Published in final edited form as:

Pediatr Transplant. 2011 August ; 15(5): 488–494. doi:10.1111/j.1399-3046.2011.01503.x.

Doppler Tissue Imaging in Children Following Cardiac Transplantation: A Comparison to Catheter Derived Hemodynamics

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Abstract

Background—Previous studies have demonstrated a correlation between $E:E_a$ and ventricular filling pressure in adults after heart transplantation. We sought to determine if $E:E_a$ correlates with filling pressure after heart transplantation in children.

Methods—A prospective analysis of children who have undergone heart transplantation was performed. Inflow and myocardial velocities were recorded and compared to catheter-derived filling pressures and rejection status.

Results—We performed 61 studies in 49 subjects. No correlation was found between septal $E:E_a$ and pulmonary capillary wedge pressure (PCWP) ($r=0.14$, $p=0.28$); or between lateral tricuspid $E:E_a$ and mean right atrial pressure (RAP) ($r=0.04$, $p=0.79$). However, the mean PCWP was higher among subjects with elevated septal $E:E_a$ (>12) compared to normal $E:E_a$ (12.3 ± 2.8 mmHg vs 10.1 ± 2.9 mmHg, $p=0.02$). Similarly, mean RAP was higher among subjects with an elevated lateral tricuspid $E:E_a$ (>10) compared to normal lateral tricuspid $E:E_a$ (7.7 ± 2.1 mmHg vs 6.0 ± 2.4 mmHg, $p=0.04$). Elevated septal $E:E_a$ was also associated with high-grade cellular rejection (OR=17.3 (95% CI 1.4–221), $p=0.028$).

Conclusion—In children following heart transplant, $E:E_a$ does not correlate well with the range of filling pressures seen after pediatric heart transplantation. However, a septal $E:E_a > 12$ is associated with elevated PCWP and high grade cellular rejection and a lateral tricuspid $E:E_a > 10$ is associated with elevated mean RAP.

Doppler tissue imaging (DTI) has emerged as a non-invasive tool capable of measuring diastolic function and predicting elevated ventricular filling pressure in adults. Previous studies suggest that a ratio of peak early diastolic mitral inflow velocity to peak early diastolic myocardial velocity ($E:E_a$) at the mitral – septal junction correlates with pulmonary capillary wedge pressure (PCWP) measured during cardiac catheterization in select populations^{1–5}. Likewise, the ratio of peak early diastolic tricuspid inflow velocity to peak early diastolic myocardial velocity at the lateral tricuspid annulus has been reported to correlate with mean right atrial pressure (RAP)¹. However, these relationships have not been fully elucidated in children. $E:E_a$ as a surrogate of PCWP would be a valuable non-invasive

tool to use in pediatric patients and could potentially reduce the need to measure hemodynamics and ventricular performance invasively.

E:E_a would be particularly useful in children who undergo heart transplantation. Pediatric heart transplant recipients require serial cardiac catheterization as a means of surveillance for allograft health. However, catheterization is invasive, costly, and associated with risk⁶. A non-invasive measure that could serve as an effective screen of graft health could reduce the frequency of catheterization and benefit this high-risk population of patients. E:E_a as a surrogate of PCWP is currently used in this clinical setting though the only published study to date suggests that this tool does not correlate with PCWP and therefore may not be appropriate to use in children after heart transplantation⁷.

The primary aim of this study was to determine whether the ratio of early mitral inflow velocity compared to annular tissue velocity (septal E:E_a) correlates with left ventricular filling pressures as measured by PCWP and whether tricuspid inflow velocity compared to annular tissue velocity (lateral tricuspid E:E_a) correlates with right ventricular filling pressure as measured by mean RAP in children who have undergone cardiac transplantation. A secondary aim was to determine if elevations in septal E:E_a are predictive of acute cellular graft rejection. We hypothesized that E:E_a would correlate with PCWP, mean RAP, and acute cellular graft rejection.

