Doppler Flow Patterns in the Right Ventricle–to–Pulmonary Artery Shunt and Neo-Aorta in Infants with Single Right Ventricle Anomalies: Impact on Outcome after Initial Staged Palliations

Peter C. Frommelt, MD, Eric Gerstenberger, MS, Jeanne Baffa, MD, William L. Border, MBChB, MPH, Tim J. Bradley, MBChB, MPH, Steven Colan, MD, Jessica Gorentz, RDCS, Haleh Heydarian, MD, J. Blaine John, MD, Wyman W. Lai, MD, MPH, Jami Levine, MD, Jimmy C. Lu, MD, Rachel T. McCandless, MD, Stephen Miller, MD, Arni Nutting, MD, Richard G. Ohye, MD, Gail D. Pearson, MD, ScD, Pierre C. Wong, MD, and Meryl S. Cohen, MD, for the Pediatric Heart Network Investigators, *Milwaukee, Wisconsin; Watertown and Boston, Massachusetts; Wilmington, Delaware; Atlanta, Georgia; Toronto, Ontario, Canada; Cincinnati, Ohio; Tampa, Florida; New York, New York; Salt Lake City, Utah; Durham, North Carolina; Charleston, South Carolina; Bethesda, Maryland; Los Angeles, California; Philadelphia, Pennsylvania*

Background: A Pediatric Heart Network trial compared outcomes in infants with single right ventricle anomalies undergoing Norwood procedures randomized to modified Blalock-Taussig shunt (MBTS) or right ventricle–to–pulmonary artery shunt (RVPAS). Doppler patterns in the neo-aorta and RVPAS may characterize physiologic changes after staged palliations that affect outcomes and right ventricular (RV) function.

Methods: Neo-aortic cardiac index (CI), retrograde fraction (RF) in the descending aorta and RVPAS conduit, RVPAS/neo-aortic systolic ejection time ratio, and systolic/diastolic (S/D) ratio were measured early after Norwood, before stage II palliation, and at 14 months. These parameters were compared with transplantation-free survival, length of hospital stay, and RV functional indices.

Results: In 529 subjects (mean follow-up period, 3.0 $\pm$ 2.1 years), neo-aortic CI and descending aortic RF were significantly higher in the MBTS cohort after Norwood. The RVPAS RF averaged <25% at both interstage intervals. Higher pre–stage II descending aortic RF was correlated with lower RV ejection fraction ($R = -0.24$; $P = .032$) at 14 months for the MBTS cohort. Higher post-Norwood CI (5.6 vs 4.4 L/min/m^2, $P = .04$) and lower S/D ratio (1.40 vs 1.68, $P = .01$) were correlated with better interstage transplantation-free survival for the RVPAS cohort. No other Doppler flow patterns were correlated with outcomes.

Conclusions: After the Norwood procedure, infants tolerated significant descending aortic RF (MBTS) and conduit RF (RVPAS), with little correlation with clinical outcomes or RV function. Neo-aortic CI, ejection time, and S/D ratios also had limited correlations with outcomes or RV function, but higher post-Norwood neo-aortic CI and lower S/D ratio were correlated with better interstage survival in those with RVPAS. (J Am Soc Echocardiogr 2013;26:521-9.)

Keywords: Hypoplastic left heart syndrome, Norwood, Echocardiography, Single ventricle

From the Medical College of Wisconsin, Milwaukee, Wisconsin (P.C.F., J.G.); the New England Research Institute, Watertown, Massachusetts (E.G.); the Alfred I. DuPont Hospital for Children, Wilmington, Delaware (J.B.); Emory University School of Medicine, Atlanta, Georgia (W.L.B.); the Hospital for Sick Children, Toronto, Ontario, Canada (T.J.B.); Boston Children's Hospital, Boston, Massachusetts (S.C., J.L.); Cincinnati Children's Hospital, Cincinnati, Ohio (H.H.); the Congenital Heart Institute of Florida/Pediatrix, Tampa, Florida (J.B.J.); Columbia University Medical Center, New York, New York (W.W.L.); the University of Michigan, Ann Arbor, Michigan (J.C.L., R.G.O.); the University of Utah, Salt Lake City, Utah (R.T.M.); Duke University, Durham, North Carolina (S.M.); Medical University of South Carolina, Charleston, South Carolina (A.N.); the National Heart, Lung, and Blood Institute, Bethesda, Maryland (G.D.P.); Children's Hospital of Los Angeles, Los Angeles, California (P.C.W.); and The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (M.S.C.).

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Reprint requests: Peter C. Frommelt, MD, Children's Hospital of Wisconsin, 9000 W. Wisconsin Avenue, MS 713, Milwaukee, WI 53226 (E-mail: *pfrommelt@chw.org*).

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Abbreviations

HLHS = Hypoplastic left heart syndrome

MBTS = Modified Blalock-Taussig shunt

MPI = Myocardial performance index

RV = Right ventricular

RVPAS = Right ventricle–to–pulmonary artery shunt

SVR = Single Ventricle Reconstruction

Initial surgical palliation for hypoplastic left heart syndrome (HLHS) and other single right ventricular (RV) anatomic variants has evolved to two different strategies that vary on the basis of the source of pulmonary blood flow: the modified Blalock-Taussig shunt (MBTS)[1] or the right ventricle–to–pulmonary artery shunt (RVPAS).[2] These surgical strategies result in different physiologic states that affect flow patterns in the reconstructed aorta (neo-aorta).[3] In a patient with HLHS and an MBTS, all RV cardiac output is exclusively ejected into the neo-aorta before being distributed to the systemic and pulmonary vascular beds; the aortopulmonary shunt allows diastolic "steal" of systemic blood into the pulmonary vascular bed. This is in contrast to a patient with HLHS and an RVPAS, in whom RV cardiac output is distributed directly to both the systemic vascular bed (through the neo-aorta) and the pulmonary vascular bed (through the RVPAS) during systole. No diastolic steal is present, but an additional volume load is placed on the right ventricle as a result of diastolic retrograde flow from the pulmonary artery back into the right ventricle through the nonvalved conduit. Changes in RV systolic and diastolic function, altered systemic and pulmonary vascular resistances, and anatomic resistance to flow into both shunts can affect these neo-aortic and RVPAS flow patterns and are identifiable by Doppler interrogation using echocardiography after initial staged palliation. Specifically, these patterns can estimate neo-aortic cardiac output, antegrade and retrograde flow profiles in the RVPAS and descending aorta (to quantify retrograde fractions through the shunt and neo-aortic arch), and systolic ejection times into the RVPAS and neoaorta (which should reflect relative resistance to flow into the two vascular beds).[4]

