Prognostic Value of Exercise Testing During Heart Transplant Evaluation in Children

Lytrivi et al: Exercise Testing for Heart Transplant Evaluation

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DOI: 10.1161/CIRCHEARTFAILURE.112.000103

Journal Subject Codes: (110) heart failure, congestive; (37) CV surgery: transplantation,
ventricular assistance, cardiomyopathy
Abstract

Background—Maximum oxygen consumption (Peak VO₂) <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 VO₂<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 VO₂<50% predicted were compared with those with peak VO₂≥50% predicted for the composite outcome of (1) death before HT, (2) initiation of mechanical circulatory support, and (3) HT at highest urgency status, using time-to-event analyses. There were 50 children in the study (median age 15 yrs, inter-quartile range 13-17 yrs, 24 female, 18 with palliated single ventricle).

Overall, 24 children reached the composite endpoint. Peak VO₂<50% predicted was associated with outcome in children with biventricular circulation (Hazard ratio [HR] 4.7, 95% confidence interval [CI] 1.8, 12.3, P<0.001) but not in those with a palliated single ventricle (HR 1.3, CI 0.1, 12.0, P=0.80). Similarly, VE/VCO₂ slope ≥34 was associated with outcome in children with biventricular circulation (HR 2.7, 95% CI 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.

Key Words: pediatrics, exercise testing, heart transplantation, heart failure, outcome
Heart transplantation (HT) is an established therapy for children in severe heart failure.\textsuperscript{1} Listing for HT is indicated when transplant offers a clinically important survival advantage compared to medical therapy for heart failure.\textsuperscript{2} Determining survival benefit with HT may appear obvious in a child in decompensated, stage D heart failure\textsuperscript{2} 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,\textsuperscript{3,4} has been described in children with heart failure.

A simpler approach to risk-stratify adults in heart failure has used data obtained during exercise testing. Two variables - oxygen consumption (VO\textsubscript{2}) at peak exercise and efficiency of ventilation during exercise – are known to stratify adults in heart failure for 1-yr survival.\textsuperscript{5,6} Based on these data and a standard practice of exercise testing during HT evaluation in adults, a recent American Heart Association (AHA) scientific statement that described indications for HT listing in children suggested that peak VO\textsubscript{2}<50\% predicted for age and gender should be considered substantial impairment in exercise performance in children with heart disease and therefore a class I indication (general agreement) for HT listing.\textsuperscript{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.\textsuperscript{7,8} Therefore, the purpose of this study was to test the hypothesis that among children evaluated for HT, those with a peak VO\textsubscript{2}<50\% predicted for age and gender will be at higher risk of death or deterioration compared to those with peak VO\textsubscript{2}\geq 50\% predicted and to assess the association of ventilatory efficiency during exercise with patient outcomes.
Methods

Subjects

We identified all children 6-20 yrs of age 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: (1) HT evaluation for re-transplant or multi-organ 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 gender to those with peak VO₂≥50% predicted for baseline characteristics and outcomes using time-to-event analyses. The primary endpoint was a composite of (1) death before receiving a HT, (2) initiation of mechanical circulatory support (extra-corporeal membrane oxygenation [ECMO] or ventricular assist device [VAD]), and (3) HT at highest urgency status defined as HT while listed as status 1A (supported by high dose single inotrope, multiple inotropes, mechanical ventilation or mechanical circulatory support). Inclusion of mechanical support in the endpoint 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 31st, 2011. Patients who received HT while 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 endpoint) had they not received HT on a non-urgent basis. The association of ventilatory efficiency during exercise test with the primary composite endpoint was also examined.

Ventricular Function

Ventricular function was assessed using trans-thoracic 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 sec 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 gender. Ventilatory anaerobic threshold (VAT) was identified by the V-slope method and the respiratory exchange ratio (RER, the ratio of VCO₂ and 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 one liter 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 (inter-quartile range [IQR]) 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’s exact test for categorical variables. The association of peak VO₂ and VE/VCO₂ slope with the composite primary endpoint 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 initial evaluation and demonstrated a significant change in their peak VO₂ (change from < 50% predicted to ≥50% predicted or vice versa) were censored at the time of the repeat test and allowed to cross-over for subsequent follow-up. A Cox proportional hazard model was developed to assess the association of exercise variables with the primary endpoint. 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 VO$_2$ value that dichotomized patients so as to maximize the likelihood ratio chi-square statistic for the composite endpoint.$^{20}$ Statistical analysis was performed using SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC). All authors have reviewed and agree with the manuscript as written.