Methods

Subjects

This study was a prospective cross-sectional analysis of pediatric heart transplant recipients who underwent cardiac catheterizations from 3/08 to 9/08 at our institution. All heart transplant recipients less than 21 years of age followed as outpatients at our institution were considered eligible. Exclusion criteria included an electronically paced cardiac rhythm, a previous diagnosis of mitral stenosis, and/or failure to reach hospital discharge following heart transplantation. Potential subjects were identified from a search of the institutional scheduling database. Informed consent was obtained from parents or guardians and patient assent was obtained when appropriate. The study was approved by the hospital Institutional Review Board.

Echocardiographic Studies

Echocardiograms were performed by one of two echocardiography sonographers with specific training for this protocol. A Phillips IE33 (Phillips, Andover, MA) machine was used for image acquisition. Appropriate transducers were selected based on subject body habitus. Images were transferred to a hospital server for digital storage. Measurements were performed offline using syngo Dynamics software version 5 (Siemens, Ann Arbor, Michigan) by a pediatric cardiologist with specialized training in echocardiography who was blinded to subject demographic information, hemodynamic data from cardiac catheterization, and endomyocardial biopsy results.

Echocardiographic images were obtained according to the standards of the American Society of Echocardiography⁸. Left ventricular dimensions were calculated from the parasternal short-axis view. Early diastolic inflow velocity (E wave) and late diastolic inflow velocity (A wave) were measured at the tips of the tricuspid and mitral valve leaflets in an apical four-chamber view (Figure 1). Pulsed DTI velocities were recorded at the lateral tricuspid annulus, the lateral mitral annulus, and the septal-annular junction from an apical four-chamber view ensuring an optimal angle of interrogation (Figure 1). Each Doppler variable was measured three times and the mean value was recorded for analysis. Data that

could not be interpreted due to lack of signal fidelity or as a result of an angle of interrogation of more than 30 degrees were discarded.

Cardiac Catheterization

Timing of surveillance cardiac catheterization was determined by institutional protocol with additional catheterizations performed if there was clinical suspicion of rejection, as well as at two weeks following treatment for allograft rejection. Hemodynamic measurements were obtained in a serial manner from distal to proximal chambers using an end-hole, balloon tipped catheter. Cardiac index was calculated using the thermodilution technique⁹. Following hemodynamic measurements, endomyocardial biopsies from the right ventricular septum were obtained using a biptome with an age appropriate jaw volume of 1.6, 1.8 or 2.0 mm³. A minimum of four biopsies was obtained at each catheterization, transported in formalin and reviewed by light microscope for cellular rejection grading according to the standards of the International Society of Heart and Lung Transplantation (ISHLT).

Sedation and Hydration Status

Sedation was performed by an anesthesiologist or by trained catheterization laboratory personnel. The degree of sedation ranged from local anesthesia only to general anesthesia with endotracheal intubation. All echocardiograms immediately preceded catheterization and were performed under the same conditions of sedation. Administration of intravenous fluids was limited to standard maintenance fluids for NPO status. No additional fluid boluses were given during the echocardiogram or in the period up to and including catheter measurements.

Histology

Cellular rejection was determined using the ISHLT criteria: grade 0 = no rejection; grade 1A = focal infiltrate without myocyte damage; grade 1B = diffuse but sparse infiltrate without myocyte damage; grade II = one focus with aggressive infiltrates and / or myocyte damage; grade IIIA = multisite aggressive infiltrate and / or myocyte damage; grade IIIB = diffuse inflammation with myocyte necrosis; grade IV = diffuse polymorphous infiltrate with hemorrhage and myocyte necrosis.

Statistical Analysis

Descriptive statistics were performed with normally distributed continuous variables expressed as mean $\pm$ standard deviation and skewed continuous variables expressed as median with range. Categorical variables were summarized as counts and percentage of total. For our primary analysis, the E:E_a from each myocardial site, the PCWP, and the mean RAP were evaluated as continuous variables. Correlation was determined using the Spearman rank correlation coefficient. For our secondary analyses, the septal and lateral tricuspid E:E_a were evaluated as dichotomous variables. Cut-points were determined based on a post-hoc review of likelihood ratios which identified a cut-point of 12 for the septal E:E_a and a cut-point of 10 for the lateral tricuspid E:E_a as best predictors of elevated filling pressure (PCWP $\geq$ 10, mean RAP $\geq$ 8). Comparisons of PCWP based on “elevated” versus “normal” E:E_a were made by one-tailed student’s t-test. Acute cellular graft rejection was evaluated as a single group (present or absent) and evaluated based on high grade vs. low grade where high grade was defined as rejection meeting the criteria for ISHLT grade 3A or higher. Logistic regression was used to test for associations between E:E_a and presence of cellular rejection. Twenty percent (12/61) of the study echocardiograms were randomly selected for review by a second reader to determine inter-observer variability. The intraclass correlation coefficient was used for this analysis. Statistical significance was established at $p < 0.05$.