Currently, there is no single measure that defines RV function by echocardiography. Two-dimensional assessment of RV volumes and ejection fraction is difficult because of the complex geometry of the chamber. The systolic-to-diastolic duration ratio, as calculated from the tricuspid regurgitation spectral Doppler signal, has been shown to be an indicator of global RV function in children with HLHS, with an increasing ratio correlated with poorer RV function.[5] The calculation of the systolic-to-diastolic duration ratio is made by measuring the systolic duration (from onset to cessation of regurgitant flow from the tricuspid insufficiency jet) and diastolic duration (the time when there is no tricuspid insufficiency flow signal). These intervals can also be calculated from spectral Doppler flow patterns in the RVPAS (measuring systolic antegrade and diastolic retrograde time intervals) in infants with HLHS who have undergone the Sano modification for stage I palliation. This new ratio is attractive because it would be available and easily obtained by echocardiography in every infant with an RVPAS; this is in contrast to calculation of the ratio from tricuspid regurgitation, for which a measureable Doppler signal is available in only about 80% of infants with HLHS.[5]

The Pediatric Heart Network Single Ventricle Reconstruction (SVR) trial compared outcomes in 549 infants undergoing Norwood procedures randomized to either MBTS or RVPAS at 15 North American centers.[6] As part of the SVR trial, two-dimensional and Doppler echocardiographic studies were evaluated at a core laboratory.[3] Echocardiographic indices were measured with the purpose of assessing the effect of MBTS versus RVPAS at four stages during the trial. Correlations of neo-aortic and RVPAS flow patterns with clinical outcomes in the SVR cohort have not been previously examined. In the present study, we analyzed Doppler indices of neo-aortic and RVPAS flow to more fully characterize the SVR cohort. We specifically wanted to compare these Doppler flow patterns with rates of transplantation-free survival, length of hospital stay, indices of RV size and systolic/global function, and degree of tricuspid regurgitation before and after the staged surgical palliations performed during the first 14 months of life.

METHODS

Study Design

The SVR study design[7], primary outcome[6] (incidence of death or cardiac transplantation at 12 months after randomization), and secondary outcomes[6] (morbidity during hospitalizations for the Norwood and stage II procedures, unintended cardiovascular interventions and rate of serious adverse events through 12 months, angiographically derived pulmonary artery size before the stage II procedure), and risk factors for mortality and cardiac transplantantion[8] have been previously published. Secondary echocardiographic markers of outcomes, including indices of RV function, cardiac and vascular dimensions, valve annular dimensions and function, and neoaortic flow patterns in survivors of the Norwood procedure, have been previously summarized and were shown to be similar for subjects with MBTS and RVPAS by 14 months of age.[3]

Echocardiographic Analysis

An echocardiography core laboratory at the Medical College of Wisconsin reviewed two-dimensional and Doppler echocardiograms performed at each clinical center to compare indices between shunt groups at four predesignated time intervals during the study: (1) baseline (before the Norwood procedure) at a mean of 2.1 ± 3.4 days of age, (2) after Norwood (either at the time of discharge or at approximately 30 days of age if still hospitalized) at a mean of 22.1 ± 12.6 days of age, (3) before stage II (during the preoperative evaluation for the stage II procedure) at a mean of 4.7 ± 1.5 months of age, and (4) 14 months of age (end of study visit) at a mean of 14.3 ± 1.2 months. Core lab procedures for image analysis and data management have been previously described.[3]

Five Doppler indices were the focus of this study:

- Neo-aortic cardiac index, calculated as stroke volume across the neo-aortic valve: [(neo-aortic velocity-time integral) × (neo-aortic valve area)] × heart rate (beats/min) indexed to body surface area (m^2).
- Descending aortic retrograde fraction, calculated as the percentage of retrograde diastolic flow in the descending aorta, using pulsed-wave Doppler from the suprasternal notch window to measure velocity-time integrals of antegrade systolic and retrograde diastolic flow in the descending aorta: (diastolic velocity-time integral/systolic velocity time integral) × 100.
- RVPAS retrograde fraction, calculated as the percentage of retrograde diastolic flow in the RVPAS, using pulsed-wave Doppler to measure velocity-time integrals of antegrade systolic and retrograde diastolic flow within the midportion of the shunt: (diastolic velocity-time integral/systolic velocity-time integral) × 100.
- Ratio of RVPAS to neo-aortic ejection times, calculated as the ratio of the durations of systolic flow from the Doppler jets at the midportion of the shunt and at the neo-aortic annulus: RVPAS systolic ejection time/neo-aortic systolic ejection time.
- Systolic-to-diastolic duration ratio in subjects with RVPAS, calculated as the ratio of the systolic duration (from onset to cessation of antegrade flow within the shunt) to diastolic duration (from cessation to onset of antegrade flow within the shunt) obtained from pulsed Doppler tracings in the midportion of the RVPAS (Figure 1): systolic duration/diastolic duration.

