5-1-2018

Longitudinal measures of deformation are associated with a composite measure of contractility derived from pressure-volume loop analysis in children.

Shahryar M. Chowdhury

Ryan J. Butts

Carolyn L. Taylor

Varsha M. Bandisode

Karen S. Chessa

See next page for additional authors

Creator(s)
Shahryar M. Chowdhury, Ryan J. Butts, Carolyn L. Taylor, Varsha M. Bandisode, Karen S. Chessa, Anthony M. Hlavacek, Arni Nutting, Girish S. Shirali, and G Hamilton Baker

European Heart Journal – Cardiovascular Imaging (2018) **19**, 562–568
doi:10.1093/ehjci/jex167

Longitudinal measures of deformation are associated with a composite measure of contractility derived from pressure–volume loop analysis in children

Shahryar M. Chowdhury[1]*, Ryan J. Butts[1], Carolyn L. Taylor[1], Varsha M. Bandisode[1], Karen S. Chessa[1], Anthony M. Hlavacek[1], Arni Nutting[1], Girish S. Shirali[2], and G. Hamilton Baker[1]

[1]Department of Pediatrics, Division of Cardiology, Medical University of South Carolina, 165 Ashley Ave, MSC 915, Charleston, SC, 29425, USA; and [2]The Ward Family Heart Center, Children's Mercy Hospital, 2401 Gillham Road, Kansas City, MO, 64108, USA

Received 14 March 2017; editorial decision 2 June 2017; accepted 5 June 2017; online publish-ahead-of-print 29 June 2017

Aims The relationship between echocardiographic measures of left ventricular (LV) systolic function and reference-standard measures have not been assessed in children. The objective of this study was to assess the validity of echocardiographic indices of LV systolic function via direct comparison to a novel composite measure of contractility derived from pressure–volume loop (PVL) analysis.

Methods and results Children with normal loading conditions undergoing routine left heart catheterization were prospectively enrolled. PVLs were obtained via conductance catheters. A composite invasive composite contractility index (ICCI) was developed using data reduction strategies to combine four measures of contractility derived from PVL analysis. Echocardiograms were performed immediately after PVL analysis under the same anesthetic conditions. Conventional and speckle-tracking echocardiographic measures of systolic function were measured. Of 24 patients, 18 patients were heart transplant recipients, 6 patients had a small patent ductus arteriosus or small coronary fistula. Mean age was 9.1 ± 5.6 years. Upon multivariable regression, longitudinal strain was associated with ICCI (β = -0.54, P = 0.02) while controlling for indices of preload, afterload, heart rate, and LV mass under baseline conditions. Ejection fraction and shortening fraction were associated with LV mass and load indices, but not contractility.

Conclusion Speckle-tracking derived longitudinal strain is associated ICCI in children with normal loading conditions. Longitudinal measures of deformation appear to accurately assess LV contractility in children.

Keywords speckle-tracking echocardiography • contractility • pressure–volume relations • systolic function

Introduction

The accurate assessment of left ventricular (LV) systolic function has long been a goal in paediatric echocardiography. This assessment is most often performed via the measurement of LV dimensions and volumes to calculate shortening fraction (SF) and ejection fraction (EF), respectively.[1] In children at risk for heart failure, such as those with cardiomyopathies, cardiotoxicity, or metabolic diseases, the assessment of LV systolic function often entails the use of measures derived from tissue Doppler imaging (TDI) and speckle-tracking echocardiography (STE) that are purportedly more sensitive to changes in contractility than conventional measures.[2–4] Some of these measures have been suggested to be load-independent measures of contractility.[5,6] If true, these indices of LV systolic function have the potential to provide valuable insights into the natural history and results of medical and surgical interventions in children with heart failure. However, the relationship between these echocardiographic

* Corresponding author. Tel: 843 792 4473; Fax: 843 792 5878. E-mail: chowdhur@musc.edu

measures and reference-standard measures of LV systolic function have not been assessed in children.

