Peak Oxygen Uptake Correlates With Survival Without Clinical Deterioration in Ambulatory Children With Dilated Cardiomyopathy

Alessandro Giardini, MD, PhD; Matthew Fenton, MB, BS; Rachel E. Andrews, MRCPCH; Graham Derrick, MD; Michael Burch, MD

Background—Children stable at home with dilated cardiomyopathy remain at risk of death; there is evidence of survival benefit for transplantation out to 4 years postoperatively. The limited supply of donor organs makes risk stratification imperative, but although cardiopulmonary exercise test is well established as a powerful tool in adults with heart failure, no published studies have linked oxygen uptake to prognosis in children.

Methods and Results—Between 2001 and 2009, using cardiopulmonary exercise test and echocardiography, we studied 82 children (mean age, 13.5 ± 2.3 years) with dilated cardiomyopathy. All were ambulatory, outpatients, and >120 cm in height. All children completed a symptom-limited maximal exercise test. Resting left ventricular shortening fraction was 20 ± 9%; peak heart rate was 87 ± 13% of predicted; peak oxygen uptake (VO2) was 67 ± 22% of predicted; and ventilatory efficiency was 32 ± 8. Follow-up was available for 100% of the children, and was a mean of 32.3 ± 7.5 months. Eighteen patients reached the defined clinical end point of death or listing for urgent heart transplantation. On univariate analysis, left ventricular shortening fraction, peak heart rate, peak VO2, peak systolic blood pressure, and ventilatory efficiency were all associated with adverse outcome. On multivariable Cox analysis, only peak VO2 (P = 0.003) was associated with the study end point. Patients with a peak VO2 < 62% of predicted had a higher 24-month event rate (50.6% versus 4.4%; hazard ratio, 10.78).

Conclusions—We have demonstrated that a cardiopulmonary exercise test is feasible in ambulatory children with dilated cardiomyopathy who are > 120 cm height and for the first time have linked peak VO2 with outcome in children. (Circulation. 2011;124:1713-1718.)

Key Words: exercise | heart failure | pediatrics | prognosis | transplantation

Even in the current era, children with heart failure secondary to heart muscle disease have a poor prognosis.1 Survival can be improved by more aggressive use of transplantation and mechanical circulatory support.2,3 Although the decision to perform a heart transplantation (HTx) for a child on inotropes or mechanical support is straightforward, risk stratification of ambulatory pediatric outpatients with dilated cardiomyopathy (DCM) remains challenging. However, it is also clear that children who are stable at home with chronic heart failure remain at risk of death with a survival benefit of transplantation out to 4 years after transplantation.4 The limited supply of donor organs makes risk stratification imperative.

Clinical Perspective on p 1718

Extensive evidence from adult studies5–7 supports the use of cardiopulmonary exercise testing (CPX) as a tool to predict which patients would have an increased short-term mortality without HTx. However, information regarding the practical clinical value of CPX as a prognostic tool in pediatric DCM is limited. Not unreasonably, the current clinical guidelines for HTx in children with DCM are extrapolated from the adult heart failure practice and suggest that a peak VO2 value < 50% of that predicted for age and sex appears to be a marker of substantial exercise intolerance in patients with pediatric heart disease.8 The aim of the present study is to assess the utility of CPX in pediatric DCM and to establish levels of exercise intolerance associated with adverse short-term prognosis.

Methods

This study was designed as a single-center retrospective investigation. The hospital institutional review committee approved the study and waived the need for consent. Since 2001, all children referred to the heart failure program with chronic heart failure related to left ventricular systolic dysfunction and who were at least 120 cm tall (minimum height to perform the exercise test on a cycle ergometer at our institution) have received a CPX as part of the disease surveillance program. Between 2001 and March 2009, 82 consecu-
tive children with DCM were studied with CPX. DCM was defined as left ventricular end-diastolic diameter Z score >2.0 and a left ventricular shortening fraction (LVSF) <30%. DCM was idiopathic in 77 (93.9%), induced by anthracycline in 4 (4.9%), and ischemic secondary to anomalous left coronary artery from the pulmonary artery in 1 (1.2%). All patients were outpatients and considered stable on oral medical therapy alone. None had been hospitalized in the month before assessment.

The data in the study were taken at the initial assessment of CPX and included the initial physiological data, medications prescribed, and echocardiography. Echocardiography was performed on the same day as the CPX.

