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LV MPI Change for Detection of Acute Cellular Rejection in Pediatric Heart Transplantation

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Abstract

Endomyocardial biopsy (EMB), the gold standard for diagnosis of acute cellular rejection (ACR), poses unique risks in children. Limited cross-sectional data has associated left ventricular myocardial performance index (LVMPI) with ACR. We hypothesize that a relative change in MPI from baseline without ACR to the time of ACR will better detect ACR than an absolute threshold LVMPI value. We identified 40 children with ACR 60 days post-transplant matching them by age and time from transplantation to 40 children without ACR. There was a significant increase in LVMPI at time of ACR vs. baseline (0.59 ± 0.17 vs. 0.41 ± 0.11 ; $p < 0.001$). There was no difference in LVMPI between baseline and follow-up (0.41 ± 0.11 vs. 0.42 ± 0.11 ; $p = 0.65$). An absolute increase in LVMPI of 0.47 had 82.5% sensitivity and 85% specificity for ACR whereas an increase in LVMPI from baseline of 20.4% was 90% sensitive and 100% specific. Serial measurement of LVMPI appears to be a sensitive and specific marker of ACR. LV MPI shows good inter-observer agreement and increases at the time of EMB proven ACR with subsequent resolution to baseline measurements upon EMB proven resolution of ACR. Future studies in larger, prospective cohorts should be undertaken to validate these findings.

Keywords

Heart Transplant; Pediatric; Acute Rejection; Myocardial Performance Index; Echocardiogram

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INTRODUCTION

Endomyocardial biopsy (EMB) remains the gold standard for surveillance of acute rejection after pediatric orthotopic heart transplantation. EMB-based surveillance in children may be associated with physical and/or psychological discomfort, requires repeated, frequent use of sedation or general anesthesia, and can result in complications such as loss of vascular access, tricuspid valve injury, conduction abnormalities, or cardiac perforation (1, 2). EMB is also expensive, costing insurers nearly \$3300 on average (3). In contrast, echocardiography is non-invasive, does not require routine use of sedation, costs approximately one-third as much an EMB (4) and can provide a detailed assessment of allograft function. Thus while there are many possible benefits of an echocardiographic alternative to EMB for routine graft surveillance, reliable echocardiographic indicators of acute rejection are lacking. Left ventricular myocardial performance index (LV MPI) is a reproducible, heart rate independent echocardiographic measure of both systolic and diastolic function that has recently gained use in the assessment of patients with various conditions, ranging from idiopathic dilated cardiomyopathy to normally functioning hearts (5-9). Currently there is scant data on the utility of LV MPI in the setting of acute cardiac allograft rejection in pediatric patients (10, 11). Thus we sought to explore the utility of LV MPI as an indicator of acute cellular rejection (ACR) following pediatric heart transplantation by comparing spectral Doppler derived LV MPI at the time of biopsy-proven ACR to LV MPI in the absence of ACR. We hypothesized that LV MPI is associated with ACR and that a relative increase in LV MPI at the time of ACR (compared to that individual's pre-rejection baseline) would better predict ACR than a fixed, threshold MPI value.

PATIENTS & METHODS

After Institutional Review Board approval was obtained, we reviewed the medical records of all heart transplant recipients who had an echocardiogram performed within 72 hours of EMB between January 2006 and March 2012 at the Children's Hospital of Pittsburgh of UPMC. To avoid potential confounding of ischemia-reperfusion on LV MPI, we excluded EMB-echocardiogram pairings that were <60 days post-transplantation. We then identified patients with ACR (International Society of Heart and Lung Transplant (ISHLT) grade 2R) (12) on EMB who lacked ACR on the immediate prior EMB. These patients were matched by age and time after transplantation to patients who lacked ACR on two sequential EMB.

Clinical echocardiograms were performed using commercial ultrasound systems (Philips iE33, Koninklijke Philips Electronics, The Netherlands; GE Healthcare Systems, Milwaukee WI; and Acuson, Siemens Medical Systems, Mountain View, CA). Each study included 2-dimensional imaging and spectral and color-flow Doppler interrogations. In patients with ACR, we retrospectively determined LV MPI at the time of ACR and on echocardiogram-EMB pairings showing no ACR (ISHLT grades 0-1R) immediately prior to (baseline) and following ACR (recovery). In patients without ACR, we determined LV MPI on two sequential echocardiograms at the time of EMB at similar times after transplantation to their ACR matched-pair. LV MPI was measured on spectral Doppler tracings offline using Xcelera (Koninklijke Philips Electronics) by one of two investigators (RF & NC) who were blinded to patient grouping (ACR vs. no ACR) and echocardiogram timing. A third investigator (GT) reviewed 48 of the studies and made blinded, independent measurements for interobserver validation. LV MPI was calculated as follows: isovolumetric contraction time (ICT, Mitral Valve closure to Aortic Valve opening) plus isovolumetric relaxation time (IRT, Aortic Valve closure to Mitral Valve Opening) divided by left ventricular ejection time (LVET, Aortic Valve opening to Aortic Valve closure) (8, 9) (Figure 1). Patients with ACR were excluded if their echocardiogram at the time of ACR lacked sufficient left

ventricular spectral Doppler tracings (as detailed above) or if there was not a pre- or post-ACR echocardiogram-EMB pairing performed at our institution that was available for review. We did not exclude patients for other reasons, including presence or absence of allograft vasculopathy.

