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Comparison of Echocardiographic and Pressure–volume Loop Indices of Systolic Function in Patients with Single Ventricle Physiology: A Preliminary Report

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Abstract

Background—Differences in ventricular geometry and physiology of patients with single ventricle anatomy complicate the application of traditional, noninvasive measurements of systolic function. We compared noninvasive measures of ventricular systolic function in single ventricle patients with invasive measures to evaluate their validity in this population.

Methods—A secondary analysis of patients with single ventricle physiology enrolled in the multi-institutional research project, “multi-scale modeling of single ventricle hearts,” was performed. Pressure–volume loops (PVLs) were recorded using microconductance catheters. Transthoracic echocardiogram and cardiac magnetic resonance imaging were performed on the same day. PVL indices of systolic function including end-systolic elastance (Ees), maximal rate of pressure increase (dP/dTmax), and stroke work indexed to end-diastolic volume (SW/EDV) were compared with noninvasive measures, including echocardiographic myocardial performance index (MPI), rate of pressure rise (AV valve dP/dT), isovolumic acceleration, longitudinal shortening fraction (longSF), and fractional area change (FAC).

Results—Fifteen patients had PVLs available for analysis. Eleven had a dominant right ventricle, three were status poststage 1 repair, five had superior cavopulmonary anastomosis, and

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Author Contributions

Drs. Baker, Buckley, Chowdhury, and Hlavacek all contributed in study design, data collection and analysis, interpretation of data, as well as drafting of manuscript and approval of final version.

Drs. Khambadkone and Hsia contributed to study design, interpretation of data, as well drafting of manuscript including approval of its final form.

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seven had a total cavopulmonary anastomosis. FAC correlated with Ees ($r = 0.69$, $P < .01$), SW/EDV ($r = 0.64$, $P = .01$), and dP/dTmax ($r = 0.59$, $P = .03$). LongSF correlated with dP/dTmax ($r = 0.61$, $P = .02$). MPI, AV valve dP/dT, and isovolumic acceleration did not correlate with pressure–volume loop indices of systolic function.

Conclusions—Obtaining PVLs via microconductance catheters can reliably be performed in the single ventricle population and serve as a method to validate echocardiographic indices in this high-risk population. Of the echocardiographic variables, FAC showed the best correlation with PVL indices. Future studies controlling for stage of palliation should be performed to further validate echocardiographic measures of systolic function in this patient population.

Keywords

Single Ventricle; Systolic Function; Echocardiography; Pressure–volume Loop; Ventricular Mechanics

Introduction

Advances in surgical techniques and medical management have greatly decreased mortality in patients born with single ventricle physiology.¹ Despite these advances, single ventricle patients still suffer from lower quality of life, decreased exercise capacity, worse neurodevelopmental outcome, increased need for heart transplantation, and many other morbidities.^{2–6} While patients with single ventricle physiology represent a small portion of all congenital heart disease (2–4%), they utilize a great deal of resources.^{7,8}

Applying traditional noninvasive measurements of cardiac function in patients with single ventricle physiology can be problematic given their unique and heterogeneous ventricular geometry.^{9–12} This leaves physicians with the difficult challenge of managing a high-risk population without validated, noninvasive measures of cardiac function. Pressure–volume loop (PVL) analysis is considered the gold standard for examining cardiac function; it is independent of the geometric assumptions inherent in most traditional noninvasive methods designed to describe “normal” left ventricular function. The lack of geometric assumption makes PVL analysis a well-suited modality for investigating cardiac function in single ventricle patients. The application of PVL analysis in congenital heart disease has successfully led to improved understanding of cardiac physiology in this population.^{13,14}

The aim of this study is to evaluate the validity of noninvasive echocardiographic measures of ventricular systolic function in single ventricle patients. Echocardiographic measures were compared with invasive pressure–volume loop measures of systolic function as part of a secondary analysis of patients enrolled in a multi-institutional study.¹⁵

Methods

Informed Consent

The protocol was approved by the Medical University of South Carolina institutional review board. Informed consent was obtained from the parent or legal guardian (age <18 years) or from the patient (age ≥18).

