The Effect of the Superior Cavopulmonary Anastomosis on Ventricular Remodeling in Infants with Single Ventricle

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Background: Infants with single ventricular physiology have volume and pressure overload that adversely affect ventricular mechanics. The impact of superior cavopulmonary anastomosis (SCPA) on single left ventricles versus single right ventricles is not known.

Methods: As part of the Pediatric Heart Network placebo-controlled trial of enalapril in infants with single ventricular physiology, echocardiograms were obtained before SCPA and at 14 months and analyzed in a core laboratory. Retrospective analysis of the following measurements included single ventricular end-diastolic volume (EDV), end-systolic volume (ESV), mass, mass-to-volume ratio (mass/volume), and ejection fraction. Qualitative assessment of atrioventricular valve regurgitation and assessment of diastolic function were also performed.

Results: A total of 156 participants underwent echocardiography at both time points. Before SCPA, mean ESV and mass *Z* scores were elevated (3.4 ± 3.7 and 4.2 ± 2.9, respectively) as were mean EDV and mass/volume *Z* scores (2.1 ± 2.5 and 2.0 ± 2.9, respectively). EDV, ESV, and mass decreased after SCPA, but mass/volume and the degree of atrioventricular valve regurgitation did not change. Subjects with morphologic left ventricles demonstrated greater reductions in ventricular volumes and mass than those with right ventricles (mean change in *Z* score: left ventricular [LV] EDV, −1.9 ± 2.1; right ventricular EDV, −0.7 ± 2.5; LV ESV, −2.3 ± 2.9; right ventricular ESV, −0.9 ± 4.6; LV mass, −2.5 ± 2.8; right ventricular mass, −1.3 ± 2.6; $P \leq .03$ for all). Approximately one third of patients whose diastolic function could be assessed had abnormalities at each time point.

Conclusions: Decreases in ventricular size and mass occur in patients with single ventricle after SCPA, and the effect is greater in those with LV morphology. The remodeling process resulted in commensurate changes in ventricular mass and volume such that the mass/volume did not change significantly in response to the volume-unloading surgery. (J Am Soc Echocardiogr 2017;30:699-707.)

Keywords: Single ventricle, Systolic ventricular function, Diastolic ventricular function, Ventricular remodeling, Superior cavopulmonary anastomosis, Congenital heart disease

In neonates and infants with single ventricle (SV) heart disease, the functioning ventricle must support both the systemic and pulmonary circulations, resulting in volume and pressure overload. One major aim in the surgical management of these patients is to mitigate the impact of the chronic volume overload that can lead to ventricular dilation and hypertrophy and ultimately to decreased systolic function. One of the effects of the superior cavopulmonary anastomosis (SCPA) procedure is to decrease the ventricular volume overload

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Abbreviations

AVV = Atrioventricular valve

AVVR = Atrioventricular valve regurgitation

EDV = End-diastolic volume

EF = Ejection fraction

ESV = End-systolic volume

ISV = Infant single ventricle

LV = Left ventricular

Mass/volume = Mass-to-volume ratio

RV = Right ventricular

SCPA = Superior cavopulmonary anastomosis

SV = Single ventricle

SVC = Superior vena cava

V_{fp} = Ventricular flow propagation

by directing systemic venous blood from the upper part of the body to the lungs, bypassing the SV. The SCPA procedure has been shown to reduce the incidence of systolic ventricular dysfunction in SV patients by providing an incremental decrease in volume overload early in infancy.[1-3]

Several investigators have attempted to define the changes in ventricular volumes, systolic function, and mass-to-volume ratio (mass/volume) in SV patients in small case series.[3-5] Others have made an effort to characterize changes in diastolic function.[6] Each of these studies has used different methods of assessment, precluding comparisons of the groups studied. Most reports focus on patients with left ventricular (LV) morphology, and if patients with LV and right ventricular (RV) morphologies are included, the results are typically combined for analysis.

The National Heart, Lung, and Blood Institute–sponsored Pediatric Heart Network completed a multicenter randomized placebo-controlled trial of the angiotensin-converting enzyme inhibitor enalapril in infants with single ventricular physiology, the Infant Single Ventricle (ISV) study.[7] Clinical and echocardiographic data were prospectively gathered on all subjects. No difference was found in the primary outcome of weight-for-age *Z* score or in ventricular volumes, mass, or ejection fraction (EF) between the placebo and enalapril-treated groups. Using this large, well-characterized cohort, we sought to describe the changes in LV and RV geometry and systolic function that occur in response to SCPA surgery, to explore factors that are associated with those changes, and to characterize diastolic function in infants with single ventricular physiology.

METHODS

Details of the study design and main results of the ISV trial have been published.[7,8] In brief, infants with single ventricular physiology were enrolled between 7 and 45 days of age, across 10 North American centers, between August 2003 and May 2007. Subjects were included if they had stable hemodynamics and if they were anticipated to undergo SCPA surgery. The trial followed subjects through the SCPA surgery to the final study visit at 14 months of age. Written informed consent was obtained from a parent or guardian. The study was approved by the institutional review or ethics board at each participating institution.

Patient data collected included detailed anatomic diagnosis, age at enrollment and at SCPA surgery, gestational age, gender, race, medication history, and medical and surgical data from the SCPA procedure. Ventricular morphology was characterized as LV dominant (e.g., tricuspid atresia) or RV dominant (e.g., hypoplastic left heart syndrome). Patients with indeterminate or mixed ventricular morphology (e.g., unbalanced atrioventricular canal defects with two ventricles present) were not included in the RV-LV comparison analyses for this report.

Echocardiographic Data

A detailed quantitative echocardiographic evaluation was performed, including ventricular volumes and systolic and diastolic function, at two time points during the study: before SCPA and at 14 months (final study visit). Sedation was used according to local practice. Echocardiography was performed according to a prospective, standardized imaging protocol, and studies were sent to the echocardiographic core laboratory for interpretation by a single reader.