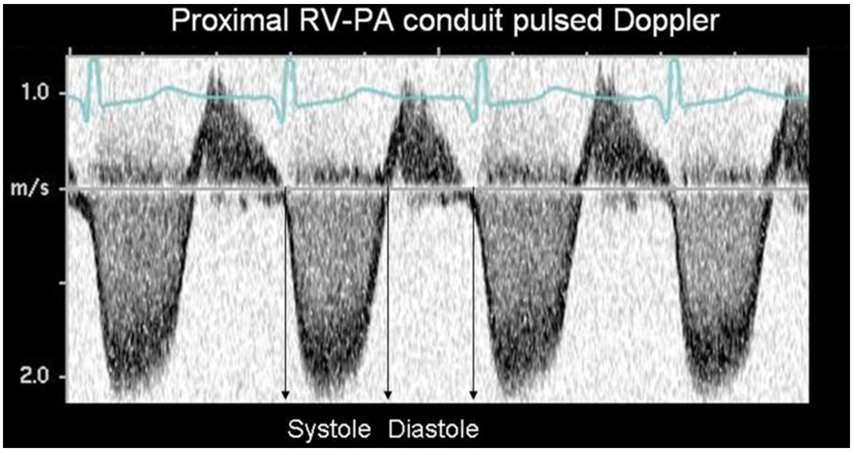

Figure 1 Systolic and diastolic time intervals obtained from flow signals in the mid-RVPAS with pulsed-wave Doppler echocardiography in an infant with HLHS after the Norwood procedure. The systolic duration is defined as the time from onset to cessation of antegrade flow (the flow signal below the baseline) and the diastolic duration as the time from cessation to onset of antegrade flow within the shunt (see *arrows*). *PA*, Pulmonary artery; *RV*, right ventricle.

Outcomes to compare with these Doppler measures included the following:

1. Transplantation-free survival for the following intervals:
   a. Interstage (Norwood discharge to stage II admission)
   b. Baseline and post-Norwood echocardiographic studies to stage II admission
   c. Pre–stage II echocardiographic study to stage II discharge
   d. Stage II discharge to latest follow-up
   e. Long-term (from the time of each echocardiographic study to latest follow-up)
2. Length of intensive care unit stay after Norwood (for the baseline and post-Norwood echocardiographic studies); length of intensive care unit stay after stage II (for the pre–stage II echocardiographic study)
3. Length of hospital stay after Norwood (for the baseline and post-Norwood echocardiographic studies); length of hospital stay after stage II (for the pre–stage II echocardiographic study)
4. Indexed RV end-diastolic and end-systolic volumes, RV ejection fraction, and RV fractional area change (calculated as previously described[3]) from each echocardiographic study for the RVPAS and MBTS subgroups
5. Severity of tricuspid regurgitation, graded by color Doppler jet width, creating two groups defined as those with less than moderate regurgitation (jet width < 2.5 mm) and those with moderate or greater regurgitation (jet width ≥ 2.5 mm) from each echocardiographic study for the RVPAS and MBTS subgroups
6. Myocardial performance index (MPI), calculated two ways; from blood flow Doppler and annular Doppler tissue imaging measures as previously described,[3] from each echocardiographic study for the RVPAS and MBTS subgroups

Statistical Analysis

Summary descriptive statistics of echocardiographic indices are presented (by shunt type in place at the end of the Norwood operation) at each echocardiographic interval. Hazard ratios and *P* values were calculated from a Cox proportional-hazards regression predicting time to death or transplantation for each time interval as a function of each Doppler variable. For the six continuous echocardiographic outcomes (RV end-diastolic volume indexed to body surface area, RV end-systolic volume indexed to body surface area, RV ejection fraction, RV area change expressed as a percentage, and MPI using both the pulsed Doppler and Doppler tissue imaging calculations), separate univariate regressions were performed for each combination of the Doppler measure as a predictor of the echocardiographic outcome. For the one dichotomous outcome (at least moderate tricuspid valve regurgitation), separate logistic regressions were performed predicting at least moderate tricuspid valve regurgitation as a function of each of the Doppler measures. Correlations and regression results with *P* values < .05 were considered significant. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Table 1 Numbers of subjects with at least one Doppler measurement available at each echocardiographic study interval

Visit	Echocardiography	Doppler assessment
Pre-Norwood	529	315
Post-Norwood	468	433
Pre–Stage II	379	356

RESULTS

There were 549 SVR trial subjects; as previously described,[6] five additional subjects who did not undergo the Norwood procedure and one subject who withdrew from the trial in week 1 were excluded. A total of 268 infants undergoing Norwood procedures received MBTS, and 281 infants received RVPAS; all were included in this study cohort except for 17 subjects who had both shunts in place after the initial Norwood procedure or who crossed over to a different shunt after the initial Norwood procedure. In addition, three subjects underwent biventricular repair after the initial Norwood procedure and were also excluded from these analyses.

All available data from the remaining 529 SVR subjects' baseline, post-Norwood, pre–stage II, and 14-month echocardiograms were included in the study cohort. Fifteen subjects underwent heart transplantation before their 14-month visits, so only echocardiographic data collected before the date of heart transplantation were included in these analyses. Mean follow-up for the entire cohort from the time of initial pre-Norwood echocardiography was 3.0 ± 2.1 years (median, 3.9 years). Table 1 summarizes the number of protocol echocardiograms obtained at each stage throughout the trial (the primary reasons for failure to obtain an echocardiogram being death or transplantation) and the number of echocardiograms that had at least

