Cardiac Allograft Function During the First Year after Transplantation in Rejection-Free Children and Young Adults

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Background—Allograft dysfunction is a common finding early after heart transplant (HT). We sought to assess the recovery of left (LV) and right ventricular (RV) function during the first year after HT in children and young adults using pulsed-wave tissue Doppler imaging.

Methods and Results—We analyzed serially performed echocardiography in 44 pediatric HT recipients (median age: 7.3 years at HT) who remained rejection-free during the first year post-transplant. Age-based normative values for systolic (S'), early-diastolic (E'), and late-diastolic (A') velocities obtained using pulsed-wave tissue Doppler imaging in 380 healthy children were used to transform patient data into z scores. Pulsed-wave tissue Doppler imaging studies ≤10 days post-HT demonstrated biventricular systolic and diastolic dysfunction with most prominent impairment in RV systolic function (S' z score −2.7±0.8), RV early-diastolic filling (E' z score −2.3±1.1), and LV early-diastolic filling (E' z score −2.3±1.1). LV systolic function (S' z score) and late-diastolic filling (A' z score) improved to normal in 11 to 30 days, LV early-diastolic filling (E' z score) in 4 to 6 months, and RV early-diastolic filling in 6 to 9 months (P<0.001 for all on longitudinal analysis). However, RV systolic function (RV S' z score −1.2±1.1) remained impaired 1-year post-transplant. Analysis of serial cardiac catheterization studies showed that RV and LV filling pressures were elevated early post-HT and declined gradually during the first year post-transplant.

Conclusions—Pediatric HT recipients have biventricular dysfunction using pulsed-wave tissue Doppler imaging early after HT with most significant impairment in RV systolic function and RV and LV early-diastolic filling. Although other aspects of LV and RV function normalize in 6 to 9 months, RV systolic function remains abnormal 1 year post-transplant. (Circ Cardiovasc Imaging. 2012;5:756-764.)

Key Words: transplantation • ventricular function • pediatrics • echocardiography

Heart transplantation is an established therapy in children with end-stage heart failure. Although severe graft dysfunction that leads to early graft loss is rare,1 some degree of graft dysfunction is common in children early after heart transplantation (HT).2 Abnormalities in ventricular mechanics may persist for years even in the absence of rejection.3 Furthermore, many recipients have had at least 1 episode of rejection within the first 6 months of transplant.4 Myocyte injury during rejection5 may be associated with worsening of graft function6 and may delay the recovery of ventricular function.

Clinical Perspective on p 764

Current clinical immune suppression protocols are associated with a lower incidence of rejection in pediatric HT recipients compared with earlier eras7,8 and may have contributed to improved early survival in the pediatric HT population.9 A larger pool of rejection-free recipients in clinical practice has created an opportunity to study the physiology of allograft recovery, in particular, recovery of ventricular function, in such recipients with more precision than was previously possible.2 A better understanding of allograft recovery in HT recipients may not only provide further insights into recovery of ventricular function following controlled ischemia, but also improve our understanding of ventricular dysfunction associated with acute and chronic rejection in HT recipients. Pulsed-wave tissue Doppler imaging (PW-TDI) is geometry-independent and allows quantification of both left ventricular (LV) and right ventricular function (RV) using tissue Doppler imaging (TDI). The use of PW-TDI in pediatric HT recipients allows for the evaluation of LV and RV function during the first year post-transplant.

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ventricular (RV) function during systole and diastole. Its noninvasive nature allows repeat evaluations, it has good reproducibility and is now widely used in children with structural heart lesions and after HT.

Therefore, the specific aims of this study were (1) to evaluate the degree of allograft ventricular dysfunction within the first 10 days after HT and, (2) to assess the magnitude and time-course of recovery of ventricular function during the first year post-transplant using serial echocardiograms with PW-TDI imaging and serial invasive hemodynamic studies.

Methods

Study Subjects

We screened all patients who underwent an HT at Boston Children’s Hospital between January 1, 2006 (when PW-TDI was integrated into clinical echocardiography protocol), and December 31, 2010. Patients with a post-transplant follow-up of at least 6 months and those who remained rejection-free during the first year post-transplant using a clinical protocol of serial surveillance biopsies were included in the study. Rejection was defined based on histopathologic findings as grade ≥2R cellular rejection (International Society of Heart and Lung Transplantation classification, 2004) or antibody-mediated rejection.

