Circulation

ORIGINAL RESEARCH ARTICLE

Transplant-Free Survival and Interventions at 6 Years in the SVR Trial

Editorial, see p 2254

BACKGROUND: In the SVR trial (Single Ventricle Reconstruction), 1-year transplant-free survival was better for the Norwood procedure with right ventricle-to-pulmonary artery shunt (RVPAS) compared with a modified Blalock–Taussig shunt in patients with hypoplastic left heart and related syndromes. At 6 years, we compared transplant-free survival and other outcomes between the groups.

METHODS: Medical history was collected annually using medical record review, telephone interviews, and the death index. The cohort included 549 patients randomized and treated in the SVR trial.

RESULTS: Transplant-free survival for the RVPAS versus modified Blalock–Taussig shunt groups did not differ at 6 years (64% versus 59%, *P*=0.25) or with all available follow-up of 7.1±1.6 years (log-rank *P*=0.13). The RVPAS versus modified Blalock–Taussig shunt treatment effect had nonproportional hazards (*P*=0.009); the hazard ratio (HR) for death or transplant favored the RVPAS before stage II surgery (HR, 0.66; 95% confidence interval, 0.48–0.92). The effect of shunt type on death or transplant was not statistically significant between stage II to Fontan surgery (HR, 1.36; 95% confidence interval, 0.86–2.17; *P*=0.17) or after the Fontan procedure (HR, 0.76; 95% confidence interval, 0.33–1.74; *P*=0.52). By 6 years, patients with RVPAS had a higher incidence of catheter interventions (0.38 versus 0.23/patient-year, *P*<0.001), primarily because of more interventions between the stage II and Fontan procedures (HR, 1.72; 95% confidence interval, 1.00–3.03). Complications did not differ by shunt type; by 6 years, 1 in 5 patients had had a thrombotic event, and 1 in 6 had had seizures.

CONCLUSIONS: By 6 years, the hazards of death or transplant and catheter interventions were not different between the RVPAS versus modified Blalock–Taussig shunt groups. Children assigned to the RVPAS group had 5% higher transplant-free survival, but the difference did not reach statistical significance, and they required more catheter interventions. Both treatment groups have accrued important complications.

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Jane W. Newburger, MD, MPH
Lynn A. Sleeper, ScD
J. William Gaynor, MD
Danielle Hollenbeck-Pringle, MPH
Peter C. Frommelt, MD
Jennifer S. Li, MD
William T. Mahle, MD
Ismee A. Williams, MD, MS
Andrew M. Atz, MD
Kristin M. Burns, MD
Shan Chen, MS
James Cnota, MD
Carolyn Dunbar-Masterson, BSN, RN
Nancy S. Ghanayem, MD
Caren S. Goldberg, MD, MS
Jeffrey P. Jacobs, MD
Alan B. Lewis, MD
Seema Mital, MD
Christian Pizarro, MD
Aaron Eckhauser, MD
Paul Stark, ScD
Richard G. Ohye, MD
On behalf of the Pediatric Heart Network Investigators*

*Investigators and centers in the SVR Trial (Single Ventricle Reconstruction) are listed in the Appendix in the online-only Data Supplement.

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Clinical Perspective

What Is New?

- We compared transplant-free survival and other outcomes at 6 years after the Norwood procedure with right ventricle-to-pulmonary artery shunt compared with a modified Blalock–Taussig shunt in children enrolled in the SVR trial (Single Ventricle Reconstruction).
- The right ventricle-to-pulmonary artery shunt group had similar transplant-free survival at 6 years but required more catheter interventions before the Fontan procedure.
- Right ventricular ejection fraction, New York Heart Association class, and complications did not differ by shunt type.
- Cumulative incidence of morbidities by 6 years included 20% with a thrombotic event, 15% with a seizure, and 7.5% with a stroke.

What Are the Clinical Implications?

- The right ventricle-to-pulmonary artery shunt strategy carries a survival advantage before stage II surgery but a greater hazard of catheter interventions until the Fontan procedure is performed.
- After the Fontan procedure, there is no sustained advantage of the initial systemic to pulmonary artery shunt on transplant-free survival or catheter intervention.
- Morbidity begins early in life and steadily increases for children in both shunt groups.
- These data emphasize the importance of continued follow-up of this cohort and the need to find new strategies to improve the long-term outlook for those with single ventricle anomalies.

With the development of the Norwood procedure in 1980,[1] survival became possible for infants with hypoplastic left heart syndrome (HLHS) and related single right ventricle anomalies. The Norwood procedure uses the native pulmonary artery to provide blood flow to the aorta, leaving the distal pulmonary arteries to be perfused by a systemic-to-pulmonary-artery shunt. In early years, surgeons used a modified Blalock–Taussig shunt (MBTS) from the subclavian artery to the ipsilateral pulmonary artery. Subsequently, Sano et al[2] described the right ventricular-to-pulmonary artery shunt (RVPAS), which lessens aortic diastolic runoff and coronary arterial steal in the early postoperative period but requires a ventriculotomy in patients with a single right ventricle.

In 2005, we began the SVR trial (Single Ventricle Reconstruction), a randomized trial comparing transplant-free survival and morbidities after the Norwood procedure with the RVPAS versus MBTS in children with HLHS and other single right ventricular disorders.[3] We previously reported the outcomes of study patients at 1 and 3 years of age.[3,4] Transplant-free survival proved to be superior in the first year of life among those assigned to the RVPAS. By 3 years, the shunt groups no longer differed significantly in transplant-free survival, although the hazard ratio for transplant-free survival tended to be better for the MBTS group after 1 year. Moreover, the RVPAS group had slightly worse right ventricular ejection fraction and a higher rate of unplanned reinterventions.

In this report of the primary end point of SVR II (SVR Extension Study), we sought to compare the shunt groups with respect to transplant-free survival using all available data when the last enrolled patient had reached 6 years of age. We also compared the shunt groups with respect to interventions and morbidities to 6 years of age, including echocardiographic right ventricular ejection fraction (RVEF), catheter interventions, other events and morbidities, and New York Heart Association class.

