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

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Abstract

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

Methods and Results—As part of the Pediatric Heart Network placebo-controlled trial of enalapril in infants with SV physiology, echocardiograms were obtained pre-SCPA and at 14-months and analyzed in a core laboratory. Retrospective analysis of the following measurements included: SV end-diastolic volume (EDV), end-systolic volume (ESV), mass, mass-to-volume ratio (mass/volume) and ejection fraction (EF). Qualitative assessment of atrioventricular valve regurgitation (AVVR) and assessment of diastolic function were also performed. A total of 156 participants had echocardiograms at both time points. Pre-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

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(2.1 ± 2.5 and 2.0 ± 2.9 , respectively). The EDV, ESV, and mass decreased after the SCPA, but mass/volume and the degree of AVVR did not change. Subjects with morphologic LV demonstrated a greater reduction in ventricular volumes and mass than those with RVs (change in z-score [mean $\pm$ SD]: LVEDV -1.9 ± 2.1 , RVEDV -0.7 ± 2.5 , LVESV -2.3 ± 2.9 , RVESV -0.9 ± 4.6 , LV mass -2.5 ± 2.8 , RV mass -1.3 ± 2.6 . All $p < .03$). Approximately one-third of patients whose diastolic function could be assessed had abnormalities at each time point.

Conclusions—A decrease in ventricular size and mass occurs in SV patients after the SCPA procedure, 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.

Keywords

single ventricle; systolic ventricular function; diastolic ventricular function; ventricular remodeling; superior cavopulmonary anastomosis; congenital heart disease

Introduction

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 by directing systemic venous blood from the upper part of the body to the lungs, bypassing the single ventricle. 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 authors 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 employs 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 multi-center randomized placebo-controlled trial of the angiotensin converting enzyme (ACE) inhibitor enalapril in infants with single ventricle 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 between the placebo and the enalapril treated groups. Utilizing 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 SV physiology.

Methods

Details of the study design and main results of the ISV trial have been published (7, 8). In brief, infants with SV 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 - HLHS). 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: pre- SCPA procedure and at 14-months (final study visit). Sedation was used according to local practice. Echocardiograms were performed according to a prospective, standardized imaging protocol and sent to the echocardiographic core lab 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. The end-diastolic volume (EDV), end-systolic volume (ESV) and mass were then calculated using a modified Simpson biplane method (9). The percent ventricular ejection fraction (EF) was calculated as $([EDV - ESV] / EDV) \times 100$. Ventricular mass was calculated as myocardial end-diastolic volume (epicardial volume – endocardial volume) $\times$ myocardial density (1.05 g/ml). Inter- and intra-observer variabilities for this method of assessing morphologic SVs have been reported previously (9). The degree of atrioventricular valve regurgitation (AVVR) was qualitatively assessed and grouped as none/mild and moderate/severe.

Doppler assessment of atrioventricular valve (AVV) inflow was performed for peak early velocity (E), peak atrial velocity (A), early deceleration time (E_{dt}), and a-wave duration (A_{dur}). 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. Tissue Doppler imaging of annular myocardial velocities recorded peak early (E') and late (A') diastolic velocities at the two walls and 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 TDI waveform fusion. Figure 3 demonstrates the effect of the R-R interval on fusion of the waveforms. Duration of pulmonary vein flow reversal (PV_{dur}) and ventricular flow propagation (V_{fp}) were also recorded. E/E' values >10 and a V_{fp} values >45 were considered abnormal (10). Echocardiographic data were reviewed and measurements made using custom software (Marcus Laboratories, Boston, MA).

Statistical methods

The data used in the analyses were obtained in a prospective manner; the analyses reported in this manuscript were retrospectively proposed and implemented. To adjust echocardiographic measurements to account for the effect of body size (volume, mass) and age (ejection fraction, 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 utilized are therefore based on systemic LV measurements.

Data are described as frequencies, medians with 25th and 75th percentile values, and means with standard deviations as appropriate. For some of the evaluations below, echocardiograms with partial data were included; each section lists the number of subjects included for sub analysis.

Echocardiographic measurements of the LV and RV groups were compared using the Student's t-test for non-skewed variables and the Wilcoxon rank sum test for other measures. In the subset of 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 1-sample t-test. The changes in AVVR between the 2 time points were assessed using McNemar's test. The exact Fisher and Mantel-Haenszel Chi-Square tests for linear trend were used to evaluate the effect of enalapril on the ventricle, and to compare the changes in subjects with single RVs to those with single LVs. Subgroup analyses of treatment effect on changes in mass-volume z-scores were performed between single LV vs. single RV (subgroups pre-specified 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 utilized to account for non-linearity in regression models.

