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Echocardiographic Detection of Increased Ventricular Diastolic Stiffness in Pediatric Heart Transplant Recipients: A Pilot Study

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Abstract

Background—Pediatric heart transplant recipients are at risk for increased LV diastolic stiffness. However, the non-invasive evaluation of LV stiffness has remained elusive in this population. The objective of this study was to compare novel echocardiographic measures of left ventricular (LV) diastolic stiffness vs. gold-standard measures derived from pressure-volume loop (PVL) analysis in pediatric heart transplant recipients.

Methods—Patients undergoing left heart catheterization were prospectively enrolled. PVLs were obtained via conductance. The end-diastolic pressure-volume relationship was obtained via balloon occlusion. β, the stiffness constant, was calculated. Echocardiographic measures of diastolic function were derived from spectral and tissue Doppler and 2D speckle-tracking. Ventricular volumes were measured by 3D echocardiography. The novel echocardiographic estimates of ventricular stiffness included E:e′/EDV and E:early diastolic strain rate/EDV.

Results—Of 24 children, 18 were heart transplant recipients. Six control patients had a hemodynamically insignificant patent ductus arteriosus or coronary fistula. Mean age was 9.1±5.6 years. Median EDP was 9 mmHg (IQR 8–13 mmHg). Lateral E:e′/EDV ($r=0.59$, $p<0.01$), septal E:e′/EDV ($r=0.57$, $p<0.01$) and (E:circumferential early diastolic strain rate)/EDV ($r=0.54$, $p<0.01$) correlated with β. Lateral E:e′/EDV displayed a c-statistic of 0.93 in detecting patients with abnormal LV stiffness (β >0.015 mL^{-1}). A lateral E:e′/EDV of >0.15 mL^{-1} had an 89% sensitivity and 93% specificity in detecting an abnormal β.

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Conclusion—Echocardiographic estimates of ventricular stiffness may be accurate when compared to the gold-standard in pediatric heart transplant recipients. The clinical usefulness of these non-invasive measures in assessing LV stiffness merits further study in children.

Keywords

Pressure-volume relationship; pediatric; diastolic function; echocardiography

Introduction

Patients who have undergone heart transplantation are known to be at risk for increased ventricular stiffness due prolonged ischemic time, donor-recipient size mismatch, and/or a history of rejection.[1–3] Even in the presence of preserved ejection fraction, increased ventricular stiffness results in heart failure symptoms, exercise intolerance, decreased quality of life, and increased risk of mortality.[4–6] However, the importance of ventricular stiffness in pediatric heart transplant recipients is unknown due to the challenges in the non-invasive assessment of diastolic function, specifically, in the non-invasive assessment of ventricular stiffness. Currently, the invasive evaluation of the end-diastolic pressure-volume relationship derived from pressure volume loop (PVL) analysis is the reference standard method used to assess ventricular stiffness.[7, 8] However, PVL analysis is rarely performed for clinical purposes in children because of the required invasive procedures and load alteration.

Current echocardiographic assessment of left ventricular (LV) diastolic function has focused on early active relaxation/diastolic suction (spectral Doppler mitral E and tissue Doppler e′ velocities, isovolumic relaxation time, etc.) and the estimation of filling pressures (lateral and septal E:e′).[9] These measures have been well validated against the reference standard in both adults and children.[10–13] While the assessment of filling pressures is an often used marker of diastolic function, it has limitations. Filling pressures are influenced by loading conditions, myocardial elastic properties, and pericardial properties. In addition, changes in ventricular stiffness often occur prior to an elevation in filling, making it an insensitive marker of early diastolic dysfunction.[10] Therefore, optimally one would include a measure of ventricular stiffness in the assessment of diastolic function in addition to the more conventional assessments of early active relaxation and filling pressures.

The ability to assess for the development of increased ventricular diastolic stiffness has the potential to (1) improve clinicians' ability to understand the natural history of the varied disease processes encountered in the pediatric heart transplant population, (2) detect the results of therapies aimed at rejection and myocardial remodeling, and (3) improve risk stratification prior to interventional/surgical procedures. However, no studies have validated potential echocardiographic measures of ventricular stiffness against the gold standard PVL measures. Therefore, the goal of this study was to assess the validity of non-invasive indices of ventricular stiffness by direct comparison to gold-standard indices derived from PVL analysis in children who have undergone heart transplantation. We hypothesized that non-invasive estimates of filling pressure divided by end-diastolic volume (EDV) would correlate well with the invasive PVL derived ventricular stiffness constant.

Materials and Methods

Children aged 0–21 years undergoing clinically-indicated diagnostic left heart catheterization were recruited prospectively at a single institution. We divided our cohort into two groups. The first group included children who had undergone heart transplantation. The second group included children who acted as "controls." As normal children do not undergo routine heart catheterization, these children included those with a hemodynamically insignificant patent ductus arteriosus or coronary fistula (Qp:Qs < 1.5 with normal LV EDV for body size). Exclusion criteria included: 1) medical status for which participation in the study presented more than minimal risk as determined by the attending physician, 2) non-sinus rhythm, 3) patients with right-sided heart disease, and 4) rejection episode (biopsy grade of 2R or greater, pAMR of 2 or greater, or clinical/echocardiographic changes consistent with rejection that were accompanied by an augmentation in immunosuppression) within the last six months as they were deemed to high risk to participate in the procedures involved in the protocol. The protocol was approved by our institutional review board. Informed consent was obtained from the parent or legal guardian of minors or from the participants of age ≥ 18.

