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A Multi-Center Study Comparing Shunt Type in the Norwood Procedure for Single-Ventricle Lesions: 3-Dimensional Echocardiographic Analysis

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Abstract

Background—The Pediatric Heart Network's (PHN) Single Ventricle Reconstruction Trial (SVR) randomized infants with single right ventricles (RV) undergoing a Norwood procedure to a modified Blalock-Taussig or RV-to-pulmonary artery shunt. This report compares RV parameters in the two groups using 3-dimensional echocardiography (3DE).

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Disclosures

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Methods and Results—3DE studies were obtained at 10/15 SVR centers. Of the 549 subjects, 314 underwent 3DE studies at one to four time points (pre-Norwood, post-Norwood, pre-stage II, and 14 months) for a total of 757 3DEs. Of these, 565 (75%) were acceptable for analysis. RV volume, mass, mass:volume ratio, ejection fraction (EF), and severity of tricuspid regurgitation did not differ by shunt type. RV volumes and mass did not change after the Norwood, but increased from pre-Norwood to pre-stage II (end-diastolic volume [EDV, ml]/body surface area [BSA]$^{1.3}$, end-systolic volume [ESV, ml]/BSA$^{1.3}$ and mass[g]/BSA$^{1.3}$ mean difference [95% confidence interval] = 25.0 [8.7, 41.3], 19.3 [8.3, 30.4], and 17.9 [7.3, 28.5], then decreased by 14 months (EDV/BSA$^{1.3}$, ESV/BSA$^{1.3}$ and mass/BSA$^{1.3}$ mean difference [95% confidence interval] = −24.4 [−35.0, −13.7], −9.8 [−17.9, −1.7], and −15.3 [−22.0, −8.6]. EF decreased from pre-Norwood to pre-stage II (mean difference [95% confidence interval] = −3.7% [−6.9%, −0.5%]), but did not decrease further by 14 months.

Conclusions—We found no statistically significant differences between study groups in 3DE measures of RV size and function, or magnitude of tricuspid regurgitation. Volume unloading was seen after stage II, as expected, but EF did not improve. This study provides insights into the remodeling of the operated univentricular RV in infancy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00115934.

Keywords

echocardiography; heart defect; congenital; pediatrics

The Pediatric Heart Network's Single Ventricle Reconstruction (SVR) Trial randomized newborns with single right ventricle anomalies undergoing the Norwood procedure at 15 North American sites to either the modified Blalock-Taussig shunt (MBTS) or right-ventricular-to-pulmonary-artery shunt (RVPAS) to provide pulmonary blood flow. The primary endpoint, transplantation–free survival 12 months post-randomization, was significantly higher for the RVPAS compared to the MBTS group. When follow-up beyond one year was included, however, transplantation-free survival was not different between the two groups (mean follow-up, 32 ± 11 months in non-transplanted survivors).[1]

A secondary aim of the SVR trial was to compare the effect of MBTS to RVPAS on echocardiographic indices of right ventricular (RV) function and tricuspid regurgitation (TR). Both shunt types result in RV volume overload, and are often associated with hemodynamically significant TR. In addition, the RVPAS requires a right ventriculotomy, which has the potential to result in regional wall dysfunction, aneurysm formation and dysrhythmia, all of which may negatively influence RV function. The presence of regurgitation through the RVPAS adds to RV volume overload.

Due to inherent and well-recognized difficulties in measuring single RV size and function by two-dimensional imaging, three-dimensional echocardiographic (3DE) analysis was incorporated into the SVR trial. Prior studies have validated the accuracy and reproducibility of both right and left ventricular volumetrics by 3DE in small hearts and at rapid heart rates, both *in vivo* and *in vitro*, and with small animals as well as humans. These studies demonstrated that 3DE analysis of ventricular size and function in young pediatric patients correlates well with magnetic resonance imaging (MRI), albeit with a tendency for volumes to be smaller by 3DE than by MRI.[2–4] Three-dimensional echocardiographic determination of the *vena contracta* also provides a reliable quantitative indicator of TR.[5] Thus, for the SVR trial, 3DE was incorporated to provide serial, non-invasive analysis of RV size and function, and of TR before and following the Norwood and stage II procedures. The hypothesis of the present analysis was that RV systolic function would be better and the

severity of TR would be lower in subjects having the RVPAS compared with those with the MBTS.