Data analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC). A p-value <0.05 was considered statistically significant.

Results

Patient Population

Of the 230 subjects randomized for the main trial, 28 were withdrawn prior to the pre-SCPA visit, and fourteen subjects did not undergo an SCPA. The remaining subjects underwent SCPA as follows: 134 had a bidirectional cavopulmonary anastomosis, 28 had a bilateral bidirectional cavopulmonary anastomosis, and 26 had a hemi-Fontan procedure. A total of

156 subjects had complete studies at both time points. Briefly with regard to the surgical procedures, the 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 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-RA 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 the hemi-Fontan) is the same. By directing venous return from the superior vena cava(e) directly to the pulmonary arteries, a portion of the volume load on the single ventricle is removed, while allowing reasonable pulmonary blood flow.

For the entire group, the median age at time of the SCPA and the time from the 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 comprised 46% of the cohort; 81% were classified as white, 13% as black, 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 change 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 a decrease in z-score between the pre-SCPA and 14-month visits. Mass/volume did not significantly change between the two time points. The 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 valvuloplasties at the time of the SCPA, 161 subjects had AVVR assessment at both time points, including 132 subjects with no change in the degree of AVVR between the two time points. Prior to SCPA surgery, 35 subjects (22%; 29 RV, 4 LV and 2 Mixed) had moderate/severe AVVR. Of these, 16 (15 RV and 1 LV) had continued moderate/severe AVVR at the 14-month visit, while 19 (14 RV, 3 LV and 2 Mixed) improved to none/mild. Out of 126 subjects with none/mild AVVR at pre-SCPA, ten progressed to moderate/severe AVVR (6 RV and 4 LV) at the 14-month visit; these findings were statistically not significant ($p=0.095$, McNemar's test).

Comparison of the effect of ACE inhibition to 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 RVs compared to single LVs

Table 2 includes the z-scores for the ventricular characteristics for LV vs. RV morphology and the change in z-scores between the two time points. The raw data are presented in the supplement table. As assessed by change in EDV, ESV and ventricular mass, single RVs and single LVs differed in their response to volume unloading at SCPA. A greater absolute and relative decline in z-scores (indicating more movement toward the mean) for these parameters was noted for LVs than RVs, secondary to all three variables having higher values for LVs versus RVs pre-SCPA and all three variables having lower values for LVs versus RVs 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 the 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 0.11 to 0.95 indicating that there was no significant effect of enalapril on the change in z-scores between RVs and LVs. In fact, the largest overall changes occurred in the placebo group, not the enalapril group.

Impact of age at time of SCPA on change in z- scores

The median age at SCPA surgery was 5.3 months (IQR = 4.3, 6.2). For the group as a whole, the median time from the SCPA to the 14-month visit was 8.9 months with a range of 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-scores was found using age as a continuous variable in linear modeling. When age at SCPA surgery was used categorically in a non-parametric model (age <5 months, 5–7 months and >7 months; the cut-offs are based on general additive models non-linear 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 the 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 utilize z-scores for systematic assessment of ventricular volumes and systolic function in a large cohort of infant SV patients. Pre-SCPA, the mean EDV, ESV, mass and mass/volume z-scores were >2 , confirming that patients with SV physiology have ventricles that are more dilated and concentrically hypertrophied than patients with normal biventricular cardiac anatomy. We found that, following the SCPA, the mean ESV and mass z-scores were still greater than 2 for the group as a whole, but had decreased from the pre-SCPA values, while the mean EDV and mass/volume z-scores decreased below 2. No effect of enalapril on ventricular geometry or function could be demonstrated for the overall cohort, or for the specific morphology subsets (RVs or LVs). An important difference was noted in the response of single RVs compared to single LVs, however, 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 utilizing the SCPA is an important interim step to decreasing the volume demands on the ventricle. While previous studies of ventricular size and function in SV physiology have included small cohorts, with typically less than a few dozen subjects (12, 13), few studies have used the same echocardiographic methods to evaluate subjects, and none have utilized core laboratories. The various methods used have included a 4-chamber Simpson's rule technique or Simpson's biplane to calculate ventricular volume, short-axis area change, and short-axis linear dimensions (3, 5, 14, 15). This study utilized a modified Simpson technique that has previously been shown to correlate with cardiac MRI derived ventricular measurements in functional single ventricles (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 based on 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 RV patients in this cohort had HLHS. 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 LV and single RV subjects in our cohort; the absence of clinically significant aortic arch/neo-aortic arch obstruction does not, however, exclude more subtle differences in afterload which may impact the remodeling patterns of the single ventricle.

