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Temporal changes in left ventricular strain with the development of rejection in pediatric heart transplant recipients

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Abstract

Introduction: Myocardial strain measurements are increasingly used to detect complications following heart transplantation. However, the temporal association of these changes with allograft rejection are not well defined. The aim of this study was to describe the evolution of strain measurements prior to the diagnosis of rejection in pediatric heart transplant recipients.

Methods: All pediatric heart transplant recipients (2004–2015) with at least one episode of acute rejection were identified. Longitudinal and circumferential strain measurements were assessed at the time of rejection and retrospectively on all echocardiograms until the most recent negative biopsy. Smoothing technique (LOESS) was used to visualize the changes of each variable over time and estimate the time preceding rejection at which alterations are first detectable.

Results: A total of 58 rejection episodes were included from 37 unique patients. In the presence of rejection, there were decrements from baseline in global longitudinal strain (–18.2 vs. –14.1), global circumferential strain (–24.1 vs. –19.6), longitudinal strain rate (–1 vs. –0.8), circumferential strain rate (–1.3 vs. –1.1), peak longitudinal early diastolic strain rate (1.3 vs. 1), and peak circumferential early diastolic strain rate (1.5 vs. 1.3) ($p < 0.01$ for all). The earliest detectable changes occurred 45-days prior to rejection with simultaneous alterations in myocardial strain and ejection fraction.

Conclusions: Changes in graft function can be detected non-invasively prior to the diagnosis of rejection. However, changes in strain occur concurrently with a decline in ejection fraction. Strain measurements aid in the non-invasive detection of rejection, but may not facilitate earlier diagnosis compared to more traditional measures of ventricular function.

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Conflicts of Interest:

None

Ethical Standards:

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation Belmont Report and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committee. The Institutional Review Board of Vanderbilt University Medical Center approved this study.

Keywords

Pediatric; Heart Transplant; Strain; Rejection

Introduction:

There is increasing interest in the use of two-dimensional speckle tracking echocardiography to assess cardiac pathology. This technology provides an angle-independent measure of myocardial deformation, allowing direct quantification of regional and global myocardial mechanics^{1,2}. Myocardial strain imaging has gained traction as a possible non-invasive technique to assess graft function in heart transplant recipients, and may be beneficial in the diagnosis of rejection³⁻⁵ and cardiac allograft vasculopathy^{6,7}.

Multiple reports have suggested that strain and strain rate imaging may allow for earlier detection of sub-clinical cardiac pathology^{1,8-11}. This provides clear incentive to evaluate the use of this technology in heart transplant recipients, for whom early detection of rejection is of critical importance. However, pediatric data assessing the temporal changes in strain associated with the development of rejection are lacking. The aim of this project is to assess the changes over time in strain, strain rate, and diastolic strain before a diagnosis of rejection in pediatric heart transplant recipients, and to compare these results to more traditional measures of ventricular performance.

Methods:

This was a retrospective study and was approved by the Vanderbilt University Institutional Review Board. All pediatric patients who underwent heart transplant at Vanderbilt University Medical Center with at least one episode of treated rejection (2004-2015) were included. Rejection was defined as an event that prompted augmentation of the immunosuppression regimen. This includes patients with a clinical diagnosis of rejection with or without endomyocardial biopsy evidence of rejection. A positive endomyocardial biopsy at our center is defined as International Society of Heart and Lung Transplantation grade 2R (2004 grading system¹²), grade 1B (1990 grading system¹³), or pathologic antibody-mediated rejection-2¹⁴.

At our center, 1 to 4 cardiac catheterizations with surveillance endomyocardial biopsy are performed in the first post-transplant year depending on patient age, and annually thereafter. Biopsies are also performed when there is clinical suspicion for rejection. C4d immunofluorescence is routinely performed on all specimens. Complete echocardiograms are obtained at the time of endomyocardial biopsy, whether for surveillance or suspected rejection. Echocardiograms performed in conjunction with rejection episodes were identified for inclusion in the study. All preceding echocardiograms were also identified for inclusion, up to the most recent negative endomyocardial biopsy prior to the rejection event. Echocardiograms were excluded if image quality was inadequate for accurate assessment using two-dimensional speckle tracking echocardiography.