Methods

Subjects and Echocardiographic Analyses

As previously reported, infants with single RV anomalies were randomly assigned to receive a MBTS or RVPAS during the Norwood procedure at 15 medical centers.[1] Per protocol, 3DE studies were obtained: 1) before the Norwood procedure; 2) 15.5±12.1 days following the Norwood procedure at hospital discharge; 3) 17.7±25.5 days before the stage II procedure; and 4) at 14 months following randomization (8.9±2.0 months post the stage II procedure). Ten of the 15 medical centers participating in the SVR Trial contributed to the 3DE analysis. Sedation varied according to local practice. The protocol was approved by each center's Institutional Review Board, and written consent was obtained from a parent or guardian.

All centers received a training DVD developed by the SVR Trial 3DE Core Laboratory (Boston Children's Hospital, Boston, MA) to standardize 3DE acquisitions. The protocol for the 3DE acquisitions and analysis of RV size and function was based on previous reports[2–4]. Electrocardiographically-gated full volume 3DE acquisitions were performed with 2–4 or 5–7 MHz matrix-array transthoracic probes and 3DE ultrasound systems (SONOS 7500 and iE33, Philips Medical Systems, Andover MA). Data sets were acquired with probe placement either in the subcostal or apical position, after ensuring that the entire ventricle could be viewed simultaneously in orthogonal planes. The probe was held motionless during a four-beat acquisition and the 3D volume data sets were evaluated to ensure the entire ventricle was scanned with minimal spatial and temporal artifacts. Full-volume color-flow 3DE acquisitions of the tricuspid regurgitation jet were acquired from the apex during six cardiac cycles. The full-volume digital gray-scale and color-flow acquisition data were transferred and stored to CD/DVD. These data, along with anthropometric and blood pressure measurements, were sent to the Data Coordinating Center (New England Research Institutes, Watertown, MA). The digital data sets were de-identified and then transferred by CD/DVD to the 3DE Core Laboratory for subsequent analysis, which was blinded to outcomes.

RV volume and mass were measured with dedicated off-line computers and software as previously described (4-D Echo View, TomTec, Munich, Germany).[2–4] An image of the entire RV with clear depiction of the endocardial and epicardial borders was necessary for studies to be considered acceptable for data analysis. Each study was initially analyzed by a pediatric echocardiographic technician trained in 3DE measurements, and all measurements were confirmed by the director of the core laboratory (GRM). End-diastole was chosen as the largest chamber cavity size and/or the frame immediately before atrioventricular valve closure. End-systole was chosen as the smallest chamber size and/or the frame before the onset of atrioventricular valve opening. Using the motion images for reference, the endocardial and epicardial borders of corresponding sequential cross-sectional planes were manually traced using the still images (Figure 1). A minimum of six discs were traced and volumes calculated by summation of discs methodology. [2–4] Ejection fraction (EF) was calculated as (EDV-ESV)/EDV, where EDV is end-diastolic volume and ESV is end-systolic volume. Myocardial mass was calculated as myocardial volume between the epicardial and endocardial borders multiplied by the myocardial density (1.05 g/ml).

Tricuspid regurgitation *vena contracta* was measured as the smallest systolic regurgitant jet area traversing the tricuspid valve leaflets. From the 3D color flow data sets, dedicated software (Q-lab 6.0, Philips Medical Systems, Andover MA) provided simultaneous long

axis planes of the color flow TR jet. From these images, a cut plane was placed perpendicular to the orthogonal long axis planes of the regurgitant jet, providing simultaneous visualization of the corresponding cross-sectional area (Figure 2). This perpendicular cut plane was moved along the length of the regurgitant jet to ensure choosing the narrowest cross-sectional area, as shown in the corresponding long- and short-axis views. This cross-sectional area was manually traced and represented the area of the *vena contracta*. When more than one regurgitant jet was visualized, the individual *vena contracta* areas were summed. The *vena contracta*, also known at the effective tricuspid regurgitant orifice area, was recorded as a raw area measurement (cm^2), and then indexed to body surface area (cm^2/m^2).

Statistical Analyses

Three-dimensional echo indices are shown as raw data, and also indexed to body surface area (BSA) based on the relationship to BSA previously determined for systemic left ventricles.[6] Shunt comparisons at each trial visit were performed using the actual shunt type in place at the end of the Norwood procedure with Student's t-test or the Wilcoxon rank-sum test for continuous 3DE indices and a Fisher exact test for dichotomous indices. Changes in RV volumes before and after the Norwood and stage II procedures were examined with a paired t-test. To examine whether 3DE indices varied by shunt type, changes in 3DE indices before and after the Norwood and stage II procedures were analyzed with Student's t-test. Correlations between RV end-diastolic and end-systolic volumes and tricuspid regurgitant orifice area at each trial visit were assessed with the Pearson correlation coefficient. Analyses were performed in R version 2.12.0. Two-sided p-values <0.05 were considered statistically significant.