Results

Forty-nine children met inclusion criteria and consented to participate in the study. A total of 61 echocardiographic and catheterization studies were performed on these 49 patients (six subjects underwent more than one catheterization in this time period). All echocardiographic and cardiac catheterization data were collected under the same conditions of sedation. The intraclass correlation coefficient for inter-observer agreement was ≥ 0.95 ($p < 0.01$) for all echocardiographic measurements.

Demographic information for enrolled subjects is listed in Table 1. The mean catheter-derived cardiac index was 3.7 ± 0.7 L/min/m², the mean pulmonary capillary wedge pressure was 10.3 ± 3 mmHg, and the mean RAp was 6.2 ± 2.4 mmHg. The mean measure of each echocardiographic variable is shown in Table 2. The values for ventricular dimensions, shortening fraction and atrioventricular inflow velocities fell within the normal range for the general pediatric population while the myocardial velocities were mildly diminished^{10, 11}. In this cohort, 4.4% (8/183) of images were discarded due to lack of signal fidelity.

No correlation was found between the septal E:E_a and the PCWP; $r = 0.14$, $p = 0.28$ (Figure 2) or the lateral mitral E:E_a and the PCWP; $r = 0.02$, $p = 0.9$ (Figure 3). Likewise, there was no correlation between the lateral tricuspid E:E_a and the mean right atrial pressure; $r = 0.04$, $p = 0.79$ (Figure 4). Similarly, no correlation was found between Doppler tissue derived myocardial velocities alone and PCWP (Table 3). However, when the septal E:E_a was assessed as a dichotomous variable based on likelihood ratios, those subjects with an E:E_a > 12 had a significantly higher mean PCWP compared to those subjects with an E:E_a ≤ 12 (12.3 ± 2.8 mmHg vs 10.1 ± 2.9 mmHg, $p = 0.02$, Figure 5). Similarly, when the lateral tricuspid E:E_a was evaluated as a dichotomous variable, those subjects with an E:E_a > 10 had significantly higher mean RAp (7.7 ± 2.1 mmHg vs 6.0 ± 2.4 mmHg, $p = 0.04$, Figure 5).

Histological review of the endomyocardial biopsies revealed 21 cases of acute cellular rejection (Table 4). Of the total cases of rejection, 18 were classified as low grade while three were classified as high-grade. An elevated septal E:E_a was not associated with acute cellular graft rejection (OR = 1.2 (95% CI 0.25 to 5.4), $p = 0.84$) when rejection grade was treated as an ordinal variable. However, there was a significant association between an E:E_a > 12 and high-grade cellular rejection (OR = 17.3 (95% CI 1.4 – 221), $p = 0.028$). Interestingly, in those cases with high-grade rejection, lateral mitral annular velocity and septal annular velocity trended lower than in those cases with either no rejection or low grade rejection though this did not reach significance. Tricuspid annular velocities were similar whether or not rejection of any grade was present (Figure 6). No differences were identified in shortening fraction based on degree of rejection (36% with no rejection, 35% with low-grade rejection, and 38% with high-grade rejection).

Discussion

This prospective, blinded study evaluated the relationship between Doppler tissue imaging derived measures of diastolic function and catheter obtained measurements of intracardiac pressures in a cohort of pediatric heart transplant recipients. Echocardiographic and catheterization measurements were made nearly simultaneously under the same conditions of sedation in the cardiac catheterization laboratory. While the echocardiographic technique employed was easy to perform and reproducible, we did not find correlations between E:E_a and measurements of left and right ventricular filling pressure. Though the calculation of E:E_a is frequently used as a clinical tool in the pediatric heart transplant population; this

study suggests that this tool may not be useful as a predictor of ventricular filling pressure in this patient population.

