Prognostic Value of Exercise Testing During Heart Transplant Evaluation in Children

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Background—Maximum oxygen consumption (peak VO$_2$) <50% predicted on exercise testing is a class I indication for heart transplant (HT) listing in children. This recommendation is based on exercise data in adults. We assessed the association of peak VO$_2$<50% predicted during HT evaluation with freedom from death or deterioration in children.

Methods and Results—We analyzed all children who underwent exercise testing during HT evaluation at our center between 2002 and 2011. Patients with peak VO$_2$ <50% predicted were compared with those with peak VO$_2$ ≥50% predicted for the composite outcome of death before HT, initiation of mechanical circulatory support, and HT at highest urgency status, using time-to-event analyses. There were 50 children in the study (median age, 15 years; interquartile range, 13–17 years; 24 girls; 18 with palliated single ventricle). Overall, 24 children reached the composite end point. Peak VO$_2$ <50% predicted was associated with outcome in children with biventricular circulation (hazard ratio, 4.7; 95% confidence interval, 1.8–12.3; \( P < 0.001 \)) but not in those with a palliated single ventricle (hazard ratio, 1.3; 95% confidence interval, 0.1–12.0; \( P = 0.80 \)). Similarly, VE/VCO$_2$ slope ≥34 was associated with outcome in children with biventricular circulation (hazard ratio, 2.7; 95% confidence interval, 1.1–7.1; \( P < 0.001 \)) but not in children with a palliated single ventricle.

Conclusions—Exercise testing during HT evaluation in children with biventricular circulation identified those at higher risk of death or deterioration in this small study. Larger studies are needed to assess the role of exercise testing during HT evaluation in children with a palliated single ventricle. (Circ Heart Fail. 2013;6:792-799.)

Key Words: exercise testing ■ heart failure ■ heart transplantation ■ outcome ■ pediatrics

Heart transplantation (HT) is an established therapy for children in severe heart failure.1 Listing for HT is indicated when transplant offers a clinically important survival advantage compared with medical therapy for heart failure.2 Determining survival benefit with HT may seem obvious in a child in decompensated, stage D heart failure2 but is often challenging in children with compensated heart failure referred for HT evaluation. This is so because no quantitative approach to predict survival, similar to that used in adults,3,4 has been described in children with heart failure.

Clinical Perspective on p 799
A simpler approach to risk-stratify adults in heart failure has used data obtained during exercise testing. Two variables, oxygen consumption (VO$_2$) at peak exercise and efficiency of ventilation during exercise, are known to stratify adults in heart failure for 1-year survival.5,6 On the basis of these data and a standard practice of exercise testing during HT evaluation in adults, a recent American Heart Association scientific statement that described indications for HT listing in children suggested that peak VO$_2$<50% predicted for age and sex should be considered substantial impairment in exercise performance in children with heart disease and therefore a class I indication (general agreement) for HT listing.² The statement acknowledged a lack of studies investigating the relationship of exercise performance to survival in children with heart failure. Data supporting this indication remain scant in children.7,8 Therefore, the purpose of this study was to test the hypothesis that among children evaluated for HT, those with a peak VO$_2$ <50% predicted for age and sex will be at higher risk of death or deterioration compared with those with peak VO$_2$ ≥50% predicted and to assess the association of ventilatory efficiency during exercise with patient outcomes.

Methods

Subjects
We identified all children aged 6 to 20 years old who were evaluated for their first HT at Boston Children’s Hospital between 2002 and 2011 and underwent metabolic exercise testing during that evaluation. The exclusion criteria were as follows: (1) HT evaluation for retransplant or multiorgan transplant; (2) no oxygen consumption measurement during exercise testing; and (3) lack of follow-up (such as for children referred from other HT centers for a second opinion).

