Congenital Heart Disease

Multicenter Study Comparing Shunt Type in the Norwood Procedure for Single-Ventricle Lesions

Three-Dimensional Echocardiographic Analysis

Gerald R. Marx, MD; Girish Shirali, MD, MBBS; Jami C. Levine, MD, MS; Lin T. Guey, PhD;
James F. Cnota, MD; Jeanne M. Baffa, MD; William L. Border, MBChB, MPH;
Steve Colan, MD; Gregory Ensing, MD; Mark K. Friedberg, MD; David J. Goldberg, MD;
Salim F. Idriss, MD, PhD; J. Blaine John, MD; Wyman W. Lai, MD, MPH; Minmin Lu, MS;
Shaji C. Menon, MD; Richard G. Ohye, MD; David Saudek, MD; Pierre C. Wong, MD;
Gail D. Pearson, MD, ScD; for the Pediatric Heart Network Investigators

Background**—**The Pediatric Heart Network's Single Ventricle Reconstruction (SVR) trial randomized infants with single right ventricles (RVs) undergoing a Norwood procedure to a modified Blalock-Taussig or RV-to-pulmonary artery shunt. This report compares RV parameters in the 2 groups using 3-dimensional echocardiography.

Methods and Results**—**Three-dimensional echocardiography studies were obtained at 10 of 15 SVR centers. Of the 549 subjects, 314 underwent 3-dimensional echocardiography studies at 1 to 4 time points (pre-Norwood, post-Norwood, pre–stage II, and 14 months) for a total of 757 3-dimensional echocardiography studies. Of these, 565 (75%) were acceptable for analysis. RV volume, mass, mass:volume ratio, ejection fraction, 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 [milliliters]/body surface area [BSA]$^{1.3}$, end-systolic volume [milliliters]/BSA$^{1.3}$, and mass [grams]/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 (end-diastolic volume/BSA$^{1.3}$, end-systolic volume/BSA$^{1.3}$, and mass/BSA$^{1.3}$ mean difference [95% confidence interval]=–24.4 [−35.0 to −13.7], −9.8 [−17.9 to −1.7], and −15.3 [−22.0 to −8.6]. Ejection fraction decreased from pre-Norwood to pre–stage II (mean difference [95% confidence interval]=–3.7 [−6.9 to −0.5]), but did not decrease further by 14 months.

Conclusions**—**We found no statistically significant differences between study groups in 3-dimensional echocardiography measures of RV size and function, or magnitude of tricuspid regurgitation. Volume unloading was seen after stage II, as expected, but ejection fraction 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.

(*Circ Cardiovasc Imaging*. 2013;6:934-942.)

Key Words: echocardiography ■ heart defects, congenital ■ pediatrics

The Pediatric Heart Network's (PHN) 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 end point, transplantation-free survival 12 months postrandomization, was significantly higher for the RVPAS compared with the MBTS group. When follow-up beyond 1 year was included, however, transplantation-free survival was not different between the 2 groups (mean follow-up, 32±11 months in nontransplanted survivors).[1]

Clinical Perspective on p 942

Received March 5, 2013; accepted September 27, 2013.

From the Boston Children's Hospital, MA (G.R.M., J.C.L., S.C.); The Children's Mercy Hospital and Clinics, Kansas City, MO (G.S.); New England Research Institutes, Watertown, MA (L.T.G., M.L.); Cincinnati Children's Hospital Medical Center, OH (J.F.C.); A.I. DuPont Hospital for Children, Wilmington, DE (J.M.B.); Emory University School of Medicine, Atlanta, GA (W.L.B.); University of Michigan, Ann Arbor (G.E., R.G.O.); Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada (M.K.F.); Department of Pediatrics, The Children's Hospital of Philadelphia, PA (D.J.G.); Duke University Medical Center, Durham, NC (S.F.I.); Congenital Heart Institute of Florida/Pediatric, Tampa (J.B.J.); Columbia University Medical Center, New York, NY (W.W.L.); University of Utah, Salt Lake City (S.C.M.); Medical College of Wisconsin, Milwaukee (D.S.); Children's Hospital Los Angeles, CA (P.C.W.); and National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (G.D.P.).

