Impairment of Heart Rate Recovery After Peak Exercise Predicts Poor Outcome After Pediatric Heart Transplantation

Alessandro Giardini, MD, PhD; Matthew Fenton, MBBS; Graham Derrick, MD; Michael Burch, MD

Background—A blunted heart rate recovery (HRR) from peak exercise is associated with adverse outcome in adults with ischemic heart disease. We assessed HRR after pediatric heart transplantation (HTx) and its prognostic use.

Methods and Results—Between 2004 and 2010 we performed 360 maximal exercise tests (median, 2 tests/patient; range, 1–7) in 128 children (66 men; age at test, 14±3 years) who received HTx (age, 8.5±5.1 years) because of cardiomyopathy (66%) or congenital heart defects (34%). The change in heart rate from peak exercise to 1 minute of recovery was measured as HRR and was expressed as Z score calculated from reference data obtained in 160 healthy children. HRR was impaired soon after HTx (average in first 2 years Z=−1.9±3.5) but improved afterward (Z=+0.52/y), such that HRR Z score normalized in most patients by 6 years after HTx (average, 0.6±1.8). A subsequent decline in HRR Z score was noted from 6 years after HTx (rate of Z=−0.11/y). After 27±15 months from the most recent exercise test, 19 patients died or were re-heart transplantation. For the follow-up after 6 years, HRR Z score was the only predictor of death/re-heart transplantation ($P=0.003$). Patients in the lowest quartile of HRR Z score had a much higher 5-year event rate (event-free rate, 29% versus 84%; hazard ratio, 7.0; $P=0.0013$).

Conclusions—HRR is blunted soon after HTx but normalizes at =6 years, potentially as a result of parasympathetic reinnervation of the graft, but then declines. This late decline in HRR Z score is associated with worse outcome. (Circulation. 2013;128[Suppl 1]:S199-S204.)

Key Words: exercise • pediatrics • prognosis • transplants

Heart transplantation (HTx) has dramatically improved the outcome of children diagnosed with end-stage heart failure related to congenital heart disease or cardiomyopathy, with a survival of ≈60% at 10 years after HTx.1

HTx is associated with interruption of sympathetic and parasympathetic cardiac nerves, leading to immediate cardiac denervation. Within the first 2 years after HTx, there is evidence of progressive cardiac reinnervation.2,3 Although the evidence for cardiac sympathetic reinnervation is robust,2,4 the evidence for cardiac parasympathetic reinnervation is limited, and the exact timing is uncertain.3,5

Evidence suggests that heart rate recovery (HRR) after exercise is a marker of cardiac vagal tone,6,7 with the first 30 seconds of recovery being a pure index of cardiac parasympathetic activation and the following 30 seconds representing a combination of parasympathetic activity and adrenergic withdrawal. If measured longitudinally, HRR could provide important information regarding the extent and timing of cardiac parasympathetic reinnervation. In addition, there is evidence that the speed of HRR in the first minute after peak exercise is a significant marker for unfavorable outcome in general adult populations and in patients with ischemic heart disease.8,9

The purpose of this study was to determine the extent and timing of cardiac parasympathetic reinnervation in a large group of pediatric HTx patients and to assess the prognostic use of HRR in this population.

Methods

We conducted a retrospective review of all exercise tests performed at our center between January 2004 and June 2011. Exercise tests were performed electively during annual reviews after HTx. Routine echocardiography was performed on the same day.

Transplantation

All transplants were performed using bicaval anastomosis according to a standard technique.10

Exercise Test

The exercise tests were performed on an electronically braked ergometer cycle. Oxygen uptake, carbon dioxide elimination, and minute ventilation were measured with a computerized breath-by-breath analyzer (Medgraphics, St. Paul, MN). All children performed a symptom-limited maximal exercise test using a continuous incremental bicycle protocol with a work rate increment between 10 and 20 W/min, with the aim of completing the test within 10 to 12 minutes of exercise. A 12-lead ECG and transcutaneous oxygen saturation were also monitored throughout the study, and cuff blood pressure...
was determined manually every 2 minutes. The test was considered as maximal when the child reported exhaustion (confirmed by an experienced physiologist attending the test) or when a respiratory exchange ratio ≥1.09 was reached. The technical details relating to peak \( \text{V} \text{O}_2 \) measurement and other exercise variables are previously published.3,12 Resting heart rate (HR) was measured after ≥2 minutes of complete rest in a seated position, and peak HR was defined as the maximal HR achieved during exercise. After termination of exercise, all children received continuous heart rate monitoring for the following 5 minutes. All children continued loadless, slow (20 revolutions/min) cycling in the first minute of recovery.