The systemic ventricle was imaged from the apical (ventricular long-axis) and parasternal short-axis planes. The endocardial border was traced at end-diastole and end-systole; the epicardial border was traced at end-diastole in both planes. End-diastolic volume (EDV), end-systolic volume (ESV), and mass were then calculated using a modified Simpson biplane method.[9] The percentage ventricular EF was calculated as [(EDV − ESV)/EDV] × 100. Ventricular mass was calculated as myocardial EDV (epicardial volume − endocardial volume) × myocardial density (1.05 g/mL). Inter- and intraobserver variabilities for this method of assessing morphologic SVs have been reported previously.[9] The degree of atrioventricular valve (AVV) regurgitation (AVVR) was qualitatively assessed and grouped as none/mild or moderate/severe.

Doppler assessment of AVV inflow was performed for E, A, early deceleration time, and a-wave duration. If the AVV inflow demonstrated partially fused E and A waves, which is common at infant heart rates, only the E velocity was recorded. If the waveforms were completely fused, no Doppler measurements were used. Doppler tissue imaging of annular myocardial velocities recorded E′ and A′ diastolic velocities at the two walls, which were averaged. Similar to AVV inflow assessment, if the tissue Doppler tracing demonstrated partial E′ and A′ fusion, only E′ velocity was recorded, and no measurements were used if E′ and A′ were completely fused. Figure 1 depicts examples of AVV inflow waveform fusion, and Figure 2 shows examples of Doppler tissue imaging waveform fusion. Figure 3 demonstrates the effect of the R-R interval on fusion of the waveforms. Duration of pulmonary vein flow reversal and ventricular flow propagation (V_{fp}) were also recorded. E/E′ values > 10 and V_{fp} values > 45 were considered abnormal.[10]

Echocardiographic data were reviewed and measurements made using custom software (Marcus Laboratories, Boston, MA).

Statistical Analysis

The data used in the analyses were obtained in a prospective manner; the analyses reported here were retrospectively proposed and implemented. To adjust echocardiographic measurements to account for the effect of body size (volume, mass) and age (EF, Doppler variables), *Z* score values were used.[11] *Z* score calculations were derived from the systemic left ventricle in a group of normal control subjects; the ventricular size and function *Z* scores used are therefore based on systemic LV measurements.

Data are described as frequencies, medians with 25th and 75th percentile values, and means with SDs as appropriate. For some of the evaluations below, echocardiograms with partial data were included; each section lists the number of subjects included for subanalysis. Echocardiographic measurements of the LV and RV groups were compared using Student's *t* test for nonskewed variables and the Wilcoxon rank sum test for other measures. In the subset of

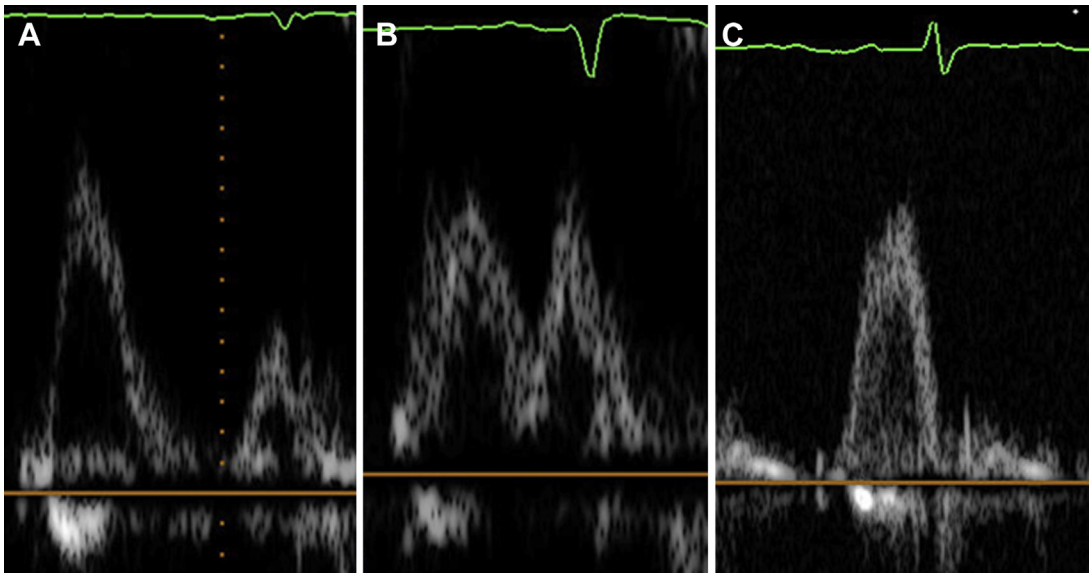

Figure 1 AVV Doppler E- and A-wave fusion: **(A)** nonfused E and A waves; **(B)** partial fusion of E and A waves; **(C)** complete fusion of E and A waves.

