Evaluation of Acute Rejection by Measuring Strain and Strain Rate in Children With Heart Transplant: A Preliminary Report

Hazim Alper Gursu, 1 Birgul Varan, 1 Elif Sade, 2 Ilkay Erdogan, 1 Atilla Sezgin, 3 Sait Aslamaci 3

Abstract

Objectives: Asymptomatic rejection after heart transplant is difficult to detect by noninvasive methods. The present study investigated the efficacy of echocardiographic strain and the strain rate imaging method in detecting rejection after pediatric heart transplant.

Materials and Methods: Fourteen pediatric patients with heart transplant were examined both with endomyocardial biopsy and strain imaging. Patients were divided into 2 groups: group 1 included patients with rejection, and group 2 included patients without rejection. Patients underwent endomyocardial biopsy at regular intervals. Regional systolic function was evaluated by longitudinal myocardial peak systolic values of strain and of strain rate. Differences between the 2 groups were assessed with unpaired t test or Mann-Whitney U test.

Results: Acute rejection was detected in 7 patients (4 were female patients). Cardiac diagnosis was restrictive cardiomyopathy in 3 patients, dilated cardiomyopathy in 3 patients, and complex congenital heart disease in 1 patient. After heart transplant, 6 patients had rejection once and 1 patient had rejection twice. Evaluation of biopsy samples revealed grade IB rejection in all patients in group 1. Systolic functions of the 6 patients were determined as normal in standard echocardiographic examination. There were no significant differences in deformation and deformation rates between group 1 and 2 except in midseptal region (P < .05).

Conclusions: One of the most significant complications in patients with heart transplant is rejection. Our results suggested that myocardial strain imaging may be valuable in defining low-grade rejection.

Key words: Biopsy, Cardiomyopathy, Cardiac function, Echocardiography, Pediatric heart transplant

Introduction

Endomyocardial biopsy is currently the criterion standard to diagnose subclinical acute rejection in patients with heart transplant; however, research is ongoing to find more sensitive and noninvasive methods to replace biopsy. In the present study, the efficacy of strain and strain rate imaging methods was investigated in detecting subclinical acute rejection in children with heart transplant. In the literature, studies on this topic are scarce.1,2

Materials and Methods

Study population

Fourteen pediatric patients who had heart transplant between the years 2010 and 2012 were included in this study. Patients were evaluated by conventional and tissue Doppler echocardiography and endomyocardial biopsy. All patients were also evaluated by the strain imaging method, synchronously with endomyocardial biopsy. Eight of 14 patients were female. Median age of patients was 14 years (range, 12-16 y). The diagnoses were congenital heart disease in 2 patients, dilated cardiomyopathy in 8 patients, and restrictive cardiomyopathy in 4 patients.

Patients were divided into 2 groups: group 1 included patients with rejection, and group 2 included patients without rejection. Rejection was detected in 7 patients (4 of them were female). Median age of patients with rejection was 14 years (range 12-15 years). The diagnoses of these patients were complex congenital heart disease in 1 patient,
dilated cardiomyopathy in 3 patients, and restrictive cardiomyopathy in 3 patients (Table 1). All patients were symptomatic as New York Heart Association class I at time of biopsy. All patients were normotensive and had normal heart rate. Because the transplanted heart might have an abnormal systolic and diastolic function, even in the absence of rejection, our study did not include a control group.

In our center, strain imaging is performed routinely along with biopsy for all patients undergoing heart transplant. Families of patients younger than 18 years of age and patients ≥ 18 years of age provided their informed consents. Because this study was a retrospective analyses, we did not obtain the approval of the ethical committee.

### Table 1. Differences Between Patients With and Without Rejection

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 7)</th>
<th>Group 2 (n = 7)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transplant, y</td>
<td>16 (14-16 y at 25% to 75% interquartile range)</td>
<td>16 (14-16 y at 25% to 75% interquartile range)</td>
<td></td>
</tr>
<tr>
<td>Sex, female/male</td>
<td>4/3</td>
<td>4/3</td>
<td></td>
</tr>
<tr>
<td>Diagnoses (No. of patients)</td>
<td>Complex CHD (1)</td>
<td>Complex CHD (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilated CMP (3)</td>
<td>Dilated CMP (5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Restrictive CMP (3)</td>
<td>Restrictive CMP (1)</td>
<td></td>
</tr>
<tr>
<td>Median rejection time after transplant, mo</td>
<td>3</td>
<td>No rejection</td>
<td></td>
</tr>
<tr>
<td>Rejection grade</td>
<td>Grade IB (for all)</td>
<td>No rejection</td>
<td>279</td>
</tr>
<tr>
<td>RVP, mm Hg</td>
<td>29.8 ± 10.2</td>
<td>29.8 ± 10.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>22.3 ± 9.2</td>
<td>16.7 ± 3.3</td>
<td>0.480</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>21.6 ± 4.7</td>
<td>12.8 ± 4.2</td>
<td>0.014</td>
</tr>
</tbody>
</table>

**Abbreviations:** CHD, congenital heart disease; CMP, cardiomyopathy; LVLW, left ventricle lateral wall; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RVP, right ventricular pressure

Differences between the 2 groups were assessed by using unpaired t test or Mann-Whitney U test.