### Calculation of HRR

HRR was calculated manually using heart rate data collected in the first minute of recovery from exercise. HRR was calculated as the first-degree slope of a single linear relationship, calculated by means of linear regression, as previously described.13 Recovery in the first minute was selected because of its recognized use as a measure of vagal reinnervation and demonstration of its strong relationship with outcome data.6,8,9

### Follow-Up and Analysis of Survival Status

After exercise tests, all patients were regularly followed up at our institution, ensuring that all outcome events were captured. Survival was defined as the time from the last exercise testing to either death or retransplant or censored at the end of the study period. The institutional review committee approved the study.

### Calculation of HRR Normal Reference Data

HRR is known to change during development in the pediatric age group when measured as an absolute value in beats/second.1 Such an age-related change in HRR in children would make any longitudinal assessment of HRR impossible, unless individual data were reported as SD scores (Z scores) from the expected value. For this reason, we analyzed the data available for 160 exercise tests performed in 160 healthy children (age, 12.8±2.0 years; 87 boys) who underwent exercise testing at the same center during the same time period to develop normal ranges for HRR. Part of this control population was reported in a previous publication.11 The control group consisted of children referred as part of the family screening of long-QT syndrome (n=31), arrhythmogenic right ventricular cardiomyopathy (n=42), hypertrophic cardiomyopathy (n=46), and children with complaints of chest pain during exercise or history of palpitation during exercise (n=6). Furthermore, 35 children were normal subjects who were part of the control group for another study. No child of the control group was on medications that could affect heart rate response or HRR or had postural hypotension or a history of syncope/dizziness during exercise. All children of the control group had normal examination, normal ECG, and normal echocardiogram. Age-specific percentiles for HRR slope were charted with the LMS method using raw data obtained in the control group for analysis and LMS ChartMaker Pro software package (available at: http://www.healthforallchildren.com/product=lmsgrowth). L, M, and S parameters were determined by maximum penalized likelihood using the LMS method.11

### Calculation of HRR Slope Z Scores in the Patient Population

Once the absolute HRR slope value in beats/second was calculated for each HTx patient for each exercise test, it was transformed into an HRR Z score value based on the previously developed normality data, and the Z score obtained was used in subsequent analysis. Figure 1 is developed to enable the reader to calculate a specific patient HRR slope Z score by knowing the absolute HRR slope value (beats/second) and the age of the patient at the time of exercise test.

### Statistical Analysis

Data distribution was tested using the Kolmogorov–Smirnov test. Normally distributed data are reported as mean±SD. Categorical variables are reported as number and percentage. The association of the primary outcome of death or re-heart transplantation (re-HTx) with different demographic, echocardiographic, and exercise test variables was assessed with univariate and multivariable analysis. Because the number of events was limited and only 1 predictor of outcome was observed at univariate analysis, no multivariable analysis was conducted. Kaplan-Meier survival curves were generated comparing the survival of those children in the lowest quartile of HRR with those in the upper 3 quartiles using log-rank test. The association between HRR Z score and left ventricular shortening fraction was assessed by calculating Pearson correlation coefficient using the values measured at the last assessment. Statistical computations were performed with MedCalc (MedCalc Software, Belgium) and GraphPad Prism (GraphPad Software, Inc, San Diego, CA) software packages. A 2-tailed \( P\leq0.05 \) was used as the criterion for statistical significance.

![Red line indicates Z score = -1.841](image-url)
Results

A total of 160 control subjects (age, 12.8±2.0 years; 87 boys) were included. As shown in Figure 1, HRR decreased progressively from 10 to 18 years of age.