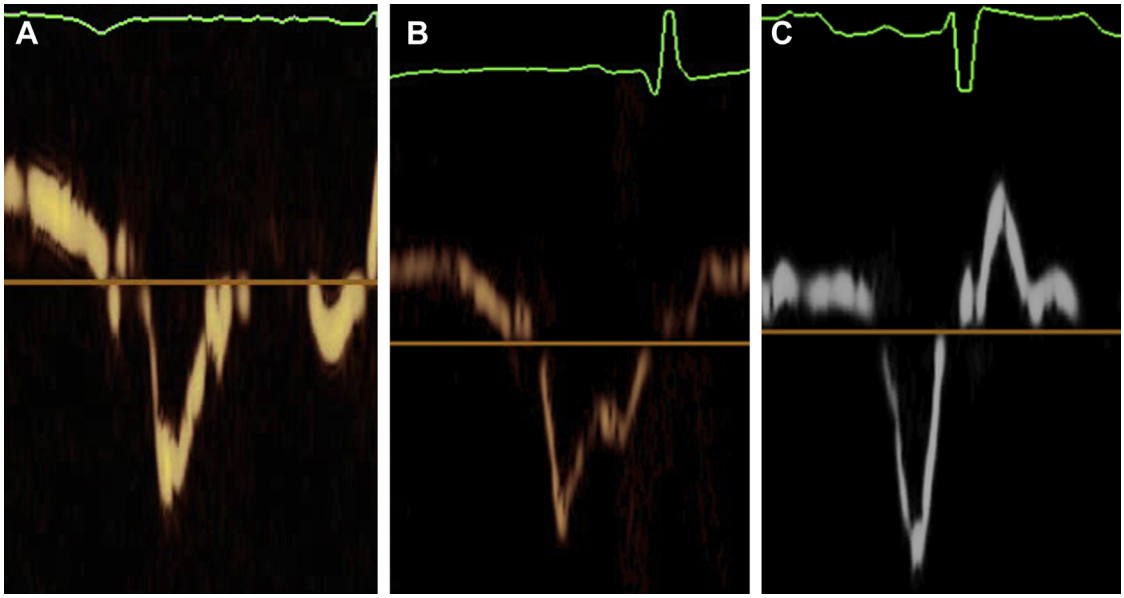

Figure 2 Doppler tissue imaging at the atrioventricular annulus E′ and A′ fusion: **(A)** nonfused E′ and A′ waves; **(B)** partial fusion of E′ and A′ waves; **(C)** complete fusion of E′ and A′ waves.

patients who had complete data available at both the pre-SCPA and 14-month time points, the distributions of changes in ventricular size and function were compared with the normal population mean of zero using the one-sample *t* test. The changes in AVVR between the two time points were assessed using the McNemar test. The Fisher exact and Mantel-Haenszel χ^2 tests for linear trend were used to evaluate the effect of enalapril on the ventricle and to compare the changes in subjects with single right ventricles with those in subjects with single left ventricles. Subgroup analyses of treatment effect on changes in mass-volume *Z* scores were performed between single left ventricle and single right ventricle (subgroups prespecified in the ISV trial) subjects. LV-RV group-by-treatment interaction tests were used to assess the treatment effect across subgroups. Generalized additive models were used to account for nonlinearity in regression models.

Data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). *P* values $< .05$ were considered to indicate statistical significance.

RESULTS

Patient Population

Of the 230 subjects randomized for the main trial, 28 were withdrawn before the pre-SCPA visit, and 14 subjects did not undergo

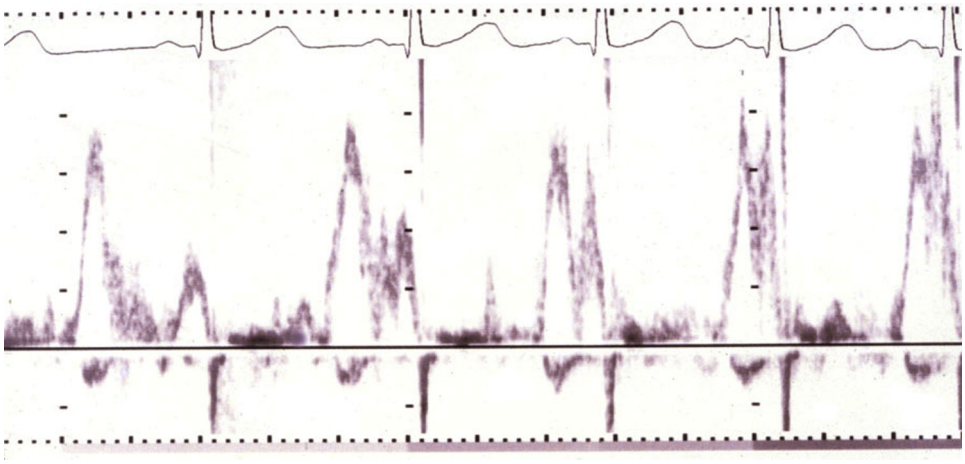

Figure 3 AVV inflow Doppler strip demonstrating that as the R-R interval shortens, the E and A waves become increasingly fused.

Table 1 Ventricular geometry and systolic function variables: pre-SCPA and 14-month visits and changes between them (ventricular types combined)

	Calculated values		*Z* score*			
	Pre-SCPA	14 months	Pre-SCPA	14 months	Change in *Z* score‡	
Variable	Mean ± SD (*n*)	Mean ± SD (*n*)	Mean ± SD (*n*)	Mean ± SD (*n*)	Mean ± SD (*n*)	*P*†
EDV (mL)	23.5 ± 9.6 (160)	29.8 ± 10.7 (163)	2.1 ± 2.5 (157)	1.2 ± 2.2 (163)	−1.0 ± 2.5 (153)	<.001
ESV (mL)	10.2 ± 5.4 (160)	12.7 ± 7.2 (163)	3.4 ± 3.7 (157)	2.2 ± 3.7 (163)	−1.2 ± 4.1 (153)	<.001
Mass (g)	26.2 ± 9.2 (158)	32.2 ± 10.3 (161)	4.2 ± 2.9 (155)	2.6 ± 2.3 (161)	−1.6 ± 2.6 (151)	<.001
EF (%)	57.4 ± 9.3 (160)	58.8 ± 9.9 (163)	−1.1 ± 1.8 (160)	−0.8 ± 1.9 (163)	0.3 ± 2.3 (156)	.02
Mass/volume (g/mL)	1.2 ± 0.5 (158)	1.2 ± 0.4 (161)	2.0 ± 2.9 (158)	1.6 ± 2.6 (161)	−0.2 ± 3.0 (154)	.33

*Three subjects were missing weight measurements at the time of echocardiography, precluding *Z* score assignment for EDV, ESV, and mass.
†To compare the distributions of change scores in our SV sample with the normal population mean of zero, we used the Wilcoxon signed rank test for EF and the one-sample *t* test for all other changes in *Z* scores.
‡*Z* score at the 14-month visit minus *Z* score at the pre-SCPA visit.