Study Catheterization and PVL Analysis Protocol

All patients underwent general anesthesia per the institution's protocol. All study data were collected following the patient's primary diagnostic and interventional procedures. A 4 Fr high fidelity microconductance catheter (CD Leycom®, Netherlands) was calibrated in normal saline for 15 seconds and then placed in the apex of the left ventricle via the femoral arterial approach. PVLs were volume-calibrated using hypertonic saline to account for parallel conductance. Cardiac output was determined by thermodilution. Conductance electrodes located outside the ventricle were excluded from analysis. Microconductance data was recorded at a sampling rate of 250 Hz. PVL data was recorded in triplicate over 10 seconds during an expiratory breath hold. Invasive data was obtained using standard equipment approved for use in human subjects (INCA® intracardiac analyzer; CD Leycom, Netherlands). PVL analysis was performed offline using specialized software (LabChart v8; ADInstruments, Colorado Springs, CO).

The end-diastolic pressure-volume relationship was obtained via balloon occlusion of the vena cavae and fitted to the equation $\alpha e^{\beta EDV}$ where β is the chamber stiffness constant, α is the curve fitting constant, and EDV = end-diastolic volume. β represents the rightward, exponential aspect of the slope of the end-diastolic pressure-volume relationship and increases as ventricular stiffness increases. Increased ventricular stiffness is considered present if $\beta > 0.015\ mL^{-1}$ in adults, however, abnormal stiffness has not been defined in the pediatric population due to the lack of data in children.[14, 15] In this pilot study, we used the adult cutoff value and indexed β to body surface area to account for differences in body sizes. Early active relaxation was evaluated using the isovolumic relaxation time constant (τ) calculated via the logistic method.[16] End-diastolic pressure (EDP) was recorded. End-systolic elastance (Ees), a measure of contractility, was assessed as the slope as the end-systolic pressure-volume relationship as we have previously described in this population.[17]

Arterial elastance (Ea), a measure of afterload, was assessed as the ratio of end-systolic pressure to stroke volume. Ventriculo-arterial coupling was calculated as Ea:Ees.

Echocardiographic Protocol

Echocardiograms were performed immediately after PVL analysis under the same anesthetic conditions using a Phillips IE33 system (Amsterdam, Netherlands). Ventricular volumes were derived from 3D echocardiography (3DE) (QLAB v10.0, Phillips). 3DE volumes were stitched together after 4-beat acquisition. Conventional echocardiographic measures of diastolic function included: spectral Doppler E and A wave velocities and their respective ratio, E deceleration time, A-wave duration, tissue Doppler e′ and a′ and their respective ratios, tissue Doppler derived isovolumic relaxation time, and pulmonary vein a-wave velocity and duration. Measurement methods conformed to recommendations by the American Society of Echocardiography and were averaged over three beats.[18]

2D speckle-tracking measures of deformation were obtained by tracing the endocardial border of the left ventricle using Cardiac Performance Analysis v 3.0 (Tomtec Imaging Systems, Chicago, IL). Analysis was performed on DICOM images at their native frame rate. Minimum frame rate for acquisition was 60 frames per second. The mean frame rate for the analyzed studies was 94 ± 11 frames per second. Longitudinal early diastolic strain rate (LEDSR) was obtained by averaging six segments from the apical 4-chamber view. Circumferential early diastolic strain rate (CEDSR) was obtained by averaging six segments from the parasternal short axis view. Studies where more than two segments could not be adequately traced were excluded.

Echocardiographic measures of stiffness

Assessment of the end-diastolic pressure-volume relationship and calculation of the ventricular stiffness constant can only be done by acutely altering loading conditions. This is not feasible in a non-invasive evaluation. In order to assess stiffness by echocardiography, we assessed operating stiffness. Conceptually, operating ventricular stiffness is described as the relationship between ventricular EDP and EDV in a patient's baseline physiologic state.[19] If one assumes that the LV volume is 0 mL when LV pressure reaches 0 mm Hg, one can calculate operating stiffness by simply dividing EDP by EDV. As β increases, operating stiffness also increases. This is conceptually displayed in Figure 1. We used echocardiographic surrogates of EDP divided by EDV derived from 3D echocardiography to assess ventricular stiffness. Surrogates of LV EDP included lateral E:e′, septal E:e′, E:LEDSR and E:CEDSR.[20] Therefore, the novel echocardiographic estimates of LV operating stiffness included lateral and septal E:e′/EDV and their average, E:LEDSR/EDV, and E:CEDSR/EDV.

Statistical analysis

The distribution of data as parametric or non-parametric was assessed using the Shapiro-Wilk test. Differences between patient groups were assessed using independent t-tests or Mann Whitney U tests, as appropriate, for continuous variables and Chi-square test or Fisher's Exact test for categorical variables. The relationship between invasive and echocardiographic measures were assessed using Pearson's correlation. Receiver operating

characteristic (ROC) curves were created and the area under the curve (AUC) was determined to assess the discriminatory ability of each echocardiographic variable to predict the presence of increased ventricular stiffness. All studies were reassessed for intra- and inter-observer variability using intraclass correlation coefficients for absolute agreement. A $p < 0.05$ was considered statistically significant. Statistics were performed using SPSS v. 23 (IBM, New York, NY).

Results

A total of 24 patients were enrolled; 18 patients were s/p orthotopic heart transplant, 5 patients had a hemodynamically insignificant patent ductus arteriosus, and one had a hemodynamically insignificant coronary fistula (6 control patients). We have previously reported associations between PVL and echocardiographic measures of contractility in this cohort.[17] All control patients had successful interventions prior to PVL and echocardiographic acquisition. A representative PVL during preload reduction and the resulting end-diastolic pressure-volume relationship is shown in Figure 2. Intra- and inter-observer variability showed intraclass correlation coefficients of r = 0.91 and 0.88, respectively for lateral E:e′/EDV, r = 0.92 and 0.86, respectively for septal E:e′/EDV, r = 0.80 and 0.72, respectively for E:LEDSR/EDV, and r = 0.71 and 0.59, respectively for E:CEDSR/EDV.