For the purpose of this analysis, all echocardiographic data were reviewed offline by a single echocardiographer (F.I.L.). Only echocardiograms with good quality PW-TDI images at a frame rate >80 frames/s were included in the analysis. PW-TDI velocities were measured using Vericis HeartSuite (Merge Healthcare, Chicago, IL) digital software. PW flow Doppler images obtained at the tip of the mitral valve leaflets were used to measure LV peak early filling (E) velocity, peak atrial filling (A) velocity, and the E/A ratio. PW-TDI derived systolic (S′), early-diastolic (E′), and late-diastolic (A′) velocity z scores on PW-TDI. The secondary end points were mean RA pressure and PCW pressure and their ratio (RA pressure/PCW pressure) obtained during cardiac catheterization studies.

Study Design

This was a retrospective cohort study of serial assessment of LV and RV function in young, predominantly pediatric, rejection-free HT recipients. The study was approved by the institutional review board with a waiver of informed consent. We analyzed serial echocardiograms and invasive hemodynamic studies performed during the first year of clinical follow-up in each patient. We categorized measurements into 7 time-intervals: (1) those obtained ≤10 days, (2) 11 to 30 days, (3) 31 to 60 days, (4) 61 to 120 days, (5) 121 to 180 days, (6) 181 to 270 days, and (7) 271 to 365 days after HT.

Echocardiography and PW-TDI

Echocardiography studies were acquired using commercially available ultrasound equipment with PW-TDI capability (Philips iE33; Koninklijke Philips Electronics, The Netherlands). Echocardiographic studies were performed either on the day of cardiac catheterization or on the day of outpatient clinic visit.

For all clinical studies, ventricular function assessment using echocardiography includes 2-dimensional imaging, color-flow Doppler, PW flow Doppler, and PW-TDI at our institution. LV systolic function using 2-dimensional echocardiography is considered normal when ejection fraction is ≥55%. The severity of tricuspid and mitral valve regurgitation is estimated by the measurement of vena contracta. PW-TDI velocities are acquired in apical 4-chamber view. The angle between myocardial motion and the ultrasound beam are kept at 30°. A 5-mm sample volume is placed at the basal aspect of the LV and RV free walls and the interventricular septum. Images are digitally stored for offline analysis.

For the purpose of this analysis, all echocardiographic data were reviewed offline by a single echocardiographer (F.L.). Only echocardiograms with good quality PW-TDI images at a frame rate >80 frames/s were included in the analysis. PW-TDI velocities were measured using Vericis HeartSuite (Merge Healthcare, Chicago, IL) digital software. PW flow Doppler images obtained at the tip of the mitral valve leaflets were used to measure LV peak early filling (E) velocity, peak atrial filling (A) velocity, and the E/A ratio. PW-TDI derived systolic (S′), early-diastolic (E′), and late-diastolic (A′) velocity z scores on PW-TDI. The secondary end points were mean RA pressure and PCW pressure and their ratio (RA pressure/PCW pressure) obtained during cardiac catheterization studies.

Within each of the 7 time-intervals, mean PW-TDI velocity z score was compared with normal (mean z score 0.0, by definition) using the 1-sample z test. The Bonferroni method was used to account for multiple comparisons. To evaluate the effect of time on PW-TDI-derived velocity peaks (and on LV and RV filling pressures), linear mixed effects models were used. These models accounted for the correlation among repeated measurements on the same subject; individual patients were treated as random effects. Interaction terms were added to the models to determine whether trends over time differed by donor age, donor ischemic time, and length of cardiopulmonary bypass.

Statistical Analysis

The primary end points were RV and LV systolic (S′), early-diastolic (E′), and late-diastolic (A′) velocity z scores on PW-TDI. The secondary end points were mean RA pressure and PCW pressure and their ratio (RA pressure/PCW pressure) obtained during cardiac catheterization studies.

Patient characteristics were summarized using median (range) or number (%). All measurements were expressed as mean±SD. To compare the severity of RV and LV dysfunction within each patient early after transplant, RV and LV z scores for S′, E′, and A′ velocities obtained ≤10 days after HT were compared using the paired t test. The Pearson correlation coefficient was used to evaluate the association between RV and LV velocity z scores obtained ≤10 days after HT and donor age, donor ischemic time, and length of cardiopulmonary bypass.

Invasive hemodynamic studies (with endomyocardial biopsy) were performed as a clinical protocol at ~2, 4, 6, 9, 12, 16, and 24 weeks, 9 months, and 1 year after HT. This schedule was modified for children <1 year of age. During each study, right heart hemodynamic data including mean right atrial (RA) pressure, RV end-diastolic and end-systolic pressures, mean pulmonary artery pressure, and pulmonary capillary wedge (PCW) pressure were measured. Cardiac index was calculated using the Fick equation and pulmonary vascular resistance (PVR; Wood Units) estimated by dividing the transpulmonary pressure gradient by cardiac index.