Study Design
This was a single-center, retrospective cohort study. The institutional review board approved the study with a waiver of informed consent.
We compared children with peak VO₂<50% predicted for age and sex with those with peak VO₂≥50% predicted for baseline characteristics and outcomes using time-to-event analyses. The primary end point was a composite of the following: (1) death before receiving a HT; (2) initiation of mechanical circulatory support (extracorporeal membrane oxygenation or ventricular assist device); and (3) HT at highest urgency status defined as HT when listed as status IA (supported by high-dose single inotrope, multiple inotropes, mechanical ventilation, or mechanical circulatory support). Inclusion of mechanical support in the end point reflects the institutional practice of initiating mechanical support in only those children who are showing rapid clinical decline with impending end-organ dysfunction. Patients were followed after exercise test until HT, initiation of mechanical support, death, or the day of last observation on December 31, 2011. Patients who received HT when listed with less urgency (as status 1B or status 2 candidates) were censored at the time of transplant. This was done to acknowledge the uncertainty of their clinical course (and the time they would take to reach the end point) had they not received HT on a nonurgent basis. The association of ventilatory efficiency during exercise test with the primary composite end point was also examined.

### Ventricular Function

Ventricular function was assessed using transthoracic echocardiography. The echocardiogram reviewed was the one performed closest to the date of the exercise test. The assessment was quantitative, if possible (left ventricular ejection fraction), or qualitative in patients with a palliated single ventricle or a systemic right ventricle. Pulmonary capillary wedge pressure and cardiac index were recorded in all children who underwent right heart catheterization for HT evaluation.

### Exercise Testing

All children underwent a symptom-limited, progressive exercise test using a bicycle or a treadmill ergometer, as previously described. Oxygen consumption (VO₂), carbon dioxide production (VCO₂), and minute ventilation (VE) were measured on a breath-by-breath basis and averaged every 15 seconds for further analysis. Peak VO₂ was defined as the highest VO₂ achieved during the test. Standard prediction equations were used to calculate percent-predicted peak VO₂ for patient age, size, and sex. Ventilatory anaerobic threshold was identified by the V-slope method and the respiratory exchange ratio (the ratio VCO₂/VO₂) measured continuously. Oxygen pulse (VO₂ heart rate) was measured at peak VO₂. Oxygen pulse is equal to the product of stroke volume and the arterial-venous O₂ content difference and is often used as a surrogate for stroke volume at peak exercise. Ventilatory efficiency (VE/VCO₂ slope), an index of efficiency of gas exchange during exercise, represents liters of air breathed out to eliminate 1 L of CO₂. VE rises linearly with VCO₂ during exercise until the respiratory compensation point, when lactic acidosis engenders an increase in VE out of proportion to the increase in VCO₂. The slope of the linear portion of the VE/VCO₂ curve was recorded as the VE/VCO₂ slope.

### Statistical Analysis

Patient characteristics are summarized as median (interquartile range) or number (%). Baseline characteristics and exercise data in children with peak VO₂<50% predicted and those with peak VO₂≥50% predicted were compared using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. The association of peak VO₂ and VE/VCO₂ slope with the composite primary end point was examined using time-to-event analyses. Kaplan–Meier survival curves and a log rank test were used to compare event-free survival between children with peak VO₂<50% predicted and those with peak VO₂≥50% predicted. A similar analysis was performed to compare children with VE/VCO₂ slope <34 and ≥34. Children who underwent repeat exercise testing after their first exercise test with the primary composite end point had peak VO₂<50% predicted (52% versus 22% of children ≥50% predicted or vice versa) were censored at the time of the repeat test and allowed to crossover for subsequent follow-up. A Cox proportional hazard model was developed to assess the association of exercise variables with the primary end point. Because both peak VO₂ and VE/VCO₂ slope are known to be abnormal in children with a palliated single ventricle, we decided a priori to examine broad diagnostic subgroups (biventricular circulation and palliated single ventricle) for the prognostic value of exercise testing in these groups. Finally, a Cox frailty model was used to identify the peak VO₂ value that dichotomized patients so as to maximize the likelihood ratio χ² statistic for the composite end point. Statistical analysis was performed using Statistical Analysis Software version 9.3 (SAS Institute Inc, Cary, NC). All authors have reviewed and agree with the article as written.