METHODS

After trial results are published, the datasets and descriptor files from the SVR II study will be made available to other researchers on the Pediatric Heart Network Public Use Dataset webpage.[5]

Subjects

Patients were enrolled between May 2005 and July 2008. Eligibility criteria and trial methods for the SVR trial have previously been published.[6] Inclusion criteria were a diagnosis of HLHS or a related single, morphological right ventricular anomaly with a planned Norwood procedure. Among 555 patients originally enrolled, 1 patient was excluded after withdrawal in week 1, and 5 did not undergo a Norwood procedure. Therefore, the analytic cohort includes 549 patients. The data include ≥6 years of follow-up since the last patient was enrolled in the trial. The Institutional Review Board of each participating center approved this study, and parents/guardians of enrolled patients provided informed consent.

Data Obtained

Medical history was collected annually using medical record review, telephone interviews with parents or guardians, and the death index. Data obtained included vital status, surgical, and catheter-based interventions, medical events, morbidities, and New York Heart Association class. The primary causes of death between 1 and 6 years of age were adjudicated by a medical monitor.[7] Echocardiograms obtained for clinical indications were interpreted in a core laboratory, and the biplane pyramidal method was used for calculation of RVEF.[8]

Statistical Analysis

Statistical methods are similar to those used in analysis of data at 3 years.[4] The comparison of study outcomes was according to treatment assignment to MBTS or RVPAS (intention to treat) unless otherwise specified. We used a Wald test for comparison

of 6-year event rates estimated by the Kaplan–Meier method and the log-rank test to determine whether the distributions of time to the earliest occurrence of death or transplantation using all available follow-up differed by assigned shunt. Three patients had their follow-up time censored at the time of biventricular repair. To test the hypothesis that the size of the treatment effect varied by time, we used Cox regression with a time-dependent treatment indicator. The time intervals were as follows: before stage II surgery, between stage II surgery until Fontan surgery, and then after Fontan surgery. Cumulative incidence rates for the competing risks of death and transplant were also estimated by shunt group.[9]

To determine whether the treatment effect differed across patient subgroups, a treatment by subgroup interaction test from Cox regression was used for the following prespecified subgroups: birth weight <2500 versus ≥2500 g, pre-Norwood tricuspid regurgitation with proximal jet width <2.5 versus ≥2.5 mm, use of deep hypothermic circulatory arrest versus regional cerebral perfusion during the Norwood procedure, annual surgeon Norwood volume, and annual center single ventricle volume based on the patients screened for the trial. We also examined a subgroup identified post hoc in a previous SVR report,[10] defined by the presence or absence of a patent aortic valve and preterm birth (4 subgroups).

Incidence rates of the secondary outcomes related to catheter-based interventions and morbidities occurring by 6 years of age were compared by shunt type using Poisson regression. The time to first catheter-based intervention was estimated using the Kaplan–Meier method. We also used Cox regression with a time-dependent treatment indicator by surgical stage to examine differential shunt type effects by time on the catheterization outcomes.

We used all available follow-up and Cox proportional hazards regression to identify pre- and intraoperative risk factors (all variables evaluated are shown in Table I in the online-only Data Supplement) for transplant-free survival. The stepwise selection procedure for the multivariable main effects model included all predictors with a univariate *P* value <0.2. A test of nonproportionality was performed for each candidate predictor. A 2-sample *t* test was used to assess whether mean RVEF differed by assigned shunt. For all analyses, including tests of interaction, a *P* value of 0.05 was considered significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc) and R version 3.2.1.

RESULTS

At the time of this report, 331 of the original 549 patients were alive without cardiac transplantation, with mean follow-up of 7.1±1.6 years. The Fontan procedure had been performed in 328 patients (159 in the MBTS group and 169 in the RVPAS group) at a mean age of 2.9±0.9 years (interquartile range, 2.3–3.4 years; range, 1.3–6.6 years). Fontan type was extracardiac in 55% and lateral tunnel in 45%; 87% were fenestrated. The distributions of these surgical approaches did not differ between the RVPAS and MBTS shunt groups. An additional 3 patients, all in the RVPAS group, had undergone biventricular repair.

Transplant-Free Survival

The assigned shunt groups did not differ in transplant-free survival (log-rank *P*=0.13; Figure 1). At 6 years, transplant-free survival rates for the RVPAS versus MBTS groups were 64% versus 59% (*P*=0.25; Table 1), and death or transplant had occurred in 99 patients with RVPAS (87 deaths, 12 transplants) and 113 patients with MBTS (103 deaths, 10 transplants). Altogether, in the RVPAS versus MBTS groups, respectively, death or transplant occurred in 72 versus 100 patients by 1 year after randomization, in 18 versus 7 patients between 1 and 3 years, and in 9 versus 6 patients after 3 years ≤6 years of age. The shunt groups did not differ significantly in rates of all-cause mortality or cardiac transplantation (Figure I in the online-only Data Supplement). Although our primary analysis was performed according to intent to treat, study inferences were similar when examining the shunt in place at the end of the Norwood procedure. An additional 6 death or transplant events occurred after 6 years, 3 each in the RVPAS and MBTS groups. Timing of deaths and cardiac transplantation in the combined shunt groups according to surgical stage is summarized in Table II in the online-only Data Supplement.

The magnitude of the treatment effect on transplant-free survival varied over the study period (proportional hazards, *P*=0.009). Follow-up was divided into 3 periods based on the time of stage II surgery and Fontan procedure. The RVPAS group, compared with the MBTS group, had a lower hazard of death or transplant before the stage II procedure (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.48–0.92; *P*=0.003). The shunt effect on death or transplant was not significant after the stage II procedure, but the estimates for the 2 later periods were in opposite directions: stage II to Fontan, RVPAS versus MBTS (HR, 1.36; 95% CI, 0.86–2.17; *P*=0.17); and after Fontan, RVPAS versus MBTS (HR, 0.76; 95% CI, 0.33–1.74; *P*=0.52).