E:E_a Compared to PCWP

Our findings are in agreement with the only previous study evaluating the relationship of E:E_a with ventricular filling pressures in children following heart transplant⁷, but are not in agreement with a number of adult studies across a variety of patient populations. In adults, a linear correlation between septal E:E_a and PCWP has been observed in patients with sinus tachycardia, hypertrophic cardiomyopathy, and compensated heart failure^{2, 3, 5}. Moreover, there are data in the adult heart transplant population that suggest a high degree of correlation between both the lateral mitral E:E_a and PCWP, and the lateral tricuspid E:E_a and the mean RAP¹. Our study adds to the previous pediatric study in suggesting that there may be something unique about the pediatric heart transplant population that makes E:E_a less useful⁷.

One clear difference between pediatric and adult heart transplantation is the potential for recipient – donor size mismatch. This mismatch may impact myocardial thickness relative to body surface area, particularly early after transplant^{12, 13}, and may therefore affect myocardial velocity. Further complicating the potential correlation in children is the finding of diminished myocardial velocities in this age group following heart transplant¹¹; a finding confirmed in this study. Additionally, the range of measured PCWP in this cohort was almost entirely normal. It is possible that a relationship between E:E_a and PCWP would have emerged if there were a larger number of subjects with elevated PCWP. Indeed, in one report from the adult transplant population, nearly half of the included subjects had a PCWP > 15 mmHg¹. However, within the population of pediatric transplant recipients, significant diastolic dysfunction manifesting with elevated ventricular filling pressure is not common. A further complicating factor in our population is the use of a cuff of native atrial tissue for the transplant anastomosis. This creates a large, combined atrial mass and, in some cases, dual atrial systoles. This unique geometry and altered electrical activity has the potential to impact inflow velocity and might alter the relationship between E:E_a and diastolic pressure¹⁴.

Though we found no correlation between E:E_a and PCWP in our cohort, a dichotomous analyses based on cut-off values of E:E_a suggested an association of an elevated E:E_a with elevated ventricular filling pressure. This association was found for septal E:E_a compared to PCWP and for lateral tricuspid E:E_a compared to mean RAP. The ability to use E:E_a in a dichotomous manner to identify clinically important differences in filling pressure has tremendous appeal; however, in our small cohort of children with generally healthy grafts, the clinical importance of this cut-off in terms of differences in filling pressures was minimal (Figure 5). Nevertheless, the presence of a statistical cut-off point in this population does raise the possibility that a clinically useful cut-off point might exist in pediatric populations in which elevations in ventricular filling pressure are more common.

E:E_a Compared to Graft Rejection

In our cohort we found no correlation between septal E:E_a and rejection treated as an ordinal value. However, we did find that high-grade rejection (ISHLT grade 3A and above) was associated with an elevated septal E:E_a. This elevation appeared to be primarily related to a decrease in myocardial velocity in those with high-grade rejection, a finding in agreement with previous reports^{15, 16}. It should be noted that rejection, in particular high-grade rejection, was extremely rare in our cohort. Therefore, while the association between high-grade rejection and E:E_a is significant in this cohort, a robust evaluation comparing rejection

to $E:E_a$ in a large sample of subjects with histologically confirmed rejection was not possible.

Although the $E:E_a$ ratio was easy to obtain and the measurements were reproducible, the challenges of estimating intracardiac pressures in the pediatric population following heart transplantation were highlighted in this study. Though this relationship has been reported for many adult cohorts, including the adult heart transplant cohort, ours is the second report to cast significant doubt on this relationship in this patient population. While it is interesting that we found cut-off values above which the $E:E_a$ ratio was associated with a statistically significant increase in mean ventricular filling pressure, the clinical importance of the small difference in filling pressures is likely limited. Nevertheless, the association of an elevated $E:E_a$ with high-grade rejection does suggest a potential role for Doppler tissue imaging as part of a multi-modality screen for graft failure.

