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Global left ventricular relaxation index in predicting cardiac cellular rejection in paediatric heart transplant patients

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Abstract

Background: Endomyocardial biopsy remains the gold standard for cardiac cellular rejection surveillance after heart transplantation. We studied a novel non-invasive index of left ventricular relaxation to detect cardiac cellular rejection in paediatric heart transplant patients. *Methods:* This is a single-centre retrospective study of paediatric heart transplant patients who underwent endomyocardial biopsy from June 2014 to September 2021. Left ventricular relaxation index was calculated as the sum of diastolic tissue Doppler imaging velocities (E) of the left ventricular lateral, septal, and posterior walls divided by the percentage of the left ventricular posterior wall thinning by M-mode. Statistical analysis included *t*-tests and Mann-Whitney tests to compare means and medians between treatment and non-treatment groups. We used the cut-off with the maximum Youden index to compare the sensitivity and specificity of left ventricular relaxation index to detect rejection. *Results:* The study included 65 patients who underwent 246 cardiac catheterizations and endomyocardial biopsies. Out of 246, 192 procedures were included and 54 were excluded due to recent transplants or lack of echocardiographic data. A total of 114 demonstrated Grade 0R, 68 Grade 1R, 8 Grade 2R, and 2 Grade 3R allograft rejection. The difference in mean left ventricular relaxation index between treatment versus non-treatment groups (2R, 3R vs. 0R, 1R) was not statistically significant ($p = 0.917$). A left ventricular relaxation index cut-off of 0.73 had the highest Youden index with good sensitivity (100%) and poor specificity (23%) for detecting rejections with grades 2R and 3R. *Conclusion:* Left ventricular relaxation index, a novel index of left ventricular relaxation, was not a sensitive or specific predictor of cardiac cellular rejection in paediatric heart transplants.

Introduction

Despite advances, cardiac cellular rejection remains a major complication of paediatric heart transplant recipients. The impact of cardiac rejection episodes on long-term graft function underscores the importance of early and precise diagnosis for the timely management of rejection.[1] The emphasis on non-invasive methods for diagnosing cardiac cellular rejection, particularly through echocardiographic parameters, has primarily stemmed from concerns regarding the time, cost, and potential risks associated with endomyocardial biopsy.[2] Inflammation resulting from the early phase of cardiac cellular rejection can lead to increased myocardial stiffness and abnormal relaxation velocities within the myocardium.[3] The diastolic function of a normal heart is influenced by factors such as heart rate, volume loading, and myocardial compliance.[4] The stable heart rate of a denervated heart in cardiac transplant patients makes it an ideal subject for diastolic studies.[5] Despite numerous studies, the utilisation of non-invasive echocardiographic parameters for diagnosing cardiac cellular rejection remains a subject of controversy.[3] At present, there is a lack of a dependable non-invasive diastolic parameter, and a single parameter alone fails to adequately represent overall diastolic function. Our institution has developed left ventricular relaxation index as a novel parameter to better reflect global diastolic function. Left ventricular relaxation index is a novel non-invasive index of left ventricular relaxation, utilising echocardiography with tissue Doppler to detect cardiac cellular rejection in paediatric and adult heart transplant patients. Previous studies have identified that a left ventricular relaxation index value >0.8 is predictive of rejection-free status.[3] Our study aimed to determine the sensitivity, specificity, and predictive value of left ventricular relaxation index in predicting cardiac cellular rejection compared to other non-invasive diagnostic parameters.