**Results**

**Study Population**

During the study period, 110 children between 6 and 20 yrs of age were evaluated for HT at Boston Children’s Hospital (Figure 1). Ten were excluded because they were evaluated for re-transplantation (8 patients), multi-organ transplantation (1 patient) or for a 2$^{nd}$ 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 yrs (IQR 13, 17 yrs) and 24 (48%) were female. There were 32 (64%) patients 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, 2 restrictive) and 2 had congenital heart disease with a systemic right ventricle (one 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 (46%) children had peak VO$_2$<50% predicted. A comparison of demographic, clinical and exercise variables between children with peak VO$_2$<50% predicted to those with VO$_2$≥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 VO$_2$<50% predicted (52% vs. 22% of children with bi-ventricular circulation).

There were no significant differences in systemic ventricular function by echocardiography between children with peak VO$_2$<50% predicted and those with peak VO$_2$≥50% predicted although the systemic ventricles in children with peak VO$_2$<50% predicted were more dilated compared to the systemic ventricles of children with peak VO$_2$≥50% predicted. Furthermore, there were no significant differences in cardiac index or pulmonary capillary wedge pressure on cardiac catheterization between the two groups. The percentage of children in the two 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 vs. 147 beats/min, P=0.05). This difference was not explained by group difference in beta blockade as the carvedilol dose was lower (median daily dose 0.24 mg/kg vs. 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 vs. 58% predicted, P<0.001); they also had less efficient ventilation during exercise (median VE/VCO$_2$ slope 43 vs. 33, P=0.009) vs. 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 RER was similar between the two groups and all children reached an RER>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 to 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,^9^ 4 of these were listed ≥4 weeks after exercise testing. One patient who was not listed after initial evaluation was listed later due to clinical decline and heart failure progression.

The primary endpoint was reached in 24 patients: there were 3 deaths, 4 patients received a mechanical support and 17 received HT while listed at highest urgency status 1A. An additional 13 patients received HT while 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 following the exercise test in study children stratified by peak VO$_2$. There was no difference in time to the composite primary endpoint 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 endpoint compared to 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 endpoint 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-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 endpoint. Cardiac index obtained at the time of cardiac catheterization was not associated with the endpoint in univariate or multivariable analysis or when analyzed as interaction with peak VO$_2$ groups.

The Cox-frailty model to maximize the likelihood ratio chi-square statistic, which considered all 63 exercise tests as baseline events but accounted for intra-subject correlation for repeat tests, identified peak VO$_2$ of 44% predicted as the best cut-off for children with biventricular circulation. Among these children, those with a peak VO$_2$<44% predicted were at 5-fold risk of death or deterioration compared to those with peak VO$_2$≥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-square statistic was obtained with a peak VO₂ cut-off of 40%; however the association between peak VO₂ and the endpoint remained non-significant (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 VO₂<50% predicted and those with peak VO₂≥50% predicted were equally likely to be listed for HT after their evaluation was completed. However, children with peak VO₂<50% predicted were at 4.7 fold risk of death or deterioration on follow-up compared to those with peak VO₂≥50% predicted among those with a biventricular circulation. This finding supports the AHA statement that peak VO₂<50% predicted should be considered a Class 1 indication for HT listing in these children. We also found that VE/VCO₂ slope of ≥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 reported ~50% 1-yr mortality in heart failure patients with peak VO₂<14 ml/kg/min managed medically. In contrast, patients with equally severe LV dysfunction but with peak VO₂≥14 ml/kg/min had 94% 1-yr survival on medical management. Peak VO₂ was later shown to be superior to clinical and hemodynamic variables in predicting transplant-free
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 beta blockers reduce mortality in heart failure while potentially reducing peak heart rate response during exercise, peak VO₂<10-12 ml/kg/min or <50% predicted are the accepted thresholds associated with poor outcome in adults on these medications.