Results

Study Population

During the study period, 61 patients underwent HT at Boston Children’s Hospital. Of these, 44 met the inclusion criteria and formed the primary analytic cohort. Of these, 21 patients (48%) were female. The median age at HT was 7.3 years (range 3 months–23 years), 11 (25%) were <1 year old, 12 (27%) were 1 to 10 years old, and 21 (48%) were >10 years old at the time of their HT. The underlying cardiac diagnosis for which HT was performed was congenital heart disease in 16, cardiomyopathy in 24, and retransplantation in 4 patients (Online-only Data Supplement Table I). The surgical technique for HT was bicaval in all patients. The mean donor ischemic time was 3.4±1.0 hours and mean cardiopulmonary bypass time 3.0±1.5 hours. A total of 334 cardiac
Echocardiography and PW-TDI

All patients had normal LV ejection fraction by 2-dimensional echocardiography in all studies. Furthermore, none of the patients had more than mild tricuspid or mitral valve regurgitation early after transplant or in follow-up studies.

Early after HT (≤10 days), both RV and LV demonstrated significant systolic and diastolic dysfunction by PW-TDI (P≤0.005 for comparison of all RV and LV PW-TDI velocity z scores to normal population). RV systolic function (S′ velocity) was more impaired compared with LV systolic function within individual patients (S′ z scores −2.7±0.8 for RV versus −0.4±1.0 for LV, P<0.001) as was RV late-diastolic filling (A′ velocity z scores −1.3±0.7 for RV versus −0.9±0.9 for LV, P=0.02). However, early-diastolic filling was impaired to a similar degree (E′ z score −2.3±1.1 versus −2.3±1.1, P=0.94). Importantly, PW-TDI velocity z scores in early post-HT period (S′, E′, and A′ for LV, RV, or interventricular septum) were similar whether recipient age or donor age was used to transform the raw data into z scores. Paired comparisons of z scores derived using the recipient age and those derived using the donor age did not reach statistical significance for any of the PW-TDI velocity z scores.

Early post-HT studies (≤10 days) demonstrated that older donor age was associated with worse LV systolic function assessed as S′ velocity z score (r=−0.42, P=0.002) and with worse LV early-diastolic filling assessed as E′ velocity z score (r=−0.46, P=0.001) but not with LV late-diastolic filling assessed as A′ z score (r=0.08, P=0.57). A similar relationship of donor age was also noted with RV systolic function assessed as S′ velocity z score (r=−0.39, P=0.007) and with RV early-diastolic filling assessed as E′ velocity z score (r=−0.54, P<0.001) but not with RV late-diastolic filling assessed as A′ z score (r=−0.09, P=0.57). Furthermore, longer donor ischemic time was associated with worse LV systolic function (LV S′ z score) and early-diastolic filling (LV E′ z scores) early post-transplant (Figure 1). No associations were found between RV or LV z scores and either donor age or duration of cardiopulmonary bypass.

Analysis of serial PW-TDI velocities demonstrated an increase in all measures of LV and RV function over time. Analyzed either as raw velocities (cm/s) or as age-adjusted velocity (z score), the improvement in RV and LV systolic function (S′), early-diastolic filling (E′), and late-diastolic filling (A′) over time was significant (P<0.001 for all in linear mixed models, Table 1, Figure 2). LV systolic function (S′ velocity) and late-diastolic filling (A′ velocity) improved to normal in 11 to 30 days, LV early-diastolic filling (E′ velocity) in 4 to 6 months, and RV early and late-diastolic filling in 6 to 9 months (Online-only Data Supplement Table III). However, RV systolic function (RV S′ z scores −1.2±1.1) remained impaired 1-year post-transplant (Figure 3, example of early and late PW-TDI velocities in a study patient). The rate of longitudinal improvement in RV or LV function was not affected by donor age, ischemic time, or cardiopulmonary bypass time.

The increase in mitral valve E- and A-wave velocity z scores by PW flow-Doppler (−0.4±1.0 to 0.2±1.2 cm/s, P=0.06 and 0.0±1.9 to 0.7±1.7, P=0.05) and the decline in their ratio (−0.1±1.2 to −0.4±0.7, P=0.05) during the study period was of borderline statistical significance (Online-only Data Supplement Table IV). However, LV E/E′ ratio (a noninvasive correlate of LV end-diastolic pressure) and RV E/E′ ratio declined gradually over time (P<0.001, linear mixed model) (Figure 4, online-only Data Supplemental Table IV).