**Follow-Up and Analysis of Survival Status**

After the exercise tests, all patients were followed up regularly at our institution, which ensured that all adverse events were captured. Additionally, patients’ medical records were reviewed to abstract the relevant data, including survival status. Survival was taken as the time from initial exercise testing. The study end point was the combination of death without HTx and clinical deterioration requiring urgent listing for HTx. Whereas criteria for elective listing were based on the presence and magnitude of symptoms, criteria for urgent listing were mechanical ventilation, high-dose intravenous inotropic agents, or need for bridging with an extracorporeal membrane oxygenator.

**Cardiopulmonary Exercise Test**

Exercise tests were performed on an electronically braked ergometer cycle. Carbon dioxide elimination (VCO2), VO2 and minute ventilation (VE) were measured with a computerized breath-by-breath analyzer (Medgraphics, St. Paul, MN). Patients performed a symptom-limited maximal exercise test using a continuous incremental bicycle protocol with a work rate increment between 5 and 20 W/min, with the aim of completing the test within 10 to 12 minutes of exercise. Criterion for test ending was considered patient exhaustion with a respiratory exchange ratio of 1.13. A 12-lead ECG and transcutaneous oxygen saturation were also monitored continuously throughout the study, and cuff blood pressure was determined manually every 2 minutes. The technical details of the measurement of peak VO2 and VE/VCO2 slope were previously published. In particular, VE/VCO2 slope was calculated from all data points until peak exercise. Resting heart rate (HR) was measured after at least 2 minutes of complete rest in a seated position, and peak HR was defined as the maximal HR achieved during exercise. Predicted maximum HR was estimated according to the following formula: 200−age in years. Chronotropic incompetence was described as a ratio of peak HR to predicted peak HR of <0.85. None of the patients had known coronary artery disease or inability to exercise for other reasons. Standard equations were used to generate predicted values for baseline spirometric and peak exercise parameters. Because of age-related differences in normal peak VO2 when expressed in milliliters per kilogram per minute in a pediatric patient cohort with a large age range, peak VO2 was expressed as percent of predicted value based on sex and age. Z-scores for peak exercise systolic blood pressure were calculated from the normative data of Alpert et al.

**Statistical Analysis**

Data distribution was tested with the Shapiro-Wilk test. Normally distributed continuous data were reported as mean±SD. Categorical variables were reported as number and percentage. The association of the primary outcome with different demographic, echocardiographic, and exercise variables (sex, age at CPX, LVSF, peak systolic blood pressure Z score, VE/VCO2 slope, peak VO2%, and peak HR%) were assessed with univariate Cox analysis. To assess the combined utility of alternatively LVSF (model 1) and VE/VCO2 slope (model 2) on top of peak VO2%, 2 multivariable Cox models were tested. The estimated hazard ratio with 2-sided 95% confidence interval is given. An empirical cutoff value of peak VO2 was selected to define groups for plotting the Kaplan-Meier curve. Event rates in patients with peak VO2 ≤62% of predicted were compared with those of patients with a peak VO2 >62% of predicted. Statistical computations were performed with MedCalc (MedCalc Software, Belgium) and GraphPad Prism (GraphPad Software, Inc, San Diego, CA) software packages. Competing outcomes survival probability was calculated with R software (available at www.r-project.org) as suggested by Scrucca et al. Possible outcomes were censored as follows: alive with no HTx = 0, elective HTx = 1, listing for urgent HTx = 2, death without HTx = 3. A 2-tailed value of P ≤0.05 was used as the criterion for statistical significance.

**Results**

The baseline characteristics of the 82 pediatric DCM patients included in this study are presented in Table 1. All patients completed the maximal CPX at a mean age of 13.5±2.3 years (range, 7.9–17.7 years), with a peak exercise respiratory exchange ratio of 1.13±0.09. Overall, LVSF was 20±9%. Exercise capacity was 28.6±10.0 mL·kg⁻¹·min⁻¹ (range, 12.3–50.4 mL·kg⁻¹·min⁻¹), which corresponded to