Table 2 Doppler measures at each study interval by shunt type

Variable	MBTS	RVPAS	*P*
Pre-Norwood			
Neo-aortic cardiac index (L/min/m^2)	9.37 ± 3.69 (*n* = 166)	8.67 ± 3.25 (*n* = 148)	.07
Post-Norwood			
Neo-aortic cardiac index (L/min/m^2)	8.10 ± 2.67 (*n* = 198)	4.43 ± 2.04 (*n* = 190)	<.001
Descending aortic retrograde fraction	0.45 ± 0.16 (*n* = 195)	0.04 ± 0.12 (*n* = 187)	<.001
RVPAS retrograde fraction	NA	0.23 ± 0.08 (*n* = 161)	—
Ratio of RVPAS to neo-aortic ejection time	NA	1.49 ± 0.20 (*n* = 155)	—
Systolic/diastolic duration ratio	NA	1.41 ± 0.34 (*n* = 170)	—
Pre–stage II			
Neo-aortic cardiac index (L/min/m^2)	9.42 ± 3.10 (*n* = 145)	6.15 ± 2.37 (*n* = 171)	<.001
Descending aortic retrograde fraction	0.41 ± 0.19 (*n* = 129)	0.06 ± 0.14 (*n* = 158)	<.001
RVPAS retrograde fraction	NA	0.20 ± 0.07 (*n* = 126)	—
Ratio of RVPAS to neo-aortic ejection time	NA	1.43 ± 0.17 (*n* = 126)	—
Systolic/diastolic duration ratio	NA	1.64 ± 0.55 (*n* = 134)	—

NA, Not applicable.
Data are expressed as mean ± SD.

one Doppler measure available for analysis. Table 2 summarizes the mean values for each Doppler measure at each time interval for both shunt groups, and Tables 3 and 4 summarize the correlation between the Doppler measures and transplantation-free survival during the different intervals for each shunt group. A brief summary of the findings for each Doppler measure as it relates to RV function and clinical outcomes is described below.

Neo-aortic Cardiac Output

Indexed neo-aortic cardiac output was significantly higher in the MBTS compared with the RVPAS cohort at both interstage intervals (Table 2). In the RVPAS cohort, the 12 subjects who died or required heart transplantation before stage II surgery had lower post-Norwood neo-aortic cardiac indices (5.6 vs 4.4 L/min/m^2; hazard ratio, 1.22; 95% confidence interval, 1.01−1.48; *P* = .04) than the interstage transplantation-free survivors. In addition, a higher pre–stage II neo-aortic cardiac index was correlated with increased RV end-diastolic (*R* = 0.25, *P* = .007) and end-systolic volume (*R* = 0.25 l, *P* = .008) at 14 months in the RVPAS cohort. In the MBTS cohort, the five patients who died or required heart transplantation before discharge after stage II surgery had a trend toward a lower pre–stage II neo-aortic cardiac index (6.4 vs 9.5 L/min/m^2 in the survivors), but this did not reach significance as a predictor of death or heart transplantation during this period (hazard ratio, 0.58; 95% confidence interval, 0.33−1.02; *P* = .06). No other differences in survival, length of hospital stay, or standard echocardiographic indices (RV size, ejection fraction, fractional area change, MPI, or degree of tricuspid regurgitation) were correlated with neo-aortic cardiac output for either the RVPAS or MBTS cohort at any interval.

Descending Aortic Retrograde Fraction

Descending aortic retrograde fractions were significantly higher in subjects with MBTS (45% after Norwood and 41% before stage II) compared with those with RVPAS (4% after Norwood and 6% before stage II). The descending aortic retrograde fraction was not associated with transplantation-free survival or length of stay for subjects with either shunt type at any interval; in fact, the retrograde fraction at the post-Norwood echocardiographic study was similar in the MBTS group for survivors and those who died or required transplantation during the interstage period (45% vs 43%), during the interval to stage II surgery (45% vs 46%), and at latest long-term follow-up (45% vs 45%). For the RVPAS cohort, higher post-Norwood descending aortic retrograde fraction was correlated with higher RV end-diastolic volume (R = 0.19, *P* = .035) at pre–stage II echocardiographic studies, and higher pre–stage II descending aortic retrograde fraction was correlated with higher RV end-diastolic (*R* = 0.36, *P* < .001) and end-systolic (*R* = 0.25, *P* = .011) volumes at 14 months. The number of RVPAS subjects with measureable retrograde fractions, however, was small. RV volumes were not correlated with descending aortic retrograde fraction for the MBTS cohort, but a higher pre–stage II retrograde fraction did correlate with lower RV ejection fraction (*R* = −0.24, *P* = .032) at 14 months for that group. No other differences in RV size or functional indices (ejection fraction, fractional area change, MPI, or degree of tricuspid regurgitation) were correlated with descending aortic retrograde fraction for either group at any interval.

RVPAS Retrograde Fraction

The mean RVPAS retrograde fraction was 23 ± 8% at the post-Norwood study and 20 ± 7% at the pre–stage II study. The RVPAS retrograde fraction was not correlated with transplantation-free survival or length of hospital stay for the RVPAS subjects at any interval. Similar to the descending aortic retrograde fraction for the MBTS, the RVPAS retrograde fraction percentage estimated at the post-Norwood echocardiographic study was similar for survivors and nonsurvivors for the intervals from the post-Norwood study to stage II surgery (23% vs 25%), during the interstage period (23% vs 22%), and at long-term follow-up (23% vs 24%). RV size and functional indices also were not correlated with RVPAS retrograde fraction except at the post-Norwood study, when a higher fraction was correlated with higher MPI as calculated by blood flow Doppler (*R* = 0.22, *P* = .015) and lower MPI as calculated by annular Doppler tissue imaging (*R* = −0.30, *P* = .027) at the pre–stage II echocardiographic study.

