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When is the right time for Fontan conversion? The role of cardiopulmonary exercise test

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ABSTRACT

Background: To determine if Fontan conversion (FC) resulted in improvement in exercise capacity (EC), and to determine the role of cardiopulmonary exercise test (CPET) in risk stratification of patients undergoing FC.
Methods: A retrospective review of patients who underwent CPET prior to FC at Mayo Clinic from 1994 to 2014. The patients who also underwent post-operative CPET were selected for the analysis of improvement in EC defined as 10% increase in baseline peak oxygen consumption (VO_2).
Results: 75 patients CPET prior to FC; mean age 24 ± 6 years; 44 males (59%); and 51 (68%) were in NYHA III/IV prior to FC. Pre-operative peak VO_2 was 15.5 ± 3.4 ml/kg/min. A comparison of pre- and post-FC CPET data was performed using 42 patients (56%) that underwent CPET after FC. Improvement in EC occurred in 18 of 42 patients (43%). Baseline peak VO_2 >14 ml/kg/min was associated with improved EC (hazard ratio [HR] 1.85; $P = .02$). Improvement in New York Heart Association (NYHA) class occurred in 12 (67%) patients with improved EC vs 2 (8%) without improved EC. Improvement in NYHA class was more likely to occur in patients with improved EC compared to those without improvement EC (odds ratio 4.11, $P = .01$). There were 10 (13%) perioperative deaths, and baseline peak VO_2 ≤14 ml/kg/min was predictive of perioperative mortality (HR 3.74; $P < .001$).
Conclusions: Baseline peak VO_2 was predictive of perioperative survival, and improvement in EC. Performance on CPET in failing Fontan patients might be a useful clinical parameter in determining appropriate timing of FC.

1. Introduction

The Fontan procedure has undergone significant modifications since its original descriptions in 1971, and each of these modifications was intended to improve hemodynamic efficiency and avoid the late complications associated with the original atriopulmonary Fontan operation [1–4]. Fontan patients, especially those with an atriopulmonary Fontan, can develop atrial arrhythmias, chronotropic incompetence, thromboembolism, liver fibrosis and protein losing enteropathy; these complications are often referred to as Fontan failure [4–9].

Several studies, including a recent study from our institution, have shown that Fontan conversion (FC) to total cavopulmonary connection is an effective rescue strategy for some patients with failing Fontan [5,10–14]. These studies have demonstrated improvement in New York Heart Association (NYHA) functional class and arrhythmia-free survival after FC [5,10–13]. However, there are no data evaluating the impact of FC on exercise capacity (EC) as measured by cardiopulmonary exercise test (CPET).

Several studies have shown that Fontan patients have poor EC, decreased peak oxygen consumption (VO_2), and decreased oxygen consumption at ventilatory anaerobic threshold compared to patients with biventricular circulation. Limited data suggest that there is a more steep decline in peak VO_2 over time in the Fontan patients with atriopulmonary connection and failing Fontan physiology compared to those with to those with total cavopulmonary connection [15,16]. Since FC transforms atriopulmonary connection to a more efficient hemodynamic circulation, we hypothesized that FC will improve objective indices of EC as measured by CPET.

Abbreviations: CPET, cardiopulmonary exercise testing; EC, exercise capacity; FC, Fontan conversion; NYHA, New York Heart Association; VO_2, oxygen consumption.

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2. Methods

2.1. Patient selection and data collection

The Mayo Clinic Institutional Review Board approved this study protocol. All adult patients (age > 18 years) that underwent FC at Mayo Clinic from January 1994 to June 2014 were identified from the electronic medical record using free text search software (Advanced Cohort Explorer). A pre-operative CPET performed within 24 months prior to FC was required for inclusion in the study. Clinical, echocardiographic, CPET and surgical data were abstracted from the medical records.

2.2. Study design

The primary study objective was to determine if FC improved EC defined as 10% increase in pre-operative peak VO_2. The secondary study objective was to determine if pre-operative CPET indices were predictive of perioperative mortality. We selected the last symptom-limited maximal CPET prior to FC as the baseline test, and the first symptom-limited maximal CPET after FC as the post intervention test. Only CPET performed within 24 months of FC were included.

2.3. Cardiopulmonary exercise test

Carbon dioxide elimination, peak VO_2, and minute ventilation were measured with a computerized breath-by-breath analyzer. Patients performed a symptom-limited maximal exercise test using an incremental protocol (Naughton protocol) that allowed reaching exhaustion in approximately 10 min of exercise. Maximal CPET was defined as a respiratory exchange ratio >1.1. A 12-lead electrocardiogram and transcutaneous oxygen saturation were continuously monitored throughout the study, and blood pressure was determined manually every 2 min. The technical details of measurement of peak VO_2 and ventilatory equivalent for carbon dioxide (VE/VCO_2-slope) have been published, and an improvement in EC was defined as 10% improvement in baseline peak VO_2 similar to prior studies [15–19]. Resting heart rate was measured after at least 2 min of complete rest in a seated position, whereas peak heart rate was defined as the maximal heart rate achieved during exercise. Heart rate reserve, chronotropic index and anaerobic threshold were calculated as previously described [17,18]. Chronotropic incompetence was defined as heart rate response <85% predicted for age using the equation (peak heart rate/220-age) [19]. Standard equations were used to generate predicted values for peak exercise parameters [19]. Because of age-related differences of normal peak VO_2 when expressed in ml/kg/min, peak VO_2 was also expressed as percentage of predicted value.

