Is a hybrid strategy a lower-risk alternative to stage 1 Norwood operation?

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ABSTRACT

Background: For neonates with critical left ventricular outflow tract obstruction (LVOTO), hybrid procedures are an alternative to the Norwood stage 1 procedure. Despite perceived advantages, however, outcomes are not well defined. Therefore, we compared outcomes after stage 1 hybrid and Norwood procedures.

Methods: In a critical LVOTO inception cohort (2005-2014; 20 institutions), a total of 564 neonates underwent stage 1 palliation with the Norwood operation with a modified Blalock-Taussig shunt (NW-BT; n = 232; 41%), Norwood operation with a right ventricle-to-pulmonary artery conduit (NW-RVPA; n = 222; 39%), or a hybrid procedure (n = 110; 20%). Post-stage 1 outcomes were analyzed via competing-risks and parametric hazard analyses and compared among all 564 patients and between patients who underwent propensity-matched hybrid and those who underwent NW-BT/NW-RVPA.

Results: By 6 years after the stage 1 operation, 50% ± 3%, 7% ± 2%, and 4% ± 1% of patients transitioned to Fontan, transplantation, and biventricular repair, respectively, whereas 7% ± 2% were alive without transition and 32% ± 2% died. Risk factors for death without transition included procedure type, smaller ascending aorta, aortic valve atresia, and lower birth weight. Risk-adjusted 4-year survival was better after NW-RVPA than after NW-BT or hybrid (76% vs 60% vs 61%; *P* < .001). Furthermore, for neonates with lower birth weight (<2 kg), an interaction between birth weight and hybrid resulted in a trend toward better survival after hybrid compared with NW-BT or NW-RVPA. For propensity-matched neonates between hybrid and NW-BT (88 pairs), 4-year survival was similar (62% vs 57%; *P* = .58). For propensity-matched neonates between hybrid and NW-RVPA (81 pairs), 4-year survival was better after NW-RVPA (59% vs 75%; *P* = .008).

Conclusions: For neonates with critical LVOTO undergoing single-ventricle palliation, NW-RVPA was associated with the best overall survival. Hybrid strategies are not a lower-risk alternative to Norwood operations overall; however, the impact of lower birth weight on survival may be mitigated after hybrid procedures compared with Norwood operations. (*J Thorac Cardiovasc Surg* 2017;153:163-72)

Risk-adjusted survival for neonates with critical LVOTO stratified by stage 1 operation.

Central Message

Overall, NW-RVPA had the best survival. Although hybrid procedures are not a lower-risk alternative overall compared with stage 1 Norwood operations, hybrids may improve survival in neonates with lower birth weight.

Perspective

Although the perception exists that hybrid procedures may be a lower-risk alternative to Norwood procedures for neonates with critical LVOTO who require stage 1 single-ventricle palliation, the Congenital Heart Surgeons' Society experience demonstrated better overall survival after NW-RVPA. Hybrid procedures may offer a survival advantage for neonates with lower birth weight, however.

See Editorial Commentary page 173.

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Abbreviations and Acronyms

BSA	= body surface area
CHSS	= Congenital Heart Surgeons' Society
CPB	= cardiopulmonary bypass
DHCA	= deep hypothermic circulatory arrest
KM	= Kaplan-Meier
LVOTO	= left ventricular outflow tract obstruction
NW-BT	= Norwood with modified Blalock-Taussig shunt
NW-RVPA	= Norwood with right ventricle–pulmonary artery conduit

Scanning this QR code will take you to supplemental data, tables, and figures for this article.

Current strategies that achieve the objectives of stage 1 palliation for neonates with critical left ventricular outflow tract obstruction (LVOTO) and right ventricle–dependent systemic circulation include the Norwood operation and a hybrid procedure. Although the Norwood operation accomplishes the goals of stage 1 palliation, it involves major surgical reconstruction and is associated with a physiology characterized by the need for a delicate circulatory balance and increased cardiac demands.^{1,2} Moreover, exposure to cardiopulmonary bypass (CPB), generally with either deep hypothermic circulatory arrest (DHCA) or regional cerebral perfusion, during aortic arch reconstruction can contribute to postoperative hemodynamic instability, morbidity, and mortality.³ In addition, the early physiological stress imposed on neonates after Norwood operations raises concerns regarding adverse neurodevelopment.⁴

The hybrid procedure has emerged as an alternative strategy for stage 1 palliation.^{5,6} In contrast to Norwood operations, the hybrid procedure generally does not require CPB and DHCA or regional cerebral perfusion. Thus, the less invasive hybrid procedure may avoid the physiological instability associated with Norwood operations for stage 1 palliation and may potentially improve survival.^{3,5-7} In this light, hybrid palliation may be perceived as a lower-risk alternative to Norwood operations, especially for patients considered at high risk for mortality. Although these perceptions exist, the impact of the hybrid procedure on survival relative to Norwood operations remains incompletely defined.^{5,7,8}

The Congenital Heart Surgeons' Society (CHSS) has one of the largest multi-institutional inception cohorts of neonates with critical LVOTO, in which the majority of patients have undergone single-ventricle palliation via either a stage 1 hybrid or Norwood operation. Given the insufficient published evidence comparing outcomes of these strategies,^{3,5,6,8-10} we sought to compare outcomes among neonates undergoing a hybrid procedure with either of the 2 commonly used techniques for establishing pulmonary blood flow (systemic artery–to–pulmonary artery shunt or right ventricle–to–pulmonary artery conduit) and those undergoing a Norwood operation.

METHODS

Between 2005 and 2014, a total of 692 neonates with critical LVOTO were admitted to the 21 CHSS institutions within 30 days of life and were prospectively enrolled in a multi-institution inception cohort (Table E1). Inclusion criteria were based on the presence of critical LVOTO in the setting of atrioventricular and ventriculoarterial concordance, such that the LVOTO precluded adequate systemic cardiac output through the aortic valve, with the initial intervention performed at a CHSS institution. The physiological criteria generally resulted in ductal-dependent systemic circulation and the need for early intervention. For 564 neonates (20 institutions; Figure E1), the initial management strategy was the Norwood operation with a modified Blalock-Taussig shunt (NW-BT; n = 232; 41%), the Norwood operation with right ventricle–to–pulmonary artery conduit (NW-RVPA; n = 222; 39%), or a hybrid procedure (n = 110; 20%). Although the hybrid strategies lacked procedural uniformity, basic criteria included restriction of pulmonary blood flow with pulmonary artery banding and maintenance of ductus arteriosus patency with either transcatheter stent placement or prostaglandin therapy (Table E2). The choice of management strategy