A number of reference-standard measures of LV systolic function are derived from pressure–volume loop (PVL) analysis. Left ventricular end-systolic elastance (Ees) is one such measure of myocardial contractility, defined as the slope of the end-systolic pressure–volume relationship.[7] Some have attempted to use this index to validate echocardiographic measures of systolic function in animals and adults.[8,9] However, using this index as a lone measure of contractility has a number of limitations. First, Ees is only one component of the end-systolic pressure–volume relationship. The other component, the ventricular volume at the point where the ventricular pressure equals 0 mmHg (V_0), is also a measure of contractility.[10] Both Ees and V_0 must be interpreted simultaneously in order to accurately assess contractility.[11] In addition, the assumption that Ees is linear at baseline contractile states does not necessarily hold in smaller hearts, such as those in children.[12,13] Other PVL measures of contractility offer advantages in the paediatric population. Preload recruitable stroke work (PRSW) is independent of body size and therefore potentially useful in a variably sized paediatric population.[14] Starling's contractility index (SCI) is more sensitive to changes in contractility than Ees and PRSW.[15] Unfortunately, V_0, PRSW, and SCI have not previously been used for validation of non-invasive measures of systolic function in children or adults, in part, for simplicity's sake, as having a single index of contractility simplifies analysis and interpretation. However, echocardiographic validation results when using a single PVL index as the reference-standard measure of contractility are bound by (i) the individual PVL measure's limitations and (ii) the fact that important data regarding a patient's contractile state may have been lost by excluding other PVL indexes of contractility. Previous studies validating echocardiographic measures of systolic function against Ees alone should be interpreted with these limitations in mind.

We propose that an invasive composite contractility index (ICCI) derived by combining the four measures of contractility from PVL analysis should be used to validate echocardiographic measures of systolic function. As such, the goal of this study was to assess the validity of echocardiographic indices of LV systolic function in children via direct comparison to a composite measure of contractility derived from PVL analysis that included Ees, V_0, PRSW, and SCI.

Methods

Children undergoing a clinically indicated diagnostic left heart catheterization at the Medical University of South Carolina were recruited prospectively. Exclusion criteria included: (i) Age > 21 years, (ii) medical status for which participation in the study presented more than minimal risk as determined by the attending physician, (iii) non-sinus rhythm, (iv) patients with right-sided cardiac pathology (tetralogy of Fallot, atrial septal defect, etc.), and (v) significantly abnormal loading conditions (Qp:Qs > 1.5 or left ventricular outflow tract gradient > 15 mmHg). 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

We have described the pressure–volume loop acquisition in this cohort previously in a study validating echocardiographic estimates of Ees.[16] In summary, patients underwent general anesthesia per institutional 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 s 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. Preload reduction was achieved via balloon occlusion of one or both vena cavae in order to assess the end-systolic pressure–volume relationship. Ees and V_0 were calculated using the iterative regression method.[17] V_0 is often a negative value, especially in children, as the iterative regression method assumes Ees to be linear, when it is in fact curvilinear. However, this curvilinearity manifests only under non-physiologic conditions in adults, hence, standard practice is to assume Ees is linear in the physiologic range.[11] PRSW is the slope of the relationship between stroke work (the area encompassed by the PVL) and end-diastolic volume (EDV) upon preload reduction. SCI is the slope of the relationship between maximum $+\,dP/dt$ and EDV upon preload reduction. Arterial elastance (Ea), a measure of afterload, was calculated as end-systolic pressure divided by invasive stroke volume.[18] The ratio of arterial elastance (Ea) to Ees is the reference-standard measure of ventriculo-arterial coupling which describes the interaction between myocardial performance and vascular function.[19] All PVL data were recorded in triplicate over 10 s during an expiratory breath hold. Microconductance data was recorded at a sampling rate of 250 Hz. 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 Pro® v.8; ADInstruments, Colorado Springs, CO, USA).

Echocardiographic acquisition and analysis protocol

Echocardiograms were performed immediately after PVL analysis under the same anesthetic conditions using a Phillips IE33 system (Andover, MA, USA). Echocardiograms were sent uncompressed and at native frame rates to the encrypted server for analysis. All measurements were made off-line by a single blinded reviewer and averaged over three beats. Non-invasive blood pressures (systolic, diastolic, and mean) were obtained supine at the time of echocardiography by automated sphygmomanometer and averaged over three measurements.

