, y	14.38 ± 5.54	15.50 ± 5.73	12.60 ± 4.99	.200
Age at Fontan, y	6.52 ± 4.44	6.84 ± 4.37	5.87 ± 4.80	.625
Time from Fontan to first CPET, y	7.79 ± 3.25	8.66 ± 3.26	6.63 ± 2.98	.154
Time from first to last CPET, y	3.63 ± 1.61	3.63 ± 1.26	3.65 ± 2.14	.970

Data are mean ± SD.
*Mann–Whitney *U* test (continuous variables) or χ^2 test (categorical variables) between HR >85% of predicted and HR <85% of predicted.

Table IV. Findings of the initial CPET in patients with single-ventricle physiology after ECC–TCPC

Variables	Fontan total (n = 70)	Fontan males (n = 35)	Fontan females (n = 35)	*P* value*
FVC, L	2.32 ± 0.92	2.68 ± 1.04	1.92 ± 0.55	**.001**
FVCP, %	71.75 ± 17.48	75.74 ± 19.64	67.35 ± 13.76	.056
FEV1, L	1.96 ± 0.78	2.25 ± 0.89	1.63 ± 0.48	**.001**
FEV1P, %	69.33 ± 18.29	73.59 ± 19.94	64.66 ± 15.28	.052
FEV1/FVC, %	85.22 ± 10.20	84.88 ± 8.70	85.60 ± 11.77	.781
MVV, L	59.14 ± 22.84	64.73 ± 24.34	52.58 ± 19.36	**.034**
MVVP, %	61.14 ± 34.16	63.13 ± 34.59	58.71 ± 34.13	.622
AT MET	4.85 ± 1.36	4.83 ± 1.53	4.87 ± 1.19	.889
AT HR, bpm	123.97 ± 18.90	121.20 ± 21.63	126.74 ± 15.54	.223
Peak MET	6.74 ± 1.88	6.71 ± 2.02	6.78 ± 1.76	.880
Peak VO_2	1166.44 ± 458.47	1265.64 ± 534.30	1045.19 ± 312.83	.063
% of peak predicted	55.90 ± 16.81	46.67 ± 13.03	65.13 ± 15.10	**<.001**
Peak HR, bpm	153.49 ± 24.56	149.89 ± 28.24	157.09 ± 20.00	.223
HRR	21.81 ± 14.96	24.59 ± 18.61	18.52 ± 8.09	.102
Peak RER	1.11 ± 0.10	1.09 ± 0.08	1.14 ± 0.11	**.024**
Peak SBP, mmHg	152.61 ± 29.05	157.20 ± 27.72	147.88 ± 30.04	.185
Peak DBP, mmHg	76.22 ± 16.10	78.97 ± 17.08	73.38 ± 14.74	.151
OUES	1.61 ± 0.63	1.72 ± 0.66	1.49 ± 0.59	.211
VE/VCO_2	32.15 ± 7.54	32.58 ± 8.44	31.60 ± 6.41	.663

AT, anaerobic threshold; *DBP*, diastolic blood pressure; *HRR*, heart rate reserve; *SBP*, systolic blood pressure.
Data are mean ± SD. Significant *P* values are in bold type.
*Mann–Whitney *U* test between the sexes.

in this study was 32.15 ± 7.54. We observed an increase in mean VE/VCO_2 slope from 31.39 ± 10.20 to 33.50 ± 8.50 in the serial CPETs, a non–statistically significant change ($P = .578$).

Previous studies have proven that exercise impairment is always present in patients after Fontan circulation, and that peak VO_2 can serve as a good predictor for outcomes after Fontan surgery.[24] A large single-center study found that a peak VO_2 of <21.0 mL/kg/min independently predicted mortality,[25] whereas another study reported that a peak VO_2 of <16.6 mL/kg/min is predictive of mortality.[26] The overall peak VO_2 in the present study was 23.59 mL/kg/min, much higher than the cutoff values for predicting mortality in each of the aforementioned studies. The mean age of the patients in this study at CPET was also lower than that in both of those studies. In healthy individuals, peak VO_2 normally increases during adolescence. Therefore, we can speculate that patients receiving ECC–TCPC have better clinical outcomes than those treated with the traditional approach.