SCPA. The remaining subjects underwent SCPA as follows: 134 had bidirectional cavopulmonary anastomoses, 28 had bilateral bidirectional cavopulmonary anastomoses, and 26 had hemi-Fontan procedures. A total of 156 subjects had complete studies at both time points. Briefly with regard to the surgical procedures, bidirectional SCPA involves dividing the superior vena cava (SVC) from the heart, oversewing the cardiac end, and attaching the SVC to the right pulmonary artery in an end-to-side fashion. A bilateral bidirectional SCPA is required when there is a persistent left-sided SVC in addition to the usual right-sided SVC. In this procedure, both cavae are removed from the heart and sewn end to side to the branch pulmonary arteries. A hemi-Fontan is a modification of the SCPA procedure performed by some surgeons in which both cranial and cardiac ends of the SVC are anastomosed to the superior and inferior surfaces of the right pulmonary artery, and a patch is placed to occlude the SVC–right atrial orifice. The intent of this modification is to streamline the subsequent Fontan procedure. The hemodynamic impact of all of these procedures (bidirectional SCPA, bilateral bidirectional SCPA, and hemi-Fontan) is the same. By directing venous return from the SVC(s) directly to the pulmonary arteries, a portion of the volume load on the SV is removed, while allowing reasonable pulmonary blood flow.

For the entire group, the median age at the time of SCPA and the time from SCPA to the 14-month visit were 5.3 months (range, 2.3–14.9 months) and 8.9 months (range, 1.7–11.9 months), respectively. Male subjects constituted 46% of the cohort; 81% were classified as white, 13% as black, and 6% as "other"; 13% reported their ethnicity as Hispanic. RV-dominant morphology was present in 71%.

Changes in Ventricular Geometry, Systolic Function, and AVVR between the Pre-SCPA and 14-Month Time Points

Calculated values for ventricular volumes, mass, mass/volume, and EF for the entire cohort at each time point are shown in Table 1; the *Z* scores for the group and the changes in *Z* scores between the two time points are also shown. Mean *Z* scores for ventricular EDV, ESV, mass, and mass/volume were all >2 at the pre-SCPA visit. EDV, ESV, and mass all demonstrated decreases in *Z* scores between the pre-SCPA and 14-month visits. Mass/volume did not significantly change between the two time points. EF demonstrated a statistically significant but small improvement.

To evaluate the change in AVVR between the pre-SCPA and 14-month time points, subjects were grouped into two categories: none/mild AVVR and moderate/severe AVVR. Excluding six subjects who underwent atrioventricular valvuloplasty at the time of SCPA, 161 subjects had AVVR assessments at both time points, including 132 subjects with no change in the degree of AVVR between the two time points. Before SCPA surgery, 35 subjects (22%; 29 RV,

Table 2 Ventricular geometry and systolic function variables by ventricular type: *Z* scores at the pre-SCPA and 14-month time points and changes between them

	LV *Z* score		RV *Z* score		Change in *Z* scores (value at 14 months minus value at pre-SCPA)			
	Pre-SCPA Mean ± SD (*n*)	14 mo Mean ± SD (*n*)	Pre-SCPA Mean ± SD (*n*)	14 mo Mean ± SD (*n*)	Left ventricle Mean ± SD (*n*)	Right ventricle Mean ± SD (*n*)	Mean difference*	*P*†
EDV	2.8 ± 2.4 (32)	0.9 ± 1.5 (33)	2.0 ± 2.6 (111)	1.3 ± 2.4 (114)	−1.9 ± 2.1 (32)	−0.7 ± 2.5 (108)	−1.2	.01
ESV	4.2 ± 3.2 (32)	1.9 ± 2.0 (33)	3.4 ± 4.0 (111)	2.6 ± 4.2 (114)	−2.3 ± 2.9 (32)	−0.9 ± 4.6 (108)	−1.4	.03
Mass	4.5 ± 3.1 (32)	2.2 ± 1.9 (33)	4.0 ± 2.9 (109)	2.7 ± 2.4 (114)	−2.5 ± 2.8 (32)	−1.3 ± 2.6 (107)	−1.2	.03
EF	−1.2 ± 1.2 (33)	−0.9 ± 1.5 (33)	−1.2 ± 2.0 (113)	−0.9 ± 2.1 (114)	0.3 ± 1.7 (33)	0.3 ± 2.6 (110)	0.0	.98
Mass/volume	1.3 ± 2.2 (33)	1.2 ± 1.5 (33)	1.9 ± 2.8 (111)	1.6 ± 2.8 (114)	−0.1 ± 2.6 (33)	−0.3 ± 3.1 (109)	0.2	.76

*LV mean minus RV mean.
†*t* test.

four LV, and two mixed) had moderate/severe AVVR. Of these, 16 (15 RV and one LV) had continued moderate/severe AVVR at the 14-month visit, while 19 (14 RV, three LV, and two mixed) improved to none/mild. Of 126 subjects with none/mild AVVR before SCPA, 10 progressed to moderate/severe AVVR (six RV and four LV) at the 14-month visit; these findings were statistically not significant ($P = .095$, McNemar test).