### Results

#### Study Population

During the study period, 110 children aged between 6 and 20 years were evaluated for HT at Boston Children’s Hospital (Figure 1). Ten were excluded because they were evaluated for retransplantation (8 patients), multiorgan transplantation (1 patient), or for a second opinion with no follow-up data (1 patient). Of the remaining 100 patients, 31 were in the cardiac intensive care unit with refractory heart failure at the time of the evaluation and did not undergo exercise testing. Of the remaining 69 patients, 11 did not undergo exercise testing and 8 had incomplete exercise data. The study cohort consisted of 50 children who were evaluated for primary HT, underwent metabolic exercise testing during evaluation, and had adequate exercise data for the study. Their median age at the time of exercise test was 15 years (interquartile range, 13–17 years) and 24 (48%) were girls. There were 32 patients (64%) with a biventricular circulation and 18 (36%) who had undergone single ventricle palliation. Of patients with biventricular circulation, 30 had cardiomyopathy (25 dilated, 3 hypertrophic, and 2 restrictive) and 2 had congenital heart disease with a systemic right ventricle (1 patient had L-transposition of the great arteries; the second patient had D-transposition of the great arteries and a history of Senning operation).

#### Baseline Characteristics

At the time of their first exercise test, 23 children (46%) had peak VO₂<50% predicted. A comparison of demographic, clinical, and exercise variables between children with peak VO₂<50% predicted and those with VO₂≥50% predicted at the time of their first exercise test is presented in the Table. A higher percentage of children with palliated single ventricle had peak VO₂<50% predicted (52% versus 22% of children with biventricular circulation).

There were no significant differences in systemic ventricular function by echocardiography between children with peak VO₂<50% predicted and those with peak VO₂≥50% predicted, although the systemic ventricles in children with peak VO₂<50% predicted were more dilated compared with the systemic ventricles of children with peak VO₂≥50% predicted. Furthermore, there were no significant differences in cardiac index or pulmonary capillary wedge pressure on cardiac catheterization between the 2 groups. The percentage of children in the 2 groups who received various heart failure medications were similar for all medications. The difference in peak heart rate between the groups was of borderline significance (median, 135 beats/min versus 147 beats/minute).
This difference was not explained by group difference in beta blockade because the carvedilol dose was lower (median daily dose, 0.24 mg/kg versus 0.45 mg/kg) in the group with lower peak heart rate. Despite lower peak heart rates, children with peak VO_2 < 50% predicted had a significantly lower peak O_2 pulse (median, 39% predicted versus 58% predicted; \( P < 0.001 \)); they also had less efficient ventilation during exercise (median VE/VCO_2 slope, 43 versus 33; \( P = 0.009 \)) versus children with peak VO_2 ≥ 50% predicted (Table). Ten of 23 children (43%) with peak VO_2 < 50% predicted and 10 of 27 children (37%) with peak VO_2 ≥ 50% predicted had atrial or ventricular ectopy during exercise or in recovery; no child in either group experienced atrial or ventricular tachycardia. Peak respiratory exchange ratio was similar between the 2 groups, and all children reached a respiratory exchange ratio > 1.0 at peak exercise.

Thirty-nine patients underwent exercise testing only once during the study period. The test was repeated once in 9 patients and twice in 2 patients. In 10 of these 13 follow-up exercise tests, the patient’s peak VO_2 did not change compared with the first test with respect to group assignment and remained either < 50% predicted or ≥ 50% predicted.

**Clinical Outcomes**

Overall, 35 patients were listed after initial HT evaluation. Children with peak VO_2 < 50% predicted (15 of 23) and those with peak VO_2 ≥ 50% predicted (20 of 27) were equally likely to be listed (\( P = 0.55 \)). The decision to list was described as clinical progression of heart failure in all patients with additional, specific concerns for rising pulmonary vascular resistance in 4, ventricular tachycardia in 1, plastic bronchitis in 2, and protein-losing enteropathy in 2 patients. Although 5 patients were initially listed at the highest urgency listing status 1A, 4 of these were listed after ≥ 4 weeks of exercise testing. One patient who was not listed after initial evaluation was listed later because of clinical decline and heart failure progression.