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Cohort</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Age at test, y</td>
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<tr>
<td>Male sex, n (%)</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Body surface area, m²</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>Peak workload, W</td>
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<td>Peak SBP, mm Hg</td>
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<td>Z score</td>
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<td>Peak heart rate, bpm</td>
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<td>Percent of predicted</td>
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<tr>
<td>Prevalence of chronotropic incompetence, n (%)</td>
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<tr>
<td>Peak VO₂, mL·kg⁻¹·min⁻¹</td>
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<tr>
<td>Percent of predicted</td>
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<tr>
<td>VO₂/workload slope</td>
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<td>Peak minute ventilation, L/min</td>
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<td>VE/VCO₂ slope</td>
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<td>Peak respiratory exchange ratio</td>
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<td>Pacemakers/ICD, n (%)</td>
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<tr>
<td>Medications, n (%)</td>
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<tr>
<td>Furosemide</td>
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<td>Spironolactone</td>
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<td>Warfarin</td>
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LVSF indicates left ventricular shortening fraction; SBP, systolic blood pressure; VO₂, oxygen uptake; VE/VCO₂ slope, ventilatory efficiency; and ICD, implantable cardioverter-defibrillator.
67±22% of predicted (range, 27%–107%). Peak HR in the overall study cohort was 162±26 bpm (range, 117–207 bpm), which corresponded to 87±13% of predicted (range, 62%–111%). Thirty patients (36.6%) had chronotropic incompetence. Peak exercise systolic blood pressure was 119±25 mm Hg, which corresponded to a Z score of 4.3±4.0. Forty-one patients (50%) were receiving β-blockers at the time of the CPX, and 56 patients (68%) were receiving angiotensin-converting enzyme inhibitors.

Outcome
All patients had complete follow-up until November 2010. Details on the outcome of the study cohort are shown in Figure 1. Competing outcomes survival probability is shown in Figure 2.

At an average follow-up of 32.3±7.5 months (range, 0.3 [early transplantation] to 93.4 months after the CPX), 18 patients reached the end point of death or urgent listing for HTx. In detail, 7 patients died (sudden death in 2 and rapid clinical deterioration in 5), whereas 11 patients needed urgent listing for HTx because of severe clinical deterioration and were bridged to HTx on high-dose intravenous inotropic support (n=6) or on extracorporeal membrane oxygenator support (n=5). The range of time between urgent listing and HTx was 3 to 25 days. Twelve additional patients underwent nonurgent HTx.

**Correlates of Outcome**
At univariate analysis, LVSF (P=0.0001), peak HR% (P=0.002), peak VO₂% (P<0.0001), peak systolic blood pressure Z score (P=0.001), and VE/VCO₂ slope (P=0.0001) were all associated with a higher rate of death or need for HTx, whereas sex (P=0.197) and age at CPX (P=0.292) were not. In the multivariable analysis that included peak VO₂% and LVSF as independent variables (model 1), peak VO₂% (P=0.003) was the only variable associated with the composite end point (Table 2). LVSF did not add significant information. In multivariable Cox model 2, peak VO₂% was also the only variable associated with outcome (P=0.008), with VE/VCO₂ slope not being retained in the model.

Using the empirical peak VO₂ cutoff point of 62% of predicted, Kaplan-Meier survival curves showed a higher rate of death/listing for urgent HTx in patients with a peak VO₂ ≤62% (event rate at 24 months, 50.6% versus 4.4%; hazard ratio, 10.78; 95% confidence interval, 4.04–27.98; Figure 3).
Discussion

We have shown that in stable, ambulatory pediatric DCM patients, a symptom–limited CPX can be achieved in all patients referred. The mean age at testing was comfortably in the pediatric age range (13.5±2.3 years), with a lower range of only 7.9 years. The patients in this study were children who were ambulatory and at home. Yet, unlike adults, ambulatory children at home with chronic heart failure have a clear survival benefit from transplantation out to 4 years after transplantation.4 Therefore, risk stratification is integral to the effective management of these children, and the limited supply of donor organs in the pediatric age group reinforces the clinical need to identify those likely to benefit most from transplantation. This study is the first to show that exercise intolerance (expressed as peak VO2%) may be helpful to identify children in whom the rate of death or clinical deterioration requiring urgent listing for transplantation is higher. As in adults, exercise testing is of prognostic value up to 2 years after testing.5–7 Importantly, the information provided by peak VO2 was able to complement that provided by other established risk factors such as the extent of left ventricular systolic dysfunction.

Clinical Utility of Peak VO2%

Our findings are in keeping with the large body of evidence that CPX is useful to risk stratify adult patients with DCM who have heart failure.5–7 However, until now, this has not been validated in the pediatric age range. Only 1 study has assessed the relationship between CPX variables and outcome in pediatric DCM. Guimarães and colleagues16 studied 31 children with DCM at a mean age of 8.6±1.9 years. Unlike our patients, all children were on the active list for transplantation at the time of the study. Peak VO2 values were similar in patients who died or had HTx and in those who did not (18.3±5.7 versus 22.0±5.4 mL · kg⁻¹ · min⁻¹; P=NS). The expression of peak VO2 as an absolute value, rather than as a percentage of predicted normal value based on sex and age, might explain this finding, particularly because there is an overall trend for increasing peak VO2 (in mL · kg⁻¹ · min⁻¹) in the young.17 Similarly, Das and colleagues18 showed that only 21% of children on the waiting list for HTx have a peak VO2 below the 14 mL · kg⁻¹ · min⁻¹ cutoff currently used to recommend HTx in adults. Their small study also showed that the use of absolute peak VO2 value (in mL · kg⁻¹ · min⁻¹) can be misleading in children because of differences in body size and muscle mass.