Measures of LV systolic function were derived from 2D and 3D echocardiography, M-mode, and spectral tissue Doppler imaging (TDI) (Xcelera, Phillips, Andover, MA, USA). Measurement methods conformed to recommendations by the American Society of Echocardiography.[1] Measurements included SF (M-mode), TDI s' velocity from the lateral and septal LV walls, heart-rate corrected velocity of circumferential fiber shortening vs. wall stress (VCFc vs. WS z-score), isovolumic contraction time derived from TDI (IVCT'), and isovolumic acceleration at the lateral and septal LV walls. 2D speckle-tracking was performed using Cardiac Performance Analysis v. 3.0 (Tomtec Imaging Systems). Six segments each from the apical 2, 3, and 4 chamber views were averaged to measure global longitudinal strain and strain rate. Six segments each from the parasternal short axis view at the base, mid, and apex were averaged to obtain global circumferential strain and strain rate. Ventricular volumes and ejection fraction were derived from 3D echocardiography (QLAB v. 9.0, Phillips, Andover, MA, USA). ECG-gated 3DE volumes were acquired during expiratory breath-hold over four beats and the sub-volumes were stitched together. The average frame rate of the 3D volumes was 29.7 ± 5.1 frames/sec with an average heart rate during acquisition of 86.8 ± 17.2 bpm.

Table 1 Patient demographics and invasive data

	Heart transplant (*n* = 18)	Non-heart transplant (*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
Systolic blood pressure (mmHg)	89 ± 9	87 ± 9	0.75
Diastolic blood pressure (mmHg)	46 ± 7	51 ± 8	0.23
Baseline heart rate (bpm)	87 ± 15	78 ± 25	0.28
Ejection fraction (%)	58.2 (7.6)	55.4 (16.8)	0.82
Shortening fraction (%)	30.4 (9.8)	31.2 (14.9)	0.77
LV mass (g)	31.9 (41.7)	51.1 (36.9)	0.35
EDP (mmHg)	10.9 ± 3.5	9.7 ± 3.0	0.45
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)	1.0 (0.9)	0.02
Rs (Wood units)	19.5 (9.6)	19.2 (14.0)	0.67
Qp:Qs	1.0 (0)	1.0 (0.3)	0.45
Ees (mmHg/mL)	2.2 (3.3)	1.0 (2.1)	0.12
V_0 (mL)	-8.8 (29.9)	-26.8 (45.7)	0.28
PRSW (mmHg)	45.3 ± 19.7	38.6 ± 18.0	0.47
SCI (mmHg/s/mL)	8.6 (9.4)	7.4 (6.5)	0.58
Ea (mmHg/mL)	2.4 ± 0.9	1.6 ± 0.4	0.05
Ea/Ees	1.3 (0.9)	1.5 (1.5)	0.63
Preload composite	-0.05 ± 1.06	0.14 ± 0.88	0.71
Afterload composite	-0.08 ± 1.05	0.23 ± 0.88	0.53
Contractility composite	0.14 ± 0.95	-0.41 ± 1.13	0.25

Results reported as mean ± standard deviation for parametric data and median (interquartile range) for non-parametric data.
BSA, body surface area; EDP, end-diastolic pressure; Ea, arterial elastance; Ees, end-systolic elastance; MvO_2, mixed venous oxygen saturation; PRSW, preload recruitable stroke work; Qp:Qs, ratio of pulmonary to systemic blood flow; Rp, pulmonary vascular resistance; Rs, systemic vascular resistance; SCI, Starling's contractility index; V_0, ventricular volume at pressure of 0 mmHg.

Statistics

In order to develop the ICCI from PVL indices, we integrated Ees, V_0, PRSW, and SCI into a synthetic surrogate of contractility using data reduction strategies via principal component analysis.[20] This method of variable clustering simplifies regression modeling by avoiding the separate analysis of multiple factors that are theoretically measuring the same phenomenon. Thus, we calculated the ICCI as the first principal component of the principal component analysis based on the correlation matrix of Ees, V_0, PRSW, and SCI. The correlations between ICCI and each of its individual components were $r = 0.84$, $r = 0.87$, $r = 0.60$, and $r = 0.84$, respectively. A similar analysis was performed to assess preload and afterload as neither of these variables can be absolutely characterized by a single haemodynamic measurement.[21] The composite index of preload was developed by integrating LV EDV and end-diastolic pressure using the same method. Correlation coefficients of these individual variables with the composite index of preload were both $r = 0.76$. The composite index of afterload was developed by integrating Ea, systemic vascular resistance, and wall stress. The correlation coefficients of these individual variables with the composite index of afterload were $r = 0.87$, $r = 0.89$, and $r = 0.92$, respectively.