Transplant vs. control patients

Demographic, clinical, and catheterization data from these patients are presented in Table 1. There were no differences in EDP between groups. However, transplant patients did have higher LV stiffness compared to controls. Echocardiographic data comparing the two groups are presented in Table 2. Transplant patients had higher LV mass/volume Z-score, lateral E:e′/EDV, and septal E:e′/EDV compared to controls. There were no differences in E:LEDSR/EDV or E:CEDSR/EDV between groups. In all patients, β displayed a correlation with Ea (r = 0.50, p = 0.01).

Transplant patients with normal vs. abnormal stiffness

Of 18 transplant patients, nine (50%) had increased LV stiffness, i.e. $\beta > 0.015$ mL^{-1}. Patients with increased LV stiffness were younger (5.6 ± 3.2 vs. 13.4 ± 5.3 yo, $p < 0.01$) and had a lower body surface area (0.6 ± 0.1 vs. 1.3 ± 0.4 m^2, $p < 0.01$) than patients with normal LV stiffness. These patients also had a history of longer ischemic time (288 ± 38 vs. 234 ± 46 minutes, p = 0.02). There were no differences in presence of single ventricle prior to transplantation, history of Norwood arch reconstruction, history of rejection, or graft age between these groups. No patients displayed coronary vasculopathy.

During catheterization, there were no differences in blood pressure, mixed venous oxygen saturation, pulmonary vascular resistance, EDP, Ees, or Ea/Ees between patients with and without abnormal stiffness. Patients with elevated stiffness had a lower cardiac index (2.8 ± 0.8 vs. 4.2 ± 0.6 L/min/m^2, $p < 0.01$), higher Ea (3.0 ± 0.7 vs. 1.9 ± 0.8 mm Hg/mL, p = 0.01), and lower τ (22.0 (IQR 2.4) vs. 25.3 (IQR 5.6) ms, p = 0.01) compared to patients with normal stiffness.

By echocardiography, patients with abnormal stiffness had lower LV EDV (37 ± 10 vs. 77 ± 28 mL, $p < 0.01$), higher lateral E:e′/EDV (0.23 ± 0.08 vs. 0.11 ± 0.05 mL^{-1}, $p < 0.01$), septal E:e′/EDV (0.32 ± 0.12 vs. 0.17 ± 0.08 mL^{-1}, $p < 0.01$), and E:CEDSR/EDV (1.2 ± 0.5 vs. 0.6 ± 0.3 $cm/s^2/mL$, $p = 0.02$) compared to patients with normal stiffness. No differences were detected in ejection fraction, shortening fraction, LV mass/volume Z-score, or other Doppler or tissue Doppler measures of diastolic function.

Echocardiographic vs. invasive measures of diastolic function

Lateral E:e′/EDV correlated well with β ($r = 0.59$, $p < 0.01$) (Figure 3). β also correlated with septal E:e′/EDV ($r = 0.59$, $p < 0.01$) and average E:e′/EDV ($r = 0.57$, $p < 0.01$). E:CEDSR/EDV correlated slightly less strongly with β ($r = 0.54$, $p < 0.01$) while E:LEDSR did not display a correlation ($r = 0.28$, $p = 0.19$). No other echocardiographic measures of diastolic function correlated with β. Correlations were similar when only transplant patients were included in the analysis (n = 18): lateral E:e′/EDV ($r = 0.57$, $p < 0.01$), septal E:e′/EDV ($r = 0.57$, $p < 0.01$), and E:CEDSR/EDV ($r = 0.51$, $p < 0.01$). In order to assess lateral E:e′/EDV as a measure of operating stiffness we assessed its correlation with the ratio of invasive PVL-derived EDP/EDV and found a strong correlation ($r = 0.87$, $p < 0.01$).

ROC analysis was performed to determine each echocardiographic variable's discriminatory ability to detect an abnormal β of > 0.015 mL^{-1}. The area under the curve for lateral E:e′/EDV was 0.93, $p < 0.01$. A lateral E:e′/EDV cutoff value of > 0.15 mL^{-1} would have 89% sensitivity and 93% specificity in detecting an abnormal β. The area under the curves for septal and average E:e′/EDV were 0.91, $p < 0.01$. The area under the curves for E:LEDSR/EDV and E:CESDR/EDV were 0.75 and 0.89, respectively, both with $p < 0.01$.

Echocardiographic variables that showed statistically significant correlations to EDP or τ are reported in Appendix Table 1. Importantly, both lateral E:e′ ($r = 0.55$, $p < 0.01$) and septal E:e′ ($r = 0.47$, $p = 0.02$) correlated with EDP, while E:LEDSR and E:CEDSR did not.

Discussion

To our knowledge, this is the first study to evaluate the relationship of echocardiographic vs. invasive measures of ventricular stiffness using true gold-standard methods for PVL acquisition in pediatric heart transplant recipients. The main finding of this pilot study is that tissue Doppler E:e′ divided by 3D echocardiographic EDV has the potential to allow a simple non-invasive assessment of LV stiffness.

Echocardiographic evaluation of diastolic function

The assessment of diastolic function by echocardiography has been focused on the detection of abnormal filling pressures. However, due to the fact that filling pressures are load dependent, patients may have abnormal ventricular stiffness yet normal filling pressures due to a left shift on the diastolic pressure-volume relationship secondary to auto-regulatory mechanisms or through the use of diuretics. This leads to underestimation of disease severity when risk stratifying patients.[21] By accounting for preload by indexing E:e′ to EDV, we were able to accurately detect abnormal myocardial stiffness in pediatric heart transplant recipients, only two of which displayed an EDP > 12 mm Hg.