A total of 128 HTx patients (age, 14±3 years; 66 men) underwent 360 exercise tests in the study period (median, 2 tests/patient; range, 1–7 tests). Age at HTx in the study group was 8.5±5.1 years, and time from HTx was 6.0±4.1 years (median, 5.1 years; quartiles, 2.5–9.3 years). HTx was performed because of cardiomyopathy in 84 children (66%) and congenital heart disease in 44 children (34%). Left ventricular shortening fraction was 36±6%. No participants were treated with heart rate–lowering drugs, and all maintained sinus rhythm during exercise. No patient had an implanted pacemaker.

Exercise Test Results

All tests were maximal, with a peak respiratory exchange ratio of 1.14±0.10. Overall peak $V_O_2$ was 29.6±7.2 mLO$_2$/kg per minute, which corresponded to 73.1±17.7% of predicted value, whereas peak HR was 161±18 beats/min, which corresponded to 86.8±9.5% of predicted value. No patient had ST-segment changes suggestive of ischemia during exercise. One patient had negative T waves in V$_4$ through V$_5$ at rest, which became positive during exercise. Details of all exercise test results performed in the study patients are shown in Table 1. Of the demographic, clinical, and echocardiographic variables, only left ventricular shortening fraction was associated with HRR $Z$ score ($r=+0.269$; 95% confidence interval, 0.014–0.491; $P=0.039$).

Timing of Cardiac Autonomic Reinnervation After Pediatric HTx

HRR was abnormally distributed in the first 2 years from HTx as suggested by an average HRR $Z$ score of −1.9±3.5 (Figure 2). This was followed by a progressive average increase in HRR $Z$ score of +0.52/y, which led to normalization of HRR at ≈6 years from HTx (average $Z$, 0.6±1.8). After 6 years from HTx, the trend suggested a progressive decrease in HRR in the population as a whole at a rate of −0.11/y.

In Figure 2, the longitudinal changes in HRR observed in the 88 patients who had ≥2 exercise tests (solid lines) followed a similar pattern to the one produced when considering all exercise tests as individual data points.

Outcome

After follow-up of 27±15 months from exercise testing, 19 patients (age, 17±3 years) died (n=18) or underwent re-HTx (n=1). Nine patients died within 6 years from HTx. Ten patients died or were re-HTx after >6 years from HTx (death was sudden unexpected in 4 children, was because of graft failure in 4, and could not be ascertained in 2). Coronary angiography performed before the event showed diffuse coronary disease in 1 patient and mild left anterior descending coronary artery stenosis in 2 patients.

The prognostic value of demographic, echocardiographic, and exercise test variables was determined in the group of HTx patients who exercised from 6 years after HTx, after which HRR would have normalized according to the behavior observed in the population. Only data from the most recent exercise test were used for this analysis.

Table 1. Clinical and Exercise Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at exercise test, y</td>
<td>13.9±2.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>50±17</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160±5</td>
</tr>
<tr>
<td>Body surface area, m$^2$</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>19.7±4.2</td>
</tr>
<tr>
<td>Baseline heart rate, beats/min</td>
<td>100±14</td>
</tr>
<tr>
<td>Exercise time, seconds</td>
<td>780±167</td>
</tr>
<tr>
<td>Peak heart rate, beats/min</td>
<td>161±18</td>
</tr>
<tr>
<td>Percentage of predicted peak heart rate, %</td>
<td>86.8±9.5</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>110±52</td>
</tr>
<tr>
<td>Peak oxygen consumption, mLO$_2$/kg per minute</td>
<td>29.6±7.2</td>
</tr>
<tr>
<td>Percentage of predicted peak oxygen consumption, %</td>
<td>73.1±17.7</td>
</tr>
<tr>
<td>Peak minute ventilation, L/min</td>
<td>57±22</td>
</tr>
<tr>
<td>Peak respiratory exchange ratio, mmHg</td>
<td>1.14±0.11</td>
</tr>
<tr>
<td>Heart rate recovery in first minute</td>
<td>−0.64±2.76</td>
</tr>
</tbody>
</table>

*Data are presented as mean±SD.
Sixty patients had an exercise test from 6 years after HTx (age, 14.7±2.5 years; 28 men). Univariate Cox analysis demonstrated that only HRR was associated with the combined end point of death or re-HTx (Table 2). Kaplan–Meier curve showed a higher rate of death/re-HTx in patients in the lowest quartile of HRR Z score (<−1.841; event rate at 5 years, 84% versus 29%; hazard ratio, 7.0; 95% confidence interval, 2.7–64.0; P=0.0013; Figure 3).

