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Left ventricular myocardial response to exercise in children after heart transplant

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BACKGROUND: Data on myocardial response to exercise after pediatric heart transplant (HTx) are limited. In this study we used semi-supine bicycle ergometry (SSCE) stress echocardiography to evaluate left ventricular (LV) systolic and diastolic reserve in pediatric HTx recipients.
METHODS: Forty-three HTx patients and 23 controls underwent stepwise SSCE stress echocardiography. Color tissue Doppler imaging (TDI) peak systolic (s′) and early diastolic (e′) velocities in the LV lateral wall and basal septum, and LV peak global longitudinal and circumferential strain were measured at rest and during different stages of exercise. LV myocardial acceleration during isovolumic contraction (IVA) was measured at incremental heart rates (HRs) to determine the force–frequency relationship (FFR).
RESULTS: At rest, compared with controls, HTx patients showed lower TDI velocities in the basal septum (s′: 4.7 ± 1.1 vs 5.8 ± 0.8 cm/s, $p = 0.002$; e′: 8.5 ± 2.1 vs 11.3 ± 1.7 cm/s, $p < 0.001$), whereas in the LV lateral wall only e′ was lower (11.2 ± 2.6 vs 13.8 ± 2.3 cm/s, $p < 0.001$). LV IVA was not different between the groups ($p = 0.10$). LV peak global longitudinal strain was lower in HTx patients (18 ± 1.9% vs 20 ± 2.2%, $p = 0.001$), but peak circumferential strain was not different ($p = 0.50$). At peak, HR was lower in the HTx group (141 ± 12 vs 165 ± 15, $p < 0.001$), and all systolic and diastolic parameters, except circumferential strain, were lower in HTx recipients. When assessing the increase in TDI and strain values in relation to HR, the slopes were not significantly different between patients and controls.
CONCLUSIONS: Despite resting differences in myocardial functional parameters, pediatric HTx recipients have preserved LV diastolic and systolic myocardial reserve in response to exercise.
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Cardiac response to exercise in pediatric heart transplant (HTx) recipients has not been well described. In adults, a decreased heart rate (HR) response and decreased maximum oxygen consumption have been described after transplant,[1] but reports on exercise performance in pediatric HTx recipients are less consistent. Although some reports described decreased exercise capacity,[2] others showed that pediatric HTx recipients have a near-normal exercise capacity with normal oxygen consumption, HR and blood pressure response.[3] In adults, diastolic dysfunction at rest is highly correlated with reduced exercise capacity after HTx. Diastolic dysfunction in HTx recipients is thought to be multifactorial, with ischemic damage at the time of transplant causing fibrosis and myocardial stiffening, acute and chronic low-grade rejection augmenting myocardial injury,

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and transplant vasculopathy causing limited coronary flow reserve and sub-clinical ischemia. Diastolic dysfunction at rest has been found in children after HTx by tissue Doppler imaging (TDI) echocardiography,[4] based mainly on reduced e′ TDI velocities. However, myocardial response to exercise has been poorly studied in these patients.

In this study we sought to assess left ventricular (LV) systolic and diastolic myocardial response to exercise in a larger cohort of pediatric HTx recipients using semi-supine cycle ergometry (SSCE) stress echocardiography combined with color TDI and 2-dimensional speckle-tracking echocardiography (2D STE).

SSCE stress echocardiography allows for real-time assessment of hemodynamic and myocardial function during physiologic exercise, thereby potentially identifying sub-clinical dysfunction in patients with known or suspected heart disease. In addition, SSCE stress echocardiography allows for evaluation of myocardial function at different exercise stages, including peak exercise and recovery,[5] minimizing the loss of important values, especially at peak and immediately after exercise.[6]

The aims of this study were to: (1) assess the feasibility and reproducibility of SSCE stress echocardiography in pediatric HTx recipients; (2) observe LV systolic and diastolic reserve and myocardial mechanics during exercise, using color TDI and 2D STE techniques, and compare the myocardial response in HTx recipients to that of normal controls; and (3) evaluate the effect of previous acute rejection episodes on the myocardial response to exercise.