The distribution of data as parametric or non-parametric was assessed using the Shapiro–Wilk test. Differences between patient groups (heart transplant vs. non-heart transplant) were assessed using independent t-tests or Mann Whitney U tests. The correlation between echocardiographic measures of systolic function and the composite contractility index was assessed using Pearson's correlation and corrected to avoid overfitting by bootstrap validation of 1000 repetitions. Multiple variable linear regression was used to assess the effects of load confounders on each echocardiographic measure of systolic function by entering each echocardiographic variable as the dependent variable, the ICCI as the independent variable, and LV mass, heart rate, the composite afterload indexes, and the composite preload index as covariables. Regression validation (outlier exclusion, residual homoscedasticity, and evaluation for significant interactions and nonlinearities) was performed for all models. Intra- and inter-observer variability was assessed using intraclass correlation coefficients. A *P*-value <0.05 was considered statistically significant. All statistics were performed using IBM® SPSS® Statistics software v. 23 (New York, NY, USA).

Results

Twenty-four patients were enrolled; 18 patients were status post heart transplant, 5 patients had a trivial or small patent ductus arteriosus, and one had a small coronary fistula. Patent ductus arteriosus and coronary fistula patients were referred for catheterization for intervention - all were successfully intervened upon. Heart transplant patients were referred for catheterization for their routine yearly assessment - no transplant patients had evidence of coronary artery disease or rejection. Demographic, clinical, and catheterization data from these patients, and a comparison between patients with heart transplant and those without, are presented in *Table 1*. Representative analyses of PVLs during preload reduction, and the derivative measures of contractility, are shown in *Figure 1*. Comparisons of less-conventional echocardiographic measures of ventricular function are reported in Supplementary data online, *Appendix Table S1*. Interobserver variability of the speckle-tracking measures are reported in Supplementary data online, *Appendix Table S2*.

Correlations between echocardiographic measures of systolic function and contractility

Correlations between ICCI and echocardiographic measures of systolic function are reported in *Table 2*. Correlations between echocardiographic variables and the four invasive components of ICCI are reported in Supplementary data online, *Appendix Table S3*. Global longitudinal strain (*Figure 2*) and strain rate displayed the strongest correlations with ICCI. Global circumferential strain rate showed a significant, but weaker, correlation with ICCI. Ees_{NI} showed a moderate correlation with ICCI. Conventional measures of systolic function, EF and SF showed no significant correlation with ICCI. Advanced measures of systolic function derived from tissue Doppler (peak s', isovolumic contraction time, isovolumic acceleration slope) and VCFC vs. WS Z-score also showed no significant correlation with ICCI.

