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Serial Cardiopulmonary Exercise Testing in Patients with Previous Fontan Surgery

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Abstract

Patients with previous Fontan surgery have reduced peak oxygen consumption (V_{O_2}), and data regarding progression of exercise intolerance is limited. The purpose of this study was to assess the evolution of exercise tolerance in patients with previous Fontan surgery. We performed a retrospective cohort study of patients with previous Fontan surgery who underwent cardiopulmonary exercise testing between November 2002 and January 2009. Patients were required to have completed at least two tests, with adequate levels of effort, 6 months apart. We identified 78 patients (55% male) who had undergone a total of 215 cardiopulmonary exercise tests. Age at initial study was 19.7 ± 10.2 years; time interval since previous Fontan surgery 13.3 ± 5.7 years; and time interval between the initial and the most recent exercise test was 3.0 ± 1.4 years. Morphologic left ventricle was present in 58 (74.4%) patients. At baseline, peak V_{O_2} averaged 24.7 ± 7.0 ml/kg/min ($63.7\% \pm 15.8\%$ predicted). At most recent study, peak V_{O_2} averaged 23.2 ± 7.2 ml/kg/min, ($60.4\% \pm 13.9\%$ predicted). Percent predicted peak V_{O_2} declined slowly, with a mean rate of decline of 1.25 ± 0.36 percentage points/y ($p < 0.001$). Most of the decline occurred in patients < 18 years of age (mean rate of decline 1.78 ± 0.46 percentage points/y; $p = 0.0004$). Thereafter, the rate of decline was less marked (mean rate of decline 0.54 ± 0.57 percentage points/y; $p =$ not significant). Ventricular morphology, type of Fontan procedure, and cardiac medications were not predictive of progressive exercise intolerance. In conclusion, although the exercise function of previous Fontan patients tends to decline during late adolescence, it appears to stabilize during early adulthood.

Keywords

Congenital heart disease; Exercise tests; Fontan procedure

Introduction

Since its introduction in the early 1970s the Fontan procedure has become the preferred surgical strategy for the management of patients with functional single ventricles [6]. Although this innovation has improved life expectancy, numerous studies have documented

that the exercise function of patients with post-Fontan circulation is significantly impaired [5, 7, 9, 10, 14–16, 19]. Some of these studies have found an association between exercise dysfunction and increased age [5, 7, 15, 16]. However, in general, evidence for this association has come from cross-sectional studies and has not been based on data from serial exercise tests. Consequently, the extent to which the observed association between age and exercise dysfunction is attributable to an era effect (i.e., younger patients having had surgery and medical care more recently and therefore benefiting from recent technologic and therapeutic advances) rather than a time-related deterioration in exercise capacity, remains uncertain.

Since 2002, our institution has incorporated exercise testing with expiratory gas analysis into the routine clinical assessment of children, adolescents, and adults with post-Fontan circulation. Therefore, we have accumulated a unique database of serial exercise test data. The purpose of this study was to better characterize the natural history of the post-Fontan patient's exercise function as assessed by serial testing.

Methods

We conducted a retrospective cohort study of patients with previous Fontan surgery who underwent cardiopulmonary exercise testing between November 2002 and January 2009. The study was approved by the Committee on Clinical Investigation at Children's Hospital.

Patients

The database of the exercise physiology laboratory at Children's Hospital was reviewed, and all post-Fontan patients who had undergone at least two exercise tests with expiratory gas analysis, separated by at least 6 months, between November 2002 and January 2009, were identified. To exclude studies in which a patient did not expend a good effort, or in which the patient terminated exercise before reaching the cardiovascular limit, only studies in which the patient achieved a respiratory exchange ratio at peak exercise >1.05 , or a heart rate at peak exercise $>85\%$ predicted, were included in the analyses.

