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A preliminary comparison of two-dimensional speckle tracking echocardiography and pressure–volume loop analysis in patients with Fontan physiology: The role of ventricular morphology

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Abstract

Objective—Speckle tracking echocardiography (STE) may be a useful modality for assessing ventricular performance in patients with single ventricle physiology. However, STE's ability to accurately assess ventricular performance in this population is unknown. The objective of this study was to perform a preliminary comparison of STE measures of myocardial deformation to reference standard measures of function derived from pressure–volume loop (PVL) analysis.

Design—This was a secondary analysis of a prospective study investigating PVLs in patients with Fontan physiology. PVLs were recorded using microconductance catheters. PVL indices included end-systolic elastance (Ees), arterial elastance (Ea), ventriculo-arterial coupling (Ea/Ees), and the isovolumic relaxation time constant (τ). Patients were included if they had an echocardiogram within 1 month of their catheterization. STE was performed retrospectively using vendor independent software.

Results—Seventeen patients had echocardiograms available for analysis, 12 were right ventricular (RV) dominant. The median age was 8 years (IQR 5–17 years). Circumferential strain ($r=-.72$, $P=.01$) and strain rate ($r=-.61$, $P=.04$) correlated with Ea/Ees in those with RV-dominant morphology. Longitudinal strain rate correlated with Ees in those with LV-dominant morphology ($r=-.98$, $P=.01$). Longitudinal EDSR correlated with τ in those with LV-dominant morphology ($r=-.90$, $P=.04$).

Conclusions—In this limited sample, circumferential measures of deformation correlated with PVL measures better in patients with RV morphology, while longitudinal measures correlated better with PVL measures in patients with LV morphology. Further validation and investigation into the clinical usefulness of these measures are warranted.

Keywords

Fontan; pressure-volume loop; speckle tracking echocardiography; ventricular function

1 INTRODUCTION

Abnormal ventricular function is a predictor of morbidity and mortality in patients with single ventricle physiology.¹ However, applying conventional echocardiographic measurements of ventricular function, such as ejection fraction, in patients with single ventricle physiology can be difficult given their variable and unique ventricular geometry.^{2–5} Frequently, clinicians must rely on their subjective assessment of function, which suffers from poor observer variability. Cardiologists are left with the daunting challenge of managing a population at high risk for heart failure without validated, objective echocardiographic indices of cardiac function.

Speckle tracking echocardiography (STE) is an attractive modality for quantifying function in the single ventricle population. It is not reliant on ventricular geometry compared to ejection fraction. It is less reliant on angle of insonation and a high frame rate compared with tissue Doppler.⁶ Compared to cardiac magnetic resonance imaging, it is easily obtainable. In addition, STE has been found to be more sensitive than ejection fraction and fractional shortening in detecting abnormal left ventricular (LV) systolic function in patients with biventricular anatomy who have suffered a myocardial infarction, anthracycline toxicity, and dilated cardiomyopathy.^{7–9}

Despite its strengths, barriers still exist to using STE in clinical practice when evaluating single ventricle patients. First, because STE is geometry independent, it can evaluate deformation in a number of directions. Choosing which measure of deformation to follow in single ventricle patients (ie, longitudinal vs circumferential) is currently unclear. This is further complicated by the observation that systemic left ventricles (LV) have different contraction patterns than normal right ventricles (RV) and that systemic right ventricles have contraction patterns that change over time as they adapt to abnormal loading conditions. Therefore, it is conceivable that deformation measures that accurately assess ventricular function in a systemic LV do not necessarily accurately assess ventricular function in a systemic RV.

The objective of this preliminary study was to evaluate the validity of STE measures of systolic and diastolic function in single ventricle patients. Our goal was to compare STE measures of ventricular function vs reference standard measures derived from invasive pressure–volume loop (PVL) analysis and determine the role of ventricular morphology in the relationship between STE and PVL measures in patients with single ventricle physiology.

2 METHODS

This was a secondary analysis of a single-center prospective cross-sectional study investigating the effects of a single dose of sildenafil vs placebo on PVL measures of

ventricular function in patients with Fontan physiology. The methods for patient enrollment, study drug administration, and catheterization protocol were reported previously and are summarized below.¹⁰ In addition, for this study, we retrospectively analyzed clinically indicated echocardiograms acquired near the time of catheterization and compared the results to measures of ventricular function derived from PVL analysis. In the previous study, there were no differences in PVL measures of ventricular function between the sildenafil vs placebo groups. Therefore, the groups were combined for this analysis.