In a secondary analysis, we compared longitudinal changes in graft systolic function in the primary cohort (n=44) with a smaller cohort of 9 patients (median age 16 years) transplanted during the study period who had at least 1 episode of acute rejection during the first year after transplant. The group-difference in recovery of function was borderline significant for LV (interaction-term P=0.07) and significant for RV (P=0.001) and interventricular septum (P<0.001) (Figure 5).

Intraobserver variability was low with intraclass correlation of 0.88 for all velocities combined (95% CI 0.83, 0.90).
Table 2 depicts serial right heart hemodynamic data in study of LV systolic function and LV late-diastolic filling within a improvement in biventricular function with normalization with most significant impairment of RV systolic function and biventricular systolic and diastolic dysfunction early after HT 3 major findings of this study. First, HT recipients develop ies to assess trends in biventricular filling pressures. There are LV: z, cm/s 8.0 (1.8) 8.8 (1.7) 9.3 (1.9) 10.2 (2.3) 10.6 (2.2) 11.0 (2.2) 10.8 (2.2) <0.001 ′ z, cm/s 6.5 (1.6) 7.2 (1.5) 8.4 (1.7) 9.0 (1.7) 9.7 (1.8) 10.2 (2.3) 9.8 (1.8) <0.001 ′ z, cm/s 6.1 (1.6) 6.6 (1.2) 6.9 (1.4) 7.3 (1.4) 7.7 (1.3) 7.9 (1.4) 7.9 (1.4) <0.001 S RV: ′ z, cm/s 6.1 (1.6) 6.6 (1.2) 6.9 (1.4) 7.3 (1.4) 7.7 (1.3) 7.9 (1.4) 7.9 (1.4) <0.001 ′ z, cm/s 7.9 (2.1) 8.7 (2.1) 9.8 (1.8) 10.6 (1.7) 11.2 (1.7) 11.2 (1.9) 11.5 (1.8) <0.001 ′ z, cm/s 7.9 (2.1) 8.7 (2.1) 9.8 (1.8) 10.6 (1.7) 11.2 (1.7) 11.2 (1.9) 11.5 (1.8) <0.001 ′ z, cm/s 6.1 (1.6) 6.6 (1.2) 6.9 (1.4) 7.3 (1.4) 7.7 (1.3) 7.9 (1.4) 7.9 (1.4) <0.001 S IVS: ′ z, cm/s 5.3 (1.7) 6.3 (1.5) 6.9 (1.6) 7.5 (1.4) 8.1 (1.4) 7.7 (1.3) 7.9 (1.7) <0.001 ′ z, cm/s 5.3 (1.7) 6.3 (1.5) 6.9 (1.6) 7.5 (1.4) 8.1 (1.4) 7.7 (1.3) 7.9 (1.7) <0.001 ′ z, cm/s 4.9 (1.3) 5.6 (1.3) 6.0 (1.2) 6.3 (1.3) 6.6 (1.6) 6.5 (1.4) 6.4 (1.4) <0.001 R, late-diastolic velocity; IVS, interventricular septum; and RV, right ventricle.

Intraclass correlations for individual PW-TDI velocities ranged from 0.81 to 0.93 (Online-only Data Supplement Table V).

Cardiac Catheterization
PCW pressure declined gradually from 13±5 mmHg at the time of the first invasive study to 10±3 mmHg by 1-year post-HT. RA pressure also declined gradually from 10±4 mmHg at the time of the first study to 6±2 mmHg by 1 year . The peripheral pressure was also documented abnormal tissue velocities compared with children 15,16. We also analyzed serial invasive hemodynamic studies to assess trends in biventricular filling pressures. There are 3 major findings of this study. First, HT recipients develop biventricular systolic and diastolic dysfunction early after HT with most significant impairment of RV systolic function and LV early-diastolic filling. Second, there is a gradual improvement in biventricular function with normalization of LV systolic function and LV late-diastolic filling within a month, LV early-diastolic filling in 4 to 6 months, and RV filling in 6 to 9 months after HT. However, RV systolic function remains impaired 1-year post-transplant. These longitudinal changes in PW-TDI findings are accompanied by a concurrent decline in biventricular filling pressures on hemodynamic assessment. Finally, older donor age and longer graft ischemic time are both associated with more severe RV and LV dysfunction early post-transplant. However, they are not associated with the rate at which RV or LV function improves during the first post-transplant year.