Echocardiography:

Images were obtained on Siemens Acuson Sequoia (Siemens Medical Solutions, Erlangen, Germany), Philips IE33, or Philips EPIQ7 ultrasound machines (Philips Medical Systems, Best, The Netherlands). A standard protocol was utilized for all echocardiograms including multiple acquisitions of the short axis at the level of the papillary muscles and the apical 4-chamber view to ensure adequate visualization of the endocardial border. All echocardiograms were obtained by a core group of 6 sonographers with additional training in the heart transplant protocol. Although the heart transplant protocol includes assessment at the base and apex in the short axis and the 2-chamber and 3-chamber apical views, due to variable image quality, these images were not analyzed.

Post-processing:

All strain measurements were performed using vendor independent software (Cardiac Performance Analysis, TomTec Imaging Systems, Unterschleissheim, Germany). Images were imported in standard DICOM format with a frame rate of 30Hz. Measurements included global longitudinal strain, global circumferential strain, longitudinal strain rate, circumferential strain rate, peak longitudinal early diastolic strain rate, and peak circumferential early diastolic strain rate. Circumferential strain and strain rate measurements were obtained from a parasternal short axis image at the level of the papillary muscles and longitudinal strain and strain rate measurements were obtained from an apical 4-chamber view. Measurements were completed for one cardiac cycle, from end-diastole to end-diastole. Measurements were performed by two readers with expertise in speckle tracking echocardiography (MS and CH), blinded to rejection history. One set of measurements was performed for each echocardiogram. To ensure consistency in tracking and measurement technique, all measurements were reviewed and validated by an additional reader with expertise in speckle tracking echocardiography who was also blinded to patient history (JG). Left ventricular ejection fraction was independently measured for each study using either Simpson's biplane technique or 5/6 area length method.

Statistical analysis:

Patient demographics were described using standard descriptive statistics. For each variable, baseline measurements for each patient were defined as the average across all echocardiograms performed 180 days preceding the rejection event. Baseline values were compared to measurements at the time of rejection using the Wilcoxon signed rank test. Smoothing technique (LOESS) was used to visualize the pattern of each variable over time from 180 days prior to the time of rejection until the rejection event. Changes in ejection fraction and strain measurements were modeled using separate regression models of the form $Y_{ij} = f_i(t_{ij} | \beta) + e_{ij}$ for rejection i in a subject at time j . Ejection fraction and strain (Y_{ij}) were allowed to change smoothly over time before rejection, specified by function $f_i(t_{ij} | \beta)$ with parameters β . The time of rejection (t_{ij}) is 0, such that $t_{ij} < 0$ is pre-rejection. Since repeated measurements are taken on the same subject over time and we expected the residuals, e_{ij} , may be correlated, error structure of AR-1 was used in the model. Restricted cubic splines with 4 knots were used in each model on the time variable. Predicted values vs. time with 95% confidence intervals were plotted to present the overall time effect. The

timing of the inflection for each variable prior to rejection was estimated to assess the timing of alterations preceding rejection events ¹⁵.

All statistical analyses were performed in R version 3.3.3 (R core team (2017), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) or STATA version 15 (StataCorp LLC; College Station, TX) with $p < 0.05$ considered statistically significant. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Vanderbilt ¹⁶.

Results:

A total of 58 rejection episodes were identified in 37 unique patients (Table 1). A single episode of rejection was present in 23 (62.2%) patients and 14 (37.8%) patients had multiple included rejection events. Of the rejection events, 45 (77.6%) were >1-year posttransplant. An endomyocardial biopsy was performed for 55 (94.8%) rejection episodes. Cellular rejection was confirmed in 46 (83.6%) and evidence of antibody mediated rejection was documented in 12 (21.8%) biopsy specimens. A total of 10 biopsy specimens had features of both cellular and antibody mediated rejection. Endomyocardial biopsy was negative for evidence of either cellular or antibody mediated rejection for 7 (12.7%) of the treated rejection events. A total of 4 patients (accounting for 5 rejection events) had evidence of cardiac allograft vasculopathy at the time of the included rejection. Two patients were diagnosed with allograft vasculopathy preceding the rejection event and 2 were diagnosed concurrent with rejection.