2.1 Patients

Patients were screened for enrollment during workup for clinically indicated catheterization. Inclusion criteria included single ventricle physiology status post the Fontan palliation. Exclusion criteria included a history of an adverse reaction to sildenafil or other PDE5 inhibitors; arrhythmia within 2 months of previous catheterization; extracardiac anatomy that would preclude the placement of a microconductance catheter; the use of PDE5 inhibitor within 1 month of catheterization. The institutional review board at the Medical University of South Carolina approved the protocol. Informed consent was obtained from the parent or legal guardian (age<18 years) or from the patient (age>18). Assent was obtained for all patients aged 12–17 years. (Clinicaltrials.gov Identifier: NCT01815502).

2.2 Study catheterization and PVL analysis protocol

All patients had general anesthesia per institutional protocol. A 4 Fr high fidelity microconductance catheter (CD Leycom, Hengelo, The Netherlands) was placed in the apex of the dominant ventricle via the femoral approach. Microconductance catheters were placed in the ventricle via an antegrade approach in those with a patent fenestration. The catheter was stabilized with a 5Fr transseptal sheath. A retrograde approach was used to place the microconductance catheter into the single ventricle for patients without a patent fenestration. The conductance catheter's micromanometer was calibrated in normal saline for 15 seconds prior to placement. PVLs were volume calibrated using hypertonic saline to account for parallel conductance. The Fick equation was used to calculate cardiac output after deriving oxygen consumption from indirect calorimetry (Ultima metabolic cart, MGC Diagnostics, Saint Paul, MN, USA). All PVL data were recorded in triplicate over 10 seconds during an expiratory breath hold. Microconductance data were recorded at a sampling rate of 250 Hz. Invasive data were gathered using standard equipment approved for use in human subjects (INCA intracardiac analyzer; CD Leycom). Pressure–volume loop analysis was performed off line by a blinded reviewer (RB) using specialized software (LabScribe2, iWorx, Dover, NH, USA).

End-systolic elastance (Ees), a measure of contractility, was derived from PVL analysis using a single-beat estimation as described by Shishido et al.¹¹ to avoid the risks associated with load alterations. Arterial elastance (Ea), a measure of afterload, was calculated as end-systolic pressure divided by stroke volume.¹² Ventricular–arterial (VA) coupling, an important determinant of global pump function, was calculated as the ratio of Ea to Ees. Ees and Ea were indexed to body surface area to account for differences in body size between patients. To assess diastolic function, we calculated the isovolumic relaxation time constant (τ) to evaluate early active ventricular relaxation using the method of Weiss.¹³

2.3 Echocardiographic analysis

Echocardiograms were analyzed if they occurred within 1 month of catheterization. Echocardiograms were obtained using a Philips iE33 system (Andover, MA, USA) then stored in DICOM format at a frame rate of 30 fps on the clinical server. These studies were retrieved to perform two-dimensional speckle tracking echocardiography offline using vendor independent software (Tomtec Cardiac Performance Analysis v3.0). Six segments from the apical four-chamber view were averaged to measure global longitudinal strain, strain rate, and early diastolic strain rate (EDSR). Six segments from the parasternal short-axis view at the mid-ventricular level were averaged to obtain global circumferential strain, strain rate, and EDSR. Radial strain was not used in this analysis due to its high measurement variability.¹⁴ If the myocardium was not visualized well, the specific segments were excluded. Strain measures were excluded if more than two cardiac segments were excluded from the analysis due to poor tracking. Examples of speckle tracking analysis in a single left ventricle and single right ventricle are shown in Figures 1 and 2, respectively. A single blinded reviewer (DS) made all measurements. Intra- and inter-observer variabilities were assessed for longitudinal and circumferential measures of myocardial deformation on 10 echocardiograms.

2.4 Statistics

Comparisons between patients with left vs right ventricular dominance were performed using the Mann–Whitney *U* test or Fisher's exact test. The relationships between echocardiographic and PVL measures of ventricular function were determined using a Pearson's correlation analysis. Assessments of intra- and inter-observer variabilities were made by intraclass correlation coefficient using a random effects model measuring absolute agreement in 10 random echocardiograms. A second observer, blinded to the original observers results, made measurements 1 month after the initial measurements were made. An intraclass correlation coefficient $>.80$ was viewed to be acceptable intra- or inter-observer variabilities. A *P*-value lower than .05 was considered significant. All statistics were performed using SPSS Statistics software v. 23 (IBM, Chicago, IL, USA).

3 RESULTS

Of 19 patients enrolled in the primary study, 17 patients had echocardiograms within 1 month of catheterization. Twelve patients (71%) were right ventricular (RV). The median age was 8 years (IQR 5–17 years). In 14 of 17 patients, the echocardiograms occurred on the same day under the same anesthetic conditions prior to the catheterization. Two of the echocardiograms occurred within 2 days of the catheterization, and one echocardiogram occurred within a month. Comparisons between those with left vs right dominant ventricular morphology can be viewed in Table 1. One RV-dominant patient could not have longitudinal measures of deformation measured due to an inadequate amount of ventricular free wall being in the echocardiographic window. A different RV-dominant patient could not have circumferential deformation parameters measured as no short-axis view at the level of the mid-ventricle was obtained. Intraclass correlation coefficient was $>.80$ in all longitudinal and circumferential measures of deformation in both intraobserver and inter-observer variabilities analysis.