The 6-year composite event rates conditional on transplant-free survival to 1 year (a prespecified landmark analysis) were 13.8% for RVPAS and 7.7% for MBTS (overall log-rank test *P*=0.056). The shunt groups did not differ with respect to primary causes of death after 1 year (Table III in the online-only Data Supplement).

In prespecified subgroup analyses (Table IV in the online-only Data Supplement), interaction of shunt by subgroup was statistically significant only for annual Norwood surgeon volume (*P*=0.046), with MBTS having superior transplant-free survival (*P*=0.04) in the highest volume stratum, which only included 2 surgeons. In the lower volume strata, the RVPAS was beneficial or no shunt difference could be detected.

We performed multivariable Cox regression to determine predictors of worse transplant-free survival, in-

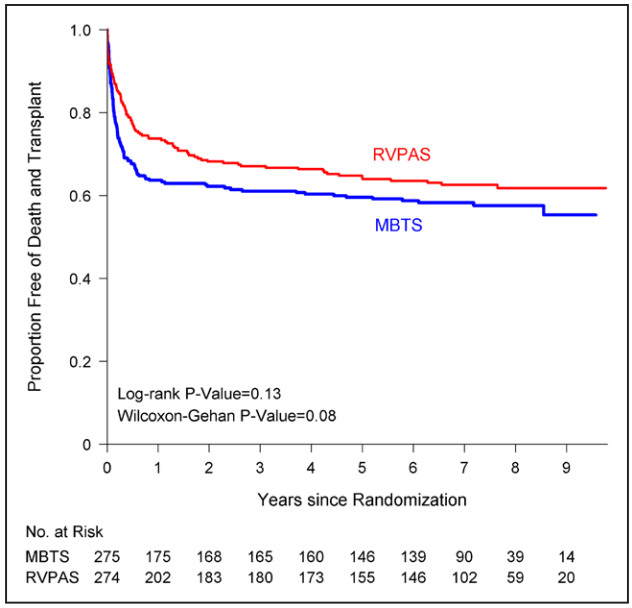

Figure 1. Comparison of the assigned shunt types in their freedom from the composite end point of death or cardiac transplantation (ie, transplantation-free survival). MBTS indicates modified Blalock–Taussig shunt; and RVPAS, right ventricle-to-pulmonary artery shunt.

cluding only covariates measured before and during the Norwood procedure (Table 2). An interaction of shunt type by time periods defined by surgical stage was fixed in the model. The MBTS was a risk factor only before the stage II procedure. The RVPAS group had a higher event rate between the stage II and Fontan procedures, but the association was not significant (HR, 1.50; *P*=0.09). Other independent predictors of adverse outcome included the presence of total anomalous pulmonary venous return, presence of a genetic syndrome or unknown genetic status (compared with absence of a genetic syndrome), moderate-to-severe tricuspid regurgitation before the Norwood procedure, use of extracorporeal membrane oxygenation during the Norwood procedure, and lower surgeon annual Norwood volume.

Cardiac Catheterization

In the period from the Norwood procedure to 6 years of age, the incidence of catheter interventions was higher in patients in the RVPAS versus MBTS group (*P*<0.001; Figure 2). Compared with the MBTS group, patients with RVPAS underwent their first catheter intervention of any type at an earlier time (*P*=0.01, 67% versus 53% by 6 years of age). They also underwent earlier coil occlusion of collaterals (*P*=0.001, 36% versus 23% by 6 years of age); this difference for the RVPAS versus MBTS groups was primarily because of coiling of aortopulmonary collaterals (*P*<0.001, 31% versus 17% by 6 years of age) and to a lesser degree because of coiling of veno-venous collaterals (*P*=0.10, 12% versus 7% by 6

Table 1. Clinical Events From Norwood to 6 Years of Age, by Shunt Type

Outcome	All (n=549)	Right Ventricular-to-Pulmonary-Artery Shunt (n=274)	Modified Blalock–Taussig Shunt (n=275)	*P* Value*
Number of patients				
Death or cardiac transplant	212	99	113	0.25
Death (before transplant)	190	87	103	
Cardiac transplant	22	12	10	
Death/transplant ≤1 y	172	72	100	
Death/transplant >1 to ≤3 y	25	18	7	
Death/transplant >3 to ≤6 y	15	9	6	
Incidence per 100 patient-years				
Cardiac surgeries	100.6	100.8	100.4	0.93
Catheter procedures	30.7	37.8	23.0	<0.001
Interventional catheterizations	21.5	25.3	17.4	<0.001
Complications	176.3	175.7	177.0	0.83
Number of patients, n (%)				
Pacemaker placed	14 (2.6)	8 (2.9)	6 (2.2)	0.60
Thrombotic event	86 (15.7)	42 (15.3)	44 (16.0)	0.91
Stroke	38 (6.9)	23 (8.4)	15 (5.5)	0.18
Seizure	71 (12.9)	40 (14.6)	31 (11.3)	0.26
Protein-losing enteropathy	17 (3.1)	12 (4.4)	5 (1.8)	0.09
Plastic bronchitis	3 (0.5)	1 (0.4)	2 (0.7)	1.00

**P* values for incidence rate and proportion comparisons are based on Poisson regression and Fisher exact test, respectively. *P* value for comparison of 6-y death/transplant is based on Wald test of the pointwise Kaplan–Meier event rate estimates at 6 y.