Echocardiographic examination

Echocardiographic examination was performed within 24 hours of endomyocardial biopsy in all patients. Echocardiography was performed at the left decubitus position by using the Vivid i (GE Medical Systems, Tirat Carmel, Israel) device and a 3-MHz transducer. Global systolic functions of the left ventricle were evaluated with standard M-mode echocardiographic examination by measuring ejection fraction and fractional shortening values. Values below 56% for ejection fraction and below 28% for fractional shortening were accepted as systolic dysfunction. Regional systolic functions were evaluated by peak systolic values of longitudinal myocardial strain and strain rates in basal, mid-, and apical segments of the left ventricular lateral wall and midsegment of the interventricular septum during periods with and without rejection. We did not perform a 17-segment analysis including the images from the apical 2 chambers and detection of radial and circumferential deformation because of the sternal incision, low accommodation, and discomfort to our heart transplant recipients. To measure peak systolic strain and strain rate, 3 consecutive cardiac cycles.
were recorded, and the average value was calculated. The EchoPac PC (GE Healthcare, Waukesha, WI, USA) software program was used for data analyses. Measurements were obtained from standard apical 4-chamber view to provide an overview of the anatomy. This is especially important in patients with a poorly functioning ventricle and low-velocity intracardiac flow. The image sector was adjusted as narrow so that structures were viewed better. The possible lowest gain that could help separate the border between the myocardium and blood and avoid signals from the blood pool was selected. A frame rate of 200 to 300 frames/s was used to acquire the data. The Doppler measurements were made, keeping the angle of insonation between the myocardium and the angle of the ultrasonography beam at 15 degrees at most.

Our patients also had electrocardiographic monitoring. Normal longitudinal myoccardial Doppler strain and strain rate values were accepted as -25 ± 7% and -1.9 ± 0.7 s⁻¹ for midsegment of the left ventricular lateral wall, 20.7 ± 1.1% and -2.3 ± 1.1 s⁻¹ for the basal segment, and -17 ± 7% and -1.3 ± 0.5 s⁻¹ for midportion of interventricular septum. Decreases of peak systolic strain and strain rate values were accepted as abnormal myocardial deformation.

**Statistical analyses**

Data were evaluated using the Statistical Package for Social Sciences software program for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Abnormality for quantitative variables in groups was determined by the Shapiro-Wilks test. For normally distributed values, mean and standard deviation were used, whereas skewed distribution was expressed by median and 25% to 75% interquartile ranges. Because the total number of cases was less than 30, the variables were considered to be distributing irregularly, and comparisons within groups were made using unpaired nonparametric t test, whereas comparisons between groups were made using nonparametric Mann-Whitney U test. Categorical variables in proportions or percentages were analyzed by chi-squared test or Fisher exact test when appropriate. P < .05 was considered to be statistically significant.

**Results**

Although 7 of 14 patients with heart transplant did not have rejection (group 2), we did have 8 rejection episodes detected in the remaining 7 patients (group 1), as shown by endomyocardial biopsies performed 21 times in total. All rejections were diagnosed during the first year after transplant (median of 3 mo). Six of the 7 patients had 1 rejection, and the other patients had 2 rejections. All patients in group 1 were at grade IB (International Society of Heart and Lung Transplantation criteria) when biopsy samples were evaluated. Left ventricular ejection fraction and fractional shortening values were normal in 6 patients with rejection and below normal in 1 patient.