Correspondence to Gail D. Pearson, MD, ScD, National Heart, Lung, and Blood Institute, 6701 Rockledge Dr, Room 8132, Bethesda, MD 20892. E-mail pearsong@mail.nih.gov

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**

DOI: 10.1161/CIRCIMAGING.113.000304

A secondary aim of the SVR trial was to compare the effect of MBTS with RVPAS on echocardiographic indices of 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.

Because of inherent and well-recognized difficulties in measuring single RV size and function by 2-dimensional imaging, 3-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 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, noninvasive analysis of RV size and function and of TR before and after 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 an 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 after the Norwood procedure at hospital discharge, (3) 17.7±25.5 days before the stage II procedure, and (4) at 14 months after 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 to 4 or 5 to 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 4-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 TR jet were acquired from the apex during 6 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 deidentified 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 (4D 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 (G.R.M.). End diastole was chosen as the largest chamber cavity size and the frame immediately before atrioventricular valve closure. End systole was chosen as the smallest chamber size and 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 6 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).

TR 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 >1 regurgitant jet was visualized, the individual vena contracta areas were summed. The vena contracta, also known as the effective tricuspid regurgitant orifice area, was recorded as a raw area measurement (centimeter squared) and then indexed to body surface area (BSA; centimeter squared per meter squared).

Statistical Analyses

Three-dimensional echo indices are shown as raw data and also indexed to 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 *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 *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 ≥1 3DE was deemed acceptable by the Core Laboratory in 314 subjects (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 2DE indices were

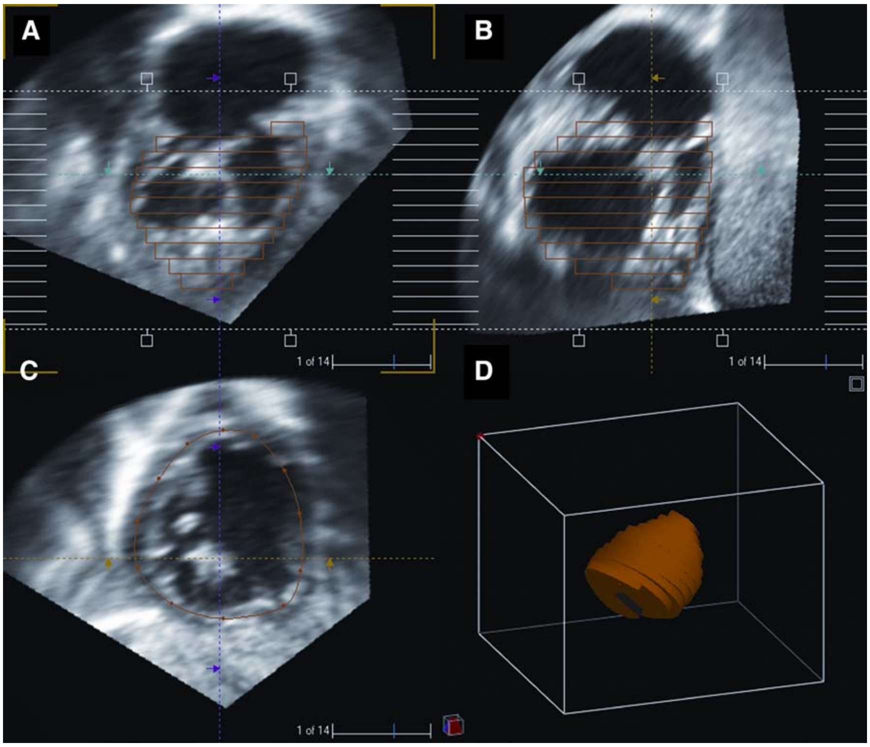

Figure 1. Summation of disc methodology for measurement of right ventricular diastolic volume in hypoplastic left heart syndrome. **A**, Long-axis view of right ventricle with multiple discs; **B**, Corresponding orthogonal view of right ventricle with multiple discs; **C**, Single cross-sectional area from disc as shown in **A** and **B**; **D**, Corresponding summation of discs as shown in **A**, **B**, and **C**.