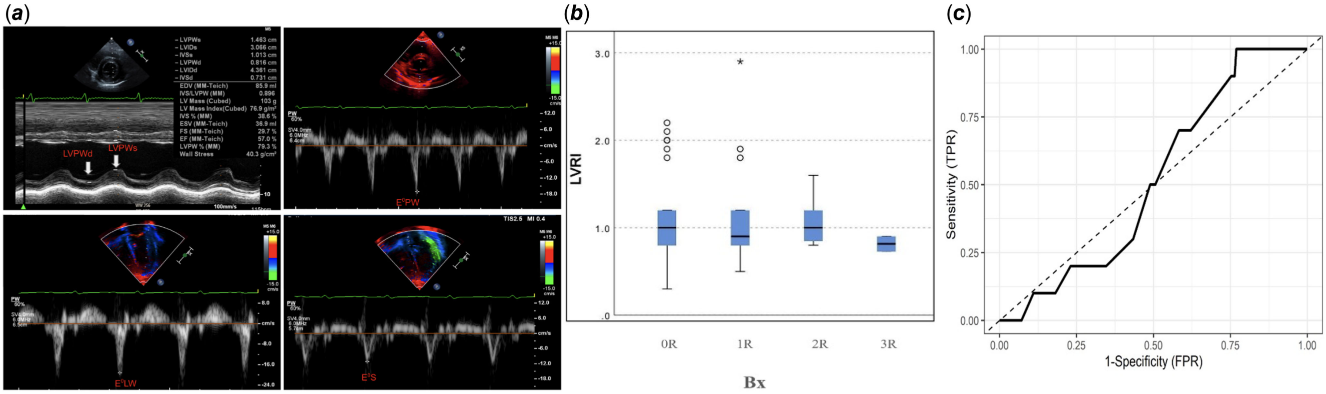

Figure 1. (***a***) Tissue doppler and M-MODE measurements used in LVRi calculation. E^0S - diastolic velocity of interventricular septum; E^0LW - diastolic velocity of left ventricle lateral wall; E^0PW - diastolic velocity of left ventricle posterior wall; M-mode trace demonstrates the measurement of the left ventricular posterior wall in systole (S) and diastole (D) for the calculation of left ventricular posterior wall thinning. (***b***) LVRi distribution among the four cardiac rejection groups (0R,1R,2R,3R). LVRi = left ventricular relaxation index; Bx = biopsy rejection grade. (***c***) Receiver operating characteristic curve for predicting biopsy results via LVRi. The area under the curve was 0.52 indicating poor potential for LVRi to predict rejection.

Methods

A single-centre retrospective study of paediatric heart transplant patients who underwent cardiac catheterisation with myocardial biopsy from June 2014 to September 2021 was performed. Patients were identified from the post-transplant database at the University of Minnesota Masonic Children's Hospital. Patients who underwent heart transplant or myocardial biopsy at least 90 days post-transplant as part of routine follow-up or for clinical evidence of cardiac cellular rejection were included.

Patients underwent endomyocardial biopsy as part of the post-heart transplant evaluation based on the standard institutional protocol. Our institutional protocol involves performing an endomyocardial biopsy every two weeks during the first three months, once a month from months 3 to 6, every three months from months 6 to 12, and annually thereafter. During each cardiac catheterisation procedure, 3–4 samples from the right ventricular side of the interventricular septum were biopsied and sent to pathology for analysis. Allograft rejection was graded according to the International Society of Heart and Lung Transplantation, grade 0 indicating no rejection, grade 1R mild, grade 2R moderate, and grade 3R severe allograft rejection. Additional haemodynamic and laboratory data including pulmonary capillary wedge pressure and Pro Brain natriuretic peptide were collected as additional markers of allograft rejection. Patients had blood drawn on the same day as endomyocardial biopsy.