3.1 Correlations between echocardiographic and PVL measures: RV-dominant group

There were no statistically significant associations between Ees and longitudinal strain ($r=.43$, $P=.19$) or strain rate (0.43 , $P=.19$). There were also no correlations between Ees and circumferential strain or strain rate. In contrast, Ea/Ees correlated with circumferential strain ($r=.72$, $P=.02$; Figure 3) and strain rate ($r=.61$, $P=.047$; Figure 4) but not with longitudinal strain or strain rate. Tau did not correlate with longitudinal or circumferential EDSR in RV-dominant patients.

3.2 Correlations between echocardiographic and PVL measures: LV-dominant group

There was no statistically significant association between Ees and longitudinal strain ($r=-.65$, $P=.23$). However, Ees did correlate strongly with longitudinal strain rate in patients with LV-dominant morphology ($-.98$, $P<.01$; Figure 5). There were no correlations between Ees and circumferential strain or strain rate. Ea/Ees did not correlate with longitudinal or circumferential strain or strain rate in LV-dominant patients. Tau correlated strongly with longitudinal EDSR ($r=-.90$, $P=.04$; Figure 6) but not with circumferential EDSR.

4 DISCUSSION

Two-dimensional STE holds promise in accurately assessing single ventricular function. In this preliminary study, we found that STE measures correlate with PVL measures of function. Our results provide insight into how this technology may be applied in patients with single right and left dominant ventricular morphologies. We found that in patients with RV-dominant morphology, circumferential measures of systolic deformation correlated best with PVL measures of ventriculo-arterial coupling. In contrast, in patients with LV-dominant morphology, longitudinal measures of deformation correlated best with PVL measures of systolic and diastolic function. These results suggest that, in clinical practice, it may be most useful to follow circumferential measures of deformation in patients with single right ventricles and longitudinal measures of deformation in patients with single left ventricles.

Previous comparisons of echocardiographic vs PVL measures of function in single ventricle patients are rare.^{15,16} Schlangen et al.¹⁷ compared 2-D speckle tracking measures of longitudinal deformation to Ees in patients with RV-dominant single ventricles. Their group found that a weak correlation between that global longitudinal strain rate and Ees. Their correlation coefficient was similar to that found in the current study; however, our findings were not statistically significant, likely due to inadequate power. Schlangen et al., however, did not evaluate circumferential measures of deformation, which based on our results seem to be a better surrogate for invasive measures in the single RV.

The fact that circumferential, and not longitudinal, strain correlated with single RV ventriculo-arterial coupling may actually support evidence regarding the mechanism by which the single right ventricle adapts to systemic pressure. The systemic RV increases circumferential relative to longitudinal contraction—this increased number of circumferential fibers help generate a greater inward radial force.¹⁸ This adaptation appears to occur relatively early in life in the single RV and has been hypothesized as a boon to overall ventricular function in these patients.¹⁹ The transition is likely complete by the time

of the Fontan operation. This adaptation to a predominant circumferential contraction pattern may provide an explanation as to why circumferential markers of deformation correlated with PVL measures in the systemic right ventricle.

In biventricular circulation, a worsening in longitudinal measures of deformation has been shown to precede a decrease in LV ejection fraction in a number of disease processes that predispose patients to impaired contractility. Based on our results, albeit in a very small sample, it appears that this relationship between longitudinal deformation and changes in contractility persists in the single ventricle patient with LV-dominant morphology.

Our results, if ideally validated in a larger sample, may be useful in guiding clinical decisions. Conventional measures of ventricular function, such as ejection fraction, are difficult to obtain by echocardiography in patients with a single ventricle. In contrast, STE is quite feasible to perform. Although there is no normative data for STE measures of deformation in patients with single ventricle physiology, previous studies have demonstrated that changes in strain from baseline are associated with outcomes in biventricular patients.²⁰ Although further research is warranted, STE may be similarly useful in single ventricle patients. Our data suggest when following these patients, circumferential measures of deformation should be assessed in those with single right ventricle morphology, while longitudinal measures should be used in those with single left ventricle morphology. Changes in these measures may be used to guide medical, interventional, and surgical decision making.