similar for subjects with and without a 3DE. Hispanic ethnicity was more common in subjects with a 3DE (*P*=0.05), attributable to a high proportion of Hispanic patients at 1 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 3DE studies were obtained across all 4 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 after 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%

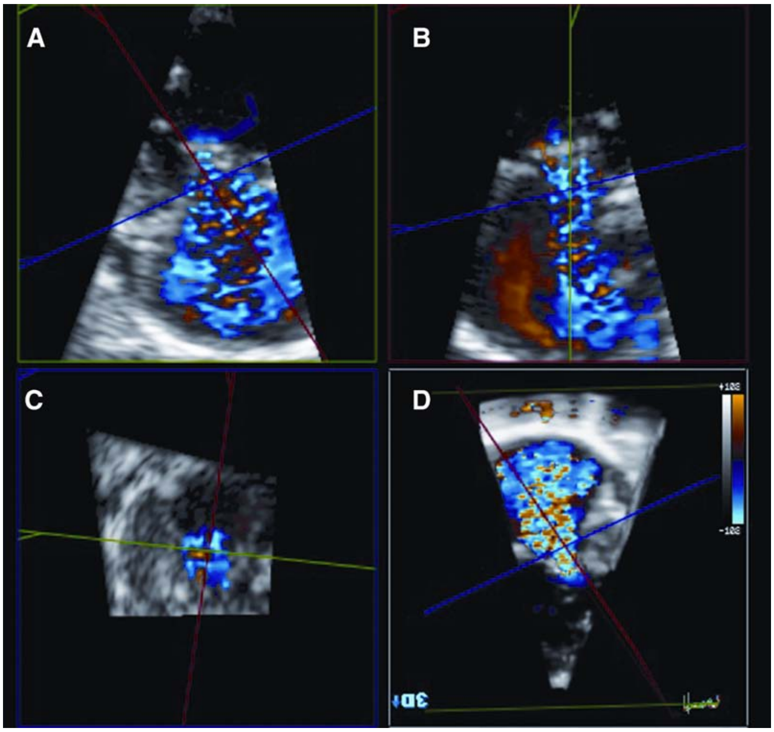

Figure 2. Measurement of vena contracta cross-sectional area in patient with severe tricuspid regurgitation in hypoplastic left heart syndrome. **A**, Long-axis color-flow jet of severe tricuspid regurgitation; **B**, Corresponding orthogonal long-axis view of tricuspid regurgitation color-flow jet; **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 Single Ventricle Reconstruction Trial Subjects With and Without a 3D Echocardiogram

	Subjects With ≥1 Acceptable 3D Echo (n=314)	All Other Randomized (n=235)	*P* Value
Age at randomization, d	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, wk	38 (38 to 39)	38 (37 to 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 to 0.5)	0.3 (0.2 to 0.5)	0.58
Native ascending aorta *z* score	−3.9 (−4.5 to −2.4)	−3.6 (−4.5 to −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 to 100.4)	82.8 (66.5 to 96.9)	0.42
RV end-systolic volume (mL)/BSA$^{1.3}$	45.8 (36.2 to 56.4)	45.3 (34.9 to 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 to 32.1)	19.7 (14.2 to 28.3)	0.12

Data presented as mean±SD, median (first quartile to third quartile), or n (%). BSA indicates body surface area; LV, left ventricle; and RV, right ventricle.

acceptable at 14 months versus 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).

RV 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 pairwise comparisons from pre-Norwood to discharge after the Norwood procedure (Table 3). Pairwise 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*<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 analyze the efficacy of valve repair further in reducing TR.