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 post-operative period following the 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 to normal two-ventricle circulations, systolic function was not adversely affected over this time frame as assessed by ejection fraction. Additional parameters have been used to assess ventricular function in single ventricle populations, including dP/dt , myocardial performance index, and TDI 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 utilized the measurement of ejection fraction 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 to 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 (RAAS) in this group of infants with ventricular volume overload compared to that seen in adults with congestive heart failure, where ACE inhibition has been shown to promote reverse remodeling. It is possible that in the infant single ventricle the physiology does not result in the marked neurohumoral activation which is characteristic of congestive heart failure associated with myocardial dysfunction.

Response of RVs vs. LVs

An important difference was noted in the response of single RVs compared to single LVs. A greater absolute and relative decline in z-scores (indicating more movement toward the mean) for these parameters was noted for LVs than RVs (Table 2) secondary to all three variables having higher values for LVs versus RVs pre-SCPA and all three variables having lower values for LVs versus RVs 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. While we were not able to determine a mechanism for this difference, it may be reflected in the commonly held view that systemic single RV patients fare worse than those with a single LV (17, 18).

Other authors 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 single ventricle population. The imaging protocol utilized in the ISV study did not include strain assessment; we anticipate that future multicenter efforts that investigate both single RVs and single LVs 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 to 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 left ventricular contraction, is absent in the systemic right ventricle, which is predicted to contribute to higher systolic stress in the systemic right compared to 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 (RAAS) 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 the SCPA has evolved over the past few decades. Berman et al., in the early 1990s, studied the effects of the SCPA on ventricular size in 31 subjects (14). The age range of their cohort at surgery was 6–95 months, substantially older than our group. Despite this, they found a decrease in end-diastolic area that was maintained in the ten patients for whom follow-up data were available. The 1994 report by Allgood et al. investigated subjects whose mean age at SCPA surgery was also significantly older than our cohort (mean 36 months, range 6–205)(3). They demonstrated an age-related increase in ventricular mass pre-operatively, 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 months 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 multi-variable algorithms to assign a diastolic function grade (24, 25). Even in the recent guideline paper from the Journal of the American Society of Echocardiography, multiple measurements are recommended (26), some of which are not feasible in the single ventricle population (left atrial size, for example). In addition to the dearth of pediatric data comparing invasive to non-invasive 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, more than 85% of the data points were missing for E/A ratio, E_{dt} , A_{dur} , and E'/A' due to fusion of the waveforms, as well as PV_{dur} due to 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 the parameters E/E' ratio and V_{fp} were obtainable in sufficient instances to allow for 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 the SCPA in the majority of the subjects evaluated (82%). Although relatively few had moderate or more AVVR prior to SCPA (35/161), a nearly equal percentage improved to none/mild (54%) versus remaining moderate/severe (46%), while 8% of those who had none/mild at the pre-SCPA evaluation progressed to moderate/severe. A small fraction of the overall cohort underwent AV valvuloplasty at the time of SCPA, a practice which is in flux currently at many clinical centers. Mahle et al reported a series of 36 patients with SV and moderate/severe AVVR. Of the 27 who did not undergo valvuloplasty at the time of SCPA, 6 (22%) demonstrated improvement in AVVR, and the presence of moderate/severe AVVR pre-operatively was not associated with hospital survival or intermediate freedom from death/transplantation (27). Our data would tend to corroborate their caution against performing AV valvuloplasty in all patients with moderate or more AVVR at the time of SCPA.