In the standard echocardiographic examination of the patient with 2 rejection episodes, systolic dysfunction was detected (ejection fraction of 41%; fractional shortening of 21%). No statistically significant differences were observed in standard echocardiographic parameters of left ventricular systolic function between group 1 and group 2. During the rejection period, mean strain and strain rate values were -7.56 ± 3.97% and -1.04 ± 0.90 s⁻¹ for the midsegment of the septum, -7.74 ± 4.39% and -0.48 ± 0.30 s⁻¹ for the midsegment, -10.88 ± 7.08% and -0.90 ± 0.41 s⁻¹ for the basal segment, and -1.50 ± 0.89% and -0.38 ± 0.23 s⁻¹ for the apical segment of left ventricular lateral wall. During the period without rejection, the measured values were -12.08 ± 5.36% and -2.42 ± 0.17 s⁻¹ for the midsegment of the septum, -9.2 ± 2.4% and -0.57 ± 0.41 s⁻¹ for the midsegment, -12.70 ± 7.47% and -1.19 ± 0.41 s⁻¹ for the basal segment, and -2.20 ± 0.85% and -0.42 ± 0.22 s⁻¹ for the apical segment of left ventricular lateral wall (Table 2). Our measured strain and strain rate values in our heart transplant patients were lower than normal findings. Between patients with and without rejection, there was statistically significant difference only in the midsegment of the septum (P < .05). Although measured strain and strain rate values were lower than normal findings, in all segments of left ventricular lateral wall there was no statistically significant difference between patients.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
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<tbody>
<tr>
<td>IVS strain, %</td>
<td>-12.08 ± 5.36</td>
<td>-7.56 ± 3.97</td>
</tr>
<tr>
<td>IVS strain rate, s⁻¹</td>
<td>-2.42 ± 0.17</td>
<td>-1.04 ± 0.90</td>
</tr>
<tr>
<td>LVLW basal strain, %</td>
<td>-12.70 ± 7.47</td>
<td>-10.88 ± 7.08</td>
</tr>
<tr>
<td>LVLW basal strain rate, s⁻¹</td>
<td>-1.19 ± 0.41</td>
<td>-0.90 ± 0.41</td>
</tr>
<tr>
<td>LVLW mid strain, %</td>
<td>-9.2 ± 2.4</td>
<td>-7.74 ± 4.39</td>
</tr>
<tr>
<td>LVLW mid strain rate, s⁻¹</td>
<td>-0.57 ± 0.41</td>
<td>-0.48 ± 0.30</td>
</tr>
<tr>
<td>LVLW apical strain, %</td>
<td>-2.20 ± 0.85</td>
<td>-1.50 ± 0.89</td>
</tr>
<tr>
<td>LVLW apical strain rate, s⁻¹</td>
<td>-0.42 ± 0.22</td>
<td>-0.38 ± 0.23</td>
</tr>
</tbody>
</table>

**Abbreviations:** IVS, interventricular septum; LVLW, left ventricle lateral wall

Differences between the 2 groups were assessed by using unpaired t test or Mann-Whitney U test.
with and without rejection ($P > .05$). Mean pulmonary capillary wedge pressure values measured during periods with and without rejection were $21.6 \pm 4.72$ and $12.8 \pm 4.2$ mm Hg. A statistically significant difference was detected between the 2 periods; there was an increase in pulmonary capillary wedge pressure in the rejection period ($P = .014$). However, there were no significant differences between right ventricle and pulmonary artery pressures ($P > .05$) (Table 1).

**Discussion**

Heart transplant is the standard treatment at end-stage cardiac failure. A significant complication in patients with heart transplant is rejection, which is most commonly encountered during the first year after transplant. It should be diagnosed as soon as possible.

The criterion standard method for diagnoses of rejection is endomyocardial biopsy, which is an invasive method. Studies about sensitive and noninvasive diagnostic methods have been performed to reduce possible complications of biopsy. In conventional 2-dimensional echocardiography, global left ventricle function is estimated by the shortening fraction or ejection fraction. Several studies have indicated that M-mode and 2-dimensional echocardiography had low sensitivity in showing systolic and diastolic function changes in acute rejection. It was determined that the earliest acute rejection signs were flow abnormalities detected during left ventricle filling by transmirtal Doppler. However, this method allows determination of rejections only if higher than grade IIIA.\(^6\) Moreover, this method is also affected by heart rate, age, and volume load.\(^3\)

Noninvasive imaging techniques such as echocardiography have previously been used to monitor rejection. Tissue Doppler imaging is a useful method in evaluation of regional tissue velocities.\(^8\) It has been observed that early diastolic peak velocity and isovolumetric relaxation time in the basal portion of the left ventricle lateral wall measured by pulse wave tissue Doppler had a high sensitivity in diagnosing rejection, especially those higher than grade II.\(^9\) Stengel and associates\(^10\) reported that high late diastolic mitral annulus velocity was effective in diagnosis of grade III and higher severe rejections. Therefore, it was observed that tissue Doppler was effective in demonstrating diastolic dysfunction in severe rejection. However, sensitivity of tissue Doppler was lower in defining abnormal regional systolic function. Moreover, tissue Doppler-based myocardial velocities were affected by myocardial contraction, cardiac movements during respiration, pushing-drawing movements of adjacent normal myocardial segment, and exaggerated wall movements in the transplanted heart. This condition causes decreased sensitivity of tissue Doppler-measured global parameters in rejection cases that are lower than grade IIB.\(^11\)

Therefore, to show regional systolic function, newer, noninvasive, and high-sensitivity cardiac ultrasonography techniques such as strain and strain rate imaging methods have been considered. When regional myocardial dysfunction is assessed, measurement of regional strain directly reflects the regional function.