Discussion

The PHN SVR study is the first multicenter trial in congenital heart disease to report the use and feasibility of 3DE indices of RV volume and EF as secondary end points. This analysis does not support the study hypothesis that the RVPAS 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 after randomization. Analysis of 2DE data from the SVR trial also suggests that RV volume and RV function do not vary between the 2 shunt types at 14 months of age.[7]

It is conceivable that the 2 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]

Table 2. Three-Dimensional Echocardiographic Indices by Shunt Type at Each Visit

	Pre-Norwood			Post-Norwood*			Pre–Stage II†			14 Mo		
	MBTS (n=37)	RVPAS (n=41)	P Value	MBTS (n=104)	RVPAS (n=111)	P Value	MBTS (n=63)	RVPAS (n=84)	P Value	MBTS (n=50)	RVPAS (n=75)	P Value
Age at echo, d	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)	<0.001
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

Data presented as mean±SD or median (first quartile–third quartile). BSA indicates body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; MBTS, modified Blalock-Taussig shunt; RV, right ventricle; and RVPAS, right ventricular-to-pulmonary artery shunt.

*The 3-dimensional (3D) echos were obtained at 15.4±11.9 days after Norwood operation before hospital discharge.

†The 3D echos were obtained at 149±45 days after Norwood operation before stage II surgery.

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.

Before 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 attributable 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 et al,[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

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

Mean difference=mean of post-Norwood minus pre-Norwood difference in 3-dimensional echocardiographic (3DE) measure. 95% CI calculated as mean±1.96×SD/$\sqrt{n}$. 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 (first quartile to third quartile). BSA indicates body surface area; CI, confidence interval; EDV, end-diastolic volume; ESV, end-systolic volume; NA, not applicable; and 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* Value
Age at echo, d	3.0±4.2	130.5±34.6	127.5 (116.3 to 138.7)	NA
RV EDV (mL)/BSA$^{1.3}$	118.8 (86.9 to 142.5)	144.0 (112.2 to 175.8)	25.0 (8.7 to 41.3)	0.004
RV ESV (mL)/BSA$^{1.3}$	56.1 (39.4 to 70.3)	70.7 (54.7 to 90.5)	19.3 (8.3 to 30.4)	0.001
RV mass (g)/BSA$^{1.3}$	73.6 (53.0 to 83.4)	85.4 (69.7 to 104.2)	17.9 (7.3 to 28.5)	0.002
RV mass:volume	0.61 (0.56 to 0.67)	0.62 (0.57 to 0.67)	0.01 (−0.02 to 0.05)	0.37
RV ejection fraction, %	52.4±7.8	48.6±7.6	−3.7 (−6.9 to −0.5)	0.02
Tricuspid regurgitant area (cm^2)/BSA (n=15)	0.52 (0.33 to 1.0)	0.48 (0.29 to 1.27)	0.12 (−0.40 to 0.63)	0.63

Mean difference=mean of pre–stage II minus pre-Norwood difference in 3-dimensional echocardiographic (3DE) measure. 95% CI calculated as mean±1.96×SD/$\sqrt{n}$. 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 (first quartile to third quartile). BSA indicates body surface area; CI, confidence interval; EDV, end-diastolic volume; ESV, end-systolic volume; NA, not applicable; RV, right ventricle.

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 after 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 nonsignificant 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 EF is the expected response to the preload reduction as a result of the volume unloading surgery and does not necessarily imply myocardial injury because recovery of function generally occurs after myocardial reverse remodeling is complete.

It is commonly thought that a decrease in RV volumes after the stage II procedure will result in a reduction in the magnitude of TR. However, in this study, TR did not decrease between the post-Norwood study and the 14-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 TR and that RV volume overload is not the sole factor responsible for the development of TR in this cohort of patients. Only 4 patients in the 3DE cohort had tricuspid valve surgery at stage II, so the efficacy of valve repair in reducing TR could not be assessed. The MRI study by Bellsham-Revell et al[10] also found no improvement in TR 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, whereas the outflow tract contracts primarily in a circumferential manner.[14] The accuracy of 3DE RV volumetrics compared with 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 multicenter 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 multicenter 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%. Herberg et al[22] compared 3DE volumes with 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

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

Mean difference=mean of 14 mo minus pre–stage II difference in 3-dimensional echocardiographic (3DE) measure. 95% CI calculated as mean±1.96×SD/$\sqrt{n}$. 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 (first quartile to third quartile). BSA indicates body surface area; CI, confidence interval; EDV, end-diastolic volume; ESV, end-systolic volume; NA, not applicable; RV, right ventricle.