Exercise Protocol

Each subject underwent a symptom-limited, progressive exercise test [21]. Most patients (81%) exercised on a stationary cycle ergometer using a ramp protocol. The steepness of the ramp was selected according to the patient's size and estimated level of fitness, aiming to attain the patient's peak work rate within 8 to 12 minutes. The remainder of the patients exercised on a treadmill using the standard Bruce protocol [4]. Each individual patient used the same type of exercise equipment on all exercise tests. Electrocardiographic monitoring and breath-by-breath expiratory gas analysis were performed using the CardiO2 exercise testing system (Medical Graphics, Minneapolis, MN). Cuff blood pressure determinations and complete 12-lead electrocardiograms were obtained at 2- to 3-minute intervals during exercise, at peak exercise, and at 1, 3, and 5 minutes after exercise. Pulse oximetry oxygen saturation was also monitored throughout the study. Immediately before each exercise test, spirometric measurements of the patients' forced vital capacity (FVC) and volume of air

exhaled in first second of forced expiration (FEV_1) were also obtained. The exercise testing system was calibrated according to the manufacturer's specifications before each test.

The time-related change in peak oxygen consumption (V_{O_2}) was the primary outcome variable for the study. Because of the variation in patient age, size, and sex in our cohort, and because many of our subjects grew significantly and underwent pubertal-related changes in stature and body habitus during the study period, our analyses focused primarily on changes in % predicted values [3, 13] for peak V_{O_2} (and other variables subject to similar considerations) rather than changes in the absolute magnitude or weight-normalized values of this variable. Secondary-outcome parameters of exercise performance included changes in % of predicted (% predicted) peak heart rate attained, % predicted oxygen pulse at peak exercise (O_2 pulse, a surrogate for forward stroke volume at peak exercise [12]), minute ventilation-versus-carbon dioxide production (V_E/V_{CO_2}) slope (an index of the efficiency of gas exchange during exercise [20]), oxygen saturations at rest and at peak exercise, and spirometric measurements.

Clinical Variables

Clinical data were extracted from the medical records of each patient. Clinical variables recorded for each patient included cardiac anatomic diagnosis, ventricular morphology, type of initial Fontan, age at initial Fontan, status of fenestration (at the time of initial exercise test), and cardiac medication regimen at time of exercise test. We also calculated the body mass index [BMI; i.e., (weight in kg)/(height in m)²] at the time of each exercise test.

Statistical Analysis

Paired Student *t* test was used to compare the initial and final values for each exercise test variable. The relation between peak V_{O_2} versus time since first exercise test was modeled with a linear mixed-effects model containing random intercepts and slopes. To identify factors associated with steeper decline in exercise function, the linear regression line of each exercise test variable served as each patient's measure of rate of change with time. The univariate association between mean rate of change in peak V_{O_2} and dichotomous clinical variables was assessed using two-sample *t* tests. In this and subsequent analyses, observations were weighted by the amount of time between first and last exercise tests to account for varying amounts of follow-up. Pearson's correlation coefficient was used to evaluate the relation between rate of change in peak V_{O_2} and various continuous clinical and exercise test variables. Variables with a univariate $p < 0.2$ were considered for inclusion in a multivariate linear regression model; $p < 0.05$ was considered statistically significant. Analyses were performed using SAS software, version 9.1 of the SAS System for Windows (SAS, Cary, NC).

Results

A total of 288 patients with previous Fontan surgery who had undergone a cardiopulmonary exercise study during the inclusion period were identified. Serial data was available on 98 of these patients. Twenty patients were excluded due to suboptimal effort and/or an interval <6 months between the first and last tests; the study population was comprised of the remaining

78 patients (Table 1). The majority had undergone their Fontan surgery before 4 years of age, and most had undergone lateral tunnel repairs; 44 (56%) were <18 years old at the time of their initial exercise study. A total of 215 qualifying exercise tests (2.8 tests/patient) were available for analysis. The demographic and clinical features of the study cohort did not differ significantly from those of the 20 patients with serial studies who did not meet inclusion criteria.

At the time of their initial exercise tests, the patients' BMIs averaged $21.3 \pm 4.0 \text{ kg/m}^2$ (normal value 18.5 to 24.9 kg/m^2). BMI at the final exercise test was significantly higher ($22.6 \pm 4.1 \text{ kg/m}^2$; $p < 0.0001$) but remained within the normal range.