Comparison of the Effect of Angiotensin-Converting Enzyme Inhibition versus Placebo on Changes in Ventricular Size and Function

Of the subjects who underwent SCPA and who had paired echocardiographic data for ventricular size and function, 79 were on enalapril therapy and 77 were assigned to placebo. No significant difference was seen between the treatment groups in terms of change in EDV, ESV, ventricular mass, EF, or mass/volume. We also found no difference in the changes in AVVR between the two study visits by treatment arm, reported previously.[7]

Changes in Ventricular Geometry and Function in Subjects with Single Right Ventricles Compared with Single Left Ventricles

Table 2 includes the *Z* scores for the ventricular characteristics for LV versus RV morphology and the changes in *Z* scores between the two time points. The raw data are presented in Supplemental Table 1 (available at www.onlinejase.com). As assessed by change in EDV, ESV, and ventricular mass, single right ventricles and single left ventricles differed in their response to volume unloading at SCPA. Greater absolute and relative declines in *Z* scores (indicating more movement toward the mean) for these parameters were noted for left ventricles than right ventricles, secondary to all three variables' having higher values for left ventricles versus right ventricles before SCPA and all three variables' having lower values for left ventricles versus right ventricles at 14 months. Of note, there was no difference in age at SCPA, follow-up time or incidence of coarctation in the RV group relative to the LV group in our cohort to explain these findings.

We then sought to determine whether the differences in response to SCPA that were seen between the ventricular subtypes were related to treatment group (enalapril vs placebo) by performing a subgroup analysis by treatment. These results are presented in Table 3. The interaction *P* values ranged from .11 to .95, indicating that there was no significant effect of enalapril on the changes in *Z* scores between right and left ventricles. In fact, the largest overall changes occurred in the placebo group, not the enalapril group.

Impact of Age at Time of SCPA on Changes in *Z* Scores

The median age at SCPA surgery was 5.3 months (interquartile range, 4.3–6.2 months). For the group as a whole, the median time from SCPA to the 14-month visit was 8.9 months (range, 1.7–11.9 months). No association between age at SCPA surgery and the change in ventricular mass, EDV, ESV, EF, or mass/volume *Z* score was found using age as a continuous variable in linear modeling. When age at SCPA surgery was used categorically in a nonparametric model (age < 5, 5–7, and >7 months; the cutoffs are based on general additive models with nonlinear fits), a significant association with ventricular mass *Z* score was identified. A smaller decrease (i.e., less normalization) in mass *Z* score was found in patients undergoing SCPA at >7 months of age. However, there was a difference in the median time from SCPA to the 14-month visit: 9.7, 8.4, and 6.0 months for the respective age groups, suggesting that the remodeling response may have been incomplete for patients undergoing later SCPA.

Characterization of Diastolic Function

Descriptive values for diastolic function assessment are presented in Table 4. Because of the high incidence of fused E/A waves and E′/A′ waves, evaluation of diastolic function was limited to assessment of E/E′ and V_{fp} (Table 4). We found no significant difference in the number of subjects with abnormal E/E′ and V_{fp} between the pre-SCPA and 14-month time points. Approximately one third of the subjects had abnormal values for both parameters at the pre-SCPA visit and at the 14-month visit, consistent with abnormal diastolic function.

DISCUSSION

This study is one of the first to provide a range of quantitative values and to use *Z* scores for systematic assessment of ventricular volumes and systolic function in a large cohort of infant SV patients. Before SCPA, the mean EDV, ESV, mass, and mass/volume *Z* scores were >2, confirming that patients with single ventricular physiology have ventricles that are more dilated and concentrically hypertrophied than patients with normal biventricular cardiac anatomy. We found that after SCPA, the mean ESV and mass *Z* scores were still >2 for the group as a whole but had decreased from their pre-SCPA values, while the mean EDV and mass/volume *Z* scores decreased below 2.

Table 3 Changes in ventricular geometry and systolic function *Z* scores between pre-SCPA and 14-month visits by ventricular type, stratified by treatment group

Change in mass/volume *Z* score* by treatment arm	LV Δ *Z* score Mean ± SD (*n*)	RV Δ *Z* score Mean ± SD (*n*)	Mean difference between left and right ventricles†	*P*‡	ANOVA interaction *P* value§
EDV					.40
Enalapril	−1.86 ± 2.12 (18)	−1.05 ± 2.64 (53)	−0.81	.22	
Placebo	−2.01 ± 2.05 (14)	−0.37 ± 2.38 (55)	−1.64	.009	
ESV					.37
Enalapril	−1.92 ± 2.23 (18)	−1.24 ± 4.86 (53)	−0.68	.27	
Placebo	−2.87 ± 3.65 (14)	−0.57 ± 4.01 (55)	−2.3	.009	
Mass					.11
Enalapril	−1.58 ± 2.57 (18)	−1.14 ± 2.63 (53)	−0.44	.48	
Placebo	−3.62 ± 2.65 (14)	−1.48 ± 2.57 (54)	−2.14	.01	
EF					.48
Enalapril	0.09 ± 1.41 (18)	0.42 ± 2.67 (54)	−0.33	.43	
Placebo	0.51 ± 2.02 (15)	0.18 ± 2.34 (56)	0.33	.74	
Mass/volume					.95
Enalapril	0.24 ± 2.56 (18)	0.14 ± 3.23 (54)	0.1	.75	
Placebo	−0.52 ± 2.55 (15)	−0.70 ± 2.85 (55)	0.18	.57	

**Z* score at the 14-month visit minus *Z* score at the pre-SCPA visit.
†LV mean minus RV mean.
‡Wilcoxon rank sum test, left ventricle versus right ventricle.
§*P* value for interaction between treatment arms and LV/RV subgroups.