Previous reports as well as the current study suggest that many children with peak VO₂≥14 ml/kg/min are listed for HT. Because peak VO₂ is related to age and gender in children, percent-predicted values are preferable in describing performance compared to absolute values (ml/min) or values scaled to body size (ml/kg/min). 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, while shorter exercise duration was associated with death or transplantation, peak VO₂ was not. In contrast, in an important recent study from UK, peak VO₂>62% predicted for age and gender in children with dilated cardiomyopathy was associated with longer survival without clinical deterioration. Although the UK study was similar in design to the current study, the overall cohort was healthier (children not considered sick enough for HT evaluation were also included) and the endpoint was time to listing rather than time to HT. These differences in baseline characteristics and the primary endpoint 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 to the current study. The difference in the relative risk that was observed to be associated with poor exercise performance in the two studies may well have been due to chance as both studies reported large confidence intervals; however the risk estimate of the current study is more in line with that reported in previous adult studies.\(^5\), \(^24\)

An important and somewhat surprising finding of the current study is that many children with biventricular circulation and peak VO\(_2\) ≥50% predicted also reached the composite endpoint within 1-2 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 two thresholds for peak VO\(_2\) are important – first, 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 a second – 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, multi-center cohort. We considered such an analysis and invited two 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 VO₂ (63-67% predicted) and inefficient ventilation even when they are clinically well, the ability to further risk-stratify these patients using exercise data may be limited during HT evaluation. 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 VO₂ or at a higher VE/VCO₂ slope) compared to 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 confidence intervals and lack precision. Second, the study cohort—in particular the subgroup with biventricular circulation—was heterogeneous for cardiac diagnosis. Although the AHA 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 current study cohort) found a peak VO₂ of 74±28% predicted using a bicycle and 79±22 % predicted using a treadmill (P value= 0.09, paired t-test). This difference appears to be of minor clinical importance. Fourth, some of the study patients underwent a repeat exercise test on follow-up which 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 VO$_2$) 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, while children with peak VO$_2<$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 US considering the role of HT in current clinical practice. To mitigate the potential effect of exercise data on listing decisions in the current study, we censored patients who received HT while listed non-urgently (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. While this finding supports the AHA statement describing indications for HT listing in children, larger, multi-center 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.

**Sources of Funding**

This study was supported in part by the Heart Transplant Research and Education Fund, Department of Cardiology, Boston Children’s Hospital, MA.
Disclosures

None.