Methods

At our center, all transplant recipients >10 years of age and with no contraindications to an exercise test undergo SSCE stress echocardiography bi-annually as part of their routine clinical follow-up. The SSCE stress echocardiography protocol includes acquisition of color TDI velocities and storage of raw gray-scale DICOM images that can be analyzed for strain using 2D STE. This study is a retrospective analysis of prospectively collected data and was approved by institutional research ethics board.

Study participants

Forty-three children transplanted between 1994 and 2009 and followed at our institution were enrolled. Twenty-three healthy volunteers matched for age and gender were also recruited to serve as normal controls. Controls had no history of cardiovascular disease, no athletic training, and were physically capable of performing the SSCE test. Before SSCE stress echocardiography, a complete baseline echocardiographic examination was performed according to the routine clinical hospital protocol, which is consistent with the Pediatric Echocardiography Guidelines, as published by the American Society of Echocardiography.[7]

SSCE stress echocardiography protocol

A semi-supine bicycle (Lode B.V., Groningen, The Netherlands) was used for all echocardiographic stress studies. A standardized Bruce exercise protocol was followed, using 3-minute stages with a target speed of 60 revolutions/min. Twenty-watt increments every 3 minutes were used for individuals up to 14 years of age, and 25-W increments for older subjects. The target HR was 85% of maximum HR, calculated as 220 – age. All tests were supervised by a cardiologist and early termination was determined based on patient fatigue or the occurrence of pre-defined adverse events (arrhythmia, ischemia, chest pain, clinical signs of circulatory compromise, progressive fall in systolic blood pressure $>10\%$, severe hypertension). Patients were monitored with continuous 12-lead electrocardiography (ECG) and sphygmomanometry blood pressure measurements during the last 30 seconds of each stage (Dinamap USA).

Image acquisition

Echocardiographic data acquisition was performed by two dedicated exercise sonographers. Images were obtained using a Vivid 9 ultrasound system (General Electric Medical Systems, Milwaukee, WI) during the last 2 minutes of each stage using the Smartstress application. The following echocardiographic images were acquired at each stage and during recovery: a parasternal long-axis view; a gray-scale parasternal short-axis view at the level of papillary muscles and apical 4, 3 and 2 chambers optimized for off-line 2D STE analysis (frame rate >60 frames/s); pulsed-wave (PW) Doppler of mitral inflow; high-frame-rate narrow-sector color TDI of the LV lateral wall; and the interventricular septum from the apical 4-chamber view.

Image analysis

Images were digitally stored for off-line analysis, using the EchoPAC system version 110.1.3 (GE Medical Systems). Manual tracking was performed to avoid translational movements of the region of interest (ROI) during the cardiac cycle.

Velocity measurements were recorded as the average value from three consecutive cardiac cycles. Fusion of the e′ and a′ wave to a single velocity peak was seen during exercise in all subjects and this fused wave was measured as e′. Isovolumic contraction (IVA) was calculated as the difference between baseline and peak velocity divided by the time interval (m/s^2). LV global longitudinal and circumferential peak systolic strain measurements were performed as previously described.[8]

Reproducibility

Two independent observers analyzed separately 15 randomly selected studies for the assessment of interobserver variability for color TDI and longitudinal strain at each stage. The same studies were used for the assessment of intraobserver variability of the same measurements, with the observer blinded to the initial results.

Statistics

Data are presented as mean and standard deviation or as median with range and frequency, as appropriate. Comparisons between the two groups were performed using Student's *t*-test, assuming unequal variance between samples, and Fisher's exact test. Linear regression models adjusted for repeated measures through an autoregressive covariance structure and slope of changes over time were compared between HTx patients and controls. Intraclass correlation coefficients (ICCs) were calculated for inter- and intraobserver variability. All statistical analyses were performed using statistical software (SAS version 9.3; SAS Institute, Cary, NC).