The primary end point was reached in 24 patients: there were 3 deaths, 4 patients received a mechanical support, and 17 received HT when listed at highest urgency status 1A. An additional 13 patients received HT when listed at lower urgency status 1B or 2. The remaining 13 patients are alive and 12 of these were still in follow-up at our institution on the last day of the study.

**Exercise Performance and Outcome**

Figure 2 illustrates Kaplan–Meier survival after the exercise test in study children stratified by peak VO_2. There was no difference in time to the composite primary end point between children with peak VO_2 < 50% predicted and those with peak VO_2 ≥ 50% predicted analyzed for the entire cohort (hazard ratio [HR], 1.4; 95% confidence interval [CI], 0.6–3.2; \( P = 0.38 \)). However, on subgroup analysis, children with a peak VO_2 < 50% predicted were at a higher risk of reaching the composite primary end point compared with those with peak VO_2 ≥ 50% predicted if they had a biventricular circulation (HR, 4.7; 95% CI, 1.8–12.3; \( P < 0.001 \); Figure 2A) but not if they had a palliated single ventricle (HR, 1.3; 95% CI, 0.1–12.0; \( P = 0.80 \); Figure 2B).

Similarly, VE/VCO_2 slope of ≥ 34 was associated with time to composite end point in children with a biventricular circulation (HR, 2.7; 95% CI, 1.1–7.1; \( P = 0.03 \)) but not in children with palliated single ventricle (HR, 1.1; 95% CI, 0.1–10.2; \( P = 0.91 \); Figure 3A and 3B). In a multivariable model in children with biventricular circulation, peak VO_2 < 50% predicted (HR, 5.0; 95% CI, 1.8–14.1; \( P = 0.002 \)) and VE/VCO_2 slope of ≥ 34 (HR, 3.2; 95% CI, 1.2–8.4; \( P = 0.02 \)) were both independently associated with time to composite end point. Cardiac index obtained at the time of cardiac catheterization was not associated with the end point.
in univariate or multivariable analysis or when analyzed as interaction with peak VO\textsubscript{2} groups.

The Cox frailty model to maximize the likelihood ratio $\chi^2$ statistic, which considered all 63 exercise tests as baseline events but accounted for intrasubject correlation for repeat tests, identified peak VO\textsubscript{2} of 44% predicted as the best cutoff for children with biventricular circulation. Among these children, those with a peak VO\textsubscript{2}<44% predicted were at 5-fold risk of death or deterioration compared with those with peak VO\textsubscript{2}$\geq$44% predicted (HR, 5.1; 95% CI, 1.9–13.5; $P<0.001$).

For patients with a palliated single ventricle, the highest likelihood ratio $\chi^2$ statistic was obtained with a peak VO\textsubscript{2} cutoff of 40%; however, the association between peak VO\textsubscript{2} and the end point remained nonsignificant (HR, 5.0; 95% CI, 0.5–45.1; $P=0.12$).

**Discussion**

In this single-center study of children who underwent exercise testing during their HT evaluation, children with peak VO\textsubscript{2}$\leq$50% predicted and those with peak VO\textsubscript{2}$\geq$50% predicted were equally likely to be listed for HT after their evaluation was completed. However, children with peak VO\textsubscript{2}$<50%$ predicted were at 4.7-fold risk of death or deterioration on follow-up compared with those with peak VO\textsubscript{2}$\geq$50% predicted among those with a biventricular circulation. This finding supports the American Heart Association statement that peak VO\textsubscript{2}$<50%$ predicted should be considered a class I indication for HT listing in these children. We also found that VE/VCO\textsubscript{2} slope of $\geq$34 during exercise testing was independently associated with poor outcome in children with biventricular circulation. Although exercise testing was unable to risk-stratify children with a palliated single ventricle, the number of patients and the frequency of events were small. Larger studies are needed to evaluate the role of exercise testing during HT evaluation in children with a palliated single ventricle.