Results

A total of 549 patients (281 RVPAS and 268 MBTS) were evaluated in the trial.[1] An echocardiogram was attempted in 349 of 484 subjects (80%) at the 10 sites with 3DE capability, and at least one 3DE was deemed acceptable by the Core Laboratory in 314 (90%). In general, baseline characteristics were similar for those subjects with a 3DE versus those without a 3DE (Table 1). There was no statistically significant difference in shunt type between those with or without a 3DE ($p = 0.49$). All baseline two-dimensional echocardiographic (2DE) indices were similar for subjects with and without a 3DE. Hispanic ethnicity was more common in subjects with a 3DE ($p = 0.05$), due to a high proportion of Hispanic patients at one contributing site. Obstructed pulmonary venous return was less likely in subjects with a 3DE ($p = 0.03$). The lack of important statistically significant differences in the groups with and without a 3DE suggests that the 3DE analytic cohort is likely representative of the trial sample.

A total of 757 3DEs were obtained across all four trial visits; 565 (75%) were deemed acceptable for analysis (78 before Norwood procedure, 215 at Norwood discharge, 147 before stage II operation, and 125 at month 14 following randomization). The success rate for obtaining an adequate 3DE varied from 54% to 86% (mean, 73%). Three-dimensional echocardiograms obtained at the 14-month visit were less likely to be deemed acceptable for analysis than echocardiograms obtained at previous visits (63% acceptable at 14 months vs. 78% acceptable at pre- Norwood [p=0.004], 85% at Norwood discharge [p<0.001], and 72% at pre-stage II [p=0.09]). Sedation was not associated with an improvement in obtaining an acceptable 3DE overall (generalized estimating equation model p=0.84 adjusting for site) or at each visit (pre-Norwood $p = 0.99$; post-Norwood $p = 0.20$; pre-Stage II $p = 0.95$; 14-month, $p = 0.58$).

Right ventricular size and function

RV volume, mass (indexed to BSA), EF, and RV mass:volume ratio did not differ for the MBTS group and the RVPAS group at any trial visit (Table 2). Considering all subjects with 3DE regardless of shunt type, there were no changes in RV EDV, ESV, mass, or EF using pair-wise comparisons from pre-Norwood to discharge after the Norwood procedure (Table 3). Pair-wise comparisons of the pre-Norwood echo to the pre-stage II echo showed significant increases in RV EDV, ESV and mass, and a significant decrease in RV EF (Table 4). In contrast, from the pre-stage II visit to the 14-month visit, paired comparisons showed significant decreases in RV volumes and mass, although the RV EF did not change (Table 5).

Tricuspid regurgitation

The severity of TR did not differ between the shunt groups at any trial visit (Table 2). Paired comparisons showed that TR increased for both shunt groups after the Norwood procedure (Table 3), then remained stable in both groups thereafter (Tables 4 and 5). In the combined study group, RV EDV and ESV were positively associated with the tricuspid regurgitant orifice area (all parameters indexed to BSA) at all study visits except the post-Norwood visit (all p values<0.01; Pearson correlation coefficients 0.32–0.45). A small number of subjects (13/146, 9%) had concomitant tricuspid valve surgery at Stage II. This number was too small to further analyze the efficacy of valve repair in reducing tricuspid regurgitation.

Discussion

The PHN SVR study is the first multi-center trial in congenital heart disease to report the use and feasibility of 3DE indices of RV volume and EF as secondary endpoints. This analysis does not support the study hypothesis that the RVPA and MBTS groups would differ in 3DE measures of RV size and function, and magnitude of TR. No significant difference by shunt, or indeed any clinically relevant difference by shunt, was found in any of the 3DE variables examined at any stage of repair during the first 14 months following randomization. Analysis of 2DE data from the SVR trial also suggests that RV volume and RV function do not vary between the two shunt types at 14 months of age.[7]

It is conceivable that the two shunt types lead to effects on the RV that were beyond the scope of the 3DE measurements that were made. Some of these changes may include mechanical dyssynchrony or altered contraction and strain patterns.[8,9] Techniques for 3DE evaluation of regional RV wall motion were unavailable at the time that this study was performed; those tools are currently in early stages of development. Differences in RV volume and function also may become manifest over a more extended period of follow-up than was present in the current study; the ongoing longitudinal evaluation of the SVR cohort should provide additional information.