The results of this study are in line with a similar study by Kasner et al. in adults with heart failure with preserved ejection fraction.[22] Similar to that previous study, we found only a modest correlation between invasive and echocardiographic measures of left ventricular stiffness. This is likely due to a number of factors. First, agreement between the two measures was not being assessed; that is, the invasive and non-invasive measures were not using the same methods to assess stiffness. The invasive measure assessed the exponential slope of the right side of the end-diastolic pressure-volume relationship, while the non-invasive measure evaluated an estimate of operational stiffness. Therefore, the resultant correlation may not be expected to be very strong. In contrast, when we compared invasive operational stiffness to non-invasive operational stiffness we observed a strong correlation as expected when measuring agreement. Currently, a reliable non-invasive method to evaluate the end-diastolic pressure-volume relationship without load alteration does not exist. Some have attempted to validate invasive single-beat (do not require load alteration) estimates of the end-diastolic pressure-volume relationship in human ex-vivo hearts.[23] However, in-vivo validation, and translation to non-invasive methods, has not yet been performed. Second, in general, the patients we assessed were relatively healthy – only two had an EDP > 12 mmHg. This may also account for the somewhat wide spread in overlap in β values for a specific E:e′/EDV value. It is feasible that if our patients had a wider range of stiffness that the correlations would be better. Despite the modest correlations between the PVL and echocardiographic measures of stiffness and the limitations of this study, it is important to note that E:e′/EDV was the only echocardiographic measure of diastolic function to have a correlation with β. All conventional measures of diastolic function, including late measures (Doppler A, tissue Doppler a′, A/a′, etc) had no correlation with β. In addition, lateral E:e′/EDV had a high area under the curve for detecting an abnormal β. Therefore, in this pilot study, E:e′/EDV appeared to be the only echocardiographic measure to have some promise of assessing ventricular stiffness in pediatric heart transplant recipients and merits further validation studies to assess its accuracy and clinical utility.

We defined abnormal stiffness as $\beta > 0.015\ mL^{-1}$. It is important to note this value has not been validated in children. In order to make this cutoff value more applicable to children we indexed β to BSA in order to account for differences in body sizes between adults and children. In addition, there is some evidence that the cutoff value may be useful as we found that those patients with a β*BSA > 0.015 had a history of longer ischemic time, lower cardiac index, and higher afterload. These are all known predictors of stiffness after transplant in the adult population. However, we recognize that the actual cutoff value for abnormal stiffness may be different in children, which would perhaps make the cutoff values for E:e′/EDV suggested in this study less accurate.

Potential clinical uses of E:e′/EDV

The ability to non-invasively detect abnormal ventricular stiffness prior to elevation of EDP has multiple potential clinical uses that merit further study. It may possibly be used to predict the cardiac response to exercise and patient functional status, especially in children who often cannot undergo formal exercise testing and have poor communication skills.[24] In addition, the assessment of ventricular stiffness has the potential to be used to detect acute rejection and resultant myocardial recovery.[3, 25] Its strengths lie in the facts that it is a

simple measure to make, the individual measures are reproducible in children,[26] the limitations of tissue Doppler and 3D echocardiography are well studied,[18] and many echocardiographic laboratories already utilize these technologies making translation to clinical practice highly feasible.

The validation of this non-invasive measure of ventricular stiffness has the potential to provide important insights into disease progression and response to treatment in other patient populations, such as those with congenital heart disease – a patient population who spend their entire lifetime exposed to abnormal loading conditions which predispose them to myocardial fibrosis and resulting decreased ventricular compliance. The validity of E:e′/EDV as a measure of stiffness in other populations is conceptually valid. However, to be applicable in the broader congenital heart disease population, these measures must be independently validated in these separate populations. In addition, normative values will need to be established in children.

Pediatric transplant patients with increased ventricular stiffness

We detected a high rate of increased ventricular stiffness in the pediatric heart transplant sample (50%). Patients with increased stiffness had increased ischemic time compared to those with normal stiffness. This is in line with what has been reported previously and with reports of the association ischemic time with myocardial fibrosis development.[27–29] In addition, patients with increased stiffness also displayed elevated afterload. Elevated afterload is known to contribute to the development of abnormal stiffness and increased filling pressures, in line with the correlation we found between β and Ea.[30] Patients with increased stiffness were also younger. Due to the small sample size, we are unable to determine if patient age is an independent predictor of stiffness in this study as there are many confounders that may contribute to this finding, such as ischemic time, graft age, afterload, donor-recipient size mismatch, etc. This finding indeed requires further study. The detection of worsening stiffness non-invasively using E:e′/EDV may be useful to clinicians in decision-making regarding anti-hypertensive therapies. Previous studies have found that history of rejection, graft age, and donor-recipient size mismatch contribute to diastolic dysfunction in heart transplant recipients.[1] We did not detect differences in these measures between groups, likely due to our small sample size.

Limitations

As is often the case in invasive pediatric studies, one of the limiting factors in interpreting the results a small study sample. These results should ideally be validated in a larger sample. The control group was not derived from healthy children as healthy children do not undergo catheterization. However, control patients had cardiac lesions that were hemodynamically insignificant and should not have influenced ventricular stiffness. We may not have detected important differences between the transplant and control group due to inadequate power. We could not perform regression analysis to detect independent predictors of increased ventricular stiffness due to the small sample size. The sensitivity and specificity derived from of receiver operating curve analysis is a “best case scenario” as these values were not confirmed in a validation cohort. As noted above, the results from this study are not necessarily applicable to other disease states. For example, in patients with normal early

relaxation but abnormal stiffness, E:e′ may not be associated with filling pressures; therefore, E:e′/EDV would not be an appropriate measure of operational stiffness. Therefore, further studies in different patient groups to validate this method are warranted.

Conclusion

An echocardiographic measure of operating stiffness, the E:e′/EDV ratio, correlated well with the reference standard measure of LV stiffness derived from pressure-volume loop analysis. E:e′/EDV appeared to be accurate in detecting pediatric heart transplant recipients with abnormal ventricular stiffness. This non-invasive measure of ventricular stiffness may allow us to gain new insights into the physiology and natural history of pediatric heart transplant patients, detect changes in ventricular stiffness after medical interventions, and allow the opportunity investigate the relationship of ventricular stiffness to patient outcomes.