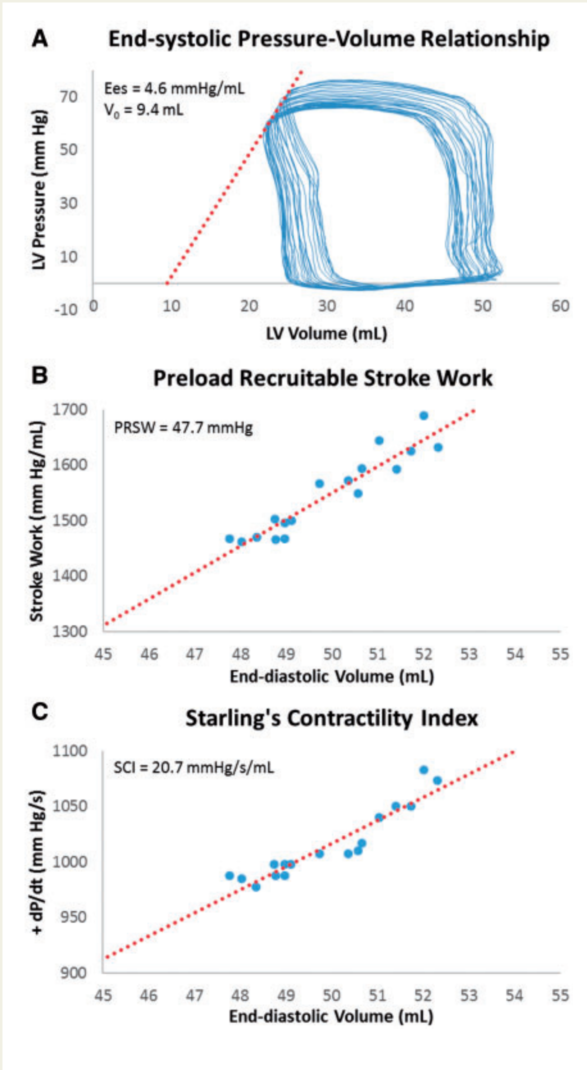

Figure 1 Assessment of pressure–volume loop measures of contractility. (*A*) Representative PVL during preload reduction. The end-systolic pressure–volume relationship is represented by the red dotted line. (*B*) Scatterplot of stroke work vs. left ventricular end-diastolic volume. The slope of this relationship (red dotted line) represents preload recruitable stroke work. (*C*) Scatterplot of peak + d*P*/d*t* vs. left ventricular end-diastolic volume. The slope of this relationship (red dotted line) represents Starling's contractility index.

Table 2 Correlations between the invasive composite measure of contractility and echocardiographic measures of systolic function

Echocardiographic measure	*R*-value	R_{boot}-value
Ejection fraction	0.19	0.22
Shortening fraction	0.09	0.04
GCS	-0.26	-0.24
GCSR	-0.52*	-0.50*
GLS	-0.59**	-0.65**
GLSR	-0.64**	-0.67**

GCS, global circumferential strain; GCSR, global circumferential strain rate; GLS, global longitudinal strain; GLSR, global longitudinal strain rate.
*$P < 0.05$.
**$P < 0.01$.

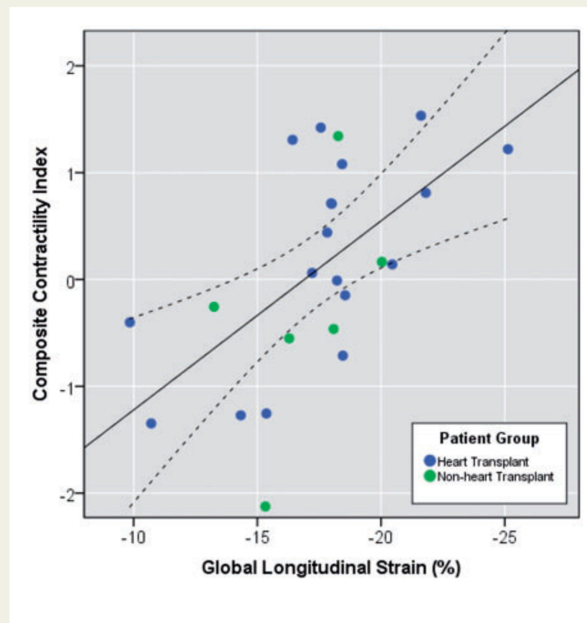

Figure 2 Scatterplot, linear fitting (solid line), and 95% confidence interval for the fitting (dotted lines) of speckle-tracking-derived longitudinal strain vs. the composite measure of contractility derived from pressure–volume loop analysis.

Load, mass, and heart rate effects on echocardiographic measures of systolic function

The association between echocardiographic measures of systolic function vs. composite measures of contractility, afterload, preload, LV mass, and heart rate derived from multiple variable linear regression are shown in *Table 3*. Variables that had no association with the composite measures (TDI lateral and septals', lateral and septal isovolumic acceleration, and VCFC Z-score) were not included in the table. LV longitudinal strain had a significant relationship with ICCI and no significant relationship with preload, afterload, LV mass, or heart rate. LV longitudinal strain rate was significantly associated with ICCI and LV mass. EF and SF were associated with load indices, but not contractility. Autocorrelations between echocardiographic measures of systolic function and composite measures of contractility, load, LV mass, and heart rate derived from principal component analysis are displayed graphically in *Figure 3*.

Discussion

This is the first study to comprehensively evaluate the association between echocardiographic measures of systolic function and a

Table 3 Determinants of echocardiographic measures of LV systolic function

	Contractility	Afterload	Preload	LV mass	Heart rate	R^2
Ejection fraction	0.13	-1.01**	0.80*	-0.74**	0.95	0.71
Shortening Fraction	0.01	-1.03**	0.51	-0.38	0.09	0.75
GCS	-0.31	0.73*	-0.69	0.47	0.03	0.41
GCSR	-0.47*	0.53*	-0.59	0.48	-0.20	0.47
GLS	-0.54*	0.36	-0.30	0.58	0.29	0.55
GLSR	-0.49*	0.36	-0.32	0.65*	0.08	0.62

Standardized β coefficients derived from multiple variable linear regression.
GCS, global circumferential strain; GCSR, global circumferential strain rate; GLS, global longitudinal strain; GLSR, global longitudinal strain rate.
*P-value < 0.05.
**P-value < 0.01.