Hoch et al,[4] both compress and gain settings significantly affected 3DE measurements.

The Core Laboratory addressed inter- and intraobserver 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,[2] in their study comparing 3DE with MRI in young infants with single ventricles, reported good correlation and agreement for intraobserver variability. Diastolic volume, systolic volume, and mass correlated and agreed well for interobserver variability. The intraclass coefficient for EF was 0.75, and the mean difference was 0.04. Although this was statistically significant ($P<0.02$), the difference is small and thus not clinically significant.

For this multicenter 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 EF 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 with 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 attributable 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 TR in infants with hypoplastic left heart syndrome, but thought the measures systematically obtained in this study provide useful data in this population.

Conclusions

The PHN SVR trial is the first multicenter effort in congenital heart disease to report the use and feasibility of 3DE indices of RV volume and EF as secondary end points. RV size and function, and severity of TR, 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 TR does not decrease, and EF remains persistently low.

Appendix

National Heart, Lung, and Blood Institute: Gail Pearson, Victoria Pemberton, Rae-Ellen Kavey*, Mario Stylianou, Marsha Mathis*.

Network Chair: University of Texas Southwestern Medical Center, Lynn Mahony.

Data Coordinating Center: New England Research Institutes, Lynn Sleeper (Principal Investigator [PI]), Sharon Tennstedt (PI), Steven Colan, Lisa Virzi*, Patty Connell*, Victoria Muratov*, Lisa Wruck*, Minmin Lu, Dianne Gallagher, Anne Devine*, Julie Schonbeck, Thomas Travison*, David F. Teitel.

Core Clinical Site Investigators: Children's Hospital Boston, Jane W. Newburger (PI), Peter Laussen*, Pedro del Nido, Roger Breitbart, Jami Levine, Ellen McGrath, Carolyn Dunbar-Masterson, John E. Mayer, Jr., Frank Pigula, Emile A. Bacha, Francis Fynn-Thompson; Children's Hospital of New York, Wyman Lai (PI), Beth Printz*, Daphne Hsu*, William Hellenbrand, Ismee Williams, Ashwin Prakash*, Seema Mital*, Ralph Mosca*, Darlene Servedio*, Rozelle Corda, Rosalind Korsin, Mary Nash*; Children's Hospital of Philadelphia, Victoria L. Vetter (PI), Sarah Tabbutt*, J. William Gaynor (Study Co-Chair), Chitra Ravishankar, Thomas Spray, Meryl Cohen, Marisa Nolan, Stephanie Piacentino, Sandra DiLullo*, Nicole Mirarchi*; Cincinnati Children's Medical Center, D. Woodrow Benson* (PI), Catherine Dent Krawczeski, Lois Bogenschutz, Teresa Barnard, Michelle Hamstra, Rachel Griffiths, Kathryn Hogan, Steven Schwartz*, David Nelson, Pirooz Eghtesady*; North Carolina Consortium: Duke University, East Carolina University, Wake Forest University, Page A. W. Anderson (PI) – deceased, Jennifer Li (PI), Wesley Covitz, Kari Crawford*, Michael Hines*, James Jaggers*, Theodore Koutlas, Charlie Sang, Jr., Lori Jo Sutton, Mingfen Xu; Medical University of South Carolina, J. Philip Saul (PI), Andrew Atz, Girish Shirali*, Scott Bradley, Eric Graham, Teresa Atz, Patricia Infinger; Primary Children's Medical Center and the University of Utah, Salt Lake City, Utah, L. LuAnn Minich (PI), John A. Hawkins-deceased, Michael Puchalski, Richard V. Williams, Peter C. Kouretas, Linda M. Lambert, Marian E. Shearrow, Jun A. Porter*; Hospital for Sick Children, Toronto, Brian McCrindle (PI), Joel Kirsh, Chris Caldarone, Elizabeth Radojewski, Svetlana Khaikin, Susan McIntyre, Nancy Slater; University of Michigan, Caren S. Goldberg (PI), Richard G. Ohye (Study Chair), Cheryl Nowak*; Children's Hospital of Wisconsin and Medical College of Wisconsin, Nancy S. Ghanayem (PI), James S. Tweddell, Kathleen A. Mussatto, Michele A. Frommelt, Peter C. Frommelt, Lisa Young-Borkowski.

