Risk factors for hospital morbidity and mortality after the Norwood procedure: A report from the Pediatric Heart Network Single Ventricle Reconstruction trial

Sarah Tabbutt, MD, PhD,[a] Nancy Ghanayem, MD,[b] Chitra Ravishankar, MD,[a] Lynn A. Sleeper, ScD,[c] David S. Cooper, MD, MPH,[d] Deborah U. Frank, MD, PhD,[e] Minmin Lu, MS,[c] Christian Pizarro, MD,[f] Peter Frommelt, MD,[b] Caren S. Goldberg, MD,[g] Eric M. Graham, MD,[h] Catherine Dent Krawczeski, MD,[i] Wyman W. Lai, MD,[j] Alan Lewis, MD,[k] Joel A. Kirsh, MD,[l] Lynn Mahony, MD,[m] Richard G. Ohye, MD,[g] Janet Simsic, MD,[n] Andrew J. Lodge, MD,[o] Ellen Spurrier, MD,[f] Mario Stylianou, PhD,[p] and Peter Laussen, MD,[q] for the Pediatric Heart Network Investigators

Objectives: We sought to identify risk factors for mortality and morbidity during the Norwood hospitalization in newborn infants with hypoplastic left heart syndrome and other single right ventricle anomalies enrolled in the Single Ventricle Reconstruction trial.

Methods: Potential predictors for outcome included patient- and procedure-related variables and center volume and surgeon volume. Outcome variables occurring during the Norwood procedure and before hospital discharge or stage II procedure included mortality, end-organ complications, length of ventilation, and hospital length of stay. Univariate and multivariable Cox regression analyses were performed with bootstrapping to estimate reliability for mortality.

Results: Analysis included 549 subjects prospectively enrolled from 15 centers; 30-day and hospital mortality were 11.5% (63/549) and 16.0% (88/549), respectively. Independent risk factors for both 30-day and hospital mortality included lower birth weight, genetic abnormality, extracorporeal membrane oxygenation (ECMO) and open sternum on the day of the Norwood procedure. In addition, longer duration of deep hypothermic circulatory arrest was a risk factor for 30-day mortality. Shunt type at the end of the Norwood procedure was not a significant risk factor for 30-day or hospital mortality. Independent risk factors for postoperative renal failure ($n = 46$), sepsis ($n = 93$), increased length of ventilation, and hospital length of stay among survivors included genetic abnormality, lower center/surgeon volume, open sternum, and post-Norwood operations.

Conclusions: Innate patient factors, ECMO, open sternum, and lower center/surgeon volume are important risk factors for postoperative mortality and/or morbidity during the Norwood hospitalization. (J Thorac Cardiovasc Surg 2012;144:882-95)

CHD

Risk factors for hospital morbidity and mortality after the Norwood procedure for patients with hypoplastic left heart syndrome (HLHS) have been reported from single centers and multicenter databases. Many centers report low birth weight, genetic abnormalities, restrictive atrial septum, duration of cardiopulmonary bypass (CPB), and extracorporeal membrane oxygenation (ECMO) as risk factors for mortality.[1-14] Multicenter reports have shown higher mortality at smaller volume centers.[2,15,16]

The Pediatric Heart Network Single Ventricle Reconstruction (SVR) trial provides a unique opportunity to analyze prospectively collected preoperative, operative, and postoperative data in the largest cohort of newborn infants with HLHS and other single right ventricle anomalies to date.

From the Children's Hospital of Philadelphia,[a] Philadelphia, Pa; Children's Hospital of Wisconsin and Medical College of Wisconsin,[b] Milwaukee, Wis; New England Research Institutes,[c] Watertown, Mass; Congenital Heart Institute of Florida,[d] St Petersburg, Fla; Primary Children's Medical Center and the University of Utah,[e] Salt Lake City, Utah; Nemours Cardiac Center,[f] Wilmington, Del; University of Michigan Medical School,[g] Ann Arbor, Mich; Medical University of South Carolina,[h] Charleston, SC; Cincinnati Children's Medical Center,[i] Cincinnati, Ohio; Morgan Stanley Children's Hospital of New York Presbyterian,[j] New York, NY; Children's Hospital Los Angeles,[k] Los Angeles, Calif; Hospital for Sick Children,[l] Toronto, Ontario, Canada; University of Texas Southwestern Medical Center,[m] Dallas, Tex; Emory University,[n] Atlanta, Ga; North Carolina Consortium: Duke University,[o] Durham, NC; National Heart, Lung, and Blood Institute,[p] Bethesda, Md; and Children's Hospital Boston,[q] Boston, Mass.

Supported by grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288, HL085057). This work is solely the responsibility of the authors and does not necessarily represent the official views of the NHLBI.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Dr Tabbutt's current affiliation is University of California San Francisco Benioff Children's Hospital, San Francisco, Calif; Dr Cooper's current affiliation is Cincinnati Children's Medical Center, Cincinnati, Ohio; and Dr Simsic's current affiliation is Nationwide Children's Hospital, Columbus, Ohio.

Clinical Trial Registration No. NCT00115934.

Received for publication Nov 7, 2011; revisions received March 21, 2012; accepted for publication May 9, 2012; available ahead of print June 18, 2012.

Address for reprints: Sarah Tabbutt, MD, PhD, University of California San Francisco Benioff Children's Hospital, Moffitt 680, 555 Parnassus Ave, San Francisco, CA 94143 (E-mail: tabbutts@peds.ucsf.edu).