Table 4 Diastolic function variables: pre-SCPA and 14-month time points and changes between them

Variable	Pre-SCPA Median (IQR) (*n*) or Mean ± SD (*n*)	14-month visit Median (IQR) (*n*) or Mean ± SD (*n*)	Change between visits* Mean ± SD (*n*)	*P*†
E/E′	10.7 ± 4.3 (140)	10.1 ± 3.8 (149)	−0.5 ± 3.9 (128)	.19
V_{fp} (cm/sec)	59.6 ± 24.6 (115)	60.3 ± 21.5 (139)	1.0 ± 30.0 (107)	.72

IQR, Interquartile range.
*Value at the 14-month visit minus value at the pre-SCPA visit.
†The one-sample *t* test was used to compare the distributions of change scores in our SV sample with the normal population mean of zero.

No effect of enalapril on ventricular geometry or function could be demonstrated for the overall cohort or for the specific morphology subsets (right or left ventricles). An important difference was noted in the response of single right ventricles compared with single left ventricles but with a greater reduction in ventricular volume in the LV group.

An important goal in the management of patients with SV congenital heart disease is the minimization of chronic volume overload, which can lead to ventricular dilation, hypertrophy, and reduced systolic function. The ventricular volume overload is most apparent in the first few years of life, before full separation of the pulmonary and systemic circulations can be achieved with the Fontan procedure. Partial separation of the circulations using SCPA is an important interim step to decreasing the volume demands on the ventricle. Although previous studies of ventricular size and function in single ventricular physiology have included small cohorts, with typically fewer than a few dozen subjects,[12,13] few studies have used the same echocardiographic methods to evaluate subjects, and none have used core laboratories. The various methods used have included a four-chamber Simpson rule technique or the Simpson biplane method to calculate ventricular volume, short-axis area change, and short-axis linear dimensions.[3,5,14,15] We used a modified Simpson technique that has previously been shown to correlate with cardiac magnetic resonance imaging–derived ventricular measurements in functional SVs.[9] Additionally, a single observer performed all measurements, further reducing potential variance in the findings. The finding of ventricular dilation in the pre-SCPA group and the fall after SCPA was the expected response given the presence of volume overload after stage I procedures and the reduction in volume overload that occurs with SCPA. The presence of concentric rather than eccentric hypertrophy suggests the coexistence of a significant prevalence of hypertension involving the ascending aorta and arch, most typically from coarctation. A large proportion of single right ventricle patients in this cohort had hypoplastic left heart syndrome. Historically, many of these patients have residual or recurrent coarctation following initial palliation. Interestingly, the incidence of coarctation at any time point was not different between single left ventricle and single right ventricle

subjects in our cohort; the absence of clinically significant aortic arch or neo–aortic arch obstruction does not, however, exclude more subtle differences in afterload that may affect the remodeling patterns of the SV.

Overall Change in Ventricular Volumes and Systolic Function with the SCPA

Our results demonstrate that the acute decrease in volume that has been previously described in the early postoperative period after SCPA[3-5,14,15] is present at the 14-month time point as well. Importantly, despite the continued presence of hypoxia and volume overload compared with normal two-ventricle circulations, systolic function was not adversely affected over this time frame as assessed by EF. Additional parameters have been used to assess ventricular function in SV populations, including dP/dt, myocardial performance index, and Doppler tissue imaging S′ values,[16] with mixed results. The emphasis on the echocardiographic analysis for the ISV trial was cardiac remodeling, not necessarily ventricular function; thus, the assessment of ventricular function used the measurement of EF by way of ventricular volumes.

Difference in Ventricular Changes between Treatment Groups

In the randomized trial, we hypothesized that enalapril-treated subjects would demonstrate a greater reduction in ventricular dilation and eccentric hypertrophy (increased ventricular mass with normal mass/volume) compared with the placebo group, but this was not the case. The lack of a difference in ventricular modeling response between enalapril and placebo groups suggests that there may be a difference in response to the renin-angiotensin-aldosterone system in this group of infants with ventricular volume overload compared with that seen in adults with congestive heart failure, in whom angiotensin-converting enzyme inhibition has been shown to promote reverse remodeling. It is possible that in the infant SV, the physiology does not result in the marked neurohumoral activation that is characteristic of congestive heart failure associated with myocardial dysfunction.

Response of Right versus Left Ventricles

An important difference was noted in the response of single right ventricle compared with single left ventricles. Greater absolute and relative declines in *Z* scores (indicating more movement toward the mean) for these parameters were noted for left ventricles than right ventricles (Table 2) secondary to all three variables' having higher values for left versus right ventricles before SCPA and all three variables' having lower values for left ventricles versus right ventricles at 14 months. Potential reasons for this, such as different age at SCPA, shorter follow-up time, or a higher incidence of coarctation in the RV group, were not present in our cohort. Although we were not able to determine a mechanism for this difference, it may be reflected in the commonly held view that systemic single right ventricle patients fare worse than those with single left ventricles.[17,18]

Other investigators have reported similar findings using other echocardiographic tools, including strain.[19,20] Efforts to date have been limited by small patient cohorts, in part a reflection of the reality that strain assessment has not been fully incorporated into clinical practice in the SV population. The imaging protocol used in the ISV study did not include strain assessment; we anticipate that future multicenter efforts that investigate both single right ventricles and single left ventricles would include strain assessment.

