Longitudinal Assessment of Cardiovascular Exercise Performance After Pediatric Heart Transplantation

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Background: No existing longitudinal data document exercise performance after pediatric heart transplantation. We report the exercise performance findings from the longitudinal study of pediatric heart transplantation patients and the association of aerobic capacity with echocardiographic measures of graft function.

Methods: We performed a retrospective analysis of 28 children after heart transplantation who underwent 87 exercise tests and echocardiograms. Subjects exercised using graded cycle or treadmill protocols. Maximal oxygen consumption (VO_2), physical working capacity, peak heart rate, and anaerobic threshold were evaluated. To measure systolic and diastolic function, shortening fraction and mitral valve pressure half-time (PHT) respectively, were obtained by echocardiography.

Results: The average age at transplantation was 10.9 ± 5.6 years, at initial exercise test was 13.8 ± 5.0 years, and at final exercise test was 15.8 ± 5.2 years. Percent-predicted values at the initial exercise test were VO_2, 59.3%; physical working capacity, 60.2%; and peak heart rate, 75.8%; these remained similarly decreased at the final exercise test. Shortening fraction and PHT were within normal limits, but PHT was significantly greater at final test ($p < 0.05$). The relationship of VO_2% with time was statistically significant, described by a quadratic equation that included initial VO_2% and time from heart transplantation. This relationship remained significant when the shortening fraction ($p < .05$) but not PHT was added as a covariate in the equation.

Conclusions: Exercise performance after pediatric heart transplantation is impaired and, despite an initial improvement, declines over time. This can be explained by increasing diastolic dysfunction independent of donor graft age. If confirmed, these findings point the direction to further research aimed at limiting this aerobic capacity decline after heart transplantation. J Heart Lung Transplant 2006;25:626–33. Copyright © 2006 by the International Society for Heart and Lung Transplantation.

Orthotopic pediatric heart transplantation (HTX) has now become an accepted intervention to prolong the lives of children with end-stage heart disease.[1,2] The long-term survival is favorable, with survival rates of approximately 85%, 75%, and 65% at 1, 5, and 10 years after HTX, respectively.[1] Studies of adult HTX survivors have demonstrated impaired exercise performance compared with otherwise healthy patients.[3–8]

Several factors are thought to be involved, including chronotropic impairment,[4,6,7,9–11] musculoskeletal abnormalities,[12–15] and acute and chronic graft dysfunction. Graft dysfunction involves abnormalities in both systolic and diastolic function at rest and during exercise.[4,9,10,16,17] Established non-invasive measures of systolic and diastolic function include shortening fraction and mitral valve pressure half-time, respectively.[18–21]

Limited data exist on exercise performance after pediatric HTX. Cross-sectional studies have shown that, similar to adult HTX patients, pediatric HTX survivors have diminished aerobic capacities compared with otherwise healthy children.[22–26] To our knowledge, no studies to date have longitudinally evaluated aerobic capacity after HTX in the pediatric population. We now report the first retrospective analysis of exercise performance findings from a longitudinal study of 28 pediatric HTX patients and the association of aerobic capacity with echocardiographic measures of graft function.

METHODS

Inclusion Criteria

Subjects were included in our study if they had undergone pediatric HTX between January 1993 and January 2002 and subsequently had their patient care at The Children's Hospital of Philadelphia (CHOP). A search of

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the Exercise Physiology Laboratory database at CHOP identified HTX patients who had exercise stress tests performed over the 4-year period between 1999 and 2003. The study only included subjects who were medically stable, without evidence of acute rejection or other chronic disease causing muscle weakness. Acute rejection was defined as grade 2 or greater by endomyocardial biopsy specimen according to the International Society of Heart and Lung Transplantation Society guidelines.[27] Biopsy specimens were obtained by cardiac catheterization within 1 week of exercise testing. All patients were assessed either annually or semiannually, depending on length of time since HTX. These evaluations generally included a clinic visit, transthoracic echocardiogram, exercise stress test, and cardiac catheterization.