Prior to the current study, data examining serial changes in ventricular volume, systolic function and mass in a large number of patients with a systemic single RV were limited. This 3DE study provides insights into the remodeling of the operated single RV in the first 14 months of life, albeit with paired rather than longitudinal comparisons due to limitations in the number of infants with serial 3D echocardiograms. We found a significant decrease in RV diastolic and systolic volume and mass, and no significant change in EF during the pre-stage II to the 14-month (pre-Fontan) interval. Bellsham-Revell and colleagues[10], in a serial MRI study in a similar patient group, also recently found a significant decrease in RV diastolic volume from pre-stage II to pre-Fontan, but observed a significant increase in EF. In their study, the post stage II MRI was done at a mean age of 2.9 years. In the current study, the post stage II echocardiograms were obtained at a mean age of 1.2 years. Similar

changes in RV volumetrics and EF may become manifest in our cohort over longer term follow up.

Until the stage II surgery, the single RV has increased volume because it is handling cardiac output for both the pulmonary and systemic circulations. After the stage II surgery, we found significant volume-unloading, but the mass:volume ratio remained the same, and the RV EF did not improve, a significant long-term concern. It is possible that remodeling may require more time than was reflected in this study. The observed decrease in indexed RV volume following stage II surgery is consistent with prior small 2DE studies by Forbes et al [11] in single left ventricles, and a similar short-term study by Selamet Tierney et al [12] in patients with systemic left or right ventricles. In a 3DE study of 18 patients with hypoplastic left heart syndrome, Kutty et al [13] reported a non-significant decrease in RV volume after the stage II surgery, and also found deterioration in the RV EF, consistent with our findings. An acute decrease in ejection fraction is the expected response to the preload reduction as a result of the volume unloading surgery and does not necessarily imply myocardial injury since recovery of function generally occurs after myocardial reverse remodeling is complete.

It is commonly believed that a decrease in RV volumes after the stage II procedure will result in a reduction in the magnitude of tricuspid regurgitation. However, in this study, tricuspid regurgitation did not decrease between the post-Norwood study and the14-month study, which is sufficiently beyond the stage II operation to have allowed for changes in tricuspid valve function in response to any RV remodeling resulting from volume-unloading. This suggests that the demonstrated volume decrease after the stage II procedure may not lead to decreased tricuspid regurgitation, and that RV volume overload is not the sole factor responsible for the development of tricuspid regurgitation in this cohort of patients. Only four patients in the 3DE cohort had tricuspid valve surgery at stage II, so the efficacy of valve repair in reducing tricuspid regurgitation could not be assessed. The magnetic resonance imaging (MRI) study by Bellsham-Revell et al[10] also found no improvement in tricuspid regurgitation despite RV volume reduction after the stage II procedure.

The location, complex anatomy and irregular shape of the RV pose a challenge to traditional imaging. The RV has complex contraction patterns, with its inflow and sinus exhibiting shortening primarily in a longitudinal direction, while the outflow tract contracts primarily in a circumferential manner.[14] The accuracy of 3DE RV volumetrics compared to MRI has been well established across a range of patient sizes (ranging from children to adults), both in normal populations and in disease states ranging from tetralogy of Fallot to univentricular hearts.[2,15–21] In anticipation of this multi-center trial, the Core Laboratory, Boston Children's Hospital, performed *in vitro* and *in vivo* studies to evaluate the reliability of 3DE to measure RV volumes, mass and EF in this young pediatric age group similar to that encountered in this multi-center trial.[2,3] The findings showed good correlation for diastolic and systolic volumes and RV mass. However, RV volumes by 3DE were consistently smaller by 9%. Helberg[22] compared 3DE volumes to small, calibrated, tissue-mimicking phantoms. Although the authors concluded that 3DE was a reliable method for calculation of small distances, areas and volumes, 3D echo volume measurements were consistently smaller. Similar to findings by Hoch et al[4], both compress and gain settings significantly affected 3DE measurements.

The Core Laboratory addressed inter- and intra-observer variability in both *in-vitro*[4] and *in-vivo* studies[2,3]. The *in vivo* studies included comparisons to MRI as the gold standard. Soriano et al in their study comparing 3DE to MRI in young infants with single ventricles, reported good correlation and agreement for intra-observer variability[2]. Diastolic volume, systolic volume, and mass correlated and agreed well for inter-observer variability. The

intra-class coefficient for EF was 0.75, and the mean difference of 0.04. Although this was statistically significant ($p<0.02$), the difference is small and thus not clinically significant.