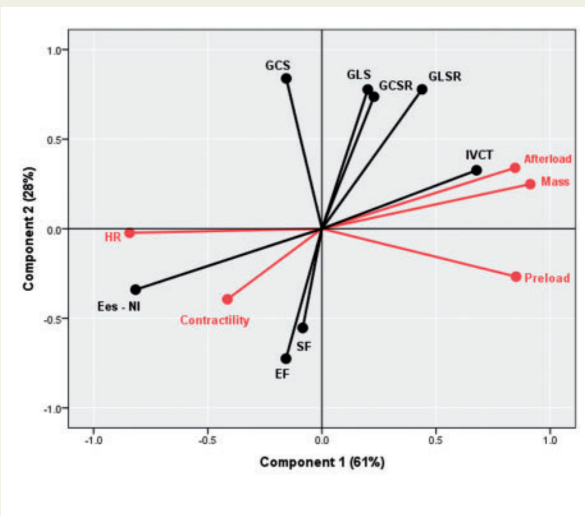

Figure 3 Principal component analysis with illustrative variables. The autocorrelation of the echocardiographic indices of systolic function (black circles) and their relationship with contractility, heart rate, mass, preload, and afterload (red circles) is presented. Axes represent the first (horizontal) and second (vertical) principal components (% of variation explained by each). The angle between two lines represents the correlation between the respective variables. There is a positive correlation if the angle is small (variables are close to each other), there is no linear correlation if the angle is 90°, and there is an inverse correlation if the angle is > 90°. The longer the length of the line the better it can be explained from the first two components. Ees_{NI}, single-beat echocardiographic estimation of end-systolic elastance; EF, ejection fraction; IVCT, isovolumic contraction time; GCS, global circumferential strain; GCSR, global circumferential strain rate; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; HR, heart rate; SF, shortening fraction.

composite measure of contractility derived from invasive PVL acquisition. The main finding of this study is that longitudinal strain derived from speckle-tracking echocardiography showed a moderate relationship with ICCI after accounting for preload, afterload, LV mass, and heart rate. In comparison, conventional measures, such as EF and shortening fraction, were significantly associated with load and LV mass.

The results of this study suggest that LV longitudinal strain is associated with contractility in children with normal loading conditions. This is in line with clinical studies suggesting longitudinal strain is a sensitive marker of early cardiac dysfunction and is associated with outcomes in disease processes known to impair contractility, such as chemotherapy cardiotoxicity, myocardial infarction, amyloidosis, etc.[4,22,23] We found no significant relationship between longitudinal strain and load or LV mass. While it is clear from previous studies that longitudinal strain is influenced by acute changes in load,[24] our findings suggest that, in the absence of acute loading changes, longitudinal strain is more closely related to contractility than load or LV mass under baseline conditions. As most patients are followed at their baseline state, longitudinal strain provides important insight into the contractile state of patients at risk for systolic dysfunction.

Few studies have compared echocardiographic vs. PVL measures of systolic function. Longitudinal measures of deformation have been associated with Ees in animals and in children with single ventricle physiology.[25,26] Yotti *et al.* compared echocardiographic measures of LV systolic function and Ees in a cohort of adults. Similar to the current study, they found significant associations between conventional echocardiographic measures of LV systolic function and load.[8] However, they found no association between longitudinal strain and Ees. There are number of potential explanations behind these discrepant results. First, longitudinal strain was only measured from the apical 4-chamber view, compared to the full 18 segment analysis performed in the current study. Second, speckle-tracking was also performed using different software packages, each of which uses a unique algorithm to calculate strain.[27] It is conceivable that different speckle-tracking software vary in their accuracy when compared to invasive measures. Finally, similar to all previous studies assessing the correlation between echocardiographic and PVL measures of systolic function, Yotti *et al.* used Ees as the lone measure of systolic function. This may be problematic because in addition to Ees, V_0 is required when using the end-systolic pressure–volume relationship to assess contractility. For example, when comparing two patients with equal Ees, preload, and afterload, the patient with a lower V_0 displays better contractility.[11]