Limitations

Our study has 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 ventricle 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 echocardiograms 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 impacts 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 LVs in biventricular circulations. Although there is no assumption that published Z scores are representative of the single ventricle “norm”, these values establish a clinically important reference point by which to follow changes expected with age and growth, and may be best utilized 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). While this is not an identical cohort, the reproducibility is highly reliant on imaging windows, which should be better in the infant age group. However, since 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, due to 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 single ventricle does occur with SCPA, this remodeling persists for at least 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 vs LV morphology. Strategies to further promote favorable remodeling, particularly for the right ventricle, should be further investigated to improve the long term outcomes of the functional single ventricle patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

A	mitral inflow atrial diastolic wave velocity
A_{dur}	duration of the mitral inflow atrial diastolic wave
A'	tissue Doppler atrial diastolic wave velocity
ACE	angiotensin converting enzyme
AVV	atrioventricular valve
AVVR	atrioventricular valve regurgitation
E	mitral inflow early diastolic wave velocity
E'	tissue Doppler early diastolic wave velocity
E_{dt}	early deceleration time
EDV	end-diastolic volume
EF	ejection fraction
ESV	end-systolic volume
HLHS	hypoplastic left heart syndrome
ISV	Infant Single Ventricle
LV	left ventricle
Mass/volume	mass to volume ratio

PV_{dur}	duration of pulmonary vein flow reversal
RV	right ventricle
SCPA	superior cavopulmonary anastomosis
SV	single ventricle
V_{fp}	ventricular flow propagation

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Highlights

- Single ventricular size and mass decrease after superior cavopulmonary anastomosis procedure.
- Mass to volume ratio does not change significantly after SCPA.
- Morphologic left ventricles demonstrated a greater reduction in ventricular volumes and mass than morphologic right ventricles.

Figure 1. Atrioventricular valve 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. Tissue Doppler 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.

Figure 3.
Atrioventricular valve 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)

Variable	Calculated values		Z-scores*		
	Pre-SCPA	14-month	Pre-SCPA	14-month	Change in z-score**
	Mean $\pm$ SD (N)	Mean $\pm$ SD (N)	Mean $\pm$ SD (N)	Mean $\pm$ SD (N)	
End diastolic volume (ml)	23.5 $\pm$ 9.6 (160)	29.8 $\pm$ 10.7 (163)	2.1 $\pm$ 2.5 (157)	1.2 $\pm$ 2.2 (163)	-1.0 $\pm$ 2.5 (153) <0.001
End systolic volume (ml)	10.2 $\pm$ 5.4 (160)	12.7 $\pm$ 7.2 (163)	3.4 $\pm$ 3.7 (157)	2.2 $\pm$ 3.7 (163)	-1.2 $\pm$ 4.1 (153) <0.001
Mass (g)	26.2 $\pm$ 9.2 (158)	32.2 $\pm$ 10.3 (161)	4.2 $\pm$ 2.9 (155)	2.6 $\pm$ 2.3 (161)	-1.6 $\pm$ 2.6 (151) <0.001
Ejection Fraction (%)	57.4 $\pm$ 9.3 (160)	58.8 $\pm$ 9.9 (163)	-1.1 $\pm$ 1.8 (160)	-0.8 $\pm$ 1.9 (163)	0.3 $\pm$ 2.3 (156) 0.02
Mass to Volume ratio (g/mL)	1.2 $\pm$ 0.5 (158)	1.2 $\pm$ 0.4 (161)	2.0 $\pm$ 2.9 (158)	1.6 $\pm$ 2.6 (161)	-0.2 $\pm$ 3.0 (154) 0.33

* 3 subjects are missing weight measurements at the time of echocardiogram precluding z-score assignment for EDV, ESV, and mass

δ To compare the distributions of change scores in our single ventricle sample with the normal population mean of zero we have used Wilcoxon signed rank test for ejection fraction and the 1 sample t-test for all other change in z-scores.

** Z-score at the 14-month minus z-score at the pre-SCPA visit

Ventricular geometry and systolic function variables by ventricular type Z-scores at Pre-SCPA and 14-month time points and changes between them