For this multi-center trial, only studies with clear delineation of endocardial borders and in which the entire RV was included in the data set were accepted for mass and volume measurements. Although this rigorous threshold may in part be responsible for the lower feasibility rate of 75%, it should have contributed to the high standards for repeatability.

In a recent consensus document from the American Society of Echocardiography and the European Association of Echocardiography,[23] the authors highlight the potential role of 3DE assessment of RV volumes and ejection fraction in postoperative patients. Despite the theoretical desirability of 3DE for the RV, however, it was difficult to obtain adequate images at all study visits, and there was considerable variability by site. Overall, the success rate declined as the subjects got older, regardless of sedation use. Recent technological advances, such as smaller transducers, improved temporal and spatial resolution of images, single-beat acquisitions, and advanced regional analysis of ventricular function are likely to improve the success of acquiring adequate 3DE images in complex congenital heart disease. In particular, frame reordering may significantly increase 3DE temporal resolution, which is seminal in improving measurements in young patients with high heart rates.[24]

Limitations

This study should be interpreted in light of its limitations. Overall, 75% of acquisitions were acceptable for data analysis, but the success rate varied widely by site. Therefore, statistical power to detect differences in RV size and function was limited compared to analyses of the trial's 2D echo database. The variability in success also meant that many subjects did not have studies at multiple time points, thus necessitating paired comparisons at individual time points rather than longitudinal modeling. The cause of unacceptable data likely relates in part to suboptimal acoustic windows due to increasing age and the history of repeated sternotomy, and in part to the inability to control respirations. Younger patients were more likely to have acceptable images, lending some credence to this view. Recent technological advances, not available at the time of the study, might have enhanced the proportion of acceptable studies. We also recognize the limitations inherent in the absence of validation data from MRI for the 3DE quantification of tricuspid regurgitation in infants with HLHS, but believe the measures systematically obtained in this study provide useful data in this population.

Conclusions

The PHN SVR trial is the first multi-center effort in congenital heart disease to report the use and feasibility of 3DE indices of RV volume and EF as secondary endpoints. Right ventricular size and function, and severity of tricuspid regurgitation, as measured by 3DE, are not different between RVPAS and MBTS patient groups from before the Norwood procedure until 14 months of age. The stage II operation results in a decrease in indexed RV volumes and mass, but the magnitude of tricuspid regurgitation does not decrease, and EF remains persistently low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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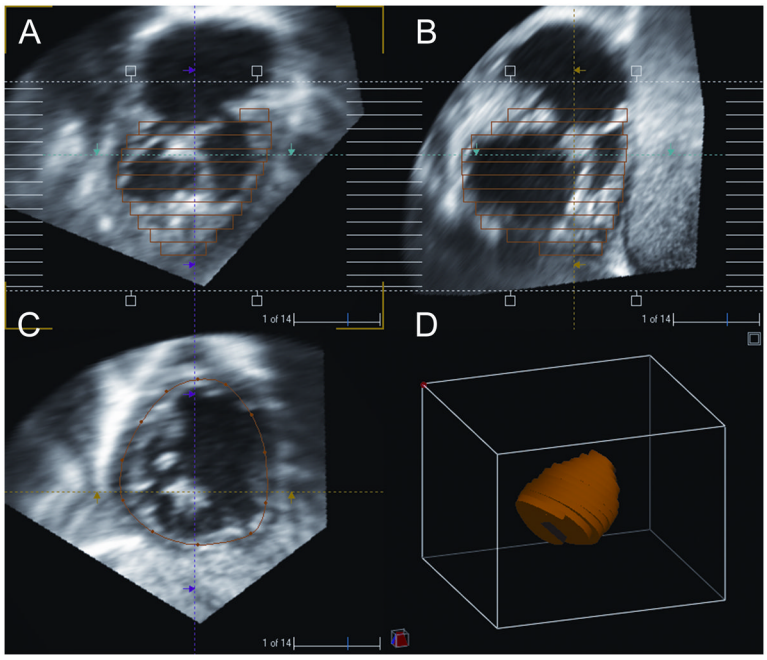

Figure 1.
Summation of disc methodology for measurement of right ventricular diastolic volume in hypoplastic left heart syndrome. A= long-axis view of right ventricle with multiple discs; B= corresponding orthogonal view of right ventricle with multiple discs; C= single cross sectional area from disc as shown in A& B; D= corresponding summation of discs as shown in ABC.