References


### Table. Baseline Characteristics of Study Patients at First Exercise Test

<table>
<thead>
<tr>
<th></th>
<th>Total (n=50)</th>
<th>Peak VO₂ ≥50% Predicted (n=27)</th>
<th>Peak VO₂ &lt;50% Predicted (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Exercise (yr)</td>
<td>15 (13, 17)</td>
<td>14 (13, 16)</td>
<td>15 (13, 17)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female Gender</td>
<td>24 (49%)</td>
<td>16 (59%)</td>
<td>8 (36%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>53 (39, 63)</td>
<td>51 (36, 62)</td>
<td>54 (44, 69)</td>
<td>0.18</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.54 (1.28, 1.73)</td>
<td>1.53 (1.19, 1.66)</td>
<td>1.58 (1.38, 1.80)</td>
<td>0.13</td>
</tr>
<tr>
<td>Single Ventricle</td>
<td>18 (36%)</td>
<td>6 (22%)</td>
<td>12 (52%)</td>
<td>0.04</td>
</tr>
<tr>
<td>End-diastolic Volume Z-Score</td>
<td>5.6 (3.0, 9.7)</td>
<td>3.9 (0.2, 7.4)</td>
<td>9.0 (4.9, 12.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>28 (23, 40)</td>
<td>36 (24, 43)</td>
<td>26 (20, 32)</td>
<td>0.16</td>
</tr>
<tr>
<td>BNP (n=12, 9)</td>
<td>314 (106, 878)</td>
<td>329 (109, 973)</td>
<td>248 (72, 745)</td>
<td>0.72</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.7 (0.6, 0.8)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.7 (0.6, 0.9)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Hemodynamic Data</strong></td>
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<td></td>
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<tr>
<td>Cardiac Index (liters/min)</td>
<td>2.5 (2.3, 2.9)</td>
<td>2.6 (2.3, 2.9)</td>
<td>2.5 (2.3, 3.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>PCW Pressure (mm Hg)</td>
<td>16 (12, 19)</td>
<td>16 (13, 20)</td>
<td>14 (11, 17)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Exercise Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>140 (125, 156)</td>
<td>147 (133, 166)</td>
<td>135 (115, 143)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak VO₂ (ml/Kg/min)</td>
<td>19.1 (14.0, 25.0)</td>
<td>24.6 (19.6, 28.1)</td>
<td>14.0 (12.7, 18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak VO₂ (% Predicted)</td>
<td>51 (39, 61)</td>
<td>58 (53, 69)</td>
<td>39 (33, 44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak O₂ Pulse (ml/min)</td>
<td>7.1 (4.8, 8.6)</td>
<td>7.7 (6.2, 8.5)</td>
<td>6.6 (4.6, 8.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Peak O₂ Pulse (% Predicted)</td>
<td>70 (53, 88)</td>
<td>84 (73, 97)</td>
<td>53 (50, 60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VE/VCO₂ Slope</td>
<td>35 (32, 44)</td>
<td>33 (29, 37)</td>
<td>43 (32, 49)</td>
<td>0.009</td>
</tr>
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<td>Peak RER</td>
<td>1.10 (1.01, 1.18)</td>
<td>1.09 (1.03, 1.13)</td>
<td>1.10 (1.01, 1.21)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
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<td></td>
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</tr>
<tr>
<td>Loop Diuretics</td>
<td>36 (72%)</td>
<td>18 (67%)</td>
<td>18 (78%)</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td></td>
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<td>-------------------</td>
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</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>25 (50%)</td>
<td>13 (48%)</td>
<td>12 (52%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>20 (40%)</td>
<td>9 (33%)</td>
<td>11 (48%)</td>
<td>0.39</td>
</tr>
<tr>
<td>ACE Inhibitors</td>
<td>39 (77%)</td>
<td>21 (78%)</td>
<td>18 (78%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>28 (56%)</td>
<td>13 (48%)</td>
<td>15 (65%)</td>
<td>0.26</td>
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</tbody>
</table>

VO$_2$ indicates oxygen consumption, BNP, brain natriuretic peptide, PCW, pulmonary capillary wedge, VE, minute ventilation, VCO$_2$, carbon dioxide production, and ACE, angiotensin converting enzyme. The numbers within parentheses represent the number of patients in each group with available data.
Figure Legends

**Figure 1.** Flow diagram illustrating patient selection for the study group. CICU (Cardiac Intensive Care Unit)

**Figure 2.** Freedom from death or deterioration stratified by percent-predicted peak VO$_2$ in children with biventricular circulation (2A) and in children with a palliated single ventricle (2B).

**Figure 3.** Freedom from death or deterioration stratified by VE/VO$_2$ slope in children with biventricular circulation (3A) and in children with a palliated single ventricle (3B).
Figure 1

HT Evaluation
N=110

Exclusion Criteria
N=10
Re-transplant (N=8), Multi-organ transplant (N=1), No follow-up (N=1)

Eligible Subjects
N=69

Refractory Heart Failure (CICU) N=31

Not Analyzed
N=19
No exercise test (N=11), Incomplete exercise data (8)

Study Subjects
N=50
Figure 2A
Figure 2B

Freedom from Outcome

Time Since Exercise (months)

0.00  0.20  0.40  0.60  0.80  1.00

<50

>=50

7  14
7  14
5  13
5  12
4  11
3  9
2  7
Figure 3A

The figure illustrates the freedom from outcome over time since exercise. Two groups are compared: those with a time since exercise of less than 34 months and those with a time since exercise of 34 months or more. The graph shows the cumulative incidence of the outcome, with the time since exercise in months indicated on the x-axis and the freedom from outcome on the y-axis. The data points for each group are marked with numbers representing the counts for each time interval.
Figure 3B
Prognostic Value of Exercise Testing During Heart Transplant Evaluation in Children
Irene D. Lytrivi, Elizabeth D. Blume, Jonathan Rhodes, Shay Dillis, Kimberlee Gauvreau and Tajinder P. Singh

Circ Heart Fail. published online April 11, 2013;
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/early/2013/04/11/CIRCHEARTFAILURE.112.000103

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