Table 2. Multivariable Cox Regression Model for Death or Cardiac Transplant

Characteristic	Hazard Ratio (95% Confidence Interval)	*P* Value
Shunt × Time interaction		0.03
RVPAS vs MBTS before stage II procedure	0.71 (0.51, 1.0)	0.03
RVPAS vs MBTS, stage II to Fontan procedure	1.50 (0.93, 2.40)	0.09
RVPAS vs MBTS, after Fontan procedure	0.84 (0.36, 1.93)	0.68
Total anomalous pulmonary venous return	3.25 (1.39, 7.60)	0.007
Genetic syndrome		<0.001
Yes	2.78 (1.56, 4.95)	
Unknown (no genetic evaluation)	3.27 (2.45, 4.36)	
No	Reference	
Pre-Norwood moderate/severe tricuspid regurgitation	1.77 (1.23, 2.56)	0.002
Extracorporeal membrane oxygenation used in operating room	4.68 (3.06, 7.15)	<0.001
Surgeon annual Norwood volume, per 1 U increase	0.95 (0.93, 0.98)	<0.001

N=534; 209 death/transplant events. MBTS indicates modified Blalock–Taussig shunt; and RVPAS, right ventricular-to-pulmonary artery shunt.

years of age). The 2 shunt groups had a similar time to first balloon angioplasty (*P*=0.54, 38% versus 33% by 6 years of age, *P*=0.55 after adjusting for center) and stenting (*P*=0.054, 22% versus 14% by 6 years of age, *P*=0.67 after adjusting for center).

We found significant nonproportional hazards for catheter intervention of any type (proportional hazards, *P*=0.02) and for coil insertion (proportional hazards, *P*=0.003), particularly coil placement for aortopulmonary collaterals (proportional hazards, *P*=0.001). The HR for catheter intervention of any type in the RVPAS versus MBTS groups varied over time (*P*=0.014; Table V in the online-only Data Supplement): before stage II (HR, 1.34; 95% CI, 0.97–1.84), stage II to Fontan (HR, 1.74; 95% CI, 1.00–3.00), and after Fontan (HR, 1.29; 95% CI, 0.67–2.48). Conversely, the effect of RVPAS versus MBTS shunt type on coil placement for any indication diminished over time (*P*=0.001): before stage II (HR, 9.55; 30 versus 3 events), stage II to Fontan (HR, 1.45; 33 versus 24 events), and after Fontan (HR, 0.91; 10 versus 12 events). A similar pattern over time was observed for coil placement for aortopulmonary collaterals. We found no significant interactions of shunt type and subgroup factors in analyses of catheter procedures.

RV Function and Clinical Events

RVEF could be accurately measured in only a small subset of patients. At 6 years of age, the RVPAS versus

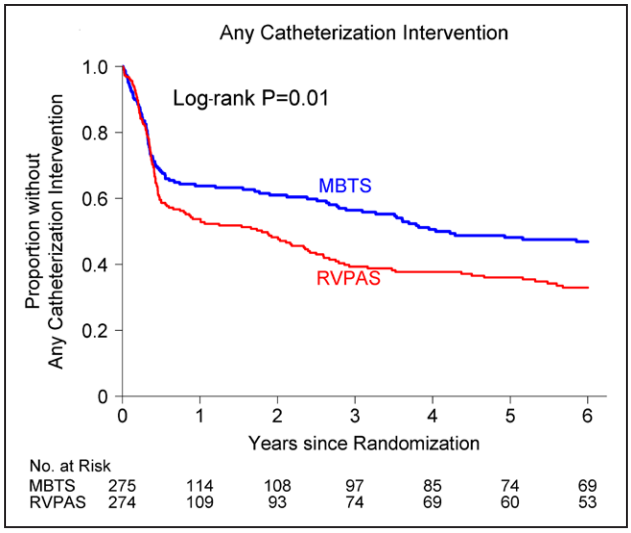

Figure 2. Comparison of the assigned shunt types in their freedom from any catheter interventions.
MBTS indicates modified Blalock–Taussig shunt; and RVPAS, right ventricle-to-pulmonary artery shunt.

MBTS groups did not differ in mean RVEF (46±6 [n=61] versus 45±6 [n=55]; *P*=0.60), even after adjustment for factors that were predictive of RVEF (*P*=0.40, adjusted for sex, socioeconomic status score,[10] and at least moderate tricuspid regurgitation).

The shunt groups did not differ significantly with respect to clinical events and morbidities (Table 1, Figure 3); the overall incidence of seizures in the first 6 years was 3.4 events per 100 patient-years; stroke, 1.8 events per 100 patient-years; protein losing enteropathy, 0.82 events per 100 patient-years; and plastic bronchitis, 0.14 events per 100 patient-years. By 6 years of age, ≈1 in 5 patients had had a thrombotic event, and ≈1 in 6 had had seizures. NYHA class was similar for the 2 shunt groups at 6 years of age, with 71% in class I, 21% in class II, 4% in class III, and 5% in class IV in the overall cohort.

DISCUSSION

Advances in surgical and catheter techniques, as well as postoperative care, have improved the survival of patients with even the most critical forms of congenital heart disease. Among congenital heart defects, HLHS serves as an exemplar of the extraordinary pharmacological, technical, and procedural innovations that have transformed the outlook of children with previously fatal defects. The SVR trial is the first multicenter randomized, prospective trial to compare the outcomes of 2 congenital heart operations, highlighting the evolution of the field of congenital heart surgery from earlier landmark achievements to evidence-based surgical practice that focuses on survival as well as longer-term complications of life-saving therapies.[11]