Left Ventricular Systolic Function and Prognosis

It is perhaps unsurprising that we have shown on univariate analysis (but not multivariable analysis) that left ventricular systolic function might have prognostic value in children with DCM. Yet, it is common practical experience that the outcome can differ in children with similarly impaired systolic function. Although an arbitrary ejection fraction/shortening fraction may identify children at risk, few would refer for transplantation on this basis alone. Importantly, our results show that CPX is able to complement the information provided by LVSF and that peak VO2% is possibly superior to LVSF to risk stratify children with DCM at risk of death or clinical worsening requiring urgent listing for HTx.

VE/\(VCO_2\) Slope and Prognosis

A large body of evidence suggests that VE/\(VCO_2\) slope provides important prognostic information in adults with chronic heart failure.19 Similarly, we could identify an association between VE/\(VCO_2\) slope and outcome on univariate analysis in the present study. However, contrary to what has been observed in the adult literature,\textsuperscript{19} VE/\(VCO_2\) slope did not provide additional information to that provided by peak VO2% in children. Even though this result might be surprising, the age range of the population studied might explain the results observed. Indeed, there is evidence that the VE/\(VCO_2\) slope is higher at young ages and tends to reach normal adult values only at ≈16 years of age.\textsuperscript{20,21} This implies that the same particular VE/\(VCO_2\) slope value could be perfectly normal in a 12-year-old patient but would clearly be pathological at 17 years of age. The exact reason for this is unknown, but this clearly is likely to have an impact on the
prognostic value of this variable when used in a pediatric population.

Clinical Implications
Our study provides supportive evidence for the use of peak VO$_2$ for risk stratification of pediatric DCM. We believe exercise test variables may become part of the standard clinical risk assessment for those children with DCM in whom we have shown it is feasible to perform CPX (ambulatory outpatients who are >120 cm).

Limitations
The present retrospective study was performed at a national tertiary referral center, which potentially introduces a bias toward inclusion of patients with more advanced disease. The data can be interpreted only in the population we studied. The children excluded were those who were not ambulatory, inpatients or recent inpatients, those on intravenous therapy, and those <120 cm tall (minimum height to perform the exercise test on a cycle ergometer at our institution). Medication status was recorded at the time of CPX, and the study was not designed to be able to assess the effects of individual medications or changes in medications on prognosis. We also have to acknowledge the likely presence of an era effect in which patients enrolled in the early era were less likely to receive what would nowadays be considered the standard pharmacological treatment for heart failure. The mortality and urgent HTx rate in the present study were relatively high, considering that the study population consisted of outpatients. However, similar results have been reported in United Network of Organ Sharing status 2 children who, despite a low mortality while awaiting transplantation (4% at 12 months), have a high risk of severe clinical deterioration (40% at 12 months), requiring bridge to urgent transplantation with either mechanical support or inotropes. There is evidence in adults with heart failure that the use of implantable defibrillators and cardiac resynchronization therapy improves outcome in patients with DCM. However, experience with the use of such therapies in children is still extremely limited, as reflected by the fact that only 3 patients in the present study had received an implantable defibrillator.

The cutoff limit selected was not validated externally and might not necessarily be optimal.

Conclusions
We have demonstrated that symptom-limited CPX is feasible in a defined population of ambulatory pediatric outpatients of >120 cm height with DCM and chronically impaired ventricular function, a group known have a survival benefit for transplantation. We have linked peak VO$_2$ with outcome in pediatric DCM; those with peak VO$_2$ ≤62% of predicted have an increased rate of death or clinical deterioration requiring urgent listing for HTx.

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Disclosures
None.

References
In adults, cardiopulmonary exercise testing is an integral part of the decision-making process for heart transplantation listing. However, experience with using cardiopulmonary exercise test as a prognostic tool in children is very limited. In the present study, using cardiopulmonary exercise testing, we studied 82 ambulatory children with dilated cardiomyopathy and found that lower peak oxygen uptake was associated with a higher rate of death (without transplantation) and clinical deterioration requiring urgent listing for transplantation. Children with a peak oxygen uptake ≤62% of the predicted value were at particularly high risk. The study provides supportive evidence for the use of cardiopulmonary exercise test for risk stratification of pediatric dilated cardiomyopathy and suggests that exercise test variables may become part of the standard clinical risk assessment of older children with dilated cardiomyopathy.
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