Limitations

The ICCI is a composite measure derived from multiple reference-standard contractile indices, however, it has not been validated experimentally as a measure of contractility independently. Therefore, its load dependency, response to inotropy and heart rate are unknown. The study population was relatively small; our results may deserve validation in a larger cohort. The majority of our patients were status post heart transplantation, and therefore cannot be considered to have absolutely normal cardiac function or loading conditions. We did not perform repeated measures after a change in loading conditions or inotropic states to avoid further complexity in the PVL catheterization procedure. However, as most patients do not undergo acute changes in loading conditions during follow-up assessment in chronic disease states, we feel the most clinically relevant analysis was performed. To be applicable to the broader congenital heart disease population, further validation may be warranted to ensure that these associations hold after acute and chronic changes in loading conditions, contractile states, a broader range of heart rates, ventricular sizes, masses, and morphologies. The associations between these echocardiographic measures of systolic function and patient outcomes need to be separately assessed to determine their usefulness in children.

Clinical implications

The validation of echocardiographic measures of systolic function has the potential to provide important insights into disease progression and response to treatment in patients at risk for heart failure, including those patients with chemotherapy cardiotoxicity, familial or acquired cardiomyopathy, heart transplantation, and congenital heart disease. As new inotropic therapies are developed, using these echocardiographic measures to understand the relationship between the resultant changes in contractility, load, and LV mass may assist in the evaluation of these therapies' efficacy.

Measures of myocardial deformation and Ees have been shown to be associated with mortality, B-type natriuretic peptide, and exercise performance in adults with cardiovascular disease.[28,29] In addition, they can be used to elucidate the mechanism of improvement in heart failure symptoms after therapy.[30,31] This is important in paediatrics because children with heart failure have not shown the same response to heart failure therapy as adults.[32] Investigating these measures may allow us to gain insight into the pathophysiology behind the lack of efficacy of standard heart failure therapies in children.

Conclusion

We developed a composite invasive measure of contractility derived from PVL analysis, the ICCI. Speckle-tracking derived longitudinal strain is associated with the ICCI in children with normal loading conditions. This association is independent from loading conditions, LV mass, and heart rate under baseline conditions. Longitudinal measures of deformation appear to accurately assess LV contractility in children under baseline conditions.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Funding

This study was funded by the American Society of Echocardiography Foundation and the Mend a Heart Foundation. Dr Chowdhury was supported by NIH/NHLBI grant T32 HL07710 and American Heart Association Mentored Clinical and Population Research Award 15MCPRP25820008.

Conflict of interest: None declared.

References

1. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK *et al*. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *J Am Soc Echocardiogr* 2010;**23**:465–95 (quiz 576-7).
2. Toro-Salazar OH, Ferranti J, Lorenzoni R, Walling S, Mazur W, Raman SV *et al*. Feasibility of echocardiographic techniques to detect subclinical cancer therapeutics-related cardiac dysfunction among high-dose patients when compared with cardiac magnetic resonance imaging. *J Am Soc Echocardiogr* 2016;**29**:119–31.
3. den Boer SL, Du Marchie Sarvaas GJ, Klitsie LM, van Iperen GG, Tanke RB, Helbing WA *et al*. Longitudinal strain as risk factor for outcome in pediatric dilated cardiomyopathy. *JACC Cardiovasc Imaging* 2016;**9**(9):1121–2.
4. Armstrong GT, Joshi VM, Ness KK, Marwick TH, Zhang N, Srivastava D *et al*. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude Lifetime Cohort Study. *J Am Coll Cardiol* 2015;**65**:2511–22.
5. Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. *J Am Coll Cardiol* 1984;**4**:715–24.
6. Vogel M, Schmidt MR, Kristiansen SB, Cheung M, White PA, Sorensen K *et al*. Validation of myocardial acceleration during isovolumic contraction as a novel noninvasive index of right ventricular contractility: comparison with ventricular pressure-volume relations in an animal model. *Circulation* 2002;**105**:1693–9.
7. Sagawa K, Suga H, Shoukas AA, Bakalar KM. End-systolic pressure/volume ratio: a new index of ventricular contractility. *Am J Cardiol* 1977;**40**:748–53.
8. Yotti R, Bermejo J, Benito Y, Sanz-Ruiz R, Ripoll C, Martinez-Legazpi P *et al*. Validation of noninvasive indices of global systolic function in patients with normal and abnormal loading conditions: a simultaneous echocardiography pressure-volume catheterization study. *Circ Cardiovasc Imaging* 2014;**7**:164–72.
9. Greenberg NL, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA *et al*. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. *Circulation* 2002;**105**:99–105.
10. Blaudszun G, Morel DR. Relevance of the volume-axis intercept, V0, compared with the slope of end-systolic pressure-volume relationship in response to large variations in inotropy and afterload in rats. *Exp Physiol* 2011;**96**:1179–95.
11. 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.
12. Georgakopoulos D, Mitzner WA, Chen CH, Byrne BJ, Millar HD, Hare JM *et al*. In vivo murine left ventricular pressure-volume relations by miniaturized conductance micromanometry. *Am J Physiol* 1998;**274**:H1416–22.
13. Wannenburg T, Schulman SP, Burkhoff D. End-systolic pressure-volume and MVO2-pressure-volume area relations of isolated rat hearts. *Am J Physiol* 1992;**262**:H1287–93.
14. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO *et al*. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation* 1985;**71**:994–1009.
15. Little WC. The left ventricular dP/dtmax-end-diastolic volume relation in closed-chest dogs. *Circ Res* 1985;**56**:808–15.
16. 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.
17. Kass DA, Midei M, Graves W, Brinker JA, Maughan WL. Use of a conductance (volume) catheter and transient inferior vena caval occlusion for rapid determination of pressure-volume relationships in man. *Cathet Cardiovasc Diagn* 1988;**15**:192–202.
18. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. *Am J Physiol* 1983;**245**:H773–80.
19. Fox JM, Maurer MS. Ventriculovascular coupling in systolic and diastolic heart failure. *Curr Heart Fail Rep* 2005;**2**:204–11.
20. Harrell FE, *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York: Springer; 2001.