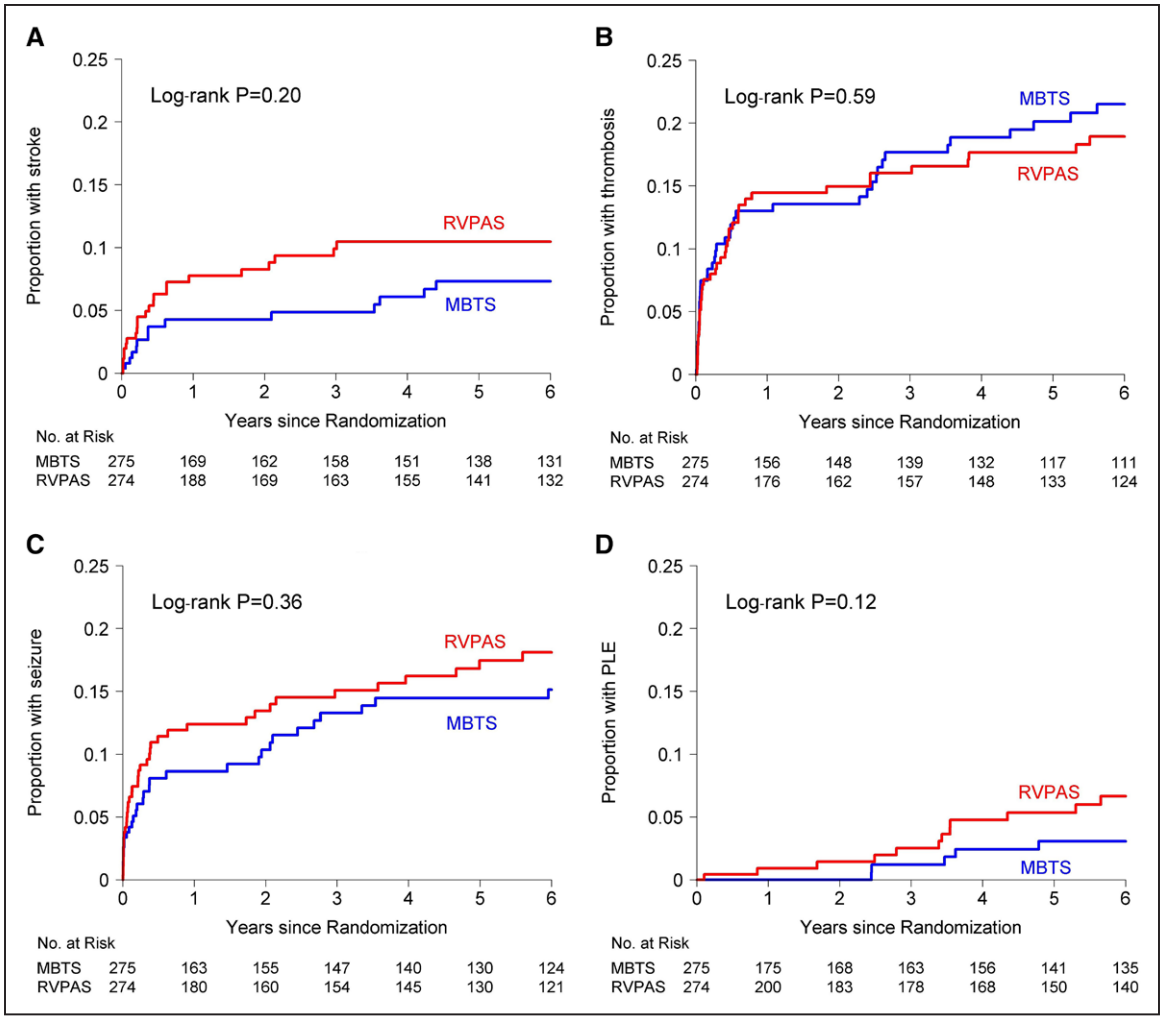

Figure 3. Kaplan–Meier estimates of the proportion of patients with stroke, thrombotic events, seizures, and PLE. **A**, Stroke: 6-year incidence for RVPAS versus MBTS (10% versus 7%). **B,** Thrombotic events: 6-year incidence RVPAS versus MBTS (19% versus 21%). **C,** Seizures: 6-year incidence for RVPAS versus MBTS (18% versus 15%). **D,** PLE: 6-year incidence for RVPAS versus MBTS (7% versus 3%). MBTS indicates modified Blalock–Taussig shunt, PLE, protein losing enteropathy; and RVPAS, right ventricle-to-pulmonary artery shunt.

We found that, by 6 years after assignment to an RVPAS versus a MBTS during the Norwood procedure, children with HLHS and other single RV anomalies no longer had a statistically significant difference in their transplant-free survival. Specifically, survival among children assigned to the RVPAS was better before the second stage of palliation was performed, but they had a similar hazard of death or transplant after this time. There was an interaction of shunt type with annual Norwood volume, with the highest volume and most senior surgeons having better outcomes using the MBTS. These data support the importance of tailoring the choice of shunt to the experience level of the surgeon and also highlight the case–volume relationship with Norwood procedure outcomes. Children in the RVPAS group had a higher incidence of catheter interventions before undergoing the Fontan procedure. After the Fontan procedure, the HRs were similar in the 2 shunt groups. Finally, right ventricular ejection fraction, clinical events and morbidities, and New York Heart Association class were similar among survivors in the 2 shunt groups.

Few studies have prospectively followed children with HLHS from birth through the early school years. Reports based on smaller cohorts have shown that the Fontan circulation is characterized by elevated filling pressure and low cardiac index, with a cascade of end-organ morbidities, including hepatic fibrosis and cirrhosis, lymphatic disorders including protein losing enteropathy and plastic bronchitis, late renal insufficiency, electrophysiological abnormalities, and thromboembolic events.[12–21] The SVR trial, which has prospectively gathered extensive data beginning before the Norwood procedure, provides a unique window into the early evolution of morbidities known to be associated with staged palliation to the Fontan procedure. The SVR trial

was conceived with the hypothesis that an early survival advantage expected from the RVPAS strategy might be balanced by adverse late outcomes of ventricular dysfunction and arrhythmia.[12] However, to date, we have found little sustained advantage of the initial systemic to pulmonary artery shunt on morbidities among survivors after the Fontan procedure. By 6 years of age, the rates of development of Fontan morbidities were similar in the 2 groups. However, cumulative Fontan morbidities in the combined shunt groups were already considerable: 1 in 5 children had had an event of thrombotic nature noted in routine clinical care, ≈15% had had ≥1 seizure, and 7.5% had had a stroke. These data highlight that morbidity begins early in life for children with single RV and has a steady increase even in the early years after Fontan.