Several cross-sectional studies on patients post-Fontan circulation have reported that these patients tend to have a more compromised exercise function with increasing age.[12,13,29] Although the reason for this decline is likely multifactorial, one factor may the cardiovascular system's inability to meet the metabolic demands of the increased muscle mass during exercise, similar to that seen in patients post-Fontan growing into adolescence and adulthood.[30] Unlike healthy peers with normal biventricular circulation, these patients' ability to increase cardiac output during exercise is limited, and thus the increased peak VO_2 normally associated with puberty is attenuated, resulting in a decreased peak PD.[14,25]

Few previous studies have evaluated the early- to mid-term follow-up data of patients receiving ECC–TCPC. In studies that have been published, either the study populations with contemporary TCPC were small or the studies combined the exercise data of patients who had undergone surgery with an older technique, such as single-stage TCPC or atriopulmonary connection.[19] In a single-center study in Japan involving 321 ECC–TCPC recipients (mean age at CPET, 13.3 ± 5.2 years), Nakano et al found that the overall cardiopulmonary exercise capacity was well maintained in these patients compared with their age- and sex-matched control subjects.[30] In a cross-sectional multicenter study in The Netherlands, Bossers et al found a mean peak VO_2 of 77 ± 15% of the predicted value in 51 post-ECC–TCPC recipients (mean age at CPET, 11.8 ± 2.1 years).[19] However, the post-Fontan procedure patients in our present study were older and had a lower peak VO_2 compared with the patients in those 2 studies. We performed serial CPET follow-up in patients after ECC–TCPC in an interval of <5 years from the first CPET to the last CPET. The mean patient age at the last CPET was <18 years. We could not ascertain whether the maintenance of a peak VO_2 similar to that in aging to adolescence in the patients who underwent ECC–TCPC resulted solely from the advantages of ECC–TCPC or from an inadequate follow-up period. In addition, only 30 patients from the original 70 patients underwent serial CPETs in the follow-up period. The medical records of the original 70 patients could be traced only from the beginning to the date at which they underwent the first CPET. There might be late morbidities and even mortality, or their cardiopulmonary function may become too severely impaired to allow subsequent CPET after the first CPET. Because this is a retrospective study, the reasons why the remaining 40 patients did not undergo serial CPET follow-up were difficult to clarify. In addition, the 30 patients who underwent serial CPETs may have come from high-income families (which might push more outdoor activities and sports), or only those who were active in sports may have agreed to do the symptom-limited exercise testing.[31,32] We can only conclude

Table VI. Comparison of the initial and final CPET data in patients after ECC–TCPC

