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Global left ventricular relaxation: A novel tissue Doppler index of acute rejection in pediatric heart transplantation

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BACKGROUND: Serial invasive cardiac catheterization with endomyocardial biopsies (EMBs) is the current standard of reference for evaluation after orthotopic heart transplant (OHTx). We developed a novel, non-invasive echocardiographic index of global left ventricular relaxation (LVRI) and assessed its sensitivity, specificity and predictive value for detecting rejection compared with EMB results in a prospective study conducted from September 2012 through May 2014.

METHODS: LVRI was calculated as the sum of diastolic tissue Doppler imaging (TDI) velocities (E′) of the left ventricular lateral, septal and posterior walls divided by the percentage of left ventricular posterior wall (LVPW) thinning by M-mode. LVRI was measured in 47 OHTx patients and 50 patients with normal hearts. Of the 33 patients who underwent clinically indicated EMB, 22 patients had Grade 0R EMB, 6 had Grade 1R and 5 had Grade 2R to 3R biopsy results. Sensitivity, specificity and predictive value of LVRI for discriminating Grade 1R to 3R EMB were calculated. The LVRI was compared before and after OHTx rejection treatment and during the early and late post-transplant period. To characterize LVRI, 1-way analysis of variance was used to compare all groups, including non-OHTx patients.

RESULTS: LVRI was lower in patients with Grade 0R EMBs compared with non-OHTx patients. Patients with Grade 1R to 3R EMBs had lower LVRI than those with Grade 0R EMBs. LVRI recovered after treatment for rejection. LVRI appeared to normalize between 40 and 90 days post-transplantation. After 90 days, sensitivity was 100% and specificity was 90.9% for detecting patients with Grade 1R to 3R EMBs using an LVRI of 0.8.

CONCLUSION: LVRI, a novel, non-invasive TDI index of global left ventricular diastolic dysfunction, appears to be useful for detecting rejection in children beyond 3 months post-OHTx.

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There has been an overall improvement in survival of pediatric cardiac transplant recipients, but cardiac function is known to decline over time and contributes significantly to mortality and need for retransplantation.[1] Segmental variation in tissue velocities derived by tissue Doppler imaging (TDI) has been attributed to the changes in cardiac translation that accompany myocardial contraction and relaxation.[2] Studies in adult and pediatric orthotopic heart transplant (OHTx) recipients have shown that myocardial velocities are altered not only at baseline, but also during acute allograft rejection.[3-7]

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After OHTx, right ventricular endomyocardial biopsy (EMB) plus histologic evaluation of obtained samples constitutes the standard of reference for detection of acute rejection.[8,9] However, EMB procedures have a risk of complications, particularly in the younger pediatric population, among whom rates of cardiac perforation can be as high as 1% to 3%.[10] Attempts at developing a non-invasive test to screen patients at risk of acute allograft rejection have so far failed to gain wide acceptance.[11–14]

We developed a novel index of global left ventricular relaxation (LVRI), that we hypothesized would predict rejection in patients who have undergone OHTx. LVRI is calculated using the sum of the diastolic TDI velocities from the interventricular septum, lateral and posterior walls of the left ventricle (Figure 1) divided by the percentage of left ventricular posterior wall thinning (LVPWthin), derived from the left ventricular wall measurements using M-mode. We evaluated the sensitivity, specificity and predictive values of the LVRI to detect early sub-clinical rejection in pediatric patients with OHTx. We also characterized the LVRI in both OHTx patients and normal controls and the response of the LVRI to treatment of rejection.

Methods

This is a prospective study conducted from September 2012 to May 2014. After approval from the institutional ethics review board, written informed consent was obtained from each of the patients before inclusion in the study.

Patients

Inclusion criteria

Patients who underwent OHTx during the study period and previously transplanted patients who underwent EMB as part of routine follow-up, or for clinical evidence of cardiac rejection, comprised the transplant group. The non-transplant group consisted of 50 children with normal cardiac structure and function who were enrolled from the outpatient cardiology clinic.