These findings expand upon previous observations by Mahle et al 2 who reported serial PW-TDI findings in pediatric HT recipients from early post-transplant period to 6 months post-transplant and in 16 controls. They found that tricuspid and mitral annular velocities remained impaired in HT recipients until >4 months post-transplant. Their group also reported reduced tricuspid annular velocities in children early and late after HT compared with controls in a cross-sectional study. 15 In another study with a cross-sectional study design, Pauliks et al 3 found abnormal RV systolic velocities in children who were rejection-free 3 years post-HT compared with age-matched controls. Other cross-sectional studies in children who were rejection-free at the time of their PW-TDI imaging but had previous rejection history have also documented abnormal tissue velocities compared with controls. 19,20 Our study expands the current knowledge-base by analyzing a larger cohort of HT recipients in a longitudinal study design, following study subjects for a longer duration, transforming raw TDI velocities into age-adjusted z scores and analyzing serial invasive hemodynamic studies performed along a similar time line. Furthermore, although some of the findings of our analysis could be anticipated from previous reports, our analysis provides a broad and integrated view of longitudinal changes in graft function in the contemporary

Table 1. Serial Tissue-Doppler Velocities in Heart Transplant Recipients During First Post-transplant Year

<table>
<thead>
<tr>
<th>Parameter</th>
<th>≤10 Days</th>
<th>11 to 30 Days</th>
<th>31 to 60 Days</th>
<th>61 to 120 Days</th>
<th>121 to 180 Days</th>
<th>181 to 270 Days</th>
<th>271 to 365 Days</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV: ′ z, cm/s</td>
<td>8.0 (1.8)</td>
<td>8.8 (1.7)</td>
<td>9.3 (1.9)</td>
<td>10.2 (2.3)</td>
<td>10.6 (2.2)</td>
<td>11.0 (2.2)</td>
<td>10.8 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV: ′ z, cm/s</td>
<td>6.5 (1.6)</td>
<td>7.2 (1.5)</td>
<td>8.4 (1.7)</td>
<td>9.0 (1.7)</td>
<td>9.7 (1.8)</td>
<td>10.2 (2.3)</td>
<td>9.8 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>6.1 (1.6)</td>
<td>6.6 (1.2)</td>
<td>6.9 (1.4)</td>
<td>7.3 (1.4)</td>
<td>7.7 (1.3)</td>
<td>7.9 (1.4)</td>
<td>7.9 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>4.9 (1.3)</td>
<td>5.6 (1.3)</td>
<td>6.0 (1.2)</td>
<td>6.3 (1.3)</td>
<td>6.6 (1.6)</td>
<td>6.5 (1.4)</td>
<td>6.4 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>2.7 (0.8)</td>
<td>2.4 (0.8)</td>
<td>2.1 (0.9)</td>
<td>2.5 (0.9)</td>
<td>2.8 (0.9)</td>
<td>2.6 (0.9)</td>
<td>2.5 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>2.3 (1.1)</td>
<td>2.1 (1.0)</td>
<td>2.0 (0.9)</td>
<td>2.1 (0.9)</td>
<td>2.3 (0.9)</td>
<td>2.4 (0.9)</td>
<td>2.3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>5.3 (1.7)</td>
<td>6.3 (1.5)</td>
<td>6.9 (1.6)</td>
<td>7.5 (1.4)</td>
<td>8.1 (1.4)</td>
<td>7.7 (1.3)</td>
<td>7.9 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV: ′ z, cm/s</td>
<td>1.3 (0.7)</td>
<td>0.9 (0.7)</td>
<td>0.7 (0.7)</td>
<td>0.4 (0.6)</td>
<td>0.1 (0.6)</td>
<td>0.3 (0.5)</td>
<td>0.2 (0.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

LV indicates left ventricle; ′ , systolic velocity; ′ , early-diastolic velocity; ′ , late-diastolic velocity; IVS, interventricular septum; and RV, right ventricle.
era during the first year from early after HT in rejection-free children. The time-related trends in systolic PW-TDI velocities in patients with a rejection event during the first year (Figure 5) suggest that the rate of recovery of ventricular function may be slower in such patients compared with rejection-free patients.