Ratio of RVPAS to Neoaortic Ejection Time

The RVPAS ejection time was prolonged relative to the neo-aortic ejection time at both the interstage intervals for the RVPAS cohort, with ratios of 1.49 ± 0.20 at the pre-Norwood study and 1.43 ± 0.17 at the pre–stage II study. The RVPAS-to-neo-aortic ejection time ratio was not correlated with transplantation-free survival, length

Table 3 Correlations of Doppler measures at each study interval with interstage survival, survival to stage II discharge, and long-term survival for the MBTS cohort

	Interstage death/heart transplantation		Death/heart transplantation from date of echocardiography to stage II surgery		Long-term death/heart transplantation from date of echocardiography	
Variable	Yes	No	Yes	No	Yes	No
Pre-Norwood predictors						
Neo-aortic cardiac index (L/min/m^2)	9.17 ± 4.32 (*n* = 22)	9.54 ± 3.78 (*n* = 112)	8.93 ± 3.69 (*n* = 47)	9.55 ± 3.69 (*n* = 119)	9.05 ± 3.49 (*n* = 58)	9.55 ± 3.80 (*n* = 108)
HR	0.97		0.96		0.97	
P	.58		.28		.37	
Post-Norwood predictors						
Neo-aortic cardiac index (L/min/m^2)	7.55 ± 2.02 (*n* = 39)	8.24 ± 2.73 (*n* = 136)	7.71 ± 2.40 (*n* = 53)	8.24 ± 2.76 (*n* = 145)	7.91 ± 2.76 (*n* = 68)	8.20 ± 2.63 (*n* = 130)
HR	0.91		0.93		0.96	
P	.15		.22		.36	
Descend aortic retrograde fraction	0.43 ± 0.16 (*n* = 38)	0.45 ± 0.14 (*n* = 135)	0.46 ± 0.21 (*n* = 50)	0.45 ± 0.15 (*n* = 145)	0.45 ± 0.19 (*n* = 66)	0.45 ± 0.15 (*n* = 129)
HR	0.54		1.58		1.21	
P	.59		.61		.81	

	Death/heart transplantation from date of echocardiography to stage II discharge		Long-term death/heart transplantation from date of stage II discharge		Long-term death/heart transplantation from date of echocardiography	
	Yes	No	Yes	No	Yes	No
Pre–stage II predictors						
Neo-aortic cardiac index (L/min/m^2)	6.43 ± 1.18 (*n* = 5)	9.53 ± 3.10 (*n* = 140)	9.28 ± 2.16 (*n* = 9)	9.54 ± 3.16 (*n* = 131)	8.26 ± 2.30 (*n* = 14)	9.54 ± 3.16 (*n* = 131)
HR	0.58		0.97		0.86	
P	.06		.76		.12	
Descending aortic retrograde fraction	0.49 ± 0.09 (*n* = 6)	0.41 ± 0.19 (*n* = 123)	0.31 ± 0.14 (*n* = 10)	0.41 ± 0.19 (*n* = 113)	0.38 ± 0.15 (*n* = 16)	0.41 ± 0.19 (*n* = 113)
HR	13.02		0.02		0.32	
P	.21		.05		.43	

HR, Hazard ratio.
Data are expressed as mean ± SD.

Table 4 Correlation of Doppler measures at each study interval with interstage survival, survival to stage II discharge, and long-term survival for the RVPAS cohort

Variable	Interstage death/heart transplantation		Death/heart transplantation from date of echocardiography to stage II surgery		Long-term death/heart transplantation from date of echocardiography	
	Yes	No	Yes	No	Yes	No
Pre-Norwood predictors						
Neo-aortic cardiac index (L/min/m^2)	11.21 ± 5.50 (*n* = 4)	8.79 ± 3.21 (*n* = 120)	8.00 ± 3.55 (*n* = 25)	8.81 ± 3.18 (*n* = 123)	8.34 ± 3.36 (*n* = 44)	8.81 ± 3.20 (*n* = 104)
HR	1.19		0.92		0.96	
P	.18		.24		.38	
Post-Norwood predictors						
Neo-aortic cardiac index (L/min/m^2)	4.37 ± 1.99 (*n* = 12)	5.58 ± 2.08 (*n* = 167)	4.87 ± 2.38 (*n* = 15)	4.41 ± 2.02 (*n* = 173)	4.21 ± 1.88 (*n* = 49)	4.51 ± 2.09 (*n* = 141)
HR	1.22		1.08		0.95	
P	.042		.43		.52	
Descending aortic retrograde fraction	0.00 ± 0.00 (*n* = 12)	0.04 ± 0.12 (*n* = 162)	0.00 ± 0.00 (*n* = 16)	0.04 ± 0.12 (*n* = 169)	0.04 ± 0.11 (*n* = 49)	0.04 ± 0.12 (*n* = 138)
HR	0.00		0.00		1.29	
P	.99		.99		.83	
RVPAS retrograde fraction	0.22 ± 0.09 (*n* = 9)	0.23 ± 0.08 (*n* = 140)	0.25 ± 0.09 (*n* = 13)	0.23 ± 0.08 (*n* = 146)	0.24 ± 0.07 (*n* = 43)	0.23 ± 0.08 (*n* = 118)
HR	2.38		37.22		5.24	
P	.83		.25		.36	
Ratio of RVPAS to neo-aortic ejection time	1.56 ± 0.12 (*n* = 9)	1.48 ± 0.19 (*n* = 135)	1.58 ± 0.18 (*n* = 13)	1.48 ± 0.19 (*n* = 140)	1.50 ± 0.18 (*n* = 42)	1.49 ± 0.20 (*n* = 113)
HR	4.68		4.63		1.27	
P	.36		.25		.75	
Systolic/diastolic time ratio	1.68 ± 0.20 (*n* = 9)	1.40 ± 0.33 (*n* = 149)	1.56 ± 0.31 (*n* = 13)	1.40 ± 0.34 (*n* = 155)	1.45 ± 0.30 (*n* = 44)	1.40 ± 0.35 (*n* = 126)
HR	10.22		2.90		1.42	
P	.010		.16		.41	