Our study should be considered in light of some limitations. We did not standardize the materials or techniques used for construction of the RVPAS, nor did we collect information in the dataset on the surgical techniques used to create or repair the right ventriculotomy in patients with RVPAS. As is typical for congenital heart surgery, surgical techniques for the RVPAS vary among surgeons between and even within institutions, and RVPAS methods have continued to evolve since study enrollment.[22–24] The most important potential long-term disadvantage of the RVPAS is diminution of RV function related to the right ventriculotomy. Because of limitations in echocardiographic techniques for evaluation of RVEF after the RVPAS, RVEF could not be calculated for many patients, nor could we assess regional RV wall motion or impact of focal scarring and dyskinesis. As this cohort continues to be observed longitudinally, cardiac magnetic resonance imaging is supplanting echocardiography as a primary cardiac outcome variable.

Additional limitations include that some effects of the 2 shunt strategies, such as effects on RV function or pulmonary artery architecture, may only become manifest in later years after the Fontan procedure. The RVPAS group underwent more interventions before the Fontan procedure and, although not statistically significant, had a somewhat higher incidence of most complications. One potential reason for these findings is that the RVPAS causes more pulmonary artery distortion. If so, alterations in pulmonary artery architecture related to the RVPAS could adversely affect the long-term functional capacity of those with an initial RVPAS. Exercise capacity is currently being tested in children at 10 to 12 years of age who were enrolled in the SVR trial. Finally, whereas the difference in transplant-free survival of children in the RVPAS versus MBTS treatment groups (64% versus 59% at 6 years of age) was not statistically significant, the magnitude of this difference could be clinically important.

In summary, at 6 years in the SVR trial, the difference in transplant-free survival for those assigned to the RVPAS versus MBTS is not statistically significant. The 6-year incidence of catheter interventions is higher in patients in the RVPAS versus MBTS group, although the increased hazard was present only before the Fontan procedure. Both treatment groups have accrued important morbidities. Participants in the SVR trial are undergoing continued surveillance to characterize their long-term outcomes and risk factors for adverse events.

ARTICLE INFORMATION

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Correspondence

Jane W. Newburger, MD, MPH, Department of Cardiology, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115. E-mail jane.newburger@cardio.chboston.org

Affiliations

Boston Children's Hospital and Harvard Medical School, MA (J.W.N., L.A.S., C.D.-M.). Children's Hospital of Philadelphia and University of Pennsylvania Medical School, Philadelphia (J.W.G.). New England Research Institutes, Watertown, MA (D.H.-P., S.C., P.S.). Children's Hospital of Wisconsin and Medical College of Wisconsin, Milwaukee (P.C.F., N.S.G.). North Carolina Consortium, Duke University, Durham (J.S.L.). East Carolina University, Greenville, NC (J.S.L.). Wake Forest University, Winston-Salem, NC (J.S.L.). Children's Healthcare of Atlanta and Emory University, GA (W.T.M.). Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia College of Physicians and Surgeons, NY (I.A.W.). Medical University of South Carolina, Charleston (A.M.A.). National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (KM.B.). Cincinnati Children's Medical Center, OH (J.C.). University of Michigan Medical School, Ann Arbor (C.S.G., R.G.O.). Congenital Heart Institute of Florida, St. Petersburg (J.P.J.). Children's Hospital Los Angeles, CA (A.B.L.). Hospital for Sick Children, Toronto, Ontario, Canada (S.M.). Nemours Cardiac Center, Wilmington, DE (C.P.). Primary Children's Hospital and the University of Utah, Salt Lake City (A.E.).

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Disclosures

None.

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Transplant-Free Survival and Interventions at 6 Years in the SVR Trial

Jane W. Newburger, Lynn A. Sleeper, J. William Gaynor, Danielle Hollenbeck-Pringle, Peter C. Frommelt, Jennifer S. Li, William T. Mahle, Ismee A. Williams, Andrew M. Atz, Kristin M. Burns, Shan Chen, James Cnota, Carolyn Dunbar-Masterson, Nancy S. Ghanayem, Caren S. Goldberg, Jeffrey P. Jacobs, Alan B. Lewis, Seema Mital, Christian Pizarro, Aaron Eckhauser, Paul Stark, Richard G. Ohye and On behalf of the Pediatric Heart Network Investigators

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Supplemental Table I. Candidate Predictors for Cox Regression of Time to Death/Transplant

Characteristics

- Intent-to-shunt
- Shunt at end of operation

Prenatal

- Prenatal Diagnosis
- Fetal intervention

Birth

- Gestational Age, weeks
- Gest. Age <37 weeks
- Apgar at 1 min
- Apgar at 5 min
- Birth weight, kg
- Birth weight < 2.5 kg
- Birth weight < 1.5 kg
- Head circumference-for-age z score at baseline

Demographic

- Male
- Hispanic
- White Race
- SES score (U.S. census)
- % below federal poverty level

Anatomy

- HLHS

- Aortic atresia, Mitral atresia
- Aortic atresia, Mitral stenosis
- Aortic stenosis, Mitral stenosis
- AS/MS & related diagnoses
- Any aortic atresia
- Obstructed PV drainage
- Total anomalous pulmonary venous return
- Ascending aorta diameter, mm
- Genetic syndrome
- Non-syndromic abnormality

Pre-Norwood Echo

- Antegrade flow in asc aorta (patent aortic valve)
- ASD mean Doppler gradient, mmHg
- RVEF, %
- Fractional area change
- LV present
- Moderate/severe mitral regurgitation[d]
- Moderate/severe tricuspid regurgitation
- Moderate/severe aortic valve regurgitation

Pre-operative

- Median highest lactate, mmol/L[c]
- Mechanical ventilation
- Pre-Norwood apnea
- Pre-Norwood shock
- Pre-Norwood respiratory failure

- Pre-Norwood metabolic acidosis
- Pre-Norwood cath intervention
- No. of Pre-Norwood cath interventions
- Pre-Norwood non-cardiac surgery
- Pre-Norwood any surgery
- No. of Pre-Norwood total surgeries
- Pre-Norwood complications
- No. of Pre-Norwood complications