Auxiliary Sites: Children's Hospital Los Angeles, Alan Lewis (PI), Vaughn Starnes, Nancy Pike; The Congenital Heart Institute of Florida (CHIF), Jeffrey P. Jacobs (PI), James A. Quintessenza, Paul J. Chai, David S. Cooper*, J. Blaine John, James C. Huhta, Tina Merola, Tracey Griffith; Emory University, William Mahle (PI), Kirk Kanter, Joel Bond*, Jeryl Huckaby; Nemours Cardiac Center, Christian Pizarro (PI), Carol Prospero; Julie Simons, Gina Baffa, Wolfgang A. Radtke; University of Texas Southwestern Medical Center, Ilana Zeltzer (PI), Tia Tortoriello*, Deborah McElroy, Deborah Town.

Angiography Core Laboratory: Duke University, John Rhodes, J. Curt Fudge*.

Echocardiography Core Laboratories: Children's Hospital of Wisconsin, Peter Frommelt; Children's Hospital Boston, Gerald Marx.

Genetics Core Laboratory: Children's Hospital of Philadelphia, Catherine Stolle.

Protocol Review Committee: Michael Artman (Chair); Erle Austin; Timothy Feltes, Julie Johnson, Thomas Klitzner, Jeffrey Krischer, G. Paul Matherne.

Data and Safety Monitoring Board: John Kugler (Chair); Rae-Ellen Kavey, Executive Secretary; David J. Driscoll, Mark Galantowicz, Sally A. Hunsberger, Thomas J. Knight, Holly Taylor, Catherine L. Webb.

*No longer at the institution listed.

Sources of Funding

This study was supported by grants (HL068269, HL068270, HL068279, HL068281, HL068285, HL068288, HL068290, HL068292, and HL085057) from the National Heart, Lung, and Blood Institute, National Institutes of Health. The views of the authors are their own and do not necessarily reflect an official position of the National Heart, Lung, and Blood Institute.

Disclosures

Dr Shirali is the advisory board member of the Philips Medical Systems. The other authors report no conflicts.