Variables	First CPET	Last CPET	*P* value[*]	Change per year
Peak VO_2, mL/min				
Total	1088.69 ± 269.08	1163.58 ± 467.64	.233	38.77 ± 129.01
HR >85% of predicted	1163.74 ± 251.35	1251.36 ± 477.59	.174	35.23 ± 104.70
HR <85% of predicted	968.91 ± 264.20	1023.13 ± 473.83	.685	44.43 ± 167.04
P value[†]	.071	.233		.864
Peak MET				
Total	6.76 ± 1.50	7.02 ± 2.29	.581	0.12 ± 0.79
HR >85% of predicted	6.79 ± 1.35	7.03 ± 1.63	.502	0.12 ± 0.56
HR <85% of predicted	6.71 ± 1.79	7.00 ± 3.18	.798	0.13 ± 1.10
P value[†]	.901	.979		.977
Peak VO_2, % of predicted				
Total	54.77 ± 16.97	58.17 ± 12.97	.210	1.67 ± 5.68
HR >85% of predicted	56.82 ± 17.23	59.21 ± 14.21	.183	1.67 ± 3.86
HR <85% of predicted	51.26 ± 15.32	55.65 ± 10.66	.153	1.66 ± 8.06
P value[†]	**.004**	.509		.995
VO_2 at AT, mL/min				
Total	781.30 ± 183.23	989.58 ± 401.01	**.012**	71.57 ± 124.01
HR >85% of predicted	808.31 ± 146.87	1036.88 ± 299.34	**.001**	75.95 ± 106.93
HR <85% of predicted	738.09 ± 232.24	913.91 ± 535.74	.376	64.60 ± 153 054
P value[†]	.352	.458		.826
MET at AT				
Total	4.83 ± 1.07	5.07 ± 1.68	.523	0.13 ± 0.55
HR >85% of predicted	4.70 ± 0.74	4.98 ± 0.89	.265	0.13 ± 0.44
HR <85% of predicted	5.03 ± 1.48	5.21 ± 2.54	.848	0.12 ± 0.73
P value[†]	.524	.783		.970
VE/VCO_2 slope				
Total	31.96 ± 10.36	33.05 ± 8.35	.667	1.90 ± 8.83
HR >85% of predicted	33.10 ± 11.13	32.16 ± 8.44	.456	−0.31 ± 1.20
HR <85% of predicted	29.68 ± 9.35	34.84 ± 8.82	.514	6.33 ± 15.26
P value[†]	.504	.638		.386
OUES				
Total	1.48 ± 0.45	1.82 ± 0.70	**.007**	0.13 ± 0.17
HR >85% of predicted	1.60 ± 0.38	1.88 ± 0.72	.053	0.12 ± 0.20
HR <85% of predicted	1.24 ± 0.51	1.72 ± 0.73	.090	0.14 ± 0.11
P value[†]	.176	.244		.907
Peak HR, bpm				
Total	161.46 ± 19.43	154.12 ± 27.78	.163	0.33 ± 19.96
HR >85% of predicted	173.00 ± 6.47	161.88 ± 20.58	**.032**	−3.01 ± 5.32
HR <85% of predicted	143.00 ± 19.06	141.70 ± 34.05	.909	5.67 ± 31.74
P value[†]	**.001**	.114		.413
HRR, bpm				
Total	22.25 ± 11.09	19.83 ± 10.35	.354	1.95 ± 19.65
HR >85% of predicted	22.86 ± 7.34	19.00 ± 9.61	.199	−2.08 ± 6.40
HR <85% of predicted	21.40 ± 15.31	21.00 ± 11.75	.935	8.41 ± 30.48
P value[†]	.853	.651		.191
FVC, % of predicted				
Total	68.39 ± 14.39	79.35 ± 17.25	**.001**	1.87 ± 8.95
HR >85% of predicted	65.14 ± 5.91	83.01 ± 11.29	**<.001**	5.69 ± 4.86
HR <85% of predicted	74.08 ± 22.32	72.93 ± 24.12	.785	−4.81 ± 10.79
P value[†]	.379	.190		**.029**
FEV1, % of predicted				
Total	66.23 ± 11.95	82.81 ± 18.85	**<.001**	3.42 ± 11.55
HR >85% of predicted	66.94 ± 5.60	87.60 ± 11.20	**<.001**	7.05 ± 7.28
HR <85% of predicted	64.98 ± 19.17	74.43 ± 26.58	.208	−2.93 ± 15.16
P value[†]	.677	.091		.115
MVV, % of predicted				
Total	66.85 ± 11.95	70.10 ± 18.30	.765	1.99 ± 15.40
HR >85% of predicted	62.01 ± 30.84	73.51 ± 15.72	.307	5.89 ± 11.30
HR <85% of predicted	76.53 ± 26.58	63.27 ± 22.34	.601	−5.81 ± 20.18
P value[†]	.322	.187		.192
BMI				
Total	20.83 ± 4.53	21.86 ± 4.94	.116	
HR >85% of predicted	20.81 ± 4.30	22.24 ± 3.89	**.005**	
HR <85% of predicted	20.85 ± 5.28	21.49 ± 5.98	.578	
P value[†]	.985	.596		

Data are mean ± SD. Significant *P* values are in bold type.
*Paired-*t* test between the first and the last CPET.
†Independent *t*-test (normally distributed variables) or Mann–Whitney *U*-test (non-normally distributed variables) between HR >85% of predicted and HR <85% of predicted.

that aerobic fitness seems to be preserved throughout adolescence in those who underwent serial testing after ECC–TCPC.

Patients after ECC–TCPC had significantly higher OUES, FVCP, and FEV1P at the last CPET compared with the first CPET. Peak VO_2 and peak MET were not included in these significant changes. Peak VO_2 measures the amount of oxygen extracted from the lungs at the point of peak exercise, whereas the OUES incorporates cardiovascular and peripheral factors that determine oxygen uptake and pulmonary factors that influence the ventilatory response to increased metabolic acidosis during incremental exercise.[33] Traditionally, patients post-Fontan procedure have a significant ventilation–perfusion mismatch, resulting in an increased physiological dead space–to–tidal volume ratio. This mismatch leads to a slow increment of oxygen consumption at the onset of exercise and accelerated low-efficiency ventilation during exercise, which presents as a lower OUES value than is seen in healthy peers. Contrary to previous findings, we observed better OUES, FVCP, and FEV1P in the serial follow-up. Post-Fontan procedure patients with fenestration patency have a greater decrease in oxygen saturation from rest to peak exercise and a higher physiological dead space at peak exercise.[34] During a medical review, we found that in the serial CPET follow-up, 6 of the 30 patients had Fontan fenestration at the first CPET, whereas none had Fontan fenestration at the last CPET. The lack of Fontan fenestration at the last CPET might contribute to these findings. Another factor might be cohort selection bias, as discussed previously, given that the patients undergoing serial CPETs represented less than one-half of the original population.