Left ventricular relaxation index

All patients included in the study underwent echocardiography within 3 days before or after endomyocardial biopsy. Echocardiograms were performed by paediatric cardiac sonographers and were reviewed by experienced paediatric cardiologists. Left ventricular relaxation index was calculated as the sum of diastolic tissue Doppler imaging velocities (E) of the left ventricular lateral, septal, and posterior walls divided by the percentage of left ventricular posterior wall thinning by M-mode. Diastolic tissue Doppler imaging velocities of lateral and septal walls were obtained from the standard apical four-chamber view. The posterior wall tissue Doppler imaging was obtained from a short axis view at the level of the mitral valve. Left ventricular posterior wall thinning is the percentage of posterior wall thinning and was obtained from M-mode measurements (Figure 1a).

$$\text{Left ventricular relaxation index} = (E^0LW + E^0S + E^0PW)/ \\ \text{left ventricular posterior wall thinning (S-D)}$$

Statistical analysis

All measurements of the individual tissue Doppler imaging velocities and of the left ventricular posterior wall thinning on M-mode were measured by one observer and were used for statistical analyses. To assess intra- and inter-observer variability, measurements were recalculated for twenty procedures by the initial observer and one additional observer blinded to previous measurements. Intraclass correlation coefficients were calculated to assess this variability and were estimated using models with procedure-specific random effects.

The mean left ventricular relaxation index, Pro Brain natriuretic peptide, and pulmonary capillary wedge pressure values and endomyocardial biopsy Grade 0R to 1R cohort versus the 2R to 3R cohort were compared using a random-effects analysis of variance with subject-specific random effects to account for repeated measurements. We identified the cut-off with the maximum Youden index to compare the sensitivity and specificity of left ventricular relaxation index, Pro Brain natriuretic peptide and pulmonary capillary wedge pressure to predict rejection and calculated the area under each receiver operating characteristic curve.

Results

Study design

Figure 2 illustrates the study design. A total of 65 patients who underwent heart transplants at less than 18 years of age were included in the study. In total, 246 cardiac catheterizations and endomyocardial biopsies were performed during the same period. Eighteen cardiac catheterisation procedures were excluded due to recent heart transplant within 90 days. Thirty-six procedures were excluded because the echocardiogram was not performed at the

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Table 1. Estimated mean values of study variables in Group 1 (0R/1R) and Group 2 (2R/3R): Estimated means (95% confidence intervals) and *p*-values were calculated using random-effects analysis of variance to account for repeated measurements within subjects. LVRI = left ventricular relaxation index; Pro BNP = brain natriuretic peptide; PCWP = pulmonary capillary wedge pressure

Variables	Group 1 (Grade 0R/1R, *n* = 182)	Group 2 (Grade 2R/3R, *n* = 10)	Difference in means (Group 2 – Group 1)	*p* value
LVRi	1.06 (0.13, 0.31)	1.04 (0.29, 0.38)	−0.01 (−0.25, 0.22)	0.917
Pro BNP	1686 (199, 4331)	13,245 (6092, 7746)	11,558 (6775, 16,240)	<0.001
PCWP	11.57 (2.08, 3.74)	17.60 (3.08, 3.93)	6.03 (3.50, 8.55)	<0.001

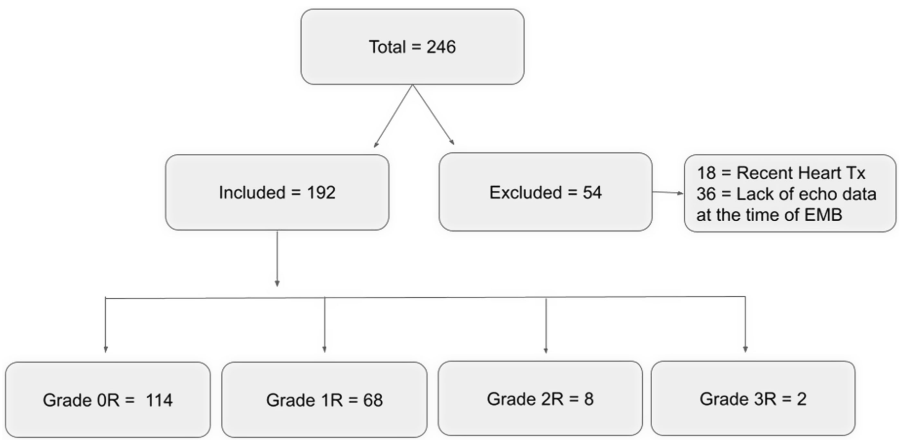

Figure 2. Study design. See text for details. Heart Tx = Heart transplant; EMB = endomyocardial biopsy.