References

1. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, Laussen PC, Rhodes JF, Lewis AB, Mital S, Ravishankar C, Williams IA, Dunbar-Masterson C, Atz AM, Colan S, Minich LL, Pizarro C, Kanter KR, Jaggers J, Jacobs JP, Krawczeski CD, Pike N, McCrindle BW, Virzi L, Gaynor JW; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992.
2. Soriano BD, Hoch M, Ithuralde A, Geva T, Powell AJ, Kussman BD, Graham DA, Tworetzky W, Marx GR. Matrix-array 3-dimensional echocardiographic assessment of volumes, mass, and ejection fraction in young pediatric patients with a functional single ventricle: a comparison study with cardiac magnetic resonance. *Circulation*. 2008;117:1842–1848.
3. Friedberg MK, Su X, Tworetzky W, Soriano BD, Powell AJ, Marx GR. Validation of 3D echocardiographic assessment of left ventricular volumes, mass, and ejection fraction in neonates and infants with congenital heart disease: a comparison study with cardiac MRI. *Circ Cardiovasc Imaging*. 2010;3:735–742.
4. Hoch M, Vasilyev NV, Soriano B, Gauvreau K, Marx GR. Variables influencing the accuracy of right ventricular volume assessment by real-time 3-dimensional echocardiography: an *in vitro* validation study. *J Am Soc Echocardiogr*. 2007;20:456–461.
5. Song JM, Jang MK, Choi YS, Kim YJ, Min SY, Kim DH, Kang DH, Song JK. The vena contracta in functional tricuspid regurgitation: a real-time three-dimensional color Doppler echocardiography study. *J Am Soc Echocardiogr*. 2011;24:663–670.
6. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol (1985)*. 2005;99:445–457.
7. Frommelt PC, Guey LT, Minich LL, Bhat M, Bradley TJ, Colan SD, Ensing G, Gorentz J, Heydarian H, John JB, Lai WW, Levine JC, Mahle WT, Miller SG, Ohye RG, Pearson GD, Shirali GS, Wong PC, Cohen MS; Pediatric Heart Network Investigators. Does initial shunt type for the Norwood procedure affect echocardiographic measures of cardiac size and function during infancy?: the Single Vventricle Reconstruction trial. *Circulation*. 2012;125:2630–2638.
8. Friedberg MK, Silverman NH, Dubin AM, Rosenthal DN. Right ventricular mechanical dyssynchrony in children with hypoplastic left heart syndrome. *J Am Soc Echocardiogr*. 2007;20:1073–1079.
9. Khoo NS, Smallhorn JF, Kaneko S, Myers K, Kutty S, Tham EB. Novel insights into RV adaptation and function in hypoplastic left heart syndrome between the first 2 stages of surgical palliation. *JACC Cardiovasc Imaging*. 2011;4:128–137.
10. Bellsham-Revell HR, Tibby SM, Bell AJ, Witter T, Simpson J, Beerbaum P, Anderson D, Austin CB, Greil GF, Razavi R. Serial magnetic resonance imaging in hypoplastic left heart syndrome gives valuable insight into ventricular and vascular adaptation. *J Am Coll Cardiol*. 2013;61:561–570.
11. Forbes TJ, Gajarski R, Johnson GL, Reul GJ, Ott DA, Drescher K, Fisher DJ. Influence of age on the effect of bidirectional cavopulmonary anastomosis on left ventricular volume, mass and ejection fraction. *J Am Coll Cardiol*. 1996;28:1301–1307.
12. Selamet Tierney ES, Glickstein JS, Altmann K, Solowiejczyk DE, Mosca RS, Quaegebeur JM, Kleinman CS, Printz BF. Bidirectional cavopulmonary anastomosis: impact on diastolic ventricular function indices. *Pediatr Cardiol*. 2007;28:372–378.
13. Kutty S, Graney BA, Khoo NS, Li L, Polak A, Gribben P, Hammel JM, Smallhorn JF, Danford DA. Serial assessment of right ventricular volume and function in surgically palliated hypoplastic left heart syndrome using real-time transthoracic three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2012;25:682–689.
14. Haber I, Metaxas DN, Geva T, Axel L. Three-dimensional systolic kinematics of the right ventricle. *Am J Physiol Heart Circ Physiol*. 2005;289:H1826–H1833.
15. Grewal J, Majdalany D, Syed I, Pellikka P, Warnes CA. Three-dimensional echocardiographic assessment of right ventricular volume and function in adult patients with congenital heart disease: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr*. 2010;23:127–133.
16. Sugeng L, Mor-Avi V, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R, Bartolles R, Baumann R, Schummers G, Lang RM, Nesser HJ. Multimodality comparison of quantitative volumetric analysis of the right ventricle. *JACC Cardiovasc Imaging*. 2010;3:10–18.
17. Gopal AS, Chukwu EO, Iwuchukwu CJ, Katz AS, Toole RS, Schapiro W, Reichek N. Normal values of right ventricular size and function by real-time 3-dimensional echocardiography: comparison with cardiac magnetic resonance imaging. *J Am Soc Echocardiogr*. 2007;20:445–455.
18. Niemann PS, Pinho L, Balbach T, Galuschky C, Blankenhagen M, Silberbach M, Broberg C, Jerosch-Herold M, Sahn DJ. Anatomically oriented right ventricular volume measurements with dynamic three-dimensional echocardiography validated by 3-Tesla magnetic resonance imaging. *J Am Coll Cardiol*. 2007;50:1668–1676.
19. Kjaergaard J, Hastrup Svendsen J, Sogaard P, Chen X, Bay Nielsen H, Køber L, Kjaer A, Hassager C. Advanced quantitative echocardiography in arrhythmogenic right ventricular cardiomyopathy. *J Am Soc Echocardiogr*. 2007;20:27–35.
20. Kjaergaard J, Petersen CL, Kjaer A, Schaadt BK, Oh JK, Hassager C. Evaluation of right ventricular volume and function by 2D and 3D echocardiography compared to MRI. *Eur J Echocardiogr*. 2006;7:430–438.
21. Acar P, Abadir S, Roux D, Taktak A, Dulac Y, Glock Y, Fournial G. Ebstein's anomaly assessed by real-time 3-D echocardiography. *Ann Thorac Surg*. 2006;82:731–733.
22. Herberg U, Brand M, Bernhardt C, Trier HG, Breuer J. Variables influencing the accuracy of 2-dimensional and real-time 3-dimensional echocardiography for assessment of small volumes, areas, and distances: an *in vitro* study using static tissue-mimicking phantoms. *J Ultrasound Med*. 2011;30:899–908.
23. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, Faletra FF, Franke A, Hung J, de Isla LP, Kamp O, Kasprzak JD, Lancellotti