Exercise testing became an important component of HT evaluation in adults after Mancini et al\textsuperscript{5} reported $\approx$50% 1-year mortality in patients with heart failure with peak VO\textsubscript{2}<14 mL/kg per minute managed medically. In contrast, patients with equally severe left ventricular dysfunction but with peak VO\textsubscript{2}$\geq$14 mL/kg per minute had 94% 1-year survival on medical management. Peak VO\textsubscript{2} was later shown to be superior to clinical and hemodynamic variables in predicting transplant-free survival.\textsuperscript{21} It is indeed remarkable that, despite
description of the heart failure survival score and the Seattle heart failure score to predict survival in heart failure, peak VO₂ has withstood the test of time as an important predictor of outcomes and is routinely used during HT evaluation in adults in contemporary clinical practice. Notably, a recent study reported that peak VO₂ adds prognostic information to the Seattle Heart Failure Score and helps in decision-making for HT listing. Because β-blockers reduce mortality in heart failure while potentially reducing peak heart rate response during exercise, peak VO₂ < 10 to 12 mL/kg per minute and <50% predicted are the accepted thresholds associated with poor outcome in adults on these medications.

Previous reports, as well as the present study, suggest that many children with peak VO₂ ≥ 14 mL/kg per minute are listed for HT. Because peak VO₂ is related to age and sex in children, percent-predicted values are preferable in describing performance compared with absolute values (mL/min) or values scaled to body size (mL/kg per minute). Few studies have assessed the prognostic value of exercise testing in pediatric HT candidates. In a study of 31 children with dilated cardiomyopathy from Brazil, although shorter exercise duration was associated with death or transplantation, peak VO₂ was not. In contrast, in an important recent study from United Kingdom, peak VO₂ > 62% predicted for age and sex in children with dilated cardiomyopathy was associated with longer survival without clinical deterioration. Although the UK study was similar in design to the present study, the overall cohort was healthier (children not considered sick enough for HT evaluation were also included) and the end point was time to listing rather than time to HT. These differences in baseline characteristics and the primary end point may explain why the UK study reported a much higher risk of poor outcome in children with low peak VO₂ (relative risk of 10.72 in those with peak VO₂ ≤ 62% predicted) compared with the present study. The difference in the relative risk that was observed to be associated with poor exercise performance in the 2 studies may well have been attributable to chance because both studies reported large CIs; however the risk estimate of the current study is more in line with that reported in previous adult studies.

An important and somewhat surprising finding of the current study is that many children with biventricular circulation and peak VO₂ ≥ 50% predicted also reached the composite end point within 1 to 2 years of their exercise test. While this finding may point to the overall disease severity or rapid
progression of heart failure in children referred for HT, it also suggests that VO$_2$ ≥ 50% predicted may not by itself assure long transplant-free survival in children being considered for HT on the basis of clinical concerns. Perhaps 2 thresholds for peak VO$_2$ are important: (1) to identify patients in whom HT listing may be deferred safely to complement the clinical impression of a well-compensated state (the focus of the UK study);$^7$ and (2) during decision-making for HT listing, to identify patients who are at particularly high risk of death or deterioration in the near-term. Risk-stratification into more than 2 groups using exercise data may also be possible by examining both the peak VO$_2$ and the ventilatory efficiency, as described previously in adults.$^6$ These approaches can only be examined in a larger, multicenter cohort. We considered such an analysis and invited 2 pediatric centers in the United States with high HT patient volume to participate in our study but found that these centers rarely used exercise testing during HT evaluation. Based on our findings, we recommend a routine use of exercise testing during HT evaluation in children.

A lack of association of peak VO$_2$ (or ventilatory efficiency) with outcome in patients with a palliated single ventricle in the current study may represent a type 2 error considering small numbers. Furthermore, because children with a palliated single ventricle have impaired peak VO$_2$ (63% to 67% predicted) and inefficient ventilation even when they are clinically well,$^{18,19}$ the ability to further risk-stratify these patients using exercise data may be limited during HT evaluation.$^7$ We speculate that if an association of exercise variables with outcome does exist in these patients, the threshold would occur at more extreme values (for example, at a lower peak VO$_2$ or at a higher VE/VCO$_2$ slope) compared with their thresholds for patients with a biventricular circulation.