A total of 325 echocardiograms were identified for inclusion and 34 (10.5%) studies were excluded due to suboptimal image quality. A total of 291 echocardiograms were analyzed with a median of 5 (interquartile range 4 – 8) studies analyzed per rejection event. Baseline strain values compared to measurements at the time of rejection are shown in Table 2. A significant decrement from baseline was noted in all strain measurements at the time of rejection. Ejection fraction also declined from baseline measurements at the time of rejection.

Regression models demonstrating the temporal association of strain measurements with rejection are shown in Figure 1 (a-f) and ejection fraction shown in Figure 2. The earliest changes prior to rejection are estimated to occur 45 days prior to the event. Measurements noted to change at this time were ejection fraction, global circumferential strain, circumferential strain rate, peak circumferential early diastolic strain rate, and longitudinal strain rate. Global longitudinal strain and peak longitudinal early diastolic strain rate demonstrated changes later in the time course, at 40 and 35 days prior to the rejection event, respectively.

Discussion:

Our analysis demonstrates the temporal association of strain measurements leading up to a diagnosis of rejection in pediatric heart transplant recipients. Significant alterations in strain occur with the development of rejection; however, these changes occur concurrently with changes in ejection fraction. Therefore, the use of strain measurements in isolation may not

predict rejection earlier compared to more traditional measures of ventricular performance. However, serial changes in strain measures may be useful as an adjunct to standard echocardiographic measures for non-invasive assessment of graft function, as ejection fraction in our study remained within the normal range despite the development of rejection.

Changes in strain measurements have been previously documented in the setting of rejection in both pediatric and adult heart transplant recipients^{3-5,10,17-20}. While the results of our analysis confirm this association, our study does not support the assertion that strain and strain rate imaging diagnose allograft rejection earlier compared to standard measurements. Multiple studies have suggested that strain is more sensitive to sub-clinical changes in ventricular performance and therefore may provide a non-invasive method for early rejection diagnosis^{10,19,21}. The contradictory findings in our study may reflect variation in the evolution of strain versus more standard echocardiographic measures with the development of rejection or may simply be secondary to differences in thresholds to define normal and abnormal between measurements.

While our analysis suggests that strain measurements in isolation may have limited ability to predict rejection early, utilization of strain in conjunction with standard echocardiographic measures may prove clinically useful. Previously developed models utilizing multiple echocardiographic measurements have proven useful in the non-invasive detection of rejection²². The addition of strain measurements into such a model may be advantageous and help to improve the sensitivity and specificity for rejection diagnosis. Other analyses have incorporated strain into similar models and demonstrated value in the prediction of all-cause mortality following heart transplantation²³.

It is important to consider that changes in strain occur following transplantation during the normal remodeling process. Abnormal strain has been documented in the early posttransplant period in both children^{24,25} and adults²⁶. This may limit the utility of strain to detect rejection in the first year post-transplant, a time when the risk of rejection is greatest^{27,28}. Strain measurements normalize by 1-year post-transplant and remain stable in the absence of rejection or cardiac allograft vasculopathy to at least 5-years^{24,29}. Therefore, strain may be better suited to detect rejection beyond 1-year, following initial stabilization in the early post-transplant period. At least one study suggests that there may be significant intra-patient variability in strain measurements²⁴, which may further impact the utility of strain in the assessment of rejection. However, others have reported that strain measurements are reliable and reproducible in the pediatric heart transplant population³⁰.