Limitations

Our study was limited by the small number of patients with elevated PCWP, mean RAp, and high-grade rejection; an indication of the relative graft health in our pediatric transplant cohort. We therefore did not have enough subjects with potential rejection or diastolic dysfunction to evaluate for a correlation in this subgroup. Moreover, the possibility that changes in the $E:E_a$ measured serially might serve as a predictor of changes in PCWP was not evaluated.

Summary

$E:E_a$ does not directly correlate with ventricular filling pressures after pediatric cardiac transplantation and therefore cannot be used as a surrogate for catheter derived measures in this population. However, an elevated septal $E:E_a$ is associated with elevated PCWP and high-grade rejection. Our study suggests that while $E:E_a$ cannot replace cardiac catheterization, an elevated $E:E_a$ may have utility as a part of a screening tool to prompt more invasive investigation for rejection in pediatric patients after heart transplantation.

Acknowledgments

Acknowledgements / Disclosures: The authors thank Kerri Lombardi, the staff of the echocardiography and catheterization laboratories, and members of the Division of Cardiac Anesthesia for their support of this work. Dr. Goldberg was supported in part by NIH T32 Training Grant #HL 07915.

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Figure 1.

A) Mitral inflow velocity. The E wave velocity corresponds to the peak velocity of passive inflow. B) Septal-annular myocardial velocity. The E_a wave velocity corresponds to the peak velocity of the septal myocardium during passive inflow.

Figure 2.
Septal E:E_a vs PCWP.

Figure 3.
Lateral mitral E:E_a vs PCWP.

Figure 4.
Lateral tricuspid E:E_a vs mean RAp.

Figure 5.

Solid diamonds represent group mean values and the bars correspond to the standard deviation. A) The relationship between normal (≤ 12) and elevated (> 12) septal E:E_a vs PCWP. B) The relationship between normal (≤ 10) and elevated (> 10) lateral tricuspid E:E_a vs mean RAP.

Figure 6.
Myocardial velocity vs rejection grade.

Table 1

Demographics of Study Participants

Total Patients	49 (61 studies)
Male	24 (49%)
Ethnicity	
White	33 (67%)
Black	9 (18%)
Hispanic	7 (14%)
Age	11.7 yrs (1.3 – 20.4)
Time from Transplant	3.9 yrs (0.06 – 14.9)

Table 2

Echocardiographic measures

Parameter	N	Mean $\pm$ SD
Blood Pool Pulse Wave Doppler (cm/sec)		
Mitral E Wave	61	91.5 $\pm$ 21.2
Tricuspid E Wave	60	60.8 $\pm$ 19.7
Tissue Doppler Velocities (cm/sec)		
Lateral Mitral E _a	60	14.7 $\pm$ 3.8
Septal E _a	61	10.2 $\pm$ 1.9
Lateral Tricuspid E _a	55	10.0 $\pm$ 3.3
Inflow Ratio		
Lateral Mitral E:E _a	60	6.7 $\pm$ 2.3
Septal E:E _a	61	9.2 $\pm$ 2.7
Lateral Tricuspid E:E _a	54	6.9 $\pm$ 4.4
Ventricular Function		
LV End Diastolic Dimension (cm)	60	3.7 $\pm$ 0.6
LV End Systolic Dimension (cm)	60	2.4 $\pm$ 0.5
Shortening Fraction (%)	60	36 $\pm$ 6

LV = left ventricle

Table 3

Myocardial velocity compared to ventricular filling pressure

Myocardial velocity	r	p
Lateral Mitral E _a [†]	0.20	0.12
Septal E _a [†]	0.11	0.38
Lateral tricuspid E _a *	0.049	0.73

[†] comparison to PCWP.

* comparison to mean RAp.

Table 4Elevated and Normal Septal E:E_a vs mean PCWP and Rejection

	Total Cases	No Rejection	Low Grade Rejection	High Grade Rejection	PCWP (mmHg)
Septal E:E _a ≤ 12	53	35	17	1	10.1 ± 2.9
Septal E:E _a > 12	8	5	1	2	12.3 ± 2.8
Total	61	40	18	3	10.3 ± 3.0