The patients' peak $\dot{V}_{O_2}$ and O_2 pulse were significantly lower on the final exercise test compared with the earliest exercise test, with a mean time interval of 3.0 ± 1.4 years (Table 2). A small decline in resting oxygen saturation was also detected. Significant changes were not observed in any of the other exercise variables studied.

Peak $\dot{V}_{O_2}$ declined slowly during the course of the study period, with a mean rate of decline of 1.25 ± 0.36 (SE) percentage points/y ($p < 0.001$). Most of the decline occurred in patients < 18 years of age (mean rate of decline 1.78 ± 0.46 percentage points/y, $p = 0.0002$). Thereafter, the rate of decline was less marked (mean rate of decline 0.54 ± 0.57 percentage points/y, $p = \text{not significant}$; Fig. 1).

Predictors of Faster Decline in Peak $\dot{V}_{O_2}$

Ventricular morphology, type of Fontan, and cardiac medications were not predictive of progressive exercise intolerance (Table 3). Bivariate correlation analysis showed a strong association between decline in peak $\dot{V}_{O_2}$ and decline in O_2 pulse (Table 4). In contrast, the relation between decline in peak $\dot{V}_{O_2}$ and decline in peak HR was weak. Changes in BMI, oxygen saturation, or baseline spirometric value also did not correlate with concomitant changes in peak $\dot{V}_{O_2}$. However, decline in peak $\dot{V}_{O_2}$ was associated with increased (worsening) $\dot{V}_E/\dot{V}_{CO_2}$ slope. The decline in peak $\dot{V}_{O_2}$ was also most pronounced among patients whose peak $\dot{V}_{O_2}$ was relatively well preserved on the initial study.

On multivariate analysis (Table 5), decline in peak O_2 pulse remained the strongest correlate of decline in peak $\dot{V}_{O_2}$. In addition, decline in peak HR, increase in $\dot{V}_E/\dot{V}_{CO_2}$ slope, higher initial peak $\dot{V}_{O_2}$, and male sex emerged as significant correlates of decline in peak $\dot{V}_{O_2}$.

Our data indicate that the exercise capacity of Fontan patients declines steeply, relative to normal predicted values, during late childhood and adolescence. The decline is much more gradual during early adulthood.

Reasons for the steep decline during childhood and adolescence remain to be defined. One likely factor implicates the large increase in skeletal muscle mass that is normally associated with puberty. In normal individuals, this increase in muscle mass is accompanied by a commensurate increase in the ability to augment cardiac output (and oxygen delivery) during exercise. Consequently, peak $\dot{V}_{O_2}$ (in ml/min) normally increases dramatically during the course of the adolescent years. However, unlike patients with normal, biventricular

circulation, the Fontan patient's ability to increase cardiac output during exercise is limited. The increased peak $\dot{V}_{O_2}$ normally associated with puberty is therefore attenuated, resulting in decreased % predicted values (i.e., the Fontan patient's peak $\dot{V}_{O_2}$ relative to that of normal subjects). The fact that the decline in peak $\dot{V}_{O_2}$ is more pronounced among male subjects may reflect the fact that the increase in muscle mass associated with male puberty typically exceeds that associated with female puberty.

Exercise function normally decreases progressively during adulthood. After adolescence, peak $\dot{V}_{O_2}$ typically decreases by approximately 0.7%/y [11]. The data from the current study imply that the decrease in peak $\dot{V}_{O_2}$ in adults with post-Fontan circulation tends to parallel that of normal subjects, albeit at a significantly lower level of function.

Decreased O_2 pulse at peak exercise, which is suggestive of a progressive inability to augment stroke volume appropriately during exercise, was the most important factor accounting for decreased peak $\dot{V}_{O_2}$. A decrease in heart rate at peak exercise also emerged as a factor related to the decreased peak $\dot{V}_{O_2}$. However, in this series, the time-related decrease in peak exercise heart rate was less pronounced than the decrease in O_2 pulse at peak exercise. These observations emphasize the deleterious effects that an impaired chronotropic response can have on exercise performance in individuals with post-Fontan circulation.