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Abbreviations

3DE	Three-dimensional echocardiography
EDP	end-diastolic pressure
EDV	end-diastolic volume
CEDSR	circumferential early diastolic strain rate
LEDSR	longitudinal early diastolic strain rate
LV	Left ventricle
PVL	pressure-volume loop

References

1. Hausdorf G, Banner NR, Mitchell A, Khaghani A, Martin M, Yacoub M. Diastolic function after cardiac and heart-lung transplantation. Br Heart J. 1989; 62:123–32. [PubMed: 2504262]
2. Young J, Leon C, Short H 3rd, Noon G, Lawrence E, Whisennand H, et al. Evolution of hemodynamics after orthotopic heart and heart-lung transplantation: early restrictive patterns persisting in occult fashion. The Journal of heart transplantation. 1986; 6:34–43.
3. Valantine H, Yeoh TK, Gibbons R, McCarthy P, Stinson E, Billingham M, et al. Sensitivity and specificity of diastolic indexes for rejection surveillance: temporal correlation with endomyocardial biopsy. The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation. 1990; 10:757–765.
4. Udelson JE. Heart Failure With Preserved Ejection Fraction. Circulation. 2011; 124:e540–e543. [PubMed: 22105201]
5. Ambrosi P, Macé L, Habib G. Predictive value of E/A and E/E′ Doppler indexes for cardiac events in heart transplant recipients. Clinical Transplantation. 2016; 30:959–963. [PubMed: 27219472]

6. Tallaj JA, Kirklin JK, Brown RN, Rayburn BK, Bourge RC, Benza RL, et al. Post-heart transplant diastolic dysfunction is a risk factor for mortality. J Am Coll Cardiol. 2007; 50:1064–9. [PubMed: 17825716]
7. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004; 350:1953–9. [PubMed: 15128895]
8. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. Am J Physiol Heart Circ Physiol. 2005; 289:H501–12. [PubMed: 16014610]
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016; 29:277–314. [PubMed: 27037982]
10. Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. Circulation. 1994; 89:2241–50. [PubMed: 8181149]
11. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000; 102:1788–94. [PubMed: 11023933]
12. Butts RJ, Chowdhury SM, Buckley J, Hlavacek AM, Hsia TY, Khambadkone S, et al. Comparison of echocardiographic and pressure-volume loop indices of systolic function in patients with single ventricle physiology: a preliminary report. Congenit Heart Dis. 2015; 10:E17–24. [PubMed: 24869911]
13. Chowdhury SM, Butts RJ, Buckley J, Hlavacek AM, Hsia TY, Khambadkone S, et al. Comparison of pressure-volume loop and echocardiographic measures of diastolic function in patients with a single-ventricle physiology. Pediatr Cardiol. 2014; 35:998–1006. [PubMed: 24584211]
14. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation. 2008; 117:2051–60. [PubMed: 18413502]
15. Sinning D, Kasner M, Westermann D, Schulze K, Schultheiss H-P, Tschöpe C. Increased Left Ventricular Stiffness Impairs Exercise Capacity in Patients with Heart Failure Symptoms Despite Normal Left Ventricular Ejection Fraction. Cardiology Research and Practice. 2011; 2011:692862. [PubMed: 21403885]
16. Matsubara H, Takaki M, Yasuhara S, Araki J, Suga H. Logistic time constant of isovolumic relaxation pressure-time curve in the canine left ventricle. Better alternative to exponential time constant. Circulation. 1995; 92:2318–26. [PubMed: 7554217]
17. Chowdhury SM, Butts RJ, Taylor CL, Bandisode VM, Chessa KS, Hlavacek AM, et al. Validation of Noninvasive Measures of Left Ventricular Mechanics in Children: A Simultaneous Echocardiographic and Conductance Catheterization Study. J Am Soc Echocardiogr. 2016; 29:640–7. [PubMed: 27025669]
18. Lai WW, Geva T, Shirali GS, Frommelt PC, Humes RA, Brook MM, et al. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. J Am Soc Echocardiogr. 2006; 19:1413–30. [PubMed: 17138024]
19. Gaasch WH, Bing OHL, Mirsky I. Chamber compliance and myocardial stiffness in left ventricular hypertrophy. European Heart Journal. 1982; 3:139–145. [PubMed: 6210539]
20. Meluzin J, Spinarova L, Hude P, Krejci J, Podrouzkova H, Pesl M, et al. Estimation of left ventricular filling pressures by speckle tracking echocardiography in patients with idiopathic dilated cardiomyopathy. Eur J Echocardiogr. 2011; 12:11–8. [PubMed: 20688766]
21. Garofalo CA, Cabreriza SE, Quinn TA, Weinberg AD, Printz BF, Hsu DT, et al. Ventricular diastolic stiffness predicts perioperative morbidity and duration of pleural effusions after the Fontan operation. Circulation. 2006; 114:I56–61. [PubMed: 16820638]
22. Kasner M, Sinning D, Burkhoff D, Tschope C. Diastolic pressure-volume quotient (DPVQ) as a novel echocardiographic index for estimation of LV stiffness in HFpEF. Clin Res Cardiol. 2015

23. ten Brinke EA, Klautz RJ, Verwey HF, van der Wall EE, Dion RA, Steendijk P. Single-beat estimation of the left ventricular end-systolic pressure-volume relationship in patients with heart failure. Acta Physiol (Oxf). 2010; 198:37–46. [PubMed: 19735484]

24. Sinning D, Kasner M, Westermann D, Schulze K, Schultheiss HP, Tschope C. Increased left ventricular stiffness impairs exercise capacity in patients with heart failure symptoms despite normal left ventricular ejection fraction. Cardiol Res Pract. 2011; 2011:692862. [PubMed: 21403885]

25. Skowronski EW, Epstein M, Ota D, Hoagland PM, Gordon JB, Adamson RM, et al. Right and left ventricular function after cardiac transplantation. Changes during and after rejection. Circulation. 1991; 84:2409–17. [PubMed: 1959196]