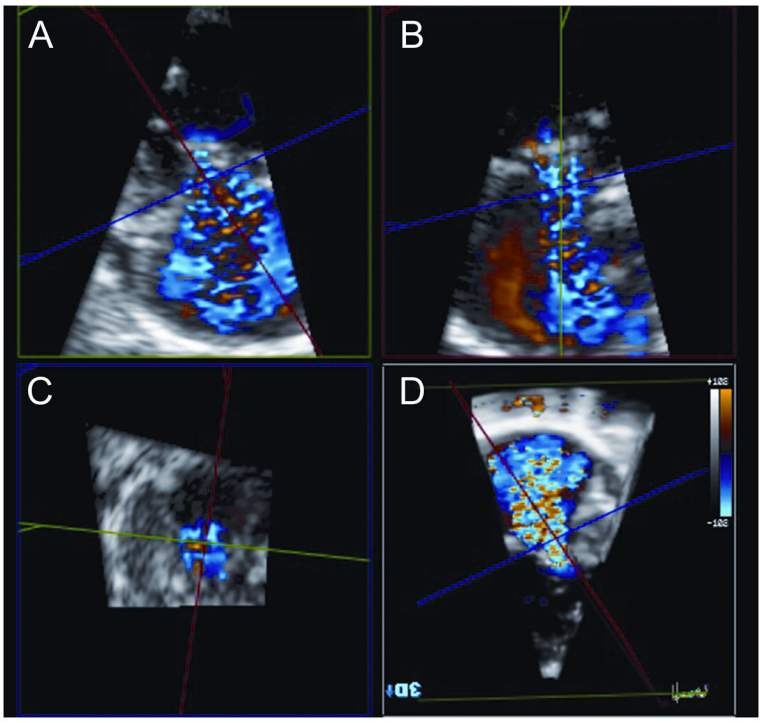

Figure 2.
Measurement of vena contracta cross sectional area in patient with severe tricuspid regurgitation in hypoplastic left heart syndrome. A=long axis color flow jet of severe tricuspid regurgitation; B=corresponding orthogonal long-axis view of tricuspid regurgitation color flow jet; C=corresponding cross-sectional view of tricuspid regurgitation color flow jet from A and B; D= three-dimensional display of corresponding tricuspid regurgitation color flow jet.

Table 1

Pre-Norwood characteristics of SVR trial subjects with and without a 3D echocardiogram

	Subjects with at least one acceptable 3D echo (N=314)	All other randomized (N=235)	P
Age at randomization, days	4.9±4.3	5.3±3.6	0.22
Male	194 (62%)	146 (62%)	1.00
Race			
White	251 (81%)	185 (79%)	0.76
Black	49 (16%)	37 (16%)	
Asian	6 (2%)	4 (2%)	
Other	5 (2%)	7 (3%)	
Hispanic	67 (21.8%)	34 (14.7%)	0.05
Birth weight, kg	3.1±0.5	3.1±0.6	0.11
Gestational age, weeks	38 (38,39)	38 (37,39)	0.32
Anatomic diagnosis			
Hypoplastic left heart syndrome	272 (87%)	202 (86%)	0.92
Other	42 (13%)	33 (14%)	
2D echo at pre-Norwood			
Native ascending aorta, cm	0.3 (0.2,0.5)	0.3 (0.2,0.5)	0.58
Native ascending aorta z-score	−3.9 (−4.5,−2.4)	−3.6 (−4.5,−2.3)	0.36
RV ejection fraction, %	46.3±9.0	46.2±8.1	0.93
RV end-diastolic volume (ml)/BSA$^{1.3}$	83.8 (72.4,100.4)	82.8 (66.5,96.9)	0.42
RV end-systolic volume (ml)/BSA$^{1.3}$	45.8 (36.2,56.4)	45.3 (34.9,55.2)	0.61
RV end-diastolic area (cm^2)/BSA$^{0.8}$	21.1±4.5	20.8±4.7	0.49
Moderate/severe tricuspid valve regurgitation	37 (12%)	28 (12%)	0.89
LV mass (g)/BSA$^{1.3}$	22.4 (15.1,32.1)	19.7 (14.2,28.3)	0.12

Data presented as mean±SD, median (1st quartile, 3rd quartile), or n (%). Abbreviations - BSA: body surface area; LV; left ventricle; RV: right ventricle