Stage 1

- Age at Norwood, days
- Norwood Perfusion type
- Total support time, min
- Total bypass time, min (excludes RCP time)
- Total DHCA time, min
- Total RCP time, min
- Lowest NP temp
- Lowest hematocrit, %
- Open sternum on day of Norwood
- Aprotinin
- a-blockade
- ECMO used in OR
- Annual Surgeon Norwood Volume
- Annual Surgeon Norwood Volume ≤ 5
- Annual Surgeon Norwood Volume category
- Annual Center Single Ventricle Volume

- Annual Center Single Ventricle Volume category

Supplemental Table II: Number of deaths and cardiac transplantations in the combined shunt groups according to surgical stage and hospitalization

	Death (prior to transplant)	All deaths	Cardiac Transplant
During Norwood Hospitalization	88	88	9
Interstage	51	55	0
During Stage II Hospitalization	17	17	3
After Stage II Discharge to Pre-Fontan	23	25	10
During Fontan Hospitalization	0	0	0
Post-Fontan Hospitalization	11	11	3

Supplemental Table III. Adjudicated Primary Cause of Death Occurring After One Year Post-Randomization According to Treatment Group

Adjudicated Cause of Death	MBTS* Group (n = 14)	RVPAS† Group (n = 20)	Total
Unknown	5	5	10
Cardiovascular	6	6	12
Pulmonary‡	0	4	4
Neurological	0	1	1
Gastroenterological/Hepatic	0	1	1
Complex/Multisystem Organ Failure§	2	1	3
Infectious	0	2	2

* MBTS = modified Blalock-Taussig shunt

† RVPAS = right-ventricular-to-pulmonary-artery shunt

‡ Pulmonary causes of death included 1 parenchymal, 1 vascular, 2 airway

§ Complex/multisystem organ failure causes of death included 1 infectious and 1 unknown in the MBTS group and 1 infectious in the RVPAS group.

Supplemental Table IV. Pre-specified Patient Subgroup Factors - Association with Death/Transplant Composite Using All Available Follow-up Data.

Subgroup Factor	N	6-year Event Rate	Hazard Ratio (95% CI)	Cox p-value	Subgroup x Shunt Interaction p-value†
Birth Weight				**<.001**	0.23 (0.12)
<2500 g	76	55%	1.93 (1.38,2.69)		
≥2500 g	473	36%	Ref		
Pre-Norwood TR*				**0.01**	0.12 (0.14)
≥2.5 mm	35	60%	1.82 (1.16,2.86)		
<2.5 mm	471	36%	Ref		
Norwood Perfusion				0.19	0.62 (0.65)
Any DHCA>10 min	414	40%	1.25 (0.90,1.73)		
RCP	130	33%	Ref		
Annual Surgeon Norwood Volume**				**0.005**	**0.05 (0.04)**
≤5 (17 surgeons)	108	51%	1.55 (1.01,2.37)		
>5 to ≤10 (12 surgeons)	113	41%	1.13 (0.73,1.75)		
>10 to ≤15 (8 surgeons)	239	33%	0.83 (0.56,1.24)		
>15 (2 surgeons)	89	38%	Ref		
Annual Site Single Ventricle Volume**				0.15	0.34 (0.40)
≤15 (4 sites)	93	44%	1.55 (1.03,2.32)		
>15 to ≤20 (5 sites)	109	42%	1.37 (0.93,2.02)		
>20 to ≤30 (4 sites)	176	41%	1.36 (0.96,1.93)		
>30 (2 sites)	171	32%	Ref		
Aortic Valve Patency				0.87	0.87 (0.22)
Non-patent aortic valve	311	37%	0.98 (0.74,1.29)		
Patent aortic valve	226	39%	Ref		
Gestational Age				**<.001**	0.47 (0.57)
<37 weeks	64	60%	2.03 (1.43,2.89)		
≥37 weeks	485	36%	Ref		
Combination of Aortic Valve Patency and Preterm Status				**<.001**	0.79 (0.52)
Non-patent aortic valve and preterm birth	39	46%	0.50 (0.26,0.99)		
Non-patent aortic valve and term birth	272	36%	0.35 (0.21, 0.60)		

Patent aortic valve and preterm birth	21	76%	Ref		
Patent aortic valve and term birth	205	35%	0.33 (0.19, 0.57)		

*Classified as tricuspid regurgitation (TR) if either location (anteroposterior proximal or transverse proximal) had jet width of at least 2.5 mm (22 and 30 subjects, respectively).

**Based on screened patient population

† Shunt group (intention-to-treat) by subgroup interaction p-value; (shunt group [non-intention-to-treat] by subgroup interaction p-value)