Patients

Fifteen patients enrolled in the multi-institutional multiscale modeling of single ventricle hearts for clinical decision support project with PVLs acquired via microconductance catheters were studied.¹⁵ Inclusion criteria included any patient with planned single ventricle palliation aged 0–40 years. Patients were excluded if they had a contraindication to performing an MRI or systemic and/or pulmonary venous abnormalities. All eligible patients were approached for participation prior to a planned surgical or catheterization procedure. All patients enrolled presented for routine catheterization per institutional protocol. For purposes of the study, Stage 1 patients were defined as patients with single ventricles who did not require surgery prior to superior cavopulmonary anastomosis or whose only cardiac surgery was a Norwood, pulmonary artery band or aortopulmonary shunt. Superior cavopulmonary connection patients were defined as having undergone one of the following surgeries: hemi-Fontan, bidirectional Glenn, or Kawashima. Total cavopulmonary connection patients were defined as those who had undergone an extracardiac or intracardiac Fontan procedure, with or without fenestration. Ventricular dominance was established by morphological characteristics of the largest ventricle, which was subjectively determined by echocardiography.

Pressure–volume Loop Data

Pressure–volume loops were obtained through direct measurement using 4-French microconductance catheters (CD Leycom, Zoetermeer, The Netherlands). In stage 1 and superior cavopulmonary connection patients, a microconductance catheter was placed in the systemic ventricle using an antegrade approach through the atrioventricular valve. A 5-French transseptal sheath was used to stabilize the catheter. In the total cavopulmonary connection patients, a microconductance catheter was placed into the single ventricle using a retrograde approach. Pressure–volume loops were obtained under general anesthesia during an expiratory hold. Careful attention was given to place the catheter in center of the ventricle and eliminate volume segments outside of the ventricle in the analysis.

Pressure–volume loop analysis was performed offline using a specialized software (ConductNT version 3.18, CD Leycom). Conductance volumes were calibrated using end-systolic and end-diastolic volumes obtained from MRI performed immediately before or after catheterization. The PVL indices were selected to represent different aspects of systolic function. To measure contractility, end-systolic elastance (E_{es}) was calculated using a previously described and validated single-beat technique.¹⁶ Briefly, the time-varying elastance curve during isovolumic contraction and ejection phase of the cardiac cycle is used to determine E_{es} . Maximum rate of pressure change (dP/dT_{max}) was used to quantify the isovolumic contraction phase of systole. Global assessment of cardiac work performed during an entire cardiac cycle was measured by stroke work (SW). SW was defined as the area enclosed by the PVL. To adjust for the wide size range of the study subjects, E_{es} was indexed to body surface area, and SW was indexed to end-diastolic volume (SW/EDV). All PVLs were analyzed by one single reviewer (RJB).

Echocardiographic Data

Transthoracic echocardiograms were performed using a Phillips iE33 system (Philips Medical Systems, Andover, MA, USA). All studies were obtained immediately prior to heart catheterization under general anesthesia with near-identical hemodynamic and physiologic states as cardiac catheterization measurements. The studies were performed by an experienced sonographer following a protocol which included a complete set of standardized views and Doppler tracings to evaluate ventricular mechanics. These included parasternal long axis, parasternal short axis, apical four-chamber, and subcostal views. All echocardiograms were then stored digitally, databased, and networked using Xcelera (Philips Medical Systems). All measurements were made off-line by a single reviewer (SC) and averaged over three beats. The echocardiographic indices were selected to represent different methods of measuring systolic function.

The single ventricular fractional area change (FAC) was defined as $(\text{end-diastolic area} - \text{end-systolic area}) / \text{end-diastolic area}$. The rate of pressure rise in the ventricle (AV valve dP/dt) was measured from the ascending limb of the dominant atrioventricular valve regurgitation continuous-wave Doppler signal between 100 and 300 cm/s. Pulsed tissue Doppler imaging at the lateral aspect of the dominant AV valve annulus was obtained from the apical four-chamber view. Myocardial performance index (MPI) was measured using tissue Doppler imaging of the free wall AV valve annulus and calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. Isovolumic acceleration was measured by dividing the peak myocardial isovolumetric contraction velocity by the acceleration time. Single ventricle longitudinal shortening fraction (longSF) was defined as difference between the single ventricle diastolic length and systolic length divided by the single ventricle diastolic length.

Magnetic Resonance Imaging

Each MRI was performed using a 1.5 Tesla scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany) using a standardized protocol including cine imaging, phase contrast analysis, magnetic resonance angiography, and respiratory-navigated 3D imaging. The cine imaging included retrospectively gated, balanced steady-state free-precession cine images in the vertical long axis, four chamber, and short axis covering the entirety of the systemic ventricle. Assessment of single ventricle volumes was performed by manual segmentation of short-axis cine images at end diastole and end systole (Argus; Siemens Medical Systems). Cine images were acquired during end-expiratory breath hold, similar to PVL acquisition. End diastolic and end systolic volumes were calculated by use of the modified Simpson's rule, and from these volumes, stroke volume and ejection fraction were calculated. Per the standard practice at our institution, all patients under the age of 10 were scanned under general anesthesia. In those patients, the MRI was performed immediately after the catheterization procedure, under the same general anesthesia. Older patients (age ≥ 10) were scanned while awake, immediately prior to the catheterization.