Figure 2. Mean velocities measured by tissue Doppler imaging at the bases of left ventricle, right ventricle, and interventricular septum during the first year after heart transplant. (A, C, E) Velocities are expressed as cm/s and as (B, D, F) age-adjusted z scores. The error bars represent 95% CIs.
RV dysfunction is an important determinant of early post-HT outcomes. The mechanism of RV dysfunction in HT recipients is multifactorial. Donor brain death, graft ischemia, and elevated PVR have all been related to early RV dysfunction. Previous studies suggest that donor brain death may affect RV contractility to a greater extent than it affects LV function. Additional RV insult from rejection, tricuspid regurgitation, and myocardial fibrosis from repeated biopsies have all been proposed to contribute to persistent RV dysfunction. The presence of near-normal PVR in the current cohort suggests that their early RV dysfunction was related to donor brain death or graft ischemia rather than to increased afterload. Furthermore, the persistence of RV dysfunction at 1-year post-transplant in rejection-free patients cannot be explained by rejection-related mechanisms. Potential mechanisms for this finding include more severe early RV dysfunction (compared to LV) and RV/tricuspid valve trauma related to repeated biopsies. With regard to LV function, although LV E' velocity measures early relaxation during diastole, A' velocity is a measure of LV compliance during late diastole. Atrial systole contributes 20% to 30% toward overall LV diastolic filling and reduced A' velocity is interpreted as poor LV compliance. Previous studies in HT recipients have reported persistent abnormality in late-diastolic LV filling and have attributed this finding to impaired left atrial function because of electrical isolation of the recipient and donor atrial components. LV late-diastolic filling was impaired in our patients early after HT but normalized within the first month post-transplant. This finding may be explained by the bicaval technique of HT in our patients, which results in a larger contribution from the donor atrium to the graft left atrial and thus more effective left atrial function than in HT recipients with a bialtral HT.

This study has several implications. First, the presence of LV and RV dysfunction early after transplant, the temporal improvement in PW-TDI velocities during the first year and the concurrent changes in LV and RV filling pressures in hemodynamic studies suggest that PW-TDI is not only more sensitive in detecting ventricular dysfunction compared with conventional echocardiography imaging (as is widely known), but also that TDI findings in HT recipients have a physiologic correlate. Whether the heterogeneity in early post-transplant ventricular dysfunction using TDI is large enough to be related to clinical outcomes requires further investigation.

Second, our findings provide insights into well-known clinical observations with respect to the importance of RV function in HT recipients. For example, the magnitude of early RV dysfunction in our study population despite their normal PVR may explain the clinical vulnerability of HT recipients with high PVR for developing acute right heart failure early post-transplant, whereas the persistence of RV dysfunction beyond the first year may explain its vulnerability to further decline in preterminal HT recipients. Our finding that LV early- and late-diastolic filling velocities normalize within the first year does not explain the restrictive response to fluid challenge in otherwise well-pediatric HT recipients reported 15 years ago. The surgical technique was universally bialtral in that era and whether the current-era recipients with no prior rejection would also demonstrate a restrictive response to fluid challenge is unknown.

Finally, an improved understanding of temporal changes in PW-TDI findings in rejection-free recipients may provide the backdrop for developing a noninvasive rejection-surveillance protocol in HT recipients, particularly in children. Previous efforts using conventional echocardiography for this purpose have not been considered broadly acceptable among HT physicians. Further studies are needed to investigate whether the higher sensitivity of PW-TDI compared with conventional echocardiography in detecting functional changes can be used to develop criteria for defining a nonrejection echocardiogram with high predictive accuracy as to allow fewer routine biopsies in pediatric recipients. This may be
particularly relevant in the current era because the frequency of rejection and thus the yield of routinely performed biopsies for detecting rejection has decreased compared with earlier eras.7,8

Study Limitations
This study has a few limitations. First, the retrospective nature of this study may create an opportunity for selection bias if the study subjects do not represent the population of interest. However, the relatively large number of imaging studies examined and use of well-defined criteria for study inclusion and for graft-rejection make it unlikely that selection bias is an
important limitation. Second, the timing of PW-TDI and invasive hemodynamic studies followed a clinical protocol, which allowed a larger variation in timing and number of studies in subjects than that expected in a prospectively established research protocol. Third, the study cohort was mostly pediatric and the findings may not be applicable to adult HT recipients. Finally, PW-TDI-measured velocities are sensitive to the sampling angle and the frame rate so that even small changes in these may alter the measured velocities. To minimize inaccuracy, we included only those images for analysis that had a frame rate >80/s and were obtained with a narrow sector. Furthermore, to minimize the effect of respiratory variability on measured velocities, 3 consecutive cycles were analyzed and their mean used in all analyses.

Conclusions
In conclusion, pediatric HT recipients demonstrate biventricular dysfunction as measured by PW-TDI early after HT with most significant impairment in RV systolic function and LV and RV early-diastolic filling. There is a gradual improvement in biventricular function with normalization of LV systolic function and LV late-diastolic filling within a month, LV early-diastolic filling in 4 to 6 months and RV early and late-diastolic filling in 6 to 9 months after transplant. Although RV systolic function also improves over time, it remains impaired 1-year post-transplant.

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Disclosures
None.