Although tissue Doppler shows tissue motion rates, strain and strain rate imaging show local rates of wall deformation. The sensitivity-limiting complications of the tissue Doppler technique do not affect strain and strain rate, which measure the gradients between the velocities of 2 myocardial segments that are 1 cm apart.\(^12\) Strain and strain rate imaging are independent from all cardiac movements and are quite sensitive to show regional systolic functional abnormalities caused by acute rejection.\(^13\)

It has been shown in several studies that these methods are sensitive and effective in early diagnosis of regional myocardial systolic dysfunction in cardiac amyloidosis, Fabry disease, Friedrich ataxia, and diabetes.\(^13-15\) Strain rate imaging is sufficiently sensitive to detect even subclinical changes in regional systolic function.

Eroglu and associates\(^6\) showed that longitudinal strain and strain rate values in all septal regions in adult patients with heart transplant were markedly lower than those in the control group. However, there was no difference in left ventricular lateral wall between patient and control groups. In the same study, it was reported that strain and strain rate values were found to be decreased in patients with normal global systolic function. Marciniak and associates\(^16\) performed a study on adult patients with heart transplant, and they reported that both radial and longitudinal peak systolic strain and strain rate values were markedly decreased in early rejection stage. In the apical 4-chamber view, they determined that the longitudinal peak systolic strain and strain rate values in patients with rejection graded ≥ IB were
-11 ± 6% and -1.4 ± 0.6 s⁻¹ in the middle segment of the left ventricular lateral wall and -16 ± 6% and -1.6 ± 0.6 s⁻¹ in the middle segment of interventricular septum. They found in the same study that peak systolic strain and strain rate values in all patients with rejection (graded < IB or graded ≥ IB) were statistically significantly lower in all segments of interventricular septum compared with the control group without heart transplant. However, they did not find any differences between heart transplant patients with rejection graded < IB and those with rejection graded ≥ IB. Peak systolic strain and strain rate values in patients with rejection graded ≥ IB were statistically significantly lower than those in the control group, especially in basal and middle segments of left ventricular lateral wall. However, no statistically significant differences were determined in any of the left ventricular lateral wall segments between patients with rejection graded < IB and the control group.

Sehgal and associates found that the peak systolic radial, longitudinal, and circumferential strain declined during an episode of rejection in pediatric heart transplant patients. In our present study, longitudinal strain and strain rate values of left ventricular lateral wall and of the middle segment of interventricular septum during rejection period were found to be lower than those during periods without rejection. However, statistically significant decreases were observed only in longitudinal strain and strain rate values of midseptum. This finding suggested that the first affected myocardial segment was the interventricular septum at low rejection grades and during asymptomatic periods. It was assumed that regional functional disorder occurred first in interventricular septum because it was the actually affected segment in all patients with cardiopulmonary bypass surgery, including those with heart transplant. The fact that prominent global systolic dysfunction in the left ventricle was not detected during rejection periods in our cases may be explained by low rejection grades. It was determined that, at low rejection grades, the evaluation of regional systolic functions by strain and strain rate imaging methods was superior to the evaluation of the global systolic functions.

Study limitations
Despite its contribution to the literature, our study has some limitations. First, because this is a preliminary report, the number of patients is rather low to really determine a meaningful outcome. In addition, the number of heart transplant patients with rejection is also low. We also could not use more advanced echocardiographic modalities such as speckle tracking technology for detection of left ventricular systolic dysfunction. Performing a 17-segment analysis including the images from the apical 2 chambers view and detecting a radial and circumferential deformation, in addition to longitudinal deformation, would have been better. Finally, the rejection grade in the affected patients was very mild. Because normal strain and strain rate values are not yet valid for children, comparisons had to be made using the normal values defined for adults.

Conclusions
Several studies about complications of heart transplant have revealed that the evaluation of regional peak systolic myocardial velocities were quite valuable in determining regional myocardial systolic function abnormalities. In our study, myocardial strain and strain rates were evaluated for the first time in pediatric patients with heart transplant, with results suggesting that these values could provide early diagnosis at low rejection grades and during asymptomatic period. We believe that increased experience on strain and strain rate imaging and further studies on a larger patient population with higher histopathological rejection grades and with a longer follow-up could show that those modalities are quite beneficial.

References