26. Colan SD, Shirali G, Margossian R, Gallagher D, Altmann K, Canter C, et al. The ventricular volume variability study of the Pediatric Heart Network: study design and impact of beat averaging and variable type on the reproducibility of echocardiographic measurements in children with chronic dilated cardiomyopathy. J Am Soc Echocardiogr. 2012; 25:842–854. e6. [PubMed: 22677278]

27. Rustad LA, Nytroen K, Andreassen A, Geiran O, Endresen K, Gullestad L, et al. Heart transplant systolic and diastolic function is impaired by prolonged pretransplant graft ischaemic time and high donor age: an echocardiographic study. Eur J Cardiothorac Surg. 2013; 44:e97–104. [PubMed: 23657552]

28. Foll D, Markl M, Menza M, Usman A, Wengenmayer T, Anjarwalla AL, et al. Cold ischaemic time and time after transplantation alter segmental myocardial velocities after heart transplantation. Eur J Cardiothorac Surg. 2014; 45:502–8. [PubMed: 24026855]

29. Pickering JG, Boughner DR. Fibrosis in the transplanted heart and its relation to donor ischemic time. Assessment with polarized light microscopy and digital image analysis. Circulation. 1990; 81:949–58. [PubMed: 2306841]

30. Leite S, Rodrigues S, Tavares-Silva M, Oliveira-Pinto J, Alaa M, Abdellatif M, et al. Afterload-induced diastolic dysfunction contributes to high filling pressures in experimental heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol. 2015; 309:H1648–54. [PubMed: 26408538]

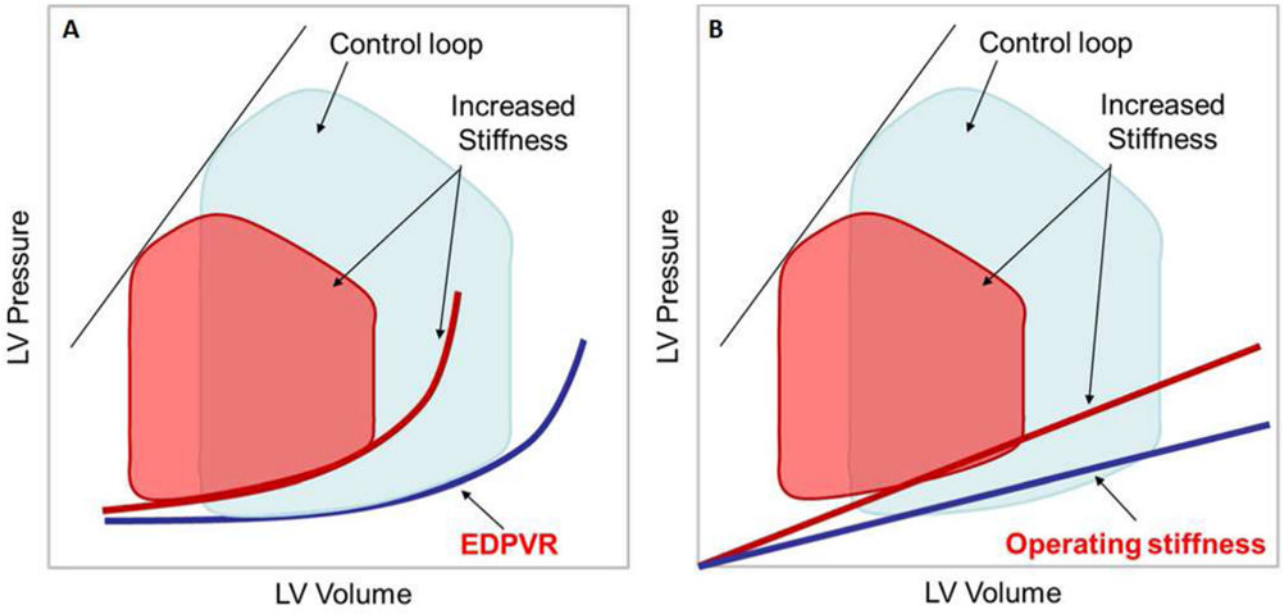

Figure 1. Conceptual framework behind echocardiographic measures of ventricular stiffness

A. Pressure-volume loop analysis using conventional invasive methods with load alteration to determine ventricular stiffness. The blue pressure-volume loop represents a patient with normal ventricular stiffness. The dark blue curved line represents the end-diastolic pressure-volume relationship upon which the pressure-volume loop would follow upon alteration of preload. The red pressure-volume loop represents a patient with elevated ventricular stiffness. The dark red curved line represents the end-diastolic pressure-volume relationship that is shifted upward and leftward in this patient with increased ventricular stiffness, representing increased end-diastolic pressure at lower ventricular volumes compared to the patient represented in blue. B. The concept of assessment of operating stiffness for use in echocardiography. The same patients are represented here in blue and red. To assess operating stiffness non-invasively, we assume the ventricular volume at 0 mm Hg is 0 mL. The operating stiffness is then the ratio of end-diastolic pressure to end-diastolic volume. Echocardiographic surrogates of end-diastolic pressure may be used. Similar to the Figure 1A, the patient with increased stiffness has a shift upward and leftward in their operating stiffness curve (dark red line) compared to the control patient (dark blue line).