Table 2

	LV z-score		RV z-score		Changes in z-scores (Value at 14-month minus value at pre-SCPA)		P-value*
	Pre-SCPA Mean $\pm$ SD (N)	14-month Mean $\pm$ SD (N)	Pre-SCPA Mean $\pm$ SD (N)	14-month Mean $\pm$ SD (N)	LV Mean $\pm$ SD (N)	RV Mean $\pm$ SD (N)	
End diastolic volume	2.8 $\pm$ 2.4 (32)	0.9 $\pm$ 1.5 (33)	2.0 $\pm$ 2.6 (111)	1.3 $\pm$ 2.4 (114)	-1.9 $\pm$ 2.1 (32)	-0.7 $\pm$ 2.5 (108)	-1.2 0.01
End systolic volume	4.2 $\pm$ 3.2 (32)	1.9 $\pm$ 2.0 (33)	3.4 $\pm$ 4.0 (111)	2.6 $\pm$ 4.2 (114)	-2.3 $\pm$ 2.9 (32)	-0.9 $\pm$ 4.6 (108)	-1.4 0.03
Mass	4.5 $\pm$ 3.1 (32)	2.2 $\pm$ 1.9 (33)	4.0 $\pm$ 2.9 (109)	2.7 $\pm$ 2.4 (114)	-2.5 $\pm$ 2.8 (32)	-1.3 $\pm$ 2.6 (107)	-1.2 0.03
Ejection fraction	-1.2 $\pm$ 1.2 (33)	-0.9 $\pm$ 1.5 (33)	-1.2 $\pm$ 2.0 (113)	-0.9 $\pm$ 2.1 (114)	0.3 $\pm$ 1.7 (33)	0.3 $\pm$ 2.6 (110)	0.0 0.98
Mass to volume ratio	1.3 $\pm$ 2.2 (33)	1.2 $\pm$ 1.5 (33)	1.9 $\pm$ 2.8 (111)	1.6 $\pm$ 2.8 (114)	-0.1 $\pm$ 2.6 (33)	-0.3 $\pm$ 3.1 (109)	0.2 0.76

LV: Left Ventricle; RV: Right Ventricle

[§] LV mean minus RV mean

* T-test

Table 3

Changes in ventricular geometry and systolic function z-scores between pre-SCPA and 14-month visit by ventricular type, stratified by treatment group

Change in mass/volume zscore* by treatment arm	LV z-score Mean $\pm$ SD (N)	RV z-score Mean $\pm$ SD (N)	Mean Difference between LV and RV [§]	P-value**	ANOVA interaction p-value [†]
EDV					0.40
Enalapril	-1.86 $\pm$ 2.12 (18)	-1.05 $\pm$ 2.64 (53)	-0.81	0.22	
Placebo	-2.01 $\pm$ 2.05 (14)	-0.37 $\pm$ 2.38 (55)	-1.64	0.009	
ESV					0.37
Enalapril	-1.92 $\pm$ 2.23 (18)	-1.24 $\pm$ 4.86 (53)	-0.68	0.27	
Placebo	-2.87 $\pm$ 3.65 (14)	-0.57 $\pm$ 4.01 (55)	-2.3	0.009	
Mass					0.11
Enalapril	-1.58 $\pm$ 2.57 (18)	-1.14 $\pm$ 2.63 (53)	-0.44	0.48	
Placebo	-3.62 $\pm$ 2.65 (14)	-1.48 $\pm$ 2.57 (54)	-2.14	0.01	
EF					0.48
Enalapril	0.09 $\pm$ 1.41 (18)	0.42 $\pm$ 2.67 (54)	-0.33	0.43	
Placebo	0.51 $\pm$ 2.02 (15)	0.18 $\pm$ 2.34 (56)	0.33	0.74	
Mass to volume ratio					0.95
Enalapril	0.24 $\pm$ 2.56 (18)	0.14 $\pm$ 3.23 (54)	0.1	0.75	
Placebo	-0.52 $\pm$ 2.55 (15)	-0.70 $\pm$ 2.85 (55)	0.18	0.57	

LV: Left Ventricle; RV: Right Ventricle

* Z-score at the 14-month visit minus z-score at the pre-SCPA visit

[§] LV mean minus RV mean

** Wilcoxon rank-sum test, LV vs. RV

[†] 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

	Pre-SCPA	14-month visit	Change between visits [*]	
Variable	Median (IQR) (N) or Mean $\pm$ SD (N)	Median (IQR) (N) or Mean $\pm$ SD (N)	Mean $\pm$ SD (N)	P-value [§]
E/E'	10.7 $\pm$ 4.3 (140)	10.1 $\pm$ 3.8 (149)	-0.5 $\pm$ 3.9 (128)	0.19
V _{ip} (cm/sec)	59.6 $\pm$ 24.6 (115)	60.3 $\pm$ 21.5 (139)	1.0 $\pm$ 30.0 (107)	0.72

IQR=inter-quartile range

^{*} Value at the 14-month visit minus value at the pre-SCPA visit[§] The 1-sample t-test is used to compare the distributions of change scores in our single ventricle sample with the normal population mean of zero.