The $\dot{V}_E/\dot{V}_{CO_2}$ slope is a measure of the efficiency of gas exchange during exercise. It has been found to correlate strongly with exercise capacity [2] and to be a sensitive predictor of mortality in patients with tetralogy of Fallot [8] as well as in patients with congestive heart failure [1, 17]. It has also been noted to be increased among post-Fontan patients [18, 19]. Therefore, our observation that progressively increased $\dot{V}_E/\dot{V}_{CO_2}$ slope was also associated with decreased peak $\dot{V}_{O_2}$ in Fontan patients is not surprising and underscores the potential clinical importance of this physiologic measurement. The mechanisms responsible for this observation deserve further study.

Patients with the highest peak $\dot{V}_{O_2}$ on their initial exercise tests tended to experience the greatest subsequent decrease in peak $\dot{V}_{O_2}$. This observation was undoubtedly due in part to the fact that younger patients (i.e., those most likely to experience a decline in % predicted peak $\dot{V}_{O_2}$) were disproportionately represented among patients with high initial peak $\dot{V}_{O_2}$. We believe that it also reflects the fact that post-Fontan patients with well preserved exercise function are uncharacteristic and that regression to the mean is their typical fate.

Comparison with Past Studies

Several cross-sectional studies of patients with post-Fontan circulation have reported that older patients tend to have more compromised exercise function. In a study of 166 pediatric patients (6 to 18 years of age) who expended a maximal effort, Paridon et al. found peak $\dot{V}_{O_2}$ to average $67\% \pm 15\%$ predicted [16]. They also observed that postpubertal age was independently associated with lower % predicted peak $\dot{V}_{O_2}$. Driscoll et al. reported that the peak $\dot{V}_{O_2}$ of 29 patients age 6 to 36 years averaged $50\% \pm 14\%$ predicted and found a negative correlation between age and % predicted peak $\dot{V}_{O_2}$ [5]. Ohuchi et al. also found a negative correlation between % predicted peak $\dot{V}_{O_2}$ and age at exercise in a series of 95

Fontan patients 5 to 28 years of age [15]. Harrison et al., in a study of 30 young adults age 26.6 ± 6.6 years, found that the post-Fontan patient's peak $\dot{V}_{O_2}$ averaged only 35% of values observed among a normal age-matched control group [10], a level of exercise dysfunction considerably worse than that observed among both Paridon's and Ohuchi's pediatric subjects [15, 16].

Fewer data from serial exercise studies in Fontan patients have been reported, and the results from these studies have been somewhat discrepant. Nir et al. [14] studied 25 patients who underwent a Fontan procedure between 1977 and 1989; the age at initial exercise testing was 5 to 41 years, and the mean interval between the first and final exercise tests was 3.5 years (range 1 to 8). They found that peak $\dot{V}_{O_2}$ changed little between the initial and final tests ($56\% \pm 18\%$ vs. $57\% \pm 17\%$ predicted). They also found a small decrease in peak oxygen saturation and % predicted peak heart rate. Giardini et al. [7] studied 55 patients who underwent serial exercise testing and reported an average age of 14 ± 6 years at the time of the first exercise test and follow-up testing 7.7 ± 4.0 years later. Peak $\dot{V}_{O_2}$ at the time of the first test was $61\% \pm 11\%$ predicted. Compared with Nir et al., they observed a steep decrease in % predicted peak $\dot{V}_{O_2}$ (2.6 ± 2.7 percentage points/y) during the course of the follow-up period. In their series, the steep decrease was not limited to the pediatric years. They did note, however, that the decrease in peak $\dot{V}_{O_2}$ was less severe among patients with an anatomic left ventricle, as well as those with a total cavopulmonary connection, and steeper in patients with a higher initial peak $\dot{V}_{O_2}$.

The discrepancy between the results of our study and those of Nir et al. [14] may be explained by an "era effect." Their subjects underwent Fontan surgery shortly after its introduction. Therefore, unlike most of the patients in our series, they did not benefit from many of the more recent advances in the management of patients with single-ventricle physiology, such as early volume unloading surgery, aggressive rehabilitation of pulmonary arteries, and more modern modifications of the Fontan procedure itself. This consideration probably accounts for their patients' unusually low initial peak $\dot{V}_{O_2}$. Because their patients started from such a low baseline, it was difficult to detect additional deterioration.