	Death/heart transplantation from date of echocardiography to stage II discharge		Long-term death/heart transplantation from date of stage II discharge		Long-term death/heart transplantation from date of echocardiography	
	Yes	No	Yes	No	Yes	No
Pre–stage II predictors						
Neo-aortic cardiac index (L/min/m^2)	6.49 ± 1.40 (*n* = 6)	6.13 ± 2.40 (*n* = 165)	5.67 ± 2.27 (*n* = 28)	6.23 ± 2.43 (*n* = 137)	5.82 ± 2.15 (*n* = 34)	6.23 ± 2.43 (*n* = 137)
HR	1.01		0.91		0.94	
P	.97		.32		.44	
Descending aortic retrograde fraction	0.00 ± 0.00 (*n* = 6)	0.06 ± 0.14 (*n* = 152)	0.08 ± 0.14 (*n* = 23)	0.06 ± 0.14 (*n* = 129)	0.06 ± 0.13 (*n* = 29)	0.06 ± 0.14 (*n* = 129)
HR	0.00		2.40		1.30	
P	>.99		.48		.83	
RVPAS retrograde fraction	0.22 ± 0.06 (*n* = 5)	0.20 ± 0.07 (*n* = 121)	0.20 ± 0.07 (*n* = 16)	0.20 ± 0.08 (*n* = 105)	0.20 ± 0.06 (*n* = 21)	0.20 ± 0.08 (*n* = 105)
HR	76.37		1.09		2.87	
P	.49		.98		.72	
Ratio of RVPAS to neo-aortic ejection time	1.53 ± 0.05 (*n* = 4)	1.43 ± 0.17 (*n* = 122)	1.44 ± 0.14 (*n* = 18)	1.42 ± 0.18 (*n* = 104)	1.46 ± 0.13 (*n* = 22)	1.42 ± 0.18 (*n* = 104)
HR	37.33		1.66		2.53	
P	.19		.69		.40	
Systolic/diastolic time ratio	1.58 ± 0.30 (*n* = 5)	1.64 ± 0.56 (*n* = 129)	1.62 ± 0.37 (*n* = 19)	1.64 ± 0.58 (*n* = 110)	1.61 ± 0.35 (*n* = 24)	1.64 ± 0.58 (*n* = 110)
HR	0.93		0.97		0.94	
P	.94		.95		.87	

HR, Hazard ratio.
Data are expressed as mean ± SD.

of hospital stay, or RV size or functional indices for the RVPAS subjects at any interval. Although the ratio tended to be lower in subjects who survived the interstage period to stage II surgery (1.48 vs 1.58, $P = .25$), it was almost identical when compared between the 113 long-term survivors who had this measure and the 42 who died or underwent transplantation (1.50 vs1.49, $P = .78$).

Systolic-to-Diastolic Duration Ratio

Systolic duration was prolonged relative to diastolic duration at both the post-Norwood (1.41 ± 0.34) and pre–stage II (1.64 ± 0.55) studies for the RVPAS cohort. A lower post-Norwood systolic-to-diastolic duration ratio was correlated with better interstage transplantation-free survival (hazard ratio, 10.22; 95% confidence interval, 1.76–59.27; $P = .01$; with a mean value of 1.40 for the survivors vs 1.68 for those who died or required transplantation during that interval). In addition, a ratio > 1.6 at the post-Norwood echocardiographic study was associated with significantly increased risk for death or transplantation during the interstage period (hazard ratio, 5.42; 95% confidence interval, 1.35–21.73; $P = .017$). This ratio was not a significant predictor of long-term death or need for transplantation (1.40 vs 1.45; hazard ratio, 1.42; 95% confidence interval, 0.62–3.26; $P = .41$). No other differences in transplantation-free survival, length of hospital stay, or RV size or functional indices were correlated with the systolic-to-diastolic duration ratio for the RVPAS subjects at the post-Norwood or pre–stage II interval.

DISCUSSION

This is the first study to characterize neo-aortic and RVPAS Doppler flow patterns and to assess their impact on clinical outcomes and RV function in a large cohort of infants with single right ventricle anomalies after Norwood palliation during the first year of life. The physiology that results after the Norwood procedure presents unique hemodynamic burdens to the single right ventricle that vary by the type of shunt used to supply pulmonary blood flow. These burdens have the potential to affect indices of RV function, as well as patient recovery and survival after surgery. A previous SVR publication[3] reported that echocardiographic indices of cardiac size and function after the Norwood procedure were similar between groups for the MBTS and RVPAS survivors by 14 months of age. The few interstage differences when the shunt was in place (smaller neo-aortic annular dimensions, shorter neo-aortic systolic ejection times, lower neo-aortic cardiac index, decreased peak aortic arch velocities, and increased Doppler-calculated MPI in the RVPAS compared with the MBTS) resolved by 14 months with removal of the shunt after stage II palliation. The present analysis specifically focused on Doppler-derived quantitative measures of neo-aortic cardiac output, volume of retrograde diastolic flow in the descending aorta, volume of retrograde flow in the RVPAS, and ratios of duration of flow into the RVPAS and neoaorta, as well as RV systolic-to-diastolic duration. We discuss findings for each of the Doppler measures in more detail below.

Neo-aortic Cardiac Output

Flow across the neo-aortic valve should reflect systemic output in patients after the Norwood procedure with an RVPAS and total RV output after the Norwood procedure with an MBTS, so it is not surprising that we found significantly lower indexed neo-aortic output in the RVPAS compared with the MBTS cohort at both interstage intervals. This difference has been previously described for the SVR cohort.[3] We also identified better interstage transplantation-free survival for the RVPAS subjects with higher post-Norwood output and better stage II surgical survival to discharge for the MBTS subjects with higher pre–stage II output, although the number of nonsurvivors was small. In addition, significantly increased RV volumes at 14 months in those RVPAS subjects was observed in association with increased neo-aortic cardiac output at the pre–stage II echocardiographic study, but that correlation is difficult to explain from better systemic output alone. It seems more likely that this dilatation is secondary to additional chronic volume-loading abnormalities that require higher RV output, such as the development of aortopulmonary collaterals (which were not quantified in this study).