The differences in hypertrophic response in the systemic left and right ventricles may relate to differences in fiber structure between the two ventricles.[21] These differences in fiber structure are associated with dominance of longitudinal strain in the normal right ventricle compared with dominant circumferential strain in the normal left ventricle.[22] However, in the systemic right ventricle, circumferential strain becomes dominant despite the fact that the percentage of circumferentially oriented fibers is less in the right ventricle. Torsion, an important component of LV contraction, is absent in the systemic right ventricle, which is predicted to contribute to higher systolic stress in the systemic right compared with the systemic left ventricle at comparable pressure, escalating the hypertrophic stimulus. This is not to imply that morphology alone is responsible for ventricular remodeling, however. The ISV study group previously reported the effect of renin-angiotensin-aldosterone system gene polymorphisms on ventricular remodeling and found that upregulation genotypes were associated with failure of reverse remodeling (failure to decrease mass/volume) after SCPA surgery; ventricular morphology did not have an effect within the high- or low-risk genotype categories.[23]

Impact of Age on Ventricular Response

Age at performance of SCPA has evolved over the past few decades. Berman and Kimball,[14] in the early 1990's, studied the effects of the SCPA on ventricular size in 31 subjects. The age range of their cohort at surgery was 6 to 95 months, substantially older than our group. Despite this, they found a decrease in end-diastolic area that was maintained in the 10 patients for whom follow-up data were available. In a 1994 study, Allgood *et al.*[3] investigated subjects whose mean age at SCPA surgery was also significantly older than our cohort (mean, 36 months; range, 6–205 months). They demonstrated an age-related increase in ventricular mass preoperatively, which is not surprising in this wide age range. However, when their cohort was divided into two groups by age at time of surgery (6–29 vs 30–205 months), no difference was seen in the magnitude of decrease in volume between the groups. Our cohort did not demonstrate a difference in remodeling within the rather narrow age range of the study.

Assessment of Diastolic Function

In adults, assessment of diastolic function typically involves multivariate algorithms to assign a diastolic function grade.[24,25] Even in the recent guideline report in *JASE*, multiple measurements are recommended,[26] some of which are not feasible in the SV population (e.g., left atrial size). In addition to the dearth of pediatric data comparing invasive with noninvasive diastolic function data, the use of these methods in pediatrics is impaired by typical infant heart rates. In our study, although all subjects had a full assessment attempted, >85% of the data points were missing for E/A ratio, early deceleration time, a-wave duration, and E′/A′ because of fusion of the waveforms, as well as duration of pulmonary vein flow reversal because of absence of diastolic flow reversal in pulmonary vein flow. Assignment of a diastolic function grade was possible in only 14 subjects at the pre-SCPA visit and in 11 at the final study visit (data not shown). Only E/E′ ratio and V_{fp} were obtainable in sufficient instances to allow interpretation. The E/E′ ratio was at the upper limits of reported normal for the group as a whole, and V_{fp} was within normal limits. However, approximately one third of the subjects

had abnormal values for both parameters at the pre-SCPA visit and at the 14-month visit, suggestive of abnormal diastolic function. Even so, the ability to detect impaired diastolic function with certainty in these patients is exceptionally limited and therefore cannot be recommended in clinical practice.

Change in the Degree of AVVR

The degree of AVVR did not change after SCPA in the majority of the subjects evaluated (82%). Although relatively few had moderate or more AVVR before SCPA (35 of 161), a nearly equal percentage improved to none/mild (54%) versus remaining moderate/severe (46%), while 8% of those who had none/mild AVVR at the pre-SCPA evaluation progressed to moderate/severe AVVR. A small fraction of the overall cohort underwent atrioventricular valvuloplasty at the time of SCPA, a practice that is in flux currently at many clinical centers. Mahle *et al.*[27] reported a series of 36 patients with SVs and moderate/severe AVVR. Of the 27 who did not undergo valvuloplasty at the time of SCPA, 6 (22%) demonstrated improvements in AVVR, and the presence of moderate/severe AVVR preoperatively was not associated with hospital survival or intermediate freedom from death or transplantation. Our data would tend to corroborate their caution against performing atrioventricular valvuloplasty in all patients with moderate or more AVVR at the time of SCPA.

Limitations

Our study had several important limitations to consider. Some of the subgroups were small, limiting our ability to detect some potential associations. Our reliance on qualitative assessment of AVVR arose from the lack of validated echocardiographic methods for quantitative evaluation of AVVR grade for children, particularly in the setting of single ventricular physiology and in the context of abnormal AVV morphologies such as a systemic tricuspid valve, which often has multiple and/or eccentric jets. The use of sedation for echocardiography in the ISV study overall was not uniform across sites or across study visits; however, no difference in the use of sedation or in the type of sedation was present between LV and RV groups. Sedation affects both preload and afterload to varying degrees, and although we posit that the overall effect is small, this remains a limitation of the analysis.

Importantly, the *Z* scores used for comparison of these SV subjects were of necessity generated for normal left ventricles in biventricular circulations. Although there is no assumption that published *Z* scores are representative of the SV "norm," these values establish a clinically important reference point by which to follow changes expected with age and growth and may be best used to assess within-patient trends. The reproducibility of the algorithm used for assessing ventricular size and function has been validated in older children with Fontan physiology.[9] Although this is not an identical cohort, the reproducibility is highly reliant on imaging windows, which should be better in the infant age group. However, because cardiac MRI was not performed as part of the ISV study, determination of "accuracy" in this cohort is not possible. Assessment of diastolic function using traditional methods in this cohort is hampered by the inapplicability of some of the recommended parameters and high prevalence of missing data for other parameters involved, because of fusion of AVV inflow and tissue Doppler waveforms at infant heart rates. Use of current diastolic function algorithms developed in adults in this group of patients cannot be recommended.

CONCLUSIONS

Our study confirms that remodeling of the SV does occur with SCPA, this remodeling persists for ≥6 months, and those with LV morphology appear more responsive to remodeling than those with RV morphology. This difference may be a factor in the discrepant outcomes that are commonly felt to be present in patients with single RV versus LV morphology. Strategies to further promote favorable remodeling, particularly for the right ventricle, should be further investigated to improve the long-term outcomes of functional SV patients.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2017.03.005.