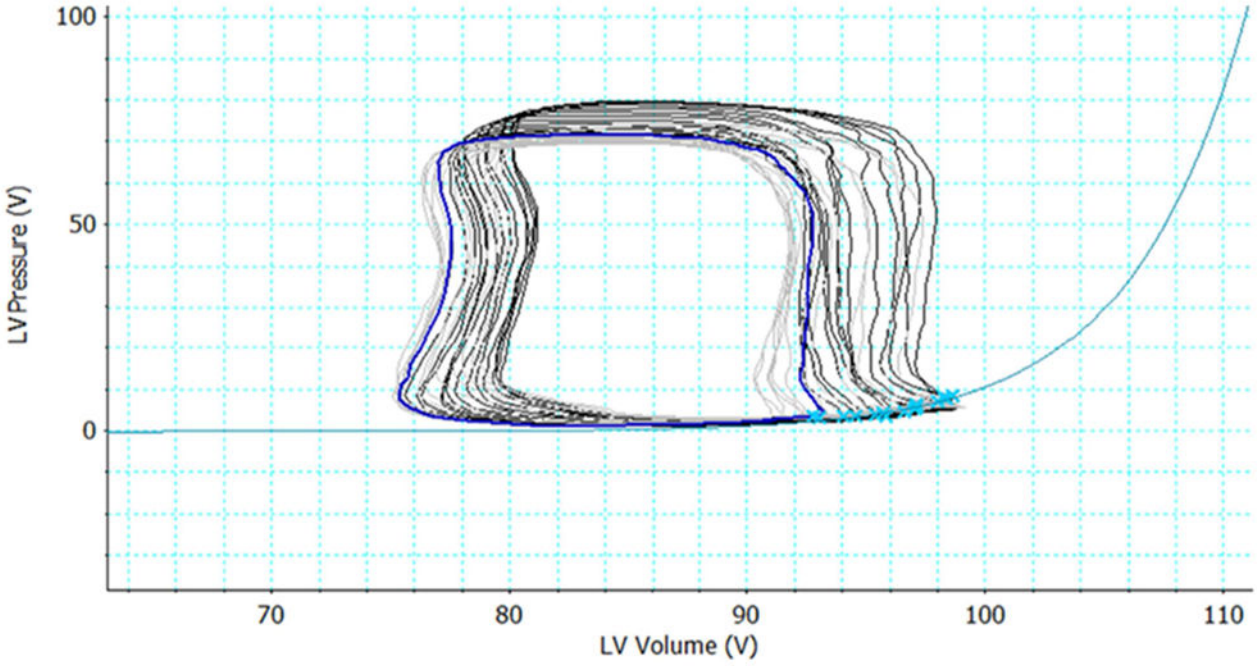

Figure 2. Representative pressure-volume loop

A representative pressure-volume loop upon preload reduction by inferior vena cava occlusion in a pediatric heart transplant recipient.

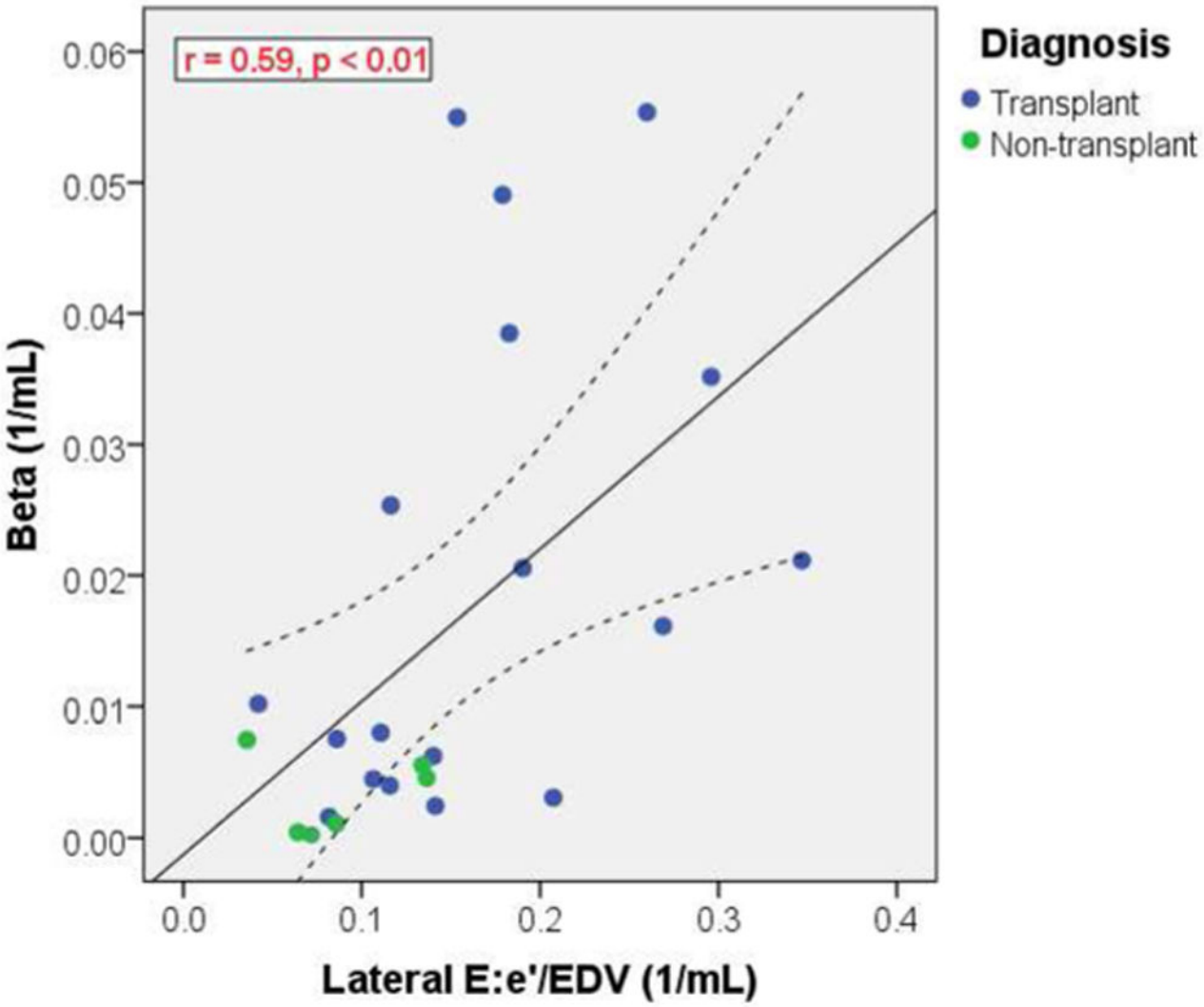

Figure 3. Correlation plot: Lateral E:e′/EDV versus β

Correlation plot of the invasively derived stiffness constant (β) vs. the echocardiographically derived measure of operant stiffness, Lateral E:e′/EDV. The dotted lines represent the 95% confidence interval of the correlation. EDV = end-diastolic volume.