Exclusion criteria

Non-transplant patients with structural heart disease or rhythm disturbances were excluded as well as patients on chemotherapy or taking medication known to affect heart function. Transplant patients with any residual structural heart disease (e.g., residual aortic arch obstruction, systemic vein obstruction, etc.) were also excluded. Patients with poor echocardiographic acoustic windows affecting accuracy of data acquisition were not enrolled.

Cardiac catheterization and EMB

EMB was utilized as the standard reference in our study, and was performed as part of the post-OHTx evaluation based on the standard institutional follow-up protocol. Four or 5 EMB samples were taken at each catheterization from the right ventricular side of the interventricular septum. Samples were sent to the pathology laboratory for analysis. EMB was not performed in patients <1 year of age.

Pathologic analysis

The pathologic results were obtained from the patient's chart. The standard grading system of the International Society for Heart and Lung Transplantation (ISHLT, from Grade 0R to 3R) was employed in our study. C3D and C4D staining was performed in all EMB tissue samples. One experienced pathologist performed the interpretation of the

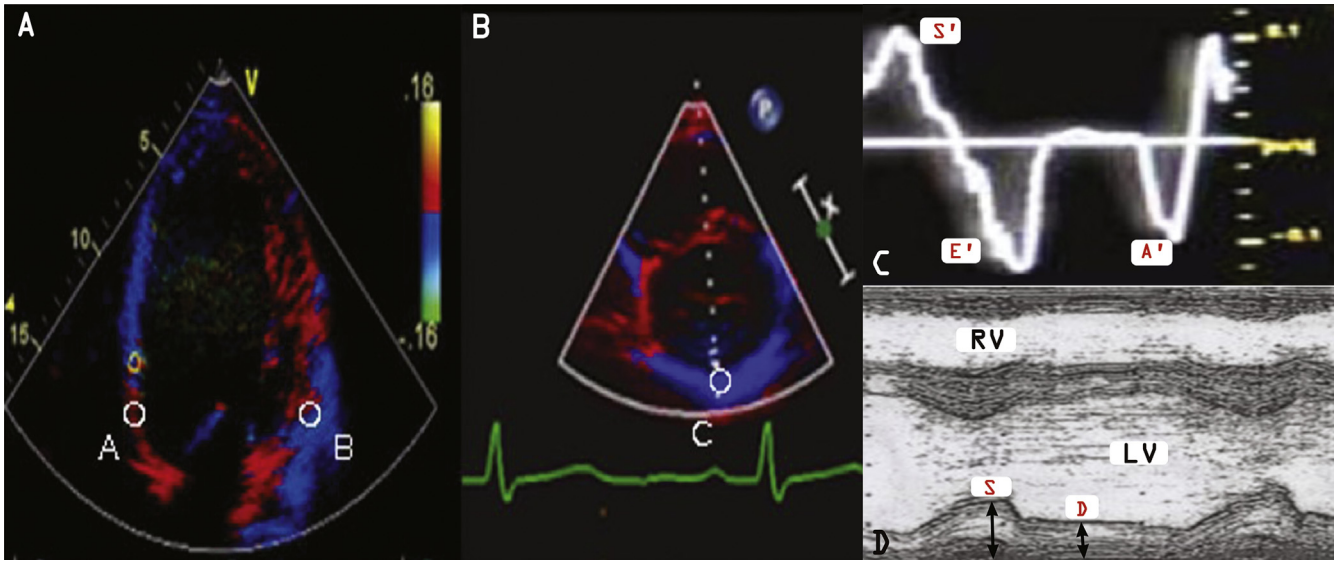

Figure 1 (A, B) Areas of the left ventricle where the spectral Doppler tissue image was obtained (points A, B and C) for the calculation of the LVRI. A = interventricular septum, B = lateral wall of the left ventricle, C = posterior wall of the left ventricle. (C) Tissue Doppler trace of the velocities derived from the color images. E′ was the only tissue velocity utilized for the calculation. (D) M-mode trace demonstrates the measurement of the LVPW in systole (S) and diastole (D) for the calculation of LVPW thinning used in the denominator of the LVRI. RV, right ventricle; LV, left ventricle.