Most of the adult patients in our series were cared for by clinicians specializing in the care of adults with congenital heart disease. The benefits of this specialized care may partially account for the relative stability of the adult patients in our series compared with those in Giardini's study [7].

In summary, the exercise capacity of patients post-Fontan procedure tends to decrease with time, especially during the adolescent years. Further studies are needed to elucidate the factors responsible for this deterioration and to identify treatments that may effectively forestall or reverse it.

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Fig. 1.

Graphic depiction of the relation between age at initial study and % predicted peak oxygen consumption (VO_2) with time. Thinner lines are subject-specific regression lines. Thicker line is the mean % predicted peak oxygen consumption (VO_2) in the population as a function of age, allowing for a change in intercept and slope at age 18 years. The slope was steep before age 18 years and much more shallow thereafter. For age <18 years: slope = -1.78 ± 0.46 (SE; 95% confidence intervals: $-2.69, -0.86$; $p = 0.0002$). For age ≥ 18 years: slope = -0.54 ± 0.57 (SE; 95% confidence intervals: $-1.68, 0.61$; $p = 0.35$)

Table 1

Patient clinical and demographic features

Characteristic	N (%)
Male sex	43 (55)
Ventricle type	
Left	58 (74.4)
Right	15 (19.2)
Both	5 (6.4)
Initial Fontan type	
Lateral tunnel	54 (69.2)
RA-PA	15 (19.2)
RA-RV	3 (3.9)
External conduit	5 (6.4)
Other	1 (1.3)
Age at initial Fontan (y)	
Mean $\pm$ SD	6.3 $\pm$ 7.55
Median (range)	3.7 (0.3 to 40.7)
Age at first ET study (y)	
Mean $\pm$ SD	19.7 $\pm$ 10.2
Median (range)	16.6 (5.8 to 50.1)
Time from Fontan to first ET (y)	13.3 $\pm$ 5.7
Time from first to last ET (y)	3.0 $\pm$ 1.4

ET exercise test, RA right atrium, PA pulmonary artery, RV right ventricle

Table 2Comparison of initial with final exercise test data (mean $\pm$ SD)

Variable	First ET	Last ET	Change	<i>p</i>
Peak V_{O_2} (ml/kg/min)	24.7 $\pm$ 7.0	23.2 $\pm$ 7.2	-1.53 $\pm$ 4.42	0.003
Peak V_{O_2} (% predicted)	63.7 $\pm$ 15.85	60.4 $\pm$ 13.9	-3.28 $\pm$ 11.62	0.015
O_2 pulse (% predicted)	82.8 $\pm$ 21.2	77.5 $\pm$ 15.8	-5.9 $\pm$ 19.77	0.011
V_E/V_{CO_2} slope	36.7 $\pm$ 6.28	35.8 $\pm$ 8.7	-0.81 $\pm$ 8.22	0.391
FVC (% predicted)	77.6 $\pm$ 14.69	77.9 $\pm$ 15.3	0.31 $\pm$ 8.61	0.753
FEV ₁ (% predicted)	78.4 $\pm$ 14.49	77.3 $\pm$ 15.3	-1.15 $\pm$ 7.75	0.192
HR (bpm)	145 $\pm$ 27	146 $\pm$ 24	0.50 $\pm$ 20.3	0.831
HR (% predicted)	76.5 $\pm$ 14.39	78.4 $\pm$ 11.5	1.83 $\pm$ 11.22	0.157
O_2 sat rest (%)	93.4 $\pm$ 4.3	92.5 $\pm$ 4.2	-0.90 $\pm$ 3.84	0.044
O_2 sat peak (%)	89.2 $\pm$ 6.1	89 $\pm$ 5.24	-0.12 $\pm$ 4.64	0.823
O_2 sat diff (%)	-4.2 $\pm$ 3.9	-3.5 $\pm$ 2.8	-0.69 $\pm$ 3.94	0.132
BMI (kg/m ²)	21.3 $\pm$ 4.0	22.6 $\pm$ 4.1	1.36 $\pm$ 2.49	<0.0001

diff difference between baseline and peak exercise, *FEV₁* volume of air exhaled in first second of forced expiration, *FVC* forced vital capacity, *HR* heart rate at peak exercise, *VE/V_{CO₂}* slope of the minute ventilation vs. carbon dioxide production relationship, *V_{O₂}* oxygen consumption, *sat* saturation, % *predicted* percentage of predicted normal value, *ET* exercise test