time of endomyocardial biopsy. Of 192 procedures, 114 had Grade 0R, 68 had Grade 1R, 8 had Grade 2R, and 2 had Grade 3R allograft rejection. Pulmonary capillary wedge pressure for all 192 procedures was collected from the haemodynamics data. Pro Brain natriuretic peptide, which was drawn at the time of endomyocardial biopsy, was collected for all patients included in the study.

Grade 0R, 1R versus Grade 2R, 3R

Patients were divided into two groups based on the rejection grades. Patients with 0R /1R were labelled as Group 1 and patients with 2R/ 3R were labelled as Group 2. Random-effects analysis of variance was used to compare the two groups. In total, 182 were under Group 1 and 10 were under Group 2. The estimated mean left ventricular relaxation index, Pro Brain natriuretic peptide, and pulmonary capillary wedge pressure measurements for Groups 1 and 2 with 95% confidence intervals and associated *p*-values are presented in Table 1. The estimated mean left ventricular relaxation index for Group 1 was 1.06 and for Group 2 was 1.04, which was not a statistically significant difference (p-value = 0.917). The estimated mean Pro Brain natriuretic peptide for Group 1 was 1686 and for Group 2 was 13,245, which was statistically significant (p-value < 0.001). The estimated mean pulmonary capillary wedge pressure for Group 1 was 11.6 and for Group 2 was 17.6, which was statistically significant (p-value < 0.001). The left ventricular relaxation index distribution among the 4 groups is shown in Figure 1b.

Sensitivity and specificity of left ventricular relaxation index for rejection

A left ventricular relaxation index cut-off of 0.73 had the highest Youden Index and was used to estimate sensitivity and specificity. The sensitivity was 100% and specificity was 23%. The area under the receiver operating characterisitic curve was 0.52 indicating poor potential for left ventricular relaxation index to predict rejection (Figure 1c).

Intra- and inter-observer variability of left ventricular relaxation index

Intraclass correlation coefficients were used to estimate intra- and inter-observer variability. Based on the intraclass correlation coefficient estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.[6]

The intra-observer variability for two sequential measurements and the ability of a single observer to reproduce the same result resulted in a correlation coefficient of 0.70 suggesting moderate reliability. Inter-observer correlation coefficient was good for diastolic velocity of left ventricle lateral wall (ELW) (0.87), diastolic velocity of interventricular septum (ES) (0.94), and diastolic velocity of left ventricle posterior wall (EPW) (0.95) but poor for left ventricular posterior wall thinning (0.46). Overall inter-observer correlation coefficient for left ventricular relaxation index was 0.41 suggesting poor reliability.

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Discussion

Our study assessed the utility of left ventricular relaxation index, a novel non-invasive index of left ventricular relaxation, to detect cardiac cellular rejection in paediatric heart transplant patients. We found that the left ventricular relaxation index values exhibited similarity across all rejection grade groups (0R, 1R, 2R, 3R), with no statistically significant difference between 0R, 1R (non-treatment) and 2R,3R (treatment groups). Left ventricular relaxation index proved to be a less dependable tool, showing considerable variability among observers. This variability was particularly notable when measuring left ventricular posterior wall and identifying E waves in the presence of fusion with A wave velocities due to tachycardia. Achieving consistency in left ventricular relaxation index measurements necessitates having the same observer and paediatric echocardiographic reader throughout, though this may be practically challenging to implement consistently. The robust association between Pro Brain natriuretic peptide and pulmonary capillary wedge pressure with cardiac cellular rejection is well documented.[7,8] In our study, we observed analogous findings, with Pro Brain natriuretic peptide and pulmonary capillary wedge pressure demonstrating statistical significance across the study groups.