The study was conducted after approval by The CHOP's Institutional Review Board.

Exclusion Criteria

A total of 65 patients fit the criteria. Thirty-seven patients were excluded for the following reasons: only 1 exercise test completed ($n = 19$), initial exercise test greater than 100 months after HTX ($n = 8$), heart-lung transplant ($n = 6$), systemic disease causing generalized myopathy ($n = 2$), and acute rejection identified at time of testing ($n = 2$).

Medications

All patients were receiving maintenance immunosuppressive medication at the time of exercise testing. Twenty-five patients (89.3%) were receiving triple immunosuppressive therapy (calcineurin inhibitor, purine inhibitor, and prednisone), and the remaining 3 patients were receiving a similar immunosuppressive regimen but without steroids. The type of immunosuppression medication did not change between tests. Steroid therapy was low-dose, from 0.05 mg/kg to 0.4 mg/kg per day. For systemic hypertension, 21 (75%) patients were taking calcium-channel blockers; 2 (7.1%) were taking additional angiotensin-converting enzyme inhibitors, and 1 was also taking a β-blocker (3.6%). Other cardioactive medications included digoxin (1 patient) and mexiletine (1 patient). For most patients, there was no change in anti-hypertensive medication between tests. Two patients had a calcium-channel blocker added after their first test, and 2 other patients had a calcium-channel blocker added before their final test. One patient was taking an angiotensin-converting enzyme inhibitor at the first test that was changed to a calcium-channel blocker before the subsequent tests.

Exercise Protocol

Subjects were exercised to maximal volition using an electronically braked cycle ergometer (SensorMedics, Yorba Linda, CA). The protocol consisted of 3 minutes of pedaling in an unloaded state followed by a ramp increase in work rate (watts) to maximal exercise capacity. The steepness of the ramp protocol was designed to achieve predicted peak work rate in 10 to 12 minutes of cycling time. Five subjects who did not meet the height requirements (height < 130 cm) for cycle ergometry were exercised using a graded treadmill (Marquette Series 2000, Milwaukee, WI) protocol. This consisted of 3 minutes of walking followed by 1-minute of incremental increases in speed and grade to maximal exercise. Of these 5 patients, 3 exercised on the bicycle on subsequent tests. Two older patients requested treadmill instead of bicycle testing.

Cardiac Monitoring

A 12-lead electrocardiogram (Marquette Case-8000, Milwaukee, WI) was obtained at rest in the supine, sitting, and standing positions during each minute of exercise and during the first 10 minutes of recovery. Cardiac rhythm was monitored continuously throughout the study. Blood pressure was measured by auscultation at rest and every 3 minutes during exercise and recovery.

Metabolic Measurements

Metabolic data were obtained throughout the exercise study and for the first 2 minutes of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics V29, Yorba Linda, CA). Measured variables included maximal oxygen consumption (VO_2), carbon dioxide production, minute ventilation, and peak heart rate (PHR). The ventilatory anaerobic threshold was measured by the V-slope method.[28] Data were expressed as percent-predicted values from age- and gender-matched normative data used in our laboratory.[29] Values were indexed for ideal body weight in those patients whose weight exceeded 110% of ideal body weight at the time of exercise test.[30]

Echocardiography Protocol

Echocardiographic evaluations were taken at or near the time of each subject's exercise test, with all but 3 echocardiograms obtained within 2 months of exercise testing. These consisted of complete 2-dimensional (2D) studies with Doppler evaluation and were recorded on videotape and digital transfer medium. Left ventricular end-diastolic and end-systolic volumes were measured from the standard parasternal short-axis views using 2D and M-mode imaging. Shortening fraction (SF) was calculated from the standard formula: (left ventricular end-diastolic dimension − left ventricular end-systolic dimension)/left ventricular end-diastolic dimension.[18] Mitral valve pressure half-time (PHT in msec equals rate of peak early mitral flow deceleration divided by 220) was obtained from Doppler interrogation