Discussion

We have shown that HRR is blunted soon after pediatric HTx but improves and normalizes in most patients after 6 years. This finding is consistent with other publications.3,10 The reason for abnormal HRR soon after HTx is unknown, but severing of parasympathetic cardiac fibers during surgery is likely to be the cause.3,15 Autonomic reinnervation of the graft is likely to be the mechanism underpinning a progressive improvement in HRR in the first 6 years after HTx.16 Indeed, 2 main components determine HRR in the first minute of recovery after exercise: the initial rapid decrease that occurs promptly when exercise ceases is entirely because of increase in cardiac vagal activity (partly mediated by arterial baroreceptors),17 and the subsequent slow exponential decay in heart rate results from algebraic summation of an increasing vagal inhibitory effect and a gradually subsiding excitatory sympathoadrenal action.6,17 One other convincing aspect is that the pattern of parasympathetic reinnervation noted herein is similar to the pattern of parasympathetic reinnervation noted by others who found progressive improvement in HRR from exercise in the first few years after HTx in children.3 A recent study from Toronto investigated cardiac autonomic reinnervation in pediatric HTx recipients by means of heart rate variability.18 Using this alternative technique to assess autonomic function, the authors were able to demonstrate various degrees of reinnervation in up to 57% of hearts, with the majority of children showing signs of reinnervation by the fourth year after HTx. Furthermore, in a limited subset of patients who underwent exercise testing in that study, the authors were able to demonstrate a faster recovery of heart rate 1 minute after exercise in children with evidence or reinnervation, strengthening further the relationship between reinnervation and HRR.

A previous study investigated the extent and time course of cardiac autonomic reinnervation after pediatric HTx using exercise testing.5 One of the limitations of that study, besides the small number of patients included, was the limited follow-up time. Indeed, functional information regarding chronotropic competence and HRR was limited to the first 5.5 years after HTx. However, that study was the first to convincingly demonstrate progressive functional reinnervation in the first few years after pediatric HTx. The major finding of the present study is to have extended the window into functional assessment of pediatric HTx to up to 15 years after HTx. This extended window demonstrated that after the initial normalization of HRR there is a progressive decrease in HRR. The

Table 2. Univariable Predictors of the Composite End Point of Death or Re-heart Transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio†</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at HTx</td>
<td>1.017</td>
<td>0.850–1.218</td>
<td>0.851</td>
</tr>
<tr>
<td>Age at exercise test</td>
<td>0.928</td>
<td>0.737–1.170</td>
<td>0.534</td>
</tr>
<tr>
<td>Time since HTx</td>
<td>0.896</td>
<td>0.696–1.153</td>
<td>0.381</td>
</tr>
<tr>
<td>Diagnosis before HTx</td>
<td>0.538</td>
<td>0.109–2.647</td>
<td>0.422</td>
</tr>
<tr>
<td>Male</td>
<td>1.466</td>
<td>0.389–5.516</td>
<td>0.570</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.070</td>
<td>0.921–1.229</td>
<td>0.370</td>
</tr>
<tr>
<td>Exercise time</td>
<td>0.999</td>
<td>0.994–1.004</td>
<td>0.710</td>
</tr>
<tr>
<td>Peak heart rate</td>
<td>0.982</td>
<td>0.951–1.014</td>
<td>0.285</td>
</tr>
<tr>
<td>% of predicted peak heart rate</td>
<td>0.994</td>
<td>0.965–1.024</td>
<td>0.709</td>
</tr>
<tr>
<td>Peak oxygen uptake</td>
<td>0.976</td>
<td>0.892–1.067</td>
<td>0.589</td>
</tr>
<tr>
<td>% of predicted peak oxygen uptake</td>
<td>0.994</td>
<td>0.965–1.024</td>
<td>0.709</td>
</tr>
<tr>
<td>HRR Z score</td>
<td>0.756</td>
<td>0.639–0.896</td>
<td>0.0001</td>
</tr>
<tr>
<td>Left ventricular shortening function</td>
<td>1.009</td>
<td>0.903–1.126</td>
<td>0.877</td>
</tr>
</tbody>
</table>

HRR indicates heart rate recovery; and HTx indicates heart transplantation.