Table 3Mean change in V_{O2}% per year by demographic and clinical variables

Demographic variables	N	Mean ± SD	95% CI	p
Sex				
Male	43	-1.58 ± 8.59	(-3.07, -0.1)	0.352
Female	35	-0.57 ± 7.47	(-2.13, 0.99)	
Ventricle				
Not left ventricle	15	-2.5 ± 9.16	(-5.38, 0.38)	0.212
Left ventricle	63	-0.83 ± 7.8	(-1.98, 0.32)	
Fontan type				
Lateral tunnel	54	-1.66 ± 8.46	(-3.01, -0.32)	0.164
Other	24	-0.05 ± 7.01	(-1.77, 1.66)	
Fenestration				
No	59	-0.9 ± 8.03	(-2.09, 0.3)	0.331
Yes	19	-2.17 ± 8.33	(-4.68, 0.33)	
Digoxin				
No	47	-0.96 ± 8.64	(-2.44, 0.52)	0.636
Yes	31	-1.48 ± 7.3	(-3.03, 0.08)	
Diuretic				
No	57	-1.16 ± 7.74	(-2.35, 0.03)	0.98
Yes	21	-1.19 ± 9.2	(-3.64, 1.26)	
Antiarrhythmic				
No	62	-1.52 ± 8.13	(-2.72, -0.32)	0.194
Yes	16	0.22 ± 7.78	(-2.21, 2.64)	
ACE inhibitor				
No	32	-1.18 ± 5.69	(-2.31, -0.04)	0.987
Yes	46	-1.16 ± 9.48	(-2.86, 0.54)	
Coumadin				
No	52	-1.66 ± 7.45	(-2.83, -0.49)	0.153
Yes	26	0.01 ± 9.13	(-2.27, 2.3)	
Aspirin				
No	31	-0.54 ± 8.71	(-2.44, 1.35)	0.362
Yes	47	-1.55 ± 7.69	(-2.85, -0.26)	

ACE = angiotensin-converting enzyme; CI = confidence interval

Table 4Correlation between rate of change in % predicted peak $\dot{V}_{O_2}$ and change in other exercise test parameters

Parameter (change/y)	Correlation	<i>p</i>
O ₂ pulse%	0.549	<0.0001
FVC%	0.096	0.40
FEV ₁ %	0.014	0.90
V_E/V_{CO_2}	-0.316	0.005
HR%	0.138	0.23
Initial $\dot{V}_{O_2}$ %	-0.453	<0.0001
O ₂ sat rest	0.186	0.10
O ₂ sat peak	0.147	0.20
O ₂ sat diff	0.008	0.95

% percentage of predicted normal value, *FVC* forced vital capacity, *FEV 1* volume of air exhaled in first second of forced expiration, V_E/V_{CO_2} slope of the minute ventilation vs. carbon dioxide production relationship, *HR* heart rate at peak exercise, $\dot{V}_{O_2}$ oxygen consumption, *sat* saturation, *diff* difference between baseline and peak exercise

Table 5

Results of multivariate analysis examining the relation between changes in peak $\dot{V}O_2$ with time and other clinical and exercise test variables

Results (% change/y)	Coefficient $\pm$ SE	<i>p</i>
O ₂ pulse	0.29 $\pm$ 0.05	<.0001
HR	0.33 $\pm$ 0.09	0.001
$\dot{V}_E/\dot{V}CO_2$	-0.33 $\pm$ 0.12	0.007
Initial $\dot{V}O_2$ % predicted	-0.08 $\pm$ 0.02	0.005
Male	-1.66 $\pm$ 0.77	0.034

HR heart rate at peak exercise, $\dot{V}_E/\dot{V}CO_2$ slope of the minute ventilation vs. carbon dioxide production relationship, $\dot{V}O_2$ oxygen consumption, % predicted percentage of predicted normal value