Statistical Analysis

Correlations between echocardiographic data and pressure-volume loop analysis were investigated using the Spearman correlation test given the small sample size. Nonparametric

statistics were used to compare echocardiographic and PVL data between stages of palliation and ventricular morphology. A P value of .05 or less was considered statistically significant. All statistics were performed using IBM SPSS Statistics software v. 21 (Armonk, NY, USA).

Results

Patient characteristics and hemodynamics from catheterization are summarized in Table 1. In summary, of the 15 patients, 11 had a dominant right ventricle, three were stage 1, five had a superior cavopulmonary connection, and seven had a total cavopulmonary connection. The age ranged from 3 months to 19 years (median 3 years).

Fourteen/15 patients enrolled in the study had adequate microconductance catheter recordings to perform PVL analysis. Since PVLs were done during expiratory breath hold, there was a very little variability between beats (Figure 1). Pressure–volume loop data did not differ between right and left ventricular dominance (Table 2). Total cavopulmonary connection patients trended toward having a higher Ees than superior cavopulmonary connection and shunted single ventricle patients (2.33 vs. 1.53 vs. 1.70, $P = .06$).

Patient 9 (superior cavopulmonary connection, LV-dominant ventricle) had inadequate echocardiographic images to calculate MPI, isovolumic acceleration, FAC, and AV valve dP/dT. Two other patients (3 and 6) had an inadequate AV valve regurgitation to perform AV valve dP/dT measurement. Patient 6 had incomplete tissue Doppler acquisition to calculate isovolumic acceleration. Therefore, 12 patients had AV valve dP/dT measured, 14 had FAC, 14 had MPI, and 13 had isovolumic acceleration. There were no differences between echocardiographic indices compared between stages of repair as well as ventricular morphology (Table 3) except that RV-dominant patients had a lower median iso-volumic acceleration of 167 cm/s² (range 112–240) vs. 335 cm/s² (range 300–370), $P = .03$.

Correlations between microconductance data and noninvasive measures are summarized in Table 4. FAC correlated with Ees, dP/dT max, and SW/EDV ($r = 0.69$, $P < .01$; $r = 0.60$, $P = .03$; and $r = 0.64$, $P = .01$, respectively). LongSF had a correlation with dP/dTmax ($r = 0.61$, $P = .02$) and trended toward a correlation with Ees ($r = 0.52$, $P = .06$). There were no statistically significant correlations between pressure–volume loop data and MPI, AV valve dP/dT, or isovolumic acceleration.

Discussion

Comparisons between conductance catheter-derived PVLs and noninvasive measures of ventricular function in patients with biventricular circulation have been performed.^{17–23} These studies have helped describe the utility of noninvasive measures of ventricular function.^{17,18,22} This study is the first to compare PVL indices derived from conductance catheters with noninvasive measures of systolic function in patients with single ventricle physiology.

The total cavopulmonary connection patients had a higher Ees than superior cavopulmonary connection patients, which would suggest improvement in contractility after total

cavopulmonary connection is performed. This agrees with the findings of a previous longitudinal study showing improvement in noninvasive estimation of contractility after total cavopulmonary connection surgery.²⁴ The small number of patients with left ventricular morphology makes comparison of PVL indices between the two populations difficult. Previous studies have highlighted the difference in ventricular function between patients with single left ventricles vs. single right ventricles, and therefore, the lack of difference in our study population is most likely due to small study population.^{6,25}

Interestingly, the Doppler-derived, geometry-independent measures of systolic function, MPI, AV valve dP/dT, and isovolumic acceleration did not correlate well with PVL measures of systolic function. A previous multicenter study of single ventricle patients found no correlation between MPI and MRI ejection fraction and only a weak correlation between AV valve dP/dT and MRI ejection fraction.²⁶ In accordance with previous studies, our findings suggest that current Doppler-derived indices may not be robust measures of systolic function in single ventricle patients.

Despite the abnormal ventricular geometry encountered in patients with single ventricles, FAC of the systemic single ventricle correlated well the three PVL systolic measures. FAC has been shown to correlate with PVL indices of systolic function in adults with biventricular circulation.²⁰ Therefore, it seems possible that FAC is a good echocardiographic measure of global systolic function in the single ventricle population.