REFERENCES

1. Parikh SR, Hurwitz RA, Caldwell RL, Girod DA. Ventricular function in the single ventricle before and after Fontan surgery. Am J Cardiol 1991;67:1390-5.
2. Sluysmans T, Sanders SP, van der Velde M, Matitiau A, Parness IA, Spevak PJ, et al. Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. Circulation 1992;86:1753-61.
3. Allgood NL, Alejos J, Drinkwater DC, Laks H, Williams RG. Effectiveness of the bidirectional Glenn shunt procedure for volume unloading in the single ventricle patient. Am J Cardiol 1994;74:834-6.
4. Donofrio MT, Jacobs ML, Spray TL, Rychik J. Acute changes in preload, afterload, and systolic function after superior cavopulmonary connection. Ann Thorac Surg 1998;65:503-8.
5. Rychik J, Jacobs ML, Norwood WI Jr. Acute changes in left ventricular geometry after volume reduction operation. Ann Thorac Surg 1995;60:1267-73. discussion 74.
6. Selamet Tierney ES, Glickstein JS, Altmann K, Solowiejczyk DE, Mosca RS, Quaegebeur JM, et al. Bidirectional cavopulmonary anastomosis: impact on diastolic ventricular function indices. Pediatr Cardiol 2007;28:372-8.
7. 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.
8. Hsu DT, Mital S, Ravishankar C, Margossian R, Li JS, Sleeper LA, et al. Rationale and design of a trial of angiotensin-converting enzyme inhibition in infants with single ventricle. Am Heart J 2009;157:37-45.
9. Margossian R, Schwartz ML, Prakash A, Wruck L, Colan SD, Atz AM, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). Am J Cardiol 2009;104:419-28.
10. Eidem BW, McMahon CJ, Cohen RR, Wu J, Finkelshteyn I, Kovalchin JP, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. J Am Soc Echocardiogr 2004;17:212-21.
11. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. J Appl Physiol (1985) 2005;99:445-57.
12. Donofrio MT, Jacobs ML, Norwood WI, Rychik J. Early changes in ventricular septal defect size and ventricular geometry in the single left ventricle after volume-unloading surgery. J Am Coll Cardiol 1995;26:1008-15.
13. Jacobs ML, Rychik J, Rome JJ, Apostolopoulou S, Pizarro C, Murphy JD, et al. Early reduction of the volume work of the single ventricle: the hemi-Fontan operation. Ann Thorac Surg 1996;62:456-61. discussion 61-2.

14. Berman NB, Kimball TR. Systemic ventricular size and performance before and after bidirectional cavopulmonary anastomosis. J Pediatr 1993;122:S63-7.
15. Forbes TJ, Gajarski R, Johnson GL, Reul GJ, Ott DA, Drescher K, et al. Influence of age on the effect of bidirectional cavopulmonary anastomosis on left ventricular volume, mass and ejection fraction. J Am Coll Cardiol 1996;28:1301-7.
16. Rhodes J, Margossian R, Sleeper LA, Barker P, Bradley TJ, Lu M, et al. Non-geometric echocardiographic indices of ventricular function in patients with a Fontan circulation. J Am Soc Echocardiogr 2011;24:1213-9.
17. Giardini A, Hager A, Pace Napoleone C, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg 2008;85:818-21.
18. Khairy P, Fernandes SM, Mayer JE Jr., Triedman JK, Walsh EP, Lock JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008;117:85-92.
19. Kaneko S, Khoo NS, Smallhorn JF, Tham EB. Single right ventricles have impaired systolic and diastolic function compared to those of left ventricular morphology. J Am Soc Echocardiogr 2012;25:1222-30.
20. Tham EB, Smallhorn JF, Kaneko S, Valiani S, Myers KA, Colen TM, et al. Insights into the evolution of myocardial dysfunction in the functionally single right ventricle between staged palliations using speckle-tracking echocardiography. J Am Soc Echocardiogr 2014;27:314-22.
21. Stevens C, Hunter PJ. Sarcomere length changes in a 3D mathematical model of the pig ventricles. Prog Biophys Mol Biol 2003;82:229-41.
22. Pettersen E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, et al. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol 2007;49:2450-6.
23. Mital S, Chung WK, Colan SD, Sleeper LA, Manlhiot C, Arrington CB, et al. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. Circulation 2011;123:2353-62.
24. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. J Am Coll Cardiol 2008;51:679-89.
25. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J Am Coll Cardiol 1997;30:8-18.
26. 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.
27. Mahle WT, Cohen MS, Spray TL, Rychik J. Atrioventricular valve regurgitation in patients with single ventricle: impact of the bidirectional cavopulmonary anastomosis. Ann Thorac Surg 2001;72:831-5.

APPENDIX

Supplemental Table 1 Ventricular geometry and systolic function variables by ventricular type at pre-SCPA and 14-month time points (raw values)

	Calculated values			
	Left ventricle		Right ventricle	
	Pre-SCPA Mean ± SD (*n*)	14 months Mean ± SD (*n*)	Pre-SCPA Mean ± SD (*n*)	14 months Mean ± SD (*n*)
EDV (mL)	27.7 ± 10.1 (33)	29.6 ± 8.3 (33)	22.5 ± 9.3 (113)	30.4 ± 11.3 (114)
ESV (mL)	12.0 ± 5.4 (33)	12.4 ± 4.6 (33)	9.9 ± 5.5 (113)	13.2 ± 8.0 (114)
Mass (g)	29.1 ± 9.9 (33)	31.6 ± 9.2 (33)	25.0 ± 9.0 (111)	32.3 ± 10.5 (114)
EF (%)	57.0 ± 6.3 (33)	58.4 ± 7.8 (33)	57.1 ± 10.4 (113)	58.3 ± 10.5 (114)
Mass/volume (g/mL)	1.1 ± 0.3 (33)	1.1 ± 0.2 (33)	1.2 ± 0.4 (111)	1.2 ± 0.4 (114)