Table 2

Three-dimensional echocardiographic indices by shunt type at each visit

	Pre-Norwood		P	Post-Norwood[1]		P	Pre-stage II[2]		P	14 months		P
	MBTS (N=37)	**RVPAS (N=41)**		**MBTS (N=104)**	**RVPAS (N=111)**		**MBTS (N=63)**	**RVPAS (N=84)**		**MBTS (N=50)**	**RVPAS (N=75)**	
Age at Echo, days	3.3 ± 4.4	3.3 ± 4.7	0.98	21.3 ± 13.2	21.0 ± 12.4	0.86	156.7 ± 45.0	152.0 ± 42.5	0.53	435.5 ± 37.7	442.7 ± 41.9	0.33
BSA, m^2	0.22 (0.20, 0.23)	0.22 (0.20, 0.22)	0.36	0.22 (0.20, 0.23)	0.21 (0.20, 0.23)	0.33	0.32 (0.29, 0.34)	0.32 (0.30, 0.35)	0.21	0.42 (0.41, 0.44)	0.45 (0.42, 0.49)	<.001
RV												
RV EDV (ml)/$BSA^{1.3}$	105.6 (93.4,127.8)	118.6 (93.7,153.9)	0.12	120.2 (99.5,141.9)	119.7 (98.6,145.5)	0.56	152.0 (120.3,176.3)	139.9 (113.8,171.2)	0.62	104.7 (86.2,133.3)	111.8 (90.1,126.4)	0.66
RV ESV (ml)/$BSA^{1.3}$	52.8 (40.1,60.5)	59.0 (46.6,71.0)	0.07	61.1 (47.0,69.5)	56.2 (44.9,68.3)	0.19	77.9 (60.4,92.6)	69.3 (53.5,91.5)	0.69	55.3 (41.8,68.9)	53.8 (44.7,71.8)	0.75
RV mass (g)/$BSA^{1.3}$	74.0 (59.3,81.4)	78.2 (58.6,92.1)	0.39	78.6 (68.6,90.4)	77.0 (63.6,94.0)	0.22	89.3 (71.7,102.9)	85.6 (70.0,102.4)	0.85	66.2 (53.6,81.0)	66.2 (55.2,79.5)	0.68
RV mass:volume ratio	0.67 (0.57,0.72)	0.62 (0.56,0.66)	0.06	0.66 (0.61,0.74)	0.65 (0.61,0.71)	0.22	0.62 (0.55,0.66)	0.62 (0.57,0.67)	0.23	0.63 (0.57,0.68)	0.62 (0.57,0.66)	0.97
RV ejection fraction, %	52.3±6.7	51.4±7.2	0.69	50.4±7.3	52.6±7.5	0.22	48.0±7.3	47.7±8.4	0.62	46.9±7.2	46.8±6.4	0.73
Tricuspid regurgitation												
Regurgitant area (cm^2)/BSA	0.57 (0.30, 1.11)	0.45 (0.32,0.91)	0.36	0.87 (0.48,1.78)	0.70 (0.46,1.29)	0.14	0.87 (0.43,1.67)	0.71 (0.38,1.00)	0.16	0.58 (0.36,0.86)	0.51 (0.33,0.91)	0.98

[1]The 3D Echos were obtained at 15.4±11.9 days post Norwood operation prior to hospital discharge.

[2]The 3D Echos were obtained at 149±45 days post Norwood operation prior to stage II surgery.

Data presented as mean±SD or median (1^{st} quartile, 3^{rd} quartile). Abbreviations – BSA: body surface area; EDV: end-diastolic volume; ESV: end-systolic volume; MBTS: modified Blalock-Taussig shunt; RV: right ventricle; RVPAS: right ventricular-to-pulmonary artery shunt

Table 3

Three-dimensional echocardiographic indices of RV size and function and tricuspid regurgitation before and after the Norwood procedure

	Pre-Norwood (n=51)	Post-Norwood (n=51)	Mean difference (95% CI) (n=51)	P
Age at Echo, days	2.7 ± 3.0	17.2 ± 6.9	14.5 (12.6, 16.3)	NA
RV EDV (ml)/BSA$^{1.3}$	110.4 (87.9,134.6)	118.1 (95.0, 151.5)	2.6 (−9.0, 14.2)	0.66
RV ESV (ml)/BSA$^{1.3}$	54.4 (44.4, 65.7)	57.8 (43.4, 69.0)	0.4 (−5.8, 6.5)	0.90
RV mass (g)/BSA$^{1.3}$	76.4 (60.0, 87.2)	78.0 (66.4, 89.8)	3.8 (−3.7, 11.4)	0.31
RV mass:volume	0.65 (0.59, 0.72)	0.66 (0.60, 0.74)	0.02 (−0.03, 0.06)	0.45
RV ejection fraction, %	51.7 ± 7.2	53.5 ± 8.2	1.8 (−1.0, 4.7)	0.21
Tricuspid regurgitant area (cm^2)/BSA (n=23)	0.35 (0.22, 0.82)	0.70 (0.29, 1.42)	0.46 (0.02, 0.89)	0.04

Mean difference = mean of post-Norwood minus pre-Norwood difference in 3D echocardiographic measure. 95% confidence interval (CI) calculated as mean ± 1.96*SD/√n.