These initial findings highlight the importance of further comparison of routinely used echocardiographic measures in single ventricle patients with PVL analysis. Given the abnormal geometry and heterogeneity of ventricular morphology in patients with single ventricles, it is reasonable to hypothesize that geometry-independent, Doppler-derived measures of systolic function would correlate best with PVL indices of systolic function. However, the three Doppler-derived measures had no correlation with PVL indices. Since echocardiographic measures, including Doppler-derived indices of function, are often primary or secondary endpoints in therapeutic studies of single ventricle patients, appropriate validation of these measures is essential to further clinical research.^{27,28} Lack of associations may be due to small study population, especially when considering AV valve dP/dT. AV valve dP/dT had an *r* value greater than 0.6 with PVL dP/dT max and SW/EDV but did not reach a statistical significance. A larger study population may have led to a statistical significance between AV valve dP/dT and PVL indices dP/dTmax and SW/EDV.

Our study utilized FDA-approved microconductance catheters to construct PVLs. However, this is a costly option for research studies and is impractical for routine clinical use. Pressure–volume loops and pressure–volume-derived indices of systolic function have also been measured using noninvasive techniques.²⁹ Employing these techniques may be the key to best describing systolic function in this population. Therefore, we advocate for further investigation of noninvasive PVL indices in single ventricle patients.

Limitations

Our study population is relatively small and, therefore, may have had inadequate power to elucidate all of the relevant correlations. Second, due the small study population, we were

not able to perform a multivariable analysis to control for ventricular morphology, stage of palliation, or other patient characteristics. Differences between PVL indices of systolic function in different stages of single ventricle palliation and ventricular morphology may exist and were not elucidated due to the small study population. Due to concerns of patient safety, volume reduction was not performed during microconductance catheter data acquisition. Therefore, Ees was not directly measured. However, previous studies have shown good correlation between single beat estimations of Ees and volume reduction derived Ees in single ventricle animal models.²⁴ Our study divided up systolic function into three distinct parts: contractility (measured by Ees), isovolumic contraction (measured by dP/dTmax), and global ventricular mechanics (measured by SW/EDV). These partitions are arbitrary, and it is important to recognize that improvement in one area will lead to changes in other measures. For instance, an increase in contractility, demonstrated by an increase in Ees, would lead to an increase in SW and would likely lead to a faster rate of pressure rise during isovolumic contraction. MRI-derived end-diastolic and end-systolic volumes were used to volume calibrate the microconductance catheters. Therefore, comparisons between MRI ejection fraction and PVL indices of systolic function would have been significantly biased. Thus, the current gold standard of noninvasive systolic function in single ventricles, MRI ejection fraction, was not compared with PVL indices of systolic function.

Conclusions

Initial results indicate that FAC correlates with microconductance catheter-derived pressure–volume loop indices of systolic function. MPI and isovolumic acceleration did not correlate well with PVL measures of systolic function. Larger studies should be performed to confirm our findings and control for additional patient characteristics, such as ventricular morphology and stage of palliation.

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Figure 1.

A representative pressure–volume loop with pressure in mm Hg on the y-axis and volume in milliliters on the x-axis. There is very little change in the pressure–volume loop between beats.

Table 1

Patient Characteristics and Hemodynamic Cath

Patient	Palliation Stage	Diagnosis	Age (Years)	Body Surface Area (m ²)	Arterial Saturation (%)	Mixed Venous Saturation (%)	PVRI (Units x m ²)	EDP (mm Hg)	AV Valve Regurgitation [†]	MRI EF (%)
1*	SHUNT	HLHS	0.4	0.3	71	56	2.6	7	0	70
2	TCPC	HLHS	17.9	1.8	93	66	2.2	10	1	58
3	SHUNT	TA	0.3	0.26	72	42	3.3	10	0	61
4	TCPC	HLHS	19.3	1.4	91	66	1.7	12	1	72
5	SCPC	HLHS	3.6	0.6	89	65	1.4	7	2	51
6	SHUNT	PA/IVS	0.4	0.3	78	58	1.9	7	0	71
7	SCPC	HLHS	7.8	0.7	86	65	2.7	5	1	43
8	SCPC	HLHS	2.3	0.53	72	55	2.1	8	1	59
9	SCPC	DILV	2.6	0.53	75	54	0.8	10	0	50
10	SCPC	HLHS	3	0.54	77	59	2.4	12	2	32
11	TCPC	HLHS	4.7	0.67	91	64	1.9	8	0	67
12	TCPC	TA	17.4	2.14	92	77	1.53	12	2	63
13	TCPC	HLHS	4.5	0.77	83	65	1.66	9	1	64
14	TCPC	HLHS	3.8	0.62	88	68	1.39	10	1	58
15	TCPC	HLHS	7.4	0.88	93	73	0.99	10	1	40

* Denotes patient with inadequate pressure-volume loop acquisition for analysis.