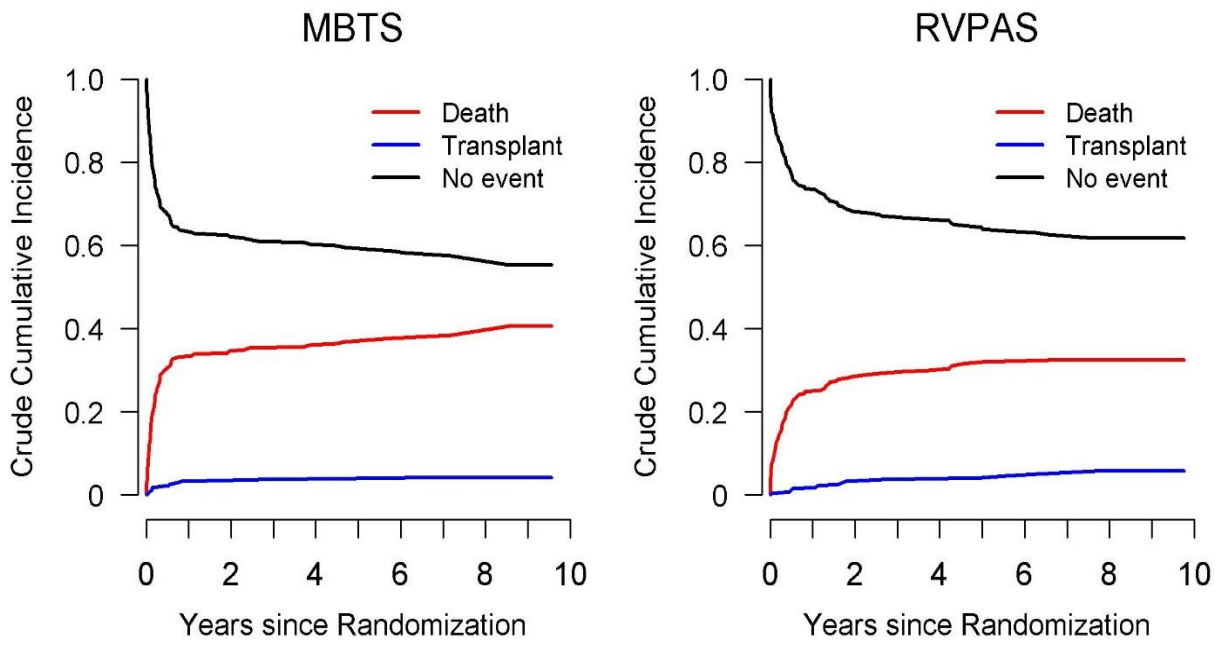
Supplemental Table V. RVPAS* v MBTS† Hazard Ratios for Time to First Catheter Intervention According to Surgical Stage									
Hazard Ratio (95% Confidence Interval), RVPAS *vs.* MBTS									
Cath Intervention	**Until Stage II**		**From Stage II to Fontan**		**After Fontan Until Latest Contact**		**Overall**		
Cath Intervention	**HR (95% CI) ‡**	**Wald P**	**HR (95% CI) ‡**	**Wald P**	**HR (95% CI) ‡**	**Wald P**	**HR (95% CI) ‡**	**Overall Wald P**	**Proportional Hazards test p-value**
All No. events (MBTS *vs.* RVPAS)	1.34 (0.97, 1.84) 65 vs. 92	0.07	1.74 (1.00, 3.00) 21 vs. 33	**0.05**	1.29 (0.67, 2.48) 18 vs. 18	0.45	1.38 (1.07, 1.77) 104 *vs.* 143	**0.01**	**0.02**
Balloon angioplasty No. events (MBTS *vs.* RVPAS)	0.95 (0.64, 1.41) 48 vs. 51	0.79	1.42 (0.73, 2.78) 14 vs. 22	0.31	2.74 (0.73, 10.31) 3 vs. 8	0.14	1.11 (0.80, 1.54) 65 *vs.* 81	0.54	0.08
Stent No. events (MBTS *vs.* RVPAS)	1.56 (0.80, 3.03) 14 vs. 23	0.19	1.71 (0.63, 4.62) 6 vs. 11	0.29	1.53 (0.63, 3.75) 8 vs. 12	0.35	1.58 (0.99, 2.53) 28 *vs.* 46	0.06	0.35
Coil (any) No. events (MBTS *vs.* RVPAS)	9.55 (2.91, 31.31) 3 vs. 30	**0.001**	1.45 (0.86, 2.45) 24 vs. 33	0.17	0.91 (0.40, 2.12) 12 vs.10	0.31	1.92 (1.30, 2.84) 39 *vs.* 73	**0.001**	**0.003**

* RVPAS = right ventricular-to-pulmonary artery shunt;

† MBTS = modified Blalock-Taussig shunt

‡ HR (95% CI) = Hazard Ratio (95% Confidence Interval)

Supplemental Figure I. Crude cumulative incidence rates of death, transplant, and neither event in subjects assigned to the MBTS = modified Blalock-Taussig shunt and to the RVPAS = right ventricular-to-pulmonary artery shunt.



Single Ventricle Reconstruction Trial participants:

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 (PI), Sharon Tennstedt (PI), Steven Colan, Lisa Virzi, Patty Connell, Victoria Muratov, Lisa Wruck, Minmin Lu, Dianne Gallagher, Anne Devine, Thomas Travison, David F. Teitel

Core Clinical Site Investigators: *Boston Children's Hospital*, Jane W. Newburger (PI), Peter Laussen, Pedro del Nido, Roger Breitbart, Jami Levine, Ellen McGrath, Carolyn Dunbar-Masterson; *Children's Hospital of New York,* Wyman Lai (PI), Beth Printz (currently at Rady Children's Hospital), Daphne Hsu (currently at Montefiore Medical Center), William Hellenbrand (currently at Yale New Haven Medical Center), Ismee Williams, Ashwin Prakash (currently at Children's Hospital Boston), Ralph Mosca (currently at New York University Medical Center), Darlene Servedio, Rozelle Corda, Rosalind Korsin, Mary Nash; *Children's Hospital of Philadelphia*, Victoria L. Vetter (PI), Sarah Tabbutt (currently at the University of California, San Francisco), 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, Kathie Hogan, Steven Schwartz (currently at the Hospital for Sick Children, Toronto), David Nelson; *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 Hospital and the University of Utah, Salt Lake City, Utah*, L. LuAnn Minich (PI), John Hawkins (deceased), Michael Puchalski, Richard

Williams, Linda Lambert, Jun Porter, Marian Shearrow; *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*, Nancy Ghanayem (PI), James Tweddell, Kathy Mussatto, Michele 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, MD (PI), James A. Quintessenza, Paul J. Chai, David S. Cooper, J. Blaine John, James C. Huhta, Tina Merola, Tracey Cox; *Emory University*, Kirk Kanter, William Mahle, Joel Bond, Leslie French, Jeryl Huckaby; *Nemours Cardiac Center*, Christian Pizarro, Carol Prospero; Julie Simons, Gina Baffa; *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 Ph*iladelphia, 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