2.4. Statistical analysis

All statistical analyses were performed with JMP version 10.0 software (SAS Institute Inc.). Categorical variables were expressed as number (percentage), and continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using the χ^2 test or Fisher exact test; continuous variables were compared with a 2-sided unpaired Student's *t*-test or Wilcoxon rank sum test, as appropriate. Univariable and multivariable Cox proportional hazard models were used to identify the predictors of improvement in EC, and the predictors of perioperative mortality. The risk associated with each variable was expressed as hazard ratio (HR) and 95% confidence interval (CI). Only the variables that were significant on univariable analysis were entered into the multivariable model. All *P* values were 2-sided, and *P* values of <.05 were considered significant.

3. Results

3.1. Baseline characteristics and Fontan conversion data

There were 78 patients who underwent FC at our institution, and 75 of them had CPET prior to FC. The mean age at the time of initial Fontan operation was 14 ± 4 years; mean age at the time of FC was 24 ± 6 years; and 44 (59%) were males. Ventricular morphology was left ventricle in 64 (66%); the most common underlying diagnosis was tricuspid atresia 29 (39%); and 51 (68%) had NYHA class III/IV symptoms prior to FC. The baseline peak VO_2 was 15.5 ± 3.4 ml/kg/min (53 ± 8% predicted), Table 1.

The most common type of total cavopulmonary connection was intraatrial conduit in 45 (60%) followed by extracardiac conduit in 19 (25%). Concomitant procedures performed during FC were atrioventricular valve repair or replacement (n = 11, 15%), pacemaker implantation (n = 39, 52%), right atrial maze (n = 27, 36%) and removal of right atrial thrombus (n = 6, 8%), Table 2.

Out of the 75 patients enrolled in the study, 33 (44%) did not undergo CPET after FC because of perioperative death (n = 10), and loss of follow-up (n = 23). There was no difference in the clinical characteristics and baseline CPET data between the 23 patients with loss of follow-up and the 42 patients that had CPET after FC.

Table 1
Baseline clinical characteristics of entire cohort (N = 75).

Age at Fontan conversion, years	24 ± 6
Age at initial Fontan operation, years	14 ± 4
Male	44 (59%)
BSA (kg/m^2)	1.9 ± 0.2
NYHA III/IV	51 (68%)
Echo data	
Left ventricle	64 (86%)
Right ventricle	10 (13%)
Indeterminate	1 (1%)
Ejection fraction*	46 ± 11
M/S AV valve regurgitation	11 (15%)
Initial diagnosis	
Tricuspid atresia	29
Common inlet ventricle	6
Double inlet left ventricle	21
Pulmonary atresia	9
Double outlet right ventricle	7
Others	3
Previous Fontan connection	
Atriopulmonary	51
Bjork modification	20
Classic Fontan	4
Indications for Fontan conversion	
Arrhythmia	55
Protein losing enteropathy	13
Fontan obstruction/thrombus	9
Hemodynamics	
Fontan pressure, mm Hg	16 ± 4
VEDP, mm Hg	11 ± 3
Cardiac index, l/min/m^2	2.3 ± 0.2
PVRi, WU × m^2	2.3 ± 0.8
Pre-operative CPET data	
Peak VO_2 (ml/min)	1162 ± 68
Peak VO_2 (ml/kg/min)	15.5 ± 3.4
Percentage predicted peak VO_2	53 ± 8
METS	5.2 ± 0.4

AV: ACPET: cardiopulmonary exercise test; MET: metabolic equivalents; NYHA: New York Heart Association; VO_2: oxygen consumption; BSA: body surface area; M/S: moderate/severe.
PVRi: pulmonary vascular resistance index; VEDP: ventricular end-diastolic pressure; WU: wood units. Ejection fraction* was based on qualitative assessment.

3.2. Cardiopulmonary exercise test

There were 42 patients who underwent CPET after FC, and these patients were used in the analysis for improvement in EC. The pre-FC CPET showed mean peak VO_2 of 15.8 ± 3.1 ml/kg/min (54 ± 5% predicted), and the mean time interval from pre-FC CPET to FC was 9 ± 6 months. Eleven patients (26%) had paced rhythm and 31 (74%) had chronotropic incompetence prior to FC.

Table 2
Fontan conversion data (N = 75).

Cavopulmonary connection	
Intraatrial conduit	45 (60%)
Extracardiac conduit	19 (25%)
Lateral tunnel	11 (15%)
Antiarrhythmic procedure	
Right atrial maze	27 (36%)
Biatrial maze	20 (27%)
Right atrial isthmus ablation	8 (11%)
Concomitant procedures	
Valve surgery	11 (15%)
Pacemaker implantation	39 (52%)
Pulmonary arterioplasty	6 (8%)
Conduit fenestration	20 (27%)
Removal of right atrial thrombus	6 (8%)