*Analysis was performed on data from the 60 patients who had an exercise test after >6 y from HTx.
†Hazard ratios were calculated for 1 U change in the univariate predictor.

Moderate improvement in cardiac autonomic reinnervation occurred in the first 6 years after HTx (Figure 3). The HRR Z score was significantly lower in the lowest quartile of HRR Z score (<−1.841; event rate at 5 years, 84% versus 29%; hazard ratio, 7.0; 95% confidence interval, 2.7–64.0; P=0.0013; Figure 3). The extended window demonstrated that after the initial normalization of HRR there is a progressive decrease in HRR. The
exact mechanism responsible for this new finding is unknown. Because there is a clear relationship between fitness level and HRR, a reduction in the overall fitness level of the population studied during follow-up could explain the decrease of HRR after 6 years from HTx. One final possibility is that changes in the graft that occur after several years might have influenced cardiac autonomic response in our population. Indeed, recent data suggest that coronary allograft vasculopathy represents the most common cause of death from 5 years after pediatric HTx, and its prevalence increases linearly during follow-up so that 43% of HTx children are affected after 12 years. Furthermore, researchers from Melbourne proved that in a group of 470 adults referred for elective coronary angiography, abnormal autonomic function demonstrated by low heart rate variability was strongly predictive of angiographic coronary disease, regardless of other comorbidities.

The main finding of our study is that a reduction in HRR after 6 years from HTx seems to be associated with a higher rate of death or retransplantation, with adverse events apparently more common in children with an HRR Z score in the lowest quartile. This could be a valuable prognostic finding and might be helpful to guide clinicians when monitoring patients by providing further insight into the differing prognosis for patients after HTx. Support for our conclusions can be found within the adult literature where HRR is a strong predictor of mortality in those with and without heart disease, including sudden death.

Regarding this last point, it has been hypothesized that variables that reflect autonomic, particularly vagal, activity like HRR would be able to effectively identify patients at risk for sudden cardiac death, presumably because parasympathetic tone is linked to electric stability of the heart.

Limitations

HRR after maximal exercise is slower than submaximal exercise in healthy individuals and is attributed to the sympathetic nervous system being stimulated significantly more during maximal exercise, with a slower withdrawal of sympathetic stimulation underpinning it. Therefore, an increased HRR in serial exercise testing may have occurred if the patient’s effort was maximal in the first but not in the last exercise tests. However, this is usually the opposite of what is noted in clinical practice, and all tests included were maximal. Furthermore, these studies were performed at a single center and used a consistent protocol and staff, which may have helped to minimize the variation in patient effort between studies.

Although most of our patients were taking calcium channel blockers, this class of medications is not known to cause significant impairment in chronotropic response or HRR. Several studies have used the difference between peak heart rate and heart rate at 1 minute of recovery to assess HRR from exercise. The technique used in this and in previous studies to calculate HRR besides providing information on the extent of the HR recovery, provides information about the kinetics of HRR because intermediate points contribute to the calculation of the slope, whereas calculations derived from the subtraction of 1 minute HR from peak HR provide only information on the extent of the change. However, despite different methodologies, the 2 techniques would produce similar results in most patients.

The time between HTx and the first exercise test was different in different patients. This is unavoidable because some patients have had HTx at young age, and because of their size they are not able to exercise until older. This elective nature of exercise testing in this population needs to be considered as a limitation of the study.

Conclusions

Our results suggest that after a period of progressive improvement in cardiac autonomic function, factors related to the graft may cause a reduction in HRR in pediatric HTx recipients. The results of the study are important because they demonstrate that HRR represents an important marker of health status in pediatric HTx patients and provides initial evidence for its use as a prognostic tool in this population. There is compelling evidence that exercise training improves HRR in many disease settings, including the adult patient with heart failure. Although low HRR is only a marker of poor outcomes in this population and not the direct cause, further research into exercise training programs for HTx children is warranted to understand whether training can improve HRR in this population and to see whether a change in HRR can translate into improved long-term outcomes.

Disclosures

None.

References


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