21. Sagawa K. *Cardiac Contraction and the Pressure-Volume Relationship*. New York: Oxford University Press; 1988.
22. Motoki H, Borowski AG, Shrestha K, Troughton RW, Tang WH, Thomas JD *et al*. Incremental prognostic value of assessing left ventricular myocardial mechanics in patients with chronic systolic heart failure. *J Am Coll Cardiol* 2012;**60**:2074–81.
23. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A *et al*. Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. *J Am Coll Cardiol* 2012;**60**:1067–76.
24. Dahle GO, Stangeland L, Moen CA, Salminen PR, Haaverstad R, Matre K *et al*. The influence of acute unloading on left ventricular strain and strain rate by speckle tracking echocardiography in a porcine model. *Am J Physiol Heart Circ Physiol* 2016;ajpheart.00947.2015.
25. Kovacs A, Olah A, Lux A, Matyas C, Nemeth BT, Kellermayer D *et al*. Strain and strain rate by speckle-tracking echocardiography correlate with pressure-volume loop-derived contractility indices in a rat model of athlete's heart. *Am J Physiol Heart Circ Physiol* 2015;**308**:H743–8.
26. Schlangen J, Petko C, Hansen JH, Michel M, Hart C, Uebing A *et al*. Two-dimensional global longitudinal strain rate is a preload independent index of systemic right ventricular contractility in hypoplastic left heart syndrome patients after fontan operation. *Circ Cardiovasc Imaging* 2014;**7**:880–6.
27. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R *et al*. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr* 2015;**28**:183–93.
28. Antonini-Canterin F, Enache R, Popescu BA, Popescu AC, Ginghina C, Leiballi E *et al*. Prognostic value of ventricular-arterial coupling and B-type natriuretic peptide in patients after myocardial infarction: a five-year follow-up study. *J Am Soc Echocardiogr* 2009;**22**:1239–45.
29. Bombardini T, Costantino MF, Sicari R, Ciampi Q, Pratali L, Picano E. End-systolic elastance and ventricular-arterial coupling reserve predict cardiac events in patients with negative stress echocardiography. *Biomed Res Int* 2013;**2013**: 2351–94.
30. Bozkurt B, Bolos M, Deswal A, Ather S, Chan W, Mann DL *et al*. New insights into mechanisms of action of carvedilol treatment in chronic heart failure patients—a matter of time for contractility. *J Card Fail* 2012;**18**:183–93.
31. Maurer MS, Sackner-Bernstein JD, El-Khoury Rumbarger L, Yushak M, King DL, Burkhoff D. Mechanisms underlying improvements in ejection fraction with carvedilol in heart failure. *Circ Heart Fail* 2009;**2**:189–96.
32. Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC *et al*. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation* 2010;**122**:333–40.