For most of the variables, echocardiographic estimates of neo-aortic cardiac output appear to have limited correlation with clinical outcomes (length of hospital stay or transplantation-free survival) or echocardiographic indices of RV size or function and tricuspid valve function at any stage or with either shunt type. The lack of correlation between echocardiography-estimated neo-aortic cardiac output and clinical outcomes and RV functional status emphasizes the influence of other factors[8] (gestational age, presence of obstructed pulmonary venous return, presence of genetic syndromes, HLHS anatomic subtype, shunt patency) that affect outcomes. Importantly, estimates of cardiac output by echocardiography can be unreliable because of errors in technique (requiring accurate estimates of neo-aortic valve cross-sectional area and laminar flow measured at the valve annulus). These errors likely led to the high-volume neo-aortic flow found in this study, which exceeded the expected neo-aortic cardiac output for this patient population. This error may be exaggerated when assessing flow through the pulmonary (neo-aortic) valve because of dynamically changing annular size during systole compared with assessment through the native aortic valve.[9]

Descending Aortic Retrograde Fraction

The MBTS results in continuous runoff from the aorta into the pulmonary arteries after the Norwood procedure,[10] and this physiology was reflected in the significant descending aortic retrograde diastolic flow seen in the MBTS cohort in this study. Although increased retrograde flow could result in more RV volume overload and potentially lower systemic (and coronary) diastolic pressure, echocardiographic estimates of retrograde descending aortic flow had limited correlation with clinical outcomes or echocardiographic indices of RV size and function in this group of patients. This is surprising, as the MBTS cohort would seem to be at highest risk for adverse events related to the diastolic steal. Altered coronary perfusion secondary to diastolic steal may help explain the decreased RV ejection fraction found at 14 months in those MBTS subjects with higher descending aortic retrograde flow. The overall lack of correlation between descending aortic retrograde flow and RV functional status and clinical outcomes again emphasizes the multiple factors that contribute to the RV hemodynamic burden after Norwood with an MBTS. As expected, significant retrograde flow was unusual in the RVPAS cohort.

Right Ventricle–to–Pulmonary Artery Conduit Retrograde Fraction

The diastolic retrograde flow through the RVPAS places an additional volume load on the single right ventricle in infants after the Norwood procedure; an increased retrograde fraction could potentially affect RV size and function as well as clinical outcomes. In the SVR cohort, we found no correlation between the Doppler-derived RVPAS retrograde fraction and any index of RV size or function; in addition, adverse clinical outcomes were not correlated with the degree of retrograde flow estimated by Doppler. The predicted retrograde fraction for the group generally ranged from 20% to 25%, suggesting a mild degree of conduit regurgitation despite the absence of a valved conduit. This may help explain our previously published finding from the SVR cohort that identified smaller RV size in the RVPAS cohort compared with the MBTS cohort,[3] as the impact of the RVPAS retrograde flow appears to be minimal when the shunt is in place. Better early survival, both interstage[11] and at 14 months,[6] for the RVPAS group would also suggest that conduit retrograde flow has little negative impact on outcomes during the first year of life.

Ratio of RVPAS to Neo-aortic Ejection Time

Doppler patterns that compare the duration of flow into the systemic and pulmonary beds from a single ventricle should be influenced by the relative resistance to flow, with expected longer duration of systolic flow into the lower resistance pulmonary outflow (RVPAS) compared with the systemic outflow (neo-aorta). The lower resistance allows earlier initiation of flow during the "preejection" isovolumic contraction phase and prolonged duration of flow into the RVPAS. This physiology of prolonged flow into the RVPAS compared with the neo-aorta was confirmed in this study, with mean ratios of RVPAS to neo-aortic ejection time at both the post-Norwood and pre–stage II echocardiograms of 1.49 and 1.43, respectively.

Abnormal systolic time intervals (characterized by prolonged preejection and shortened outflow ejection times) have been associated with pulmonary vascular disease (when assessing pulmonary systolic flow[12]) and poorer outcomes (when assessing aortic systolic flow[13,14]) in adults with acquired left ventricular dysfunction. Similarly, infants with elevated systemic vascular resistance and/or decreased RV systolic function after Norwood would also be expected to have abnormal systolic intervals with shorter neo-aortic systolic flow duration relative to pulmonary flow duration. Because this physiology suggests altered RV contractility and/or an unbalanced resistance to flow, it would be expected that a higher ratio of RVPAS to neo-aortic ejection time would predict worse outcomes and poorer indices of RV function in our cohort. The fact that we did not find these correlations suggests that this ratio does not directly reflect the relative flow distribution or RV contractility and that variations in ejection times are likely dynamic and can be influenced by other factors (such as elevated pulmonary resistance and ventricular activation pattern) as well as conditions imposed by the echocardiographic study itself (such as level of sedation).

Systolic-to-Diastolic Duration Ratios

The RV systolic-to-diastolic duration ratio has been found to correlate with indices of ventricular function and differentiate normal children from those with restrictive cardiomyopathy,[15] dilated cardiomyopathy,[16,17] and pulmonary hypertension.[18] In addition, this ratio was predictive of outcomes in children with pulmonary hypertension.[18] In children with HLHS during staged palliations, the systolic-to-diastolic duration ratio was significantly increased compared with normal children (1.65 vs 0.85)[5] and was significantly higher in those patients with qualitatively decreased RV function compared with those with normal estimated function. Our study assessed the systolic-to-diastolic duration ratio using spectral Doppler interrogation of the RVPAS flow. This technique is attractive because the flow pattern in the RVPAS is easily and consistently obtained by echocardiography in all patients. Using this technique, we found that the systolic-to-diastolic ratio was significantly elevated at the post-Norwood (mean, 1.41) and pre–stage II (mean, 1.64) echocardiographic studies compared with published values for normal children (0.95).[19] In addition, this ratio was prolonged in those subjects who did not survive the interstage period, with a ratio > 1.6 at the post-Norwood echocardiographic study predicting a significantly increased risk for death or transplantation during the interstage period. Although long-term survival, length of hospital stay, and indices of RV function were not correlated with this index, the systolic-to-diastolic duration ratio may help clinicians identify high-risk infants during the interstage period.