In cases of acute rejection, studies have shown that the systolic function is often preserved and diastolic function appears to be the first to decline.[1] Nevertheless, the utility of diastolic function assessment on echocardiogram as a tool for predicting rejection status remains disputed. In an adult study, various systolic and diastolic echocardiographic parameters of left ventricular systolic and diastolic dimensions, mitral inflow pattern and annular velocities, and the myocardial performance index) were studied, and no correlation was found between rejection and non-rejection groups.[9] Various echocardiographic parameters have been employed to study diastolic function. Galit et al. focused on peak E-wave velocity and pressure half-time across all rejection grades, noting high interpatient variability attributed to differences in atrial size, atrioventricular synchrony, and the degree of ventricular hypertrophy. The study suggested serial measurements with intrapatient comparison but acknowledged potential limitations due to inter and intraobserver variability.[10] Due to the lack of reliability of standard diastolic parameters in predicting rejection, additional echocardiographic parameters have been assessed. Myocardial performance index, which is a measure of combined systolic and diastolic function, was found to be a marker of high-grade rejection in a paediatric study.[11]

Previous paediatric studies primarily assessed diastolic function in cardiac transplant patients with rejection using individual Doppler velocities, which may not accurately reflect global ventricular relaxation. In our institution, a pilot study was conducted, resulting in the development of a new index called the left ventricular relaxation index.[3] This index incorporates Doppler velocities from three different walls of the left ventricle, in addition to per cent posterior wall thinning on M-MODE. The hypothesis was that left ventricular relaxation index could provide a more accurate estimate of global left ventricular relaxation. The initial study concluded that an left ventricular relaxation index value of <0.8 correlated with predicting cardiac cellular rejection grades 1–3R. However, there was no statistically significant difference in left ventricular relaxation index between treatment and non-treatment groups. The initial prospective study had very limited individuals in the treatable rejection group (2R,3R) and was conducted over 2 years.[3] Our study is an important addition to this pilot study in that we assessed a larger number of patients and specifically evaluated the ability of left ventricular relaxation index to distinguish the presence of rejection between treatment (2R/3R) and non-treatment (0R/1R) groups. Our findings diverge from previous conclusions regarding the reliability of left ventricular relaxation index as an echocardiographic marker for rejection in heart transplant patients, as we found no significant difference in left ventricular relaxation index between treatment and non-treatment groups. Thus we identified significant concerns regarding the reliability of left ventricular relaxation index in predicting rejection among cardiac transplant recipients.

Could non-invasive diagnostic techniques potentially supplant the gold standard endomyocardial biopsy for diagnosing cardiac cellular rejection? While several echocardiographic parameters have been explored, their effectiveness in replacing endomyocardial biopsy remains a subject of debate. Our study suggests that left ventricular relaxation index does not add diagnostic value in distinguishing patients with acute allograft rejection. Nevertheless, it's plausible that employing a standardised approach utilising multiple echocardiographic parameters, with each patient serving as their control, could offer a solution. Prospective studies focusing on standardising various non-invasive parameters alongside endomyocardial biopsy could be an avenue for future research.

Limitations

A smaller study population in the treatment groups and operator dependence of the left ventricular relaxation index calculation limits the reliability of this test. As most of the paediatric studies are smaller single institutional studies, larger prospective studies with standardised methods should be corroborated in future studies.

Conclusion

Left ventricular relaxation index, a novel index of left ventricular relaxation, was not a sensitive or specific predictor of cardiac cellular rejection in paediatric heart transplants. Serial measurements of multiple non-invasive echocardiographic parameters with patients acting as their baseline can be used as an aid in diagnosing cardiac cellular rejection but endomyocardial biopsy remains the gold standard for diagnosing cardiac cellular rejection.

Competing interests. The authors have no conflict of interest to disclose in particular to this study. This research did not require any funding.

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