0022-5223/$36.00

doi:10.1016/j.jtcvs.2012.05.019

Abbreviations and Acronyms

CPB = cardiopulmonary bypass
CPR = cardiopulmonary resuscitation
DHCA = deep hypothermic circulatory arrest
ECMO = extracorporeal membrane oxygenation
E-CPR = ECMO required to restore circulation during CPR
HLHS = hypoplastic left heart syndrome
MBTS = modified Blalock-Taussig shunt
RCP = regional cerebral perfusion
RVPAS = right ventricular–pulmonary artery shunt
SVR = Single Ventricle Reconstruction

Primary results of the SVR trial reported differences in outcome between subjects undergoing the Norwood procedure with a right ventricular–pulmonary artery shunt (RVPAS) versus a modified Blalock-Taussig shunt (MBTS).[17] The initial report focused solely on the comparative outcomes relative to shunt type. The primary aim of this prespecified secondary analysis was to examine the associations of patient-related risk factors and perioperative management variables on morbidity and mortality during the Norwood hospitalization. To facilitate comparisons with previous reports of surgical morality for the Norwood procedure, we analyzed both 30-day and hospital mortality. Our secondary aim was to explore associations with shunt type on longer-term transplant-free survival in subjects requiring cardiopulmonary resuscitation (CPR) and/or ECMO.

METHODS

Study Design

Details of the SVR trial design have been previously published.[17,18] In brief, inclusion criteria consisted of a diagnosis of HLHS or other single right ventricle anomaly and a planned Norwood procedure. Patients were excluded if the preoperative cardiac anatomy rendered either the MBTS or RVPAS technically impossible or if they had any major congenital or acquired extracardiac abnormality that could independently decrease the likelihood of transplant-free survival at 1 year of age. Subjects were randomly assigned to receive either the MBTS or the RVPAS. The institutional review board at each center approved the protocol. Written informed consent was obtained from a parent/guardian before randomization. Other than the type of shunt placed, the remainder of the perioperative care was per institutional standard. For the purposes of this analysis, subjects were categorized by the shunt in place at the end of the Norwood procedure.

Data Collection and Definitions

Data were prospectively collected. The 16 outcome variables are defined in Appendix Table 1. Other than 30-day mortality, outcomes were recorded if they occurred before hospital discharge or before stage II procedure for subjects not discharged. ECMO initiated after the Norwood procedure was considered an outcome variable. The 42 potential risk factors are defined in Appendix Table 2. Subjects underwent genetic evaluations when indicated by clinical suspicion of a genetic abnormality. In addition, a research option for a genetic evaluation was offered. Preoperative shock was defined as a composite of hepatic failure (Appendix Table 1), renal failure (Appendix Table 1), lactate greater than 10 mmol/L, or intubation for shock. Perfusion strategies included deep hypothermic circulatory arrest (DHCA) alone or regional cerebral perfusion (RCP) with or without DHCA. Open sternum included all subjects with an open sternum on the day of the Norwood procedure. These subjects were categorized as those at a "routine" center where sternums of all patients were left open at the end of the Norwood procedure or those at an "elective" center where the surgeon selectively decided to leave the patient's sternum open. ECMO for failure to separate from CPB was examined as a potential risk factor. The day of Norwood procedure was defined as day 1.

The longer-term outcome of patients requiring CPR (defined as receiving chest compressions) and/or ECMO was examined in further detail. Subjects were characterized as follows: CPR alone (CPR), ECMO alone (ECMO), ECMO required to restore circulation during CPR (E-CPR), and neither CPR nor ECMO ("none"). For the subanalysis of these 4 groups, only CPR, ECMO, or E-CPR occurring within 30 days of Norwood procedure were included. Subjects requiring ECMO for failure to separate from CPB were included in the ECMO group.

Statistical Methods

Summary statistics include mean ± standard deviation, median, and range. We analyzed 2 mortality outcomes: (1) time to death up to discharge from the Norwood hospitalization, using Kaplan-Meier estimation and Cox proportional hazards regression, with censoring at dates of cardiac transplant and at time of stage II procedure (for those not discharged) and (2) a dichotomous 30-day post-Norwood procedure mortality indicator, using logistic regression. We analyzed 4 continuous outcomes using linear regression: post-Norwood right ventricular fractional area change, log-transformed time to initial extubation, log-transformed total days ventilated, and log-transformed hospital length of stay. Subjects who died or underwent cardiac transplant during the hospitalization were excluded from analysis of the extubation, ventilation, and length of stay outcomes. We analyzed 10 dichotomous morbidity outcomes using logistic regression; for 3 of these (necrotizing enterocolitis, liver failure, mediastinitis), only univariate analyses were conducted owing to the low event rate. For construction of multivariable models, variables with a P value $\leq .2$ in univariate analysis were used as candidate predictors in regression modeling. The R^2 and maximum rescaled R^2 values are reported for linear and logistic regression models, respectively. In addition, generalized additive modeling was used to identify nonlinear associations between outcomes and continuous candidate predictors. Variables with a nonlinearity P value $< .05$ were considered in the multivariable selection procedure. Bootstrap resampling was used to estimate the reliability of each factor selected by stepwise regression for the multivariable mortality model.[19,20] We retained a term in the model if it had reliability greater than 50% and a P value of less than .05.

We used analysis of variance and the Kruskal-Wallis test for comparison of the distributions of baseline characteristics across the 4 ECMO/CPR groups. To account for potential survival bias in this secondary analysis of CPR with or without ECMO subjects, we used Cox proportional hazards regression with a time-dependent group indicator to model time to death or transplant, using all available follow-up data. A test of interaction between subject group and shunt type was used to assess differential treatment effect by group.

RESULTS

Between May 2005 and July 2008 there were 549 evaluable SVR subjects: 268 with an MBTS and 281 with an RVPAS.

Mortality

Mortality during the Norwood hospitalization was 16% (88/549). Deaths occurred at a median of 16 days, (range,