Our clinical protocols for immunosuppression and surveillance EMB have been previously described (13). Briefly, all patients received antithymocyte globulin induction therapy then maintenance immunosuppression with tacrolimus and either sirolimus or mycophenolate mofetil. Corticosteroids were given only in the immediate postoperative period for 5-7 days and as pulse therapy for treatment of biopsy-proven ACR (ISHLT grade 2R).

In the primary analysis we compared LV MPI at the time of ACR to LV MPI at the EMB immediately preceding the ACR event. Both the absolute difference (rejection – baseline) and the relative change [(rejection-baseline)/baseline] in LV MPI were quantified and compared to these same measures among the control patients. Sensitivity and specificity for each method were assessed and Receiver Operating Characteristic (ROC) curves constructed. In patients with ACR, we also made comparisons of LV MPI at baseline to recovery and ACR to recovery.

Group characteristics are expressed as median and range or count and proportion and were compared using the Wilcoxon rank-sum test or Chi square test, as appropriate. LV MPI data are expressed as mean and standard deviation and were compared using the Wilcoxon rank-sum test (between group comparisons) or Wilcoxon matched pairs signed rank test (within group comparisons). Interobserver variability was assessed by the information-based measure of disagreement (IBMD) statistic, which ranges from 0 (no disagreement) to 1 (14). Data were analyzed using STATA, version 10.1 (StataCorp LP, College Station, TX) and the IBMD on-line calculator (15). All comparisons were 2-sided with significance level of 0.05.

RESULTS

We identified 1,802 EMB performed 60 days after transplantation in 178 pts. After exclusions for inadequate echocardiogram images (n=13) or lack of precursor and/or follow-up echocardiogram-EMB pairings (n=6), we identified 40 patients with ACR. Thirty patients (75%) had 1 ACR event, 7 (17.5%) had 2 ACR events, and 1 patient each had 3, 4 and 5 ACR events. Table 1 shows the demographics of the patients with ACR and matched controls. There were no statistically significant differences in age, sex, left ventricular shortening fraction, or time from transplantation.

LV MPI was higher at the time of biopsy-proven ACR (0.59 ± 0.17) than on the preceding baseline echocardiogram performed in the absence of ACR (0.41 ± 0.11 ; $p < 0.0001$). LV MPI was also higher for patients with ACR as compared to non-ACR matched controls (0.39 ± 0.11 ; $p < 0.0001$). There was no difference in LV MPI between baseline and recovery echocardiograms in patients with ACR (0.42 ± 0.11 vs. 0.42 ± 0.10 ; $p = 0.65$). Time from ACR to recovery echocardiograms was 56.2 ± 70.2 days. In patients without ACR, LV MPI was unchanged between successive echocardiograms (0.38 ± 0.10 vs. 0.39 ± 0.10 ; $p = 0.57$).

An absolute LV MPI threshold above 0.47 had 80% sensitivity and 85% specificity for ACR whereas a relative change in LV MPI of 20.4% had 90% sensitivity and 100% specificity for ACR. As shown in figure 2, there was no statistical difference when the areas under the curve (AUC) for these criteria were compared ($p = 0.15$).

Interobserver variability was excellent with an IBMD of 0.12 (95% confidence interval 0.092-0.160).

DISCUSSION

In this study we observed an increase in LV MPI with clinically significant ACR. Both an absolute LV MPI threshold of 0.47 and a relative increase of 20.4% offered very good sensitivity and very good to excellent specificity for the detection of ACR. We found no statistically significant difference in AUC between the relative and absolute threshold for detection of ACR. We believe that a comparison of these measures between larger groups of patients may show the relative MPI threshold to have superior discriminatory abilities. This is because the relative threshold incorporates the slight variation in baseline LV MPI which exist from patient to patient that have been shown in prior studies (10, 11, 16-18).

Our findings are important because they are consistent with, and thus add credibility to, the very limited published data about LV MPI in pediatric heart transplantation (10, 11). In particular we found LV MPI in the absence of ACR in our study to have a similar mean and standard deviation as reported in 2 other studies in pediatric heart transplant recipients in the absence of ACR (10, 16). This supports the fact that LV MPI can be measured reliably and with good reproducibility by different measurers across different institutions and adds confidence to the finding by Prakash et al, that LV MPI values in the absence of ACR are elevated in pediatric heart transplant recipients as compared to children without transplant who have no cardiac disease (16). Our finding that LV MPI is increased in the setting of ACR is also consistent with the only pediatric data reported to date in the context of acute rejection (10). However our data also expands knowledge on the topic by showing that LV MPI returns to pre-ejection values upon resolution of ACR.