Limitations of our study include that it was a small heterogenous sample. In particular, we had a small number of single LVs. As such, this was a preliminary study that showed potentially important data, but a larger sample size would be necessary for validation. In addition, due to the studies retrospective nature, the time from PVL acquisition during catheterization to echo varied, with impacts from sedation and time from catheterization likely playing some role in the correlations seen. Finally, the STE images were analyzed in DICOM format with a limited frame rate from the clinical server at 30 frames per second, likely leading to an underestimation of strain rates.²¹

5 CONCLUSIONS

In this preliminary report, we found speckle tracking echocardiographic measures of deformation correlated with PVL measures of function in patients with single ventricle physiology after the Fontan procedure. Specifically, circumferential measures of deformation were a surrogate for ventriculo-arterial coupling in single ventricle patients with RV morphology. Longitudinal measures of deformation seemed to correlate with PVL measures in single ventricle patients with LV-dominant morphology. These measures warrant further study in a larger cohort to determine their clinical applicability.

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FIGURE 1.

A. Example of left ventricular (LV) endocardial tracing in apical four-chamber view. B. LV longitudinal strain curves after speckle tracking analysis. C. LV endocardial tracing in parasternal short-axis view. D. LV circumferential strain curves after speckle tracking analysis

FIGURE 2.

A. Example of right ventricular (RV) endocardial tracing in apical four-chamber view. B. RV longitudinal strain curves after speckle tracking analysis. C. RV endocardial tracing in parasternal short-axis view. D. RV circumferential strain curves after speckle tracking analysis

FIGURE 3.
Scatter plot displaying Ea/Ees vs circumferential strain in patients with right ventricular (RV)-dominant morphology

FIGURE 4. Scatter plot displaying E_a/E_{es} vs circumferential strain rate in patients with right ventricular (RV)-dominant morphology

FIGURE 5. Scatter plot displaying Ees vs longitudinal strain rate in patients with left ventricular (LV)-dominant morphology

FIGURE 6.

Scatter plot displaying Tau vs longitudinal early diastolic strain rate in patients with LV-dominant morphology

TABLE 1

Patient demographic, catheterization, and echocardiographic data

Measure	LV dominant (n=5)	RV dominant (n=12)	P-value
Age (y)	12 (6, 20)	7 (4, 11)	.20
Female, n (%)	3 (60)	2 (17)	.12
Height (cm)	167 (112, 178)	124 (106, 146)	.23
Weight (kg)	50 (17, 72)	23 (17, 54)	.72
BSA (m ²)	1.6 (0.7, 1.9)	0.9 (0.7, 1.5)	.51
SBP (mm Hg)	101 (77, 122)	103 (92, 113)	.88
DBP (mm Hg)	60 (33, 76)	60 (41, 69)	.96
PVL EDV (mL)	84 (69, 161)	74 (65, 97)	.44
PVL EF (%)	54.1 (46.6, 66.4)	45.2 (34.0, 54.2)	.16
PVL EDP (mm Hg)	5.1 (3.7, 9.1)	7.1 (4.4, 8.7)	.51
Rp (Wood units·m ²)	1.5 (1.2, 1.9)	1.3 (0.9, 2.1)	.77
Ees (mm Hg mL ⁻¹ m ⁻²)	3.1 (2.0, 3.4)	2.5 (1.8, 2.7)	.33
Ea (mm Hg mL ⁻¹ m ⁻²)	1.5 (1.3, 2.3)	1.7 (1.5, 2.2)	.65
Ea/Ees	0.59 (0.54, 0.78)	0.92 (0.65, 1.08)	.04
Tau (ms)	34.3 (28.3, 40.6)	34.7 (30.8, 40.9)	.99
LS (%)	-14.2 (-17.4, -10.5)	-12.1 (-16.3, -10.9)	.91
LSR (s ⁻¹)	-0.88 (-1.10, -0.75)	-0.86 (-1.04, -0.67)	.91
LEDSR (s ⁻¹)	0.96 (0.71, 1.22)	0.85 (0.78, 1.12)	.91
CS (%)	-16.3 (-18.2, -13.8)	-12.2 (-18.1, -11.1)	.51
CSR (s ⁻¹)	-1.03 (-1.22, -0.77)	-0.93 (-1.35, -0.81)	.91
CEDSR (s ⁻¹)	0.86 (0.75, 1.34)	0.91 (0.61, 1.30)	.91

Values reported as median (interquartile range).

BSA=body surface area; SBP=systolic blood pressure; DBP=diastolic blood pressure; PVL=pressure-volume loop; EDV=end-diastolic volume; EF=ejection fraction; EDP=end-diastolic pressure; Rp=pulmonary resistance; Ees=end-systolic elastance; Ea=arterial elastance; Ea/Ees=ventriculo-arterial coupling; LS=longitudinal strain; LSR=longitudinal strain rate; LEDSR=longitudinal early-diastolic strain rate; CS=circumferential strain; CSR=circumferential strain rate; CEDSR=circumferential early-diastolic strain rate.