Limitations:

Our study has inherent limitations. Given the variable quality of echocardiographic views, segmental analysis was not possible and therefore our study focused on global strain assessment. Additionally, 10.5% of echocardiograms identified for inclusion were excluded due to suboptimal image quality, potentially impacting the results of our analysis. The number and timing of echocardiograms included varied by patient and rejection event, an inherent limitation of a retrospective analysis. Unfortunately, prospective assessment is not feasible given the limited number of pediatric heart transplant recipients and relative

infrequency of treated rejection. The statistical modeling utilized in this analysis attempts to minimize this limitation. Given lack of robust standardization, there may be variation in strain measurements based on the software package used^{31,32}. However, the use of third-party strain analysis software improves the generalizability of this study as images from multiple vendors can be analyzed with Cardiac Performance Analysis Software. The events in our cohort consisted primarily of cellular rejection, but antibody-mediated, mixed, and biopsy negative rejection also occurred. Given the relatively small number of rejection events that were not cellular rejection, comparison among these groups was not feasible. It is also possible that subclinical rejection episodes occurred prior to the formal diagnosis of rejection, as our center utilizes surveillance biopsy sparingly. Lastly, our analysis did not focus on the changes in strain following an episode of rejection and therefore the evolution of strain parameters following a rejection event cannot be assessed.

Conclusions:

In the presence of acute allograft rejection, there are detectable alterations in myocardial strain in pediatric heart transplant recipients. These changes occur simultaneously with a decline in ejection fraction. Therefore, the assessment of strain in isolation may not facilitate earlier detection of rejection. However, strain may prove to be a useful non-invasive adjunct in the assessment of graft performance and may aid in the identification of rejection when taken into consideration with other non-invasive measures.

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Figure 1.

Regression models depicting the changes prior to a diagnosis of rejection in a) GCS - global circumferential strain, b) GLS - global longitudinal strain, c) CSR – circumferential strain rate, d) LSR – longitudinal strain rate, e) DCSR, - peak circumferential early diastolic strain rate and f) peak longitudinal early diastolic strain rate

Figure 2. Regression model depicting the changes in ejection fraction (EF) prior to a diagnosis of rejection

Table 1.**Demographics based on patients and rejection events**

Number of patients (N=37)	
Age at transplant (years)	3.6 (1.5 - 16.3)
Diagnosis	
Cardiomyopathy	16 (43.2%)
CHD	19 (51.4%)
Re-transplant	2 (5.4%)
Race	
Caucasian	19 (51.4%)
African American	16 (43.2%)
Other	2 (5.4%)
Number of rejection episodes	
1	23 (62.2%)
2	8 (21.6%)
3	5 (13.5%)
4	1 (2.7%)
Rejection events (N=58)	
Age at rejection (years)	13.5 (6.3 - 17.7)
Biopsy performed	55 (94.8%)
Type of rejection	
CMR	36 (65.5%)
AMR	2 (3.6%)
Mixed	10 (18.2%)
Biopsy negative	7 (12.7%)
CMR grade	
0R	4 (7.3%)
1R	8 (14.5%)
2R	32 (58.2%)
3R	11 (20%)
AMR grade	
pAMR-0	43 (78.2%)
pAMR-1h	4 (7.3%)
pAMR-1i	5 (9.1%)
pAMR-2	3 (5.5%)
pAMR-3	-
Hemodynamic compromise	18 (31%)

Abbreviations: CHD - congenital heart disease, CMR - cellular mediated rejection, AMR - antibody mediated rejection

Table 2.

Baseline strain measurements compared to those obtained at the time of rejection

	Baseline	At rejection	p value*
GLS	-18.2 (-16.2, -20.4)	-14.1 (-8.9, -17.7)	<0.001
LSR	-1 (-0.9, -1.1)	-0.8 (-0.5, -1)	0.002
DLSR	1.3 (1.1, 1.5)	1 (0.6, 1.4)	0.005
GCS	-24.1 (-21.9, -26.9)	-19.6 (-15.1, -23.9)	<0.001
CSR	-1.3 (-1.3, -1.4)	-1.1 (-0.8, -1.4)	<0.001
DCSR	1.5 (1.4, 1.8)	1.3 (1, 1.6)	0.002
EF	62.1 (59.3, 64.8)	58.4 (42.3, 64.3)	0.003

p values from the Wilcoxon signed rank test

Abbreviations: GLS - global longitudinal strain, GCS - global circumferential strain, LSR - longitudinal strain rate, CSR - circumferential strain rate, DLSR - peak longitudinal early diastolic strain rate, DCSR - peak circumferential early diastolic strain rate, EF - ejection fraction