The assessment of graft function following pediatric heart transplantation can be challenging, particularly when attempting to correlate echocardiographic measures of graft function with the presence or absence of rejection. Newburger et al previously looked at using isolated markers of systolic or diastolic function to predict rejection and were unable to show any (19). However they did not assess LV MPI, which assesses both systolic and diastolic function. And because the nature of ACR is that of a lymphocytic, interstitial infiltrate with myocyte injury, it is plausible that LV MPI could be sufficiently sensitive to reflect lesser degrees of diastolic or systolic impairment that may be seen with ACR.

Because untreated acute rejection can progress to allograft dysfunction and death (20), the accurate detection of ACR is of paramount importance following heart transplantation. Most centers employ a strategy of routine, surveillance EMB of decreasing frequency following heart transplantation combined with EMB upon clinical suspicion of acute rejection. However, EMB is invasive and costly (1-3) and alternate, less invasive means to detection of ACR have long been sought (21-23). While the avoidance of serial EMBs would be ideal, the potential benefits of even a reliable adjunct to help guide the suspicion of acute rejection would also be useful. The high sensitivity and specificity of LV MPI for the detection of ACR that we observed shows promise that relative change of LV MPI against baseline may be one such useful marker. Because LV MPI is easily obtained on images that exist within most basic pediatric echocardiography protocols, it is less expensive and less time consuming than other non-invasive measures of cardiac function such as 3D strain mapping or cardiac MRI. As a result of these findings we have begun to use LV MPI to aid in the decision to perform an EMB in cases where there is clinical uncertainty about the possibility of ACR. We also are assessing the utility of LV MPI in a separate, prospective cohort of echocardiogram-EMB parings to determine if the absolute and relative thresholds we observed in this analysis are applicable more broadly.

Limitations of our study include its retrospective nature, use of clinical EMB grading, and relatively small number of patients. However we established criteria for inclusion of paired

EMB-echocardiograms prior to undertaking the study, thus minimizing selection bias. Also the clinical EMB interpretations we used in this analysis were performed by 1 of 4 well-experienced pediatric pathologists who each reported at least 75 EMB annually during the study period. Because all uncertain findings were reviewed amongst the group of pathologists as they arose, we believe the potential influence of significant variability in EMB grading on our findings is limited. While our study population is small, the 80 patients we studied is the largest pediatric heart transplant LV MPI study reported to date. Nevertheless, validation of these data in a larger, prospective multi-center cohort would be an important next step to confirming the significance of our findings. Although we anticipate that use of a relative change in LV MPI will account for slow “natural” changes in diastolic function that occur post transplant, our study did not stratify based on graft vasculopathy nor did we examine the specific effects of antibody mediated rejection (AMR) on LV MPI. Lastly, we also did not assess echocardiogram-EMB pairings prior to 60 days post-transplantation and therefore our findings should not be applied to patients early after transplantation.

In conclusion, serial measurement of LV MPI appears to be a sensitive and specific marker of ACR. LV MPI is an easily obtained non-invasive measure of systolic and diastolic ventricular function that shows good inter-observer agreement and increases at the time of EMB proven ACR with subsequent resolution to baseline measurements upon EMB proven resolution of ACR. Future studies in larger, prospective cohorts should be undertaken to validate these findings.

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Abbreviations

ACR	Acute Cellular Rejection
AUC	Area Under the Curve
EMB	Endomyocardial Biopsy
LV MPI	Left Ventricular Myocardial Performance Index
m	months
OHT	Orthotopic Heart Transplantation
ROC	Receiver Operating Characteristic
y	years.

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Figure 1. Schematic representation of the cardiac cycle and time intervals that comprise the Left Ventricular Myocardial Performance Index (LV MPI). MV, Mitral Valve; IVCT, Iso-Volumetric Contraction Time; LVET, Left Ventricular Ejection Time; IVRT, Iso-Volumetric Relaxation Time.

Figure 2.
ROC curves for relative change in MPI and absolute cutoffs

Table 1

Group demographics

	Patients with ACR (n=40)	No ACR (n=40)	p-value
Age	12y (7m-24.4y)	9y (4.2m-22.4y)	0.15
Male sex	25 (63%)	24 (60%)	0.99
Time since transplantation	3.7y (2m-17.3y)	3.9y (3m-17.1y)	0.25
LV shortening fraction (%)	36.3 ± 6.9	38.8 ± 4.2	0.06
LV MPI	0.59 ± 0.17	0.39 ± 0.11	<0.0001
ACR grade			
0	--	27 (68%)	
1R	--	13 (32%)	
2R	34 (85%)	--	
3R	6 (15%)	--	

ACR, acute cellular rejection; EMB, endomyocardial biopsy; LV, left ventricle; MPI, myocardial performance index