This study has several limitations. First, this was a retrospective study and the sample size was small, particularly for children with a palliated single ventricle but also for children with a biventricular circulation, where the associations described have large CIs and lack precision. Second, the study cohort, in particular the subgroup with biventricular circulation, was...
heterogeneous for cardiac diagnosis. Although the American Heart Association statement does not differentiate among children of different ages and diagnoses when defining substantial exercise impairment, the prognostic value of exercise parameters may differ by age and in children with different diagnoses. Third, the reported values of percent-predicted peak VO₂ were generated from equations described in healthy children using a bicycle ergometer. There are no published comparisons of peak VO₂ obtained using a bicycle to that obtained using a treadmill within the same children. In our laboratory, a comparison of 2 such tests performed in a cohort of 27 children (unrelated to the present study cohort) found a peak VO₂ of 74±28% predicted using a bicycle and 79±22% predicted using a treadmill (P=0.09; paired t test). This difference seems to be of minor clinical importance. Fourth, some of the study patients underwent a repeat exercise test on follow-up that complicated the primary analysis. However, because peak VO₂ was analyzed as a binary variable, only 3 follow-up tests (where the patients crossed over with respect to their peak VO₂) contributed to the primary analysis. Furthermore, a Cox frailty analysis, which analyzed all tests and accounted for repeat testing, demonstrated associations similar to those observed in the primary analysis. Finally, although children with peak VO₂<50% predicted were no more likely to be listed for HT than those with higher values, we cannot exclude the possibility that exercise data played a role in decision-making in some children. An ideal study design to answer the research question would be to follow children in advanced heart failure on medical therapy for their natural history and assess the relationship of baseline exercise performance to survival without offering HT. Such a study design would be unethical in the United States considering the role of HT in the present clinical practice. To mitigate the potential effect of exercise data on listing decisions in the present study, we censored patients who received HT when listed nonurgently (status 1B or 2) at the time of their transplant.

In conclusion, exercise testing during HT evaluation in children with biventricular circulation identified those at higher risk of death or deterioration in this small study. Although this finding supports the American Heart Association statement describing indications for HT listing in children, larger, multicenter studies are needed to define more clearly the role of exercise testing in children with specific cardiac diagnoses and in those with a palliated single ventricle during HT evaluation.

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Disclosures
None.

References
Maximum oxygen consumption (peak VO$_2$) and efficiency of ventilation (VE) during exercise (VE/VCO$_2$ slope) are known to stratify adults in heart failure for 1-year survival. On the basis of adult data, a recent American Heart Association scientific statement suggested that peak VO$_2$<50% predicted for age and sex should be considered substantial impairment in exercise performance in children with heart disease and therefore a class I indication for heart transplant listing. This single-center study examined the association of peak VO$_2$<50% predicted with risk of death or deterioration in 50 children evaluated for heart transplant during 2002 to 2011 (32 biventricular circulation, 18 palliated single ventricle). Overall, 24 children reached the composite end point (death, urgent transplant, or initiation of mechanical support). Although children with peak VO$_2$<50% predicted and those with peak VO$_2$≥50% predicted were equally likely to be listed, children with peak VO$_2$<50% predicted were at 4.7-fold risk of death or deterioration on follow-up compared with those with peak VO$_2$≥50% predicted among those with a biventricular circulation. VE/VCO$_2$ slope ≥34 during exercise testing was also associated with poor outcome in children with biventricular circulation. Exercise testing was unable to risk-stratify children with a palliated single ventricle. The authors conclude that exercise testing during heart transplant evaluation in children with biventricular circulation identified those at higher risk of death or deterioration in this small study. Larger studies are needed to define more clearly the role of exercise testing in children with specific cardiac diagnoses and in those with a palliated single ventricle during heart transplant evaluation.
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