[†] 0 = none/trivial, 1 = mild, 2 = moderate, 3 = severe.

DILV, double-inlet left ventricle; HLHS, hypoplastic left heart syndrome; PA/IVS, pulmonary atresia with intact ventricular septum; SCPC, superior cavopulmonary anastomosis; TA, tricuspid atresia; TCPC, total cavopulmonary anastomosis.

Table 2

Pressure-volume Loop Data

Measurement	LV Dominant	RV Dominant	P Value	Stage 1	Superior Cavopulmonary Anastomosis	Total Cavopulmonary Anastomosis	P value
Ees (mm Hg/mL $\times$ m ²)	2.9 (1.5–2.7)	2.1 (1.4–4.9)	1	1.7 (1.53–1.87)	1.53 (1.39–2.70)	2.33 (1.99–4.90)	.06
SW/EDV (mm Hg)	40.9 (35.0–62.1)	36.9 (20.9–63.9)	.49	38.6 (24.6–43.2)	27.9 (24.3–63.9)	49 (20.9–62.1)	.44
dP/dTmax (mm Hg/s)	833 (781–870)	887 (613–1221)	.41	870 (813–1036)	829 (643–1183)	887 (613–1221)	.62

Data shown are median (range).

dP/dTmax, maximal rate of pressure increase; Ees, end-systolic pressure volume ratio indexed to body-surface area; ESPVR/Ea, end-systolic pressure volume ratio divided by end-arterial elastance; LV, left ventricle; RV, right ventricle; SW/EDV, stroke work divided by end-diastolic volume.

Table 3

Echocardiographic Variables

Measurement	LV Dominant	RV Dominant	P Value	Stage 1	Superior Cavopulmonary Anastomosis	Total Cavopulmonary Anastomosis	P value
MPI	0.53 (0.31–0.53)	0.55 (0.48–0.76)	.37	0.48 (0.31–0.53)	0.69 (0.35–0.68)	0.67 (0.5–1.2)	.1
IVA	335 (300–370)	167 (125–217)	.03	333 (227–440)	131 (112–217)	196 (115–300)	.14
Fractional area change	0.4 (0.25–0.44)	0.4 (0.29–0.43)	1	0.4 (0.25–0.43)	0.29 (0.18–0.43)	0.42 (0.3–0.55)	.24
AV valve dP/dT	1731*	845 (727–1435)		1435 [†]	744 (683–2272)	983 (845–1731)	
SV longSF	0.18 (0.14–0.22)	0.17 (0.09–0.26)	.75	0.17 (0.14–0.2)	0.17 (0.94–0.22)	0.19 (0.12–0.26)	.68

* Only one LV-dominant patient with adequate AV valve regurgitation for analysis; therefore, statistical comparisons were not performed.

[†] Only one patient with AV valve dP/dT measured in stage 1 palliation; therefore, statistical analysis was not performed.

AV valve dP/dT, rate of pressure rise in dominant ventricle; IVA, isovolumic acceleration; LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; SV longSF, single ventricle longitudinal shortening fraction.

Table 4

Pressure–volume Data and Echocardiographic Data Correlations

	Ees	dP/dT Max	SW/EDV
Single ventricle longitudinal shortening fraction	$r = 0.52$ $P = .06$ $n = 14$	$r = 0.61$ $P = .02$ $n = 14$	$r = 0.27$ $P = .33$ $n = 14$
Myocardial Performance Index	$r = 0.35$ $P = .24$ $n = 13$	$r = -0.31$ $P = .27$ $n = 13$	$r = 0.02$ $P = .94$ $n = 13$
Isovolumetric acceleration	$r = -0.09$ $P = .78$ $n = 12$	$r = -0.01$ $P = .99$ $n = 12$	$r = 0.27$ $P = .37$ $n = 12$
Fractional area change	$r = 0.69$ $P = <.01$ $n = 13$	$r = 0.6$ $P = .03$ $n = 13$	$r = 0.64$ $P = .01$ $n = 13$
AV valve dP/dT	$r = 0.53$ $P = .22$ $n = 11$	$r = 0.64$ $P = .09$ $n = 11$	$r = 0.67$ $P = .07$ $n = 11$

AV valve dP/dT, rate of pressure rise in dominant ventricle; dP/dTmax, maximal rate of pressure rise; Ees, end-systolic elastance; SW/EDV, stroke work indexed to end-diastolic volume.