Limitations

Careful training in protocol image acquisition was provided and reinforced at all clinical sites in this multi-institutional trial to optimize appropriate image capture. However, the more innovative measurements needed to assess the Doppler echocardiographic patterns reviewed in the present study were not possible in all the subjects at each echocardiographic study because of incomplete or inadequate image acquisition. The impact of this limitation in the characterization of neo-aortic and RVPAS flow patterns for the SVR cohort is unclear but emphasizes the challenge of multi-institutional echocardiographic trials that require extensive data acquisition, particularly when obtaining those data from infants with complex heart disease.

Doppler-derived estimates of RVPAS flow, although obtained by pulsed Doppler in the midconduit (so that the cross-sectional area where the flow is sampled could be assumed to be stable), are likely affected by the varying degrees of turbulence during systole and diastole within the restrictive shunt. Finally, multiple comparisons between variables, as performed in this analysis, increase the likelihood that differences will be found between groups by chance, and so statistical significance at a P value of .05 may overestimate relevant correlations.

CONCLUSIONS

This is the first study to characterize neo-aortic and RVPAS flow patterns in a large group of infants with single right ventricle anomalies after initial staged palliations and correlate those patterns with clinical outcome and echocardiographic indices of RV functional status. After the Norwood procedure, infants appear to tolerate significant descending aortic retrograde flow (in those with MBTS) and conduit retrograde flow (in those with RVPAS) while the shunt is in place, with little correlation between the Doppler-estimated retrograde fraction and transplantation-free survival up to 3 years of age, duration of hospital stay, or RV or tricuspid valve function during the first year of life. Doppler estimates of neo-aortic cardiac index and the ratio of RVPAS to neo-aortic ejection times also had limited clinical correlation with outcome or RV functional indices. However, a lower neo-aortic cardiac output and higher systolic-to-diastolic duration ratio at the post-Norwood echocardiographic study were correlated with poorer interstage transplantation-free survival in those with RVPAS and may provide clinicians with additional noninvasive tools to help identify patients at risk.

REFERENCES

1. Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atresia-hypoplastic left heart syndrome. N Engl J Med 1983;308:23-6.
2. Sano S, Ishino K, Kawada M, Arai S, Kasahara S, Asai T, et al. Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 2003;126:504-10.
3. Frommelt PC, Guey LL, Minich LL, Bhat M, Bradley TJ, Colan SD, et al. Does initial shunt type for the Norwood procedure impact

echocardiographic measures of cardiac size and function during infancy? The Single Ventricle Reconstruction trial. Circulation 2012;125:2630-8.
4. Frommelt PC, Sheridan DC, Mussatto KA, Hoffman GM, Ghanayem NS, Frommelt MA, et al. Effect of shunt type on echo indices after initial palliations for hypoplastic left heart syndrome: BT shunt vs. RV-PA conduit. J Am Soc Echocardiogr 2007;20:1364-73.
5. Friedberg M, Silverman N. The systolic to diastolic duration ratio in children with Hypoplastic left heart syndrome: a novel Doppler index of right ventricular function. J Am Soc Echocardiogr 2007;20:749-55.
6. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med 2010;362:1980-92.
7. Mahony L, Sleeper LA, Anderson PA, Gersony WM, McCrindle BW, Minich LL, et al. The Pediatric Heart Network: a primer for the conduct of multicenter studies in children with congenital and acquired heart disease. Pediatr Cardiol 2006;27:191-8.
8. Tweddell JS, Sleeper LA, Ohye RG, Williams IA, Mahony L, Pizarro C, et al. Intermediate-term mortality and cardiac transplantation in infants with single-ventricle lesions: risk factors and their interaction with shunt type. J Thorac Cardiovasc Surg 2012;144:152-9.
9. Stewart WJ, Jiang L, Mich R, Pandian N, Guerrero JL, Weyman AE. Variable effects of changes in flow rate through the aortic, pulmonary and mitral valves on valve area and flow velocity: impact on quantitative Doppler flow calculations. J Am Coll Cardiol 1985;6:653-62.
10. Rychik J, Bush DM, Spray TL, Gaynor JW, Wernovsky G. Assessment of pulmonary/systemic blood flow ratio after first-stage palliation for hypoplastic left heart syndrome: development of a new index with the use of Doppler echocardiography. J Thorac Cardiovasc Surg 2000;120:81-7.
11. Ghanayem NS, Allen KR, Tabbutt S, Atz AM, Clabby ML, Cooper DS, et al. Interstage mortality after the Norwood procedure: results of the multicenter Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2012;144:896-906.
12. Scapellato F, Temporelli PL, Eleuteri E, Corra U, Imparato A, Giannuzzi P. Accurate noninvasive estimation of pulmonary vascular resistance by Doppler echocardiography in patients with chronic failure heart failure. J Am Coll Cardiol 2001;37:1813-9.
13. Garrard CL Jr., Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. Circulation 1970;42:455-62.
14. Chao TF, Sung SH, Cheng HM, Yu WC, Wang KL, Huang CM, et al. Electromechanical activation time in the prediction of discharge outcomes in patients hospitalized with acute heart failure syndrome. Intern Med 2010;49:2031-7.
15. Friedberg MK, Silverman NH. The systolic to diastolic duration ratio in children with heart failure secondary to restrictive cardiomyopathy. J Am Soc Echocardiogr 2006;19:1326-31.
16. Friedberg MK, Silverman NH. Cardiac ventricular diastolic and systolic duration in children with heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 2006;97:101-5.
17. Patel DR, Cui W, Gambetta K, Roberson DA. A comparison of Tei index versus systolic to diastolic ratio to detect left ventricular dysfunction in pediatric patients. J Am Soc Echocardiogr 2009;2:152-8.
18. Alkon J, Humpl T, Manlhiot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. Am J Cardiol 2010;106:430-6.
19. Sarnari R, Kamal RY, Friedberg MK, Silverman NH. Doppler assessment of the ratio of the systolic to diastolic duration in normal children: relation to heart rate, age and body surface area. J Am Soc Echocardiogr 2009;22:928-32.