Table 1

Demographic, clinical, and catheterization data in heart transplant versus control patients

	Heart Transplant (n = 18)	Controls (n = 6)	p-value
Age (years)	10.0 ± 5.9	8.4 ± 5.6	0.56
Female, n (%)	9 (50%)	3 (50%)	0.64
Height (cm)	125 ± 33	138 ± 29	0.40
Weight (kg)	22.6 (35.8)	35.2 (43.3)	0.54
BSA (m^2)	1.03 ± 0.47	1.16 ± 0.45	0.58
SBP (mm Hg)	89 ± 9	87 ± 9	0.75
DBP (mm Hg)	46 ± 7	51 ± 8	0.23
Cardiac Index (L/min/m^2)	3.4 ± 1.0	3.7 ± 1.7	0.69
MvO_2 (%)	74 ± 4	79 ± 7	0.09
Rp (Wood units)	1.9 (0.9)	1.1 (0.3)	0.02
Qp:Qs	1.0 (0)	1.1 (0.3)	0.45
EDP (mm Hg)	10.9 ± 3.5	9.7 ± 3.0	0.45
Ees (mm Hg/mL)	2.2 (3.3)	1.0 (2.1)	0.12
Ea (mm Hg/mL)	2.4 ± 0.9	1.6 ± 0.4	< 0.01
Ea/Ees	1.0 (0.9)	1.5 (1.5)	0.63
τ (ms)	24 (5)	30 (13)	0.16
β*BSA (m^2/mL)	0.009 (0.024)	0.005 (0.006)	0.04

Values are reported in mean ± standard deviation for parametric data and median (interquartile range) for non-parametric data. A p-value < 0.05 was considered statistically significant. β = stiffness constant, BSA = body surface area, DBP = diastolic blood pressure; Ea = arterial elastance, Ees = end-systolic elastance, EDP = end-diastolic pressure, MvO_2 = mixed venous oxygen saturation, Rp = pulmonary vascular resistance, τ = isovolumic relaxation time constant.

Table 2

Echocardiographic data in heart transplant versus control patients

	Heart Transplant (n = 18)	Controls (n = 6)	p-value
EDV/BSA (mL/m^2)	57.3 ± 10.0	71.0 ± 7.3	< 0.01
EF (%)	58.2 (7.6)	59.4 (6.8)	0.82
FS (%)	30.4 (9.8)	31.1 (14.9)	0.77
LV Mass/Volume Z- score	−1.2 ± 0.9	−2.3 ± 1.2	0.04
Mitral E velocity (cm/s)	95 ± 21	83 ± 29	0.32
Mitral A velocity (cm/s)	39 ± 10	57 ± 21	0.09
Mitral E:A	2.6 ± 0.6	1.6 ± 0.6	< 0.01
Mitral E deceleration time (s)	0.14 ± 0.04	0.21 ± 0.06	0.04
Mitral A duration (s)	0.11 ± 0.03	0.12 ± 0.01	0.59
Lateral e′ velocity (cm/s)	12.6 ± 2.7	11.8 ± 2.3	0.50
Septal e′ velocity (cm/s)	8.9 ± 2.4	9.3 ± 1.5	0.70
LEDSR (s^{-1})	1.4 ± 0.4	1.2 ± 0.3	0.11
CEDSR (s^{-1})	1.7 ± 0.4	1.4 ± 0.4	0.16
Lateral E:e′	7.9 ± 2.5	7.2 ± 2.0	0.56
Septal E:e′	11.4 ± 3.8	9.2 ± 3.1	0.20
E:LEDSR (cm/s^2)	47 (26)	47 (19)	0.67
E:CEDSR (cm/s^2)	38 (20)	43 (14)	0.52
Lateral E:e′/EDV/BSA (m^2/mL)	0.14 ± 0.04	0.10 ± 0.02	0.04
Septal E:e′/EDV/BSA (m^2/mL)	0.19 (0.09)	0.11 (0.10)	0.02
E:LEDSR/EDV /BSA(cm/s^2/mL/m^2)	0.80 (0.43)	0.64 (0.29)	0.20
E:CEDSR/EDV/BSA (cm/s^2/mL/m^2)	0.73 ± 0.18	0.61 ± 0.15	0.16

Values are reported in mean ± standard deviation for parametric data and median (interquartile range) for non-parametric data. A p-value < 0.05 was considered statistically significant. CEDSR = circumferential early diastolic strain rate, EDV = end-diastolic volume, EF = ejection fraction, FS = fractional shortening, LEDSR = longitudinal early diastolic strain rate.

Appendix Table 1

Statistically significant correlations of echocardiographic measures of diastolic function versus invasive measures of diastolic function.

Echo Measure	Tau	p-value
IVRT	r = 0.79	< 0.01
Mitral E velocity	r = −0.72	< 0.01
Lateral e′	r = −0.51	0.01
CEDSR	r = −0.50	0.02
Septal e′	r = −0.45	0.03
LEDSR	r = −0.43	0.03
	EDP	**p-value**
Mitral E velocity	r = 0.56	< 0.01
Lateral E:e′	r = 0.55	< 0.01
Mitral E:A	r = 0.54	< 0.01
Mitral E decel time	r = −0.51	0.01
Septal E:e′	r = 0.47	0.02

CEDSR = circumferential early diastolic strain rate. IVRT = isovolumic relaxation time. LEDSR = longitudinal early diastolic strain rate.