P, Marwick TH, McCulloch ML, Monaghan MJ, Nihoyannopoulos P, Pandian NG, Pellikka PA, Pepi M, Roberson DA, Shernan SK, Shirali GS, Sugeng L, Ten Cate FJ, Vannan MA, Zamorano JL, Zoghbi WA; American Society of Echocardiography; European Association of Echocardiography. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2012;25:3–46.

24. Perrin DP, Vasilyev NV, Marx GR, del Nido PJ. Temporal enhancement of 3D echocardiography by frame reordering. *JACC Cardiovasc Imaging*. 2012;5:300–304.

CLINICAL PERSPECTIVE

The potential usefulness of 3-dimensional echocardiography for longitudinal evaluation of the systemic right ventricle was evaluated in a randomized study of infants with single right ventricular anomalies undergoing a Norwood procedure. Longitudinal evaluation was performed pre-Norwood, post-Norwood, pre–stage II, and at 14 months. Adequate images for quantitative analysis could be obtained in 75% of echocardiograms. Important findings included an increase in body surface area–adjusted right ventricular volume post-Norwood that decreased after a stage II procedure, reflecting the anticipated response to changes in cardiac output and pulmonary blood flow. Ejection fraction was unchanged after Norwood and fell slightly but progressively at each of the subsequent 2 evaluations. Severity of tricuspid regurgitation increased after Norwood but did not improve with the fall in right ventricular volume after stage II. No statistically significant differences were found between groups managed with modified Blalock-Taussig or right ventricle-to-pulmonary artery shunt. This experience demonstrates the feasibility of quantitative 3-dimensional echocardiographic evaluation of the single right ventricular heart in a large cohort of infants and young children as well as the pattern of evolution of right ventricular size and function and severity of tricuspid regurgitation before the Fontan procedure. Important limitations of the technique that were identified include failure to obtain adequate images in 25% of samples, the importance of prior experience in this imaging modality to obtaining adequate images, and a higher success rate in younger patients.

Circulation
Cardiovascular Imaging

American Heart Association®

Multicenter Study Comparing Shunt Type in the Norwood Procedure for Single-Ventricle Lesions: Three-Dimensional Echocardiographic Analysis

Gerald R. Marx, Girish Shirali, Jami C. Levine, Lin T. Guey, James F. Cnota, Jeanne M. Baffa, William L. Border, Steve Colan, Gregory Ensing, Mark K. Friedberg, David J. Goldberg, Salim F. Idriss, J. Blaine John, Wyman W. Lai, Minmin Lu, Shaji C. Menon, Richard G. Ohye, David Saudek, Pierre C. Wong and Gail D. Pearson
for the Pediatric Heart Network Investigators

Circ Cardiovasc Imaging. 2013;6:934-942; originally published online October 4, 2013;
doi: 10.1161/CIRCIMAGING.113.000304
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080