This study must be viewed in light of the following limitations. First, we only recruited patients from one medical center in southern Taiwan, and our results might be generalizable only to similar populations. Second, the equipment used in the CPET and the interpretation of CPET results in this study might differ from those in other studies. However, previous studies demonstrated that the results of exercise testing are not center-specific, and all studies adhered to the ACSM guidelines. Comparing the results of this study with those of other studies should be done cautiously. Third, although our sample size was larger than the minimum size required for statistical analyses, it was still small, especially the number of patients who underwent serial CPET follow-up. Finally, the interval from the first CPET to the last CPET in our serial evaluation was <5 years, and the mean patient age at the last CPET was <18 years. Future cross-national studies with larger sample sizes and longer follow-up periods are needed for further evaluation. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table V. Comparisons of findings of the initial CPET for different echocardiographic variables and correlation between variables of CPET results and ventricular fractional shortening by echocardiography

Variables	Non-mild AVR (n = 63)	Moderate-severe AVR (n = 7)	*P* value*	Non-PA stenosis (n = 29)	PA stenosis (n = 41)	*P* value*	Ventricular fractional shortening†
FVC, L	2.36 ± 0.92	2.02 ± 0.52	.545	2.41 ± 1.12	2.30 ± 0.82	.736	0.235
FVCP, %	71.75 ± 18.37	74.20 ± 6.29	.821	72.73 ± 20.30	71.63 ± 16.97	.864	0.248
FEV1, L	1.98 ± 0.78	1.58 ± 0.73	.398	1.91 ± 0.90	1.97 ± 0.74	.829	0.304
FEV1P, %	68.84 ± 18.62	63.93 ± 8.60	.657	65.27 ± 16.01	69.71 ± 18.89	.496	0.377
MVV, L	58.04 ± 22.83	43.90 ± 12.94	.300	52.82 ± 25.40	58.58 ± 21.44	.478	0.293
MVVP, %	52.65 ± 18.99	50.93 ± 7.90	.878	46.55 ± 15.42	54.87 ± 19.07	.206	0.257
AT MET	5.06 ± 1.44	4.80 ± 0.96	.724	4.86 ± 1.16	5.10 ± 1.48	.636	0.079
Peak MET	7.02 ± 1.96	7.03 ± 2.19	.994	6.62 ± 1.53	7.15 ± 2.08	.451	−0.069
Peak VO_2	11 987.59 ± 504.62	1101.81 ± 581.59	.720	1112.12 ± 364.91	1215.69 ± 546.58	.562	0.200
% of peak predicted	57.27 ± 16.77	55.07 ± 16.47	.803	50.87 ± 17.11	59.14 ± 16.11	.153	−0.256
Peak RER	1.09 ± 0.07	1.14 ± 0.13	.240	1.11 ± 0.08	1.09 ± 0.08	.449	0.188
OUES	1.68 ± 0.68	1.57 ± 0.55	.772	1.67 ± 0.55	1.68 ± 0.71	.98	0.251
VE/VCO_2	33.13 ± 7.64	30.53 ± 0.76	.566	33.02 ± 6.78	32.86 ± 7.67	.955	

AVR, atrioventricular regurgitation.
Data are mean ± SD.
*Mann-Whitney *U* test between 2 groups.
†Rho coefficient factor by Pearlman correlation analysis.

Table VII. Correlation between parameters of the initial CPET and clinical parameters

CPET parameters	Late failure*	Protein-losing enteropathy	Atrioventricular regurgitation	Pulmonary artery stenosis	Arrhythmia	Number of hospitalizations
Peak VO_2	0.006	−0.179	0.013	0.091	−0.097	−0.219
P value	.968	.240	.934	.551	.524	.105
Peak MET	0.006	−0.179	0.013	0.091	−0.097	−0.043
P value	.968	.240	.934	.551	.524	.752
Peak PD	−0.089	−0.080	−0.024	0.186	−0.002	−0.219
P value	.562	.604	.875	.221	.991	.105
OUES	−0.180	−0.173	−0.051	0.004	−0.110	−0.139
P value	.302	.221	.772	.981	.529	.363
VE/VCO_2	0.041	0.150	−0.101	−0.010	−0.269	0.130
P value	.816	.389	.566	.955	.119	.394

Data are presented as coefficient factor.
*Late failure refers to severe sequelae after ECC–TCPC necessitating reoperation.