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**CLINICAL PERSPECTIVE**

Heart transplantation (HT) is an established therapy in children with end-stage heart failure. Although severe early graft dysfunction after HT is rare, mild ventricular dysfunction is common even without rejection and may persist for years. Pulsed-wave tissue Doppler imaging (PW-TDI) is geometry-independent and allows quantification of both left ventricular and right ventricular (RV) function during systole and diastole. In this study, we analyzed serially performed PW-TDI studies in 44 pediatric HT recipients (median age at transplant 7.3 years) who remained rejection-free during the first year post-transplant to investigate the natural history of recovery of ventricular function. We used data from PW-TDI studies in 380 healthy children to transform patient data into age-adjusted z scores to allow better interpretation of raw PW-TDI data in the study children. We found biventricular systolic and diastolic dysfunction early after HT with most significant impairment in RV systolic function and RV and left ventricular early-diastolic filling. Although other aspects of left ventricular and RV function normalized in 6 to 9 months, RV systolic function remained abnormal 1-year post-transplant. Serial cardiac catheterization studies showed that RV and left ventricular filling pressures were elevated early after HT and declined gradually during the first year. These findings provide important insights into the natural history of recovery of biventricular function in pediatric HT recipients and improve our understanding of RV dysfunction in these patients. We suggest that a better understanding of ventricular function in rejection-free patients may also help in developing a PW-TDI-based rejection-surveillance protocol in pediatric HT recipients.
Cardiac Allograft Function During the First Year after Transplantation in Rejection-Free Children and Young Adults

Fatima I. Lunze, Steven D. Colan, Kimberlee Gauvreau, Ming Hui Chen, Antonio R. Perez-Atayde, Elizabeth D. Blume and Tajinder P. Singh

Circ Cardiovasc Imaging. 2012;5:756-764; originally published online September 21, 2012; doi: 10.1161/CIRCIMAGING.112.976613

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Supplemental Table I. Baseline Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation</td>
<td>7.3 years (3 mo- 23 yrs)</td>
</tr>
<tr>
<td>Follow-up time post transplantation</td>
<td>11 months (6 mo-12 mo)</td>
</tr>
<tr>
<td>Female gender</td>
<td>21 (48%)</td>
</tr>
<tr>
<td>Age &lt; 1 year</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Age 1-9 year</td>
<td>12 (27%)</td>
</tr>
<tr>
<td>Age ≥10 years</td>
<td>21 (48%)</td>
</tr>
</tbody>
</table>

**Diagnosis Pre-Transplant**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N = 44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>16 (36%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>24 (55%)</td>
</tr>
<tr>
<td>Re-transplantation</td>
<td>4 (9%)</td>
</tr>
</tbody>
</table>

Data are presented as number (percent) for categorical characteristics or median (range) for continuous characteristics.
**Supplemental Table II. Number of PW-TDI and Cardiac Catheterization Studies Analyzed in Specified Time-intervals**

<table>
<thead>
<tr>
<th>Examination</th>
<th>Time Intervals (Days after Heart Transplant)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-10 (1)</td>
<td>11-30 (2)</td>
</tr>
<tr>
<td>PW-TDI</td>
<td>71</td>
<td>151</td>
</tr>
<tr>
<td>Cardiac Catheterization</td>
<td>14</td>
<td>68</td>
</tr>
</tbody>
</table>

PW-TDI (Pulse-wave tissue Doppler imaging)
Supplemental Table III. P-values Comparing Mean Pulsed-Wave Tissue Doppler Imaging Velocity Z-Scores to Normal Children*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>≤10 days</th>
<th>11-30 days</th>
<th>31-60 days</th>
<th>61-120 days</th>
<th>121-180 days</th>
<th>181-270 days</th>
<th>271-365 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV: S’ z-score</td>
<td>p = 0.005</td>
<td>p = 0.22</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>E’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.40</td>
<td>p = 0.003</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>A’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>IVS: S’ z-score</td>
<td>P &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.02</td>
<td>p = 0.49</td>
<td>p = 0.02</td>
<td>p = 0.01</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>E’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.006</td>
<td>p &lt; 0.001</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>A’ z-score</td>
<td>p &lt; 0.001</td>
<td>p = 0.31</td>
<td>p = 0.03</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>RV: S’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>E’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.001</td>
<td>p = 0.02</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>A’ z-score</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.12</td>
<td>p &lt; 0.001</td>
<td>p = 0.09</td>
</tr>
</tbody>
</table>