Sample size limited to subjects with 3DE indices available at both pre- and post-Norwood visits (n=51). Data presented as mean±SD or median (1st quartile, 3rd quartile). Abbreviations – BSA: body surface area; CI: confidence interval; EDV: end-diastolic volume; ESV: end-systolic volume; RV: right ventricle

Table 4

Three-dimensional echocardiographic indices of RV size and function and tricuspid regurgitation before the Norwood procedure and before the stage II procedure

	Pre-Norwood (n=39)	Pre-stage II (n=39)	Mean difference (95% CI) (n=39)	P
Age at Echo, days	3.0 ± 4.2	130.5 ± 34.6	127.5 (116.3, 138.7)	NA
RV EDV (ml)/BSA$^{1.3}$	118.8 (86.9, 142.5)	144.0 (112.2, 175.8)	25.0 (8.7, 41.3)	0.004
RV ESV (ml)/BSA$^{1.3}$	56.1 (39.4, 70.3)	70.7 (54.7, 90.5)	19.3 (8.3, 30.4)	0.001
RV mass (g)/BSA$^{1.3}$	73.6 (53.0, 83.4)	85.4 (69.7, 104.2)	17.9 (7.3, 28.5)	0.002
RV mass:volume	0.61 (0.56, 0.67)	0.62 (0.57, 0.67)	0.01 (−0.02, 0.05)	0.37
RV ejection fraction, %	52.4 ± 7.8	48.6 ± 7.6	−3.7 (−6.9, −0.5)	0.02
Tricuspid regurgitant area (cm^2)/BSA (n=15)	0.52 (0.33, 1.0)	0.48 (0.29, 1.27)	0.12 (−0.40, 0.63)	0.63

Mean difference = mean of pre-stage II minus pre-Norwood difference in 3D echocardiographic measure. 95% confidence interval (CI) calculated as mean ± 1.96*SD/√n.

Sample size limited to subjects with 3DE indices available at both pre-Norwood and pre-stage II visits (n=39. Data presented as mean±SD or median (1st quartile,3rd quartile). Abbreviations – BSA: body surface area; CI: confidence interval; EDV: end-diastolic volume; ESV: end-systolic volume; RV: right ventricle

Table 5

Three-dimensional echocardiographic indices of RV size and function and tricuspid regurgitation before the stage II procedure and at 14 months

	Pre-stage II (n=63)	Month 14 (n=63)	Mean difference (95% CI) (n=63)	P
Age at Echo, days	155.7 ± 47.9	446.2 ± 47.2	153.0 (121.0, 187.0)	NA
RV EDV (ml)/BSA$^{1.3}$	136.7 (112.5, 170.2)	106.8 (86.4, 129.9)	−24.4 (−35.0, −13.7)	<0.001
RV ESV (ml)/BSA$^{1.3}$	69.4 (52.8, 91.5)	54.8 (42.4, 73.3)	−9.8 (−17.9, −1.7)	0.02
RV mass (g)/BSA$^{1.3}$	82.7 (66.0, 98.4)	66.1 (53.2, 83.1)	−15.3 (−22.0, −8.6)	<0.001
RV mass:volume	0.61 (0.58, 0.69)	0.62 (0.55, 0.68)	−0.01 (−0.04, 0.02)	0.38
RV ejection fraction, %	48.2 ± 7.6	46.4 ± 7.1	−1.8 (−4.2, 0.7)	0.16
Tricuspid regurgitant area (cm^2)/BSA (n=33)	0.71 (0.38, 1.16)	0.63 (0.43, 1.11)	−0.04 (−0.36, 0.28)	0.81

Mean difference = mean of 14 months minus pre-stage II difference in 3D echocardiographic measure. 95% confidence interval (CI) calculated as mean ± 1.96*SD/√n.

Sample size limited to subjects with 3DE indices available at both pre-stage II and 14-month visits (n=63). Data presented as mean±SD or median (1^{st} quartile, 3^{rd} quartile). Abbreviations – BSA: body surface area; CI: confidence interval; EDV: end-diastolic volume; ESV: end-systolic volume; RV: right ventricle