* P values are for comparison to normals. Due to multiple comparisons, the p value for significant difference from normal is <0.007 (Bonferroni correction). LV (left ventricle), RV (right ventricle) and IVS (interventricular septum)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>≤10 days</th>
<th>11-30 days</th>
<th>31-60 days</th>
<th>61-120 day</th>
<th>121-180 days</th>
<th>181-270 days</th>
<th>271-365 days</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP: Systolic (mmHg)</td>
<td>105 (18)</td>
<td>106 (17)</td>
<td>110 (16)</td>
<td>103 (15)</td>
<td>106 (17)</td>
<td>108 (16)</td>
<td>106 (17)</td>
<td>0.74</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>58 (13)</td>
<td>61 (16)</td>
<td>66 (13)</td>
<td>61 (14)</td>
<td>64 (15)</td>
<td>62 (12)</td>
<td>63 (12)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean (mmHg)</td>
<td>66 (16)</td>
<td>71 (14)</td>
<td>77 (13)</td>
<td>72 (13)</td>
<td>75 (16)</td>
<td>73 (12)</td>
<td>74 (13)</td>
<td>0.04</td>
</tr>
<tr>
<td>HR (bpm):</td>
<td>109 (21)</td>
<td>108 (21)</td>
<td>111 (21)</td>
<td>108 (19)</td>
<td>107 (18)</td>
<td>106 (20)</td>
<td>102 (18)</td>
<td>0.15</td>
</tr>
<tr>
<td>MV: E-wave (cm/s)</td>
<td>0.8 (0.2)</td>
<td>0.9 (0.2)</td>
<td>0.9 (0.2)</td>
<td>0.9 (0.2)</td>
<td>1.0 (0.2)</td>
<td>0.9 (0.2)</td>
<td>0.9 (0.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>z-score</td>
<td>-0.4 (1.0)</td>
<td>-0.1 (1.2)</td>
<td>0.1 (1.2)</td>
<td>0.2 (1.3)</td>
<td>0.1 (1.0)</td>
<td>0.4 (1.0)</td>
<td>0.2 (1.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>A-wave (cm/s)</td>
<td>0.5 (0.2)</td>
<td>0.5 (0.1)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.1)</td>
<td>0.6 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>z-score</td>
<td>0.0 (1.9)</td>
<td>0.5 (1.6)</td>
<td>1.1 (2.1)</td>
<td>1.3 (1.9)</td>
<td>1.2 (1.4)</td>
<td>2.0 (2.3)</td>
<td>0.7 (1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>2.0 (0.7)</td>
<td>1.8 (0.5)</td>
<td>1.7 (0.6)</td>
<td>1.6 (0.4)</td>
<td>1.7 (0.3)</td>
<td>1.7 (0.4)</td>
<td>1.8 (0.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>z-score</td>
<td>-0.1 (1.2)</td>
<td>-0.5 (0.9)</td>
<td>-0.6 (0.8)</td>
<td>-0.8 (0.7)</td>
<td>-0.7 (0.7)</td>
<td>-0.8 (0.8)</td>
<td>-0.4 (0.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>LV: E/E’ ratio</td>
<td>8.8 (3.0)</td>
<td>7.5 (2.0)</td>
<td>6.9 (2.6)</td>
<td>6.0 (1.5)</td>
<td>6.0 (1.6)</td>
<td>6.5 (2.0)</td>
<td>6.0 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TV: E-wave (cm/s)</td>
<td>0.5 (0.2)</td>
<td>0.5 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.6 (0.1)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.2)</td>
<td>0.6 (0.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>RV: E/E’ ratio</td>
<td>8.4 (5.1)</td>
<td>7.7 (4.2)</td>
<td>6.4 (2.9)</td>
<td>5.7 (2.5)</td>
<td>5.5 (2.1)</td>
<td>5.1 (2.2)</td>
<td>4.8 (1.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP (blood pressure), HR (heart rate), bpm (beats per minute) MV (mitral valve), TV (tricuspid valve)
### Supplemental Table V. Intraclass Correlations for Individual PW Tissue Doppler Measures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LV S’</th>
<th>LV E’</th>
<th>LV A’</th>
<th>IVS S’</th>
<th>IVS E’</th>
<th>IVS A’</th>
<th>RV S’</th>
<th>RV E’</th>
<th>RV A’</th>
<th>LV E/E’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraclass Correlation</td>
<td>$r=0.93$</td>
<td>$r=0.89$</td>
<td>$r=0.87$</td>
<td>$r=0.90$</td>
<td>$r=0.90$</td>
<td>$r=0.86$</td>
<td>$r=0.81$</td>
<td>$r=0.91$</td>
<td>$r=0.87$</td>
<td>$r=0.86$</td>
</tr>
</tbody>
</table>

LV (left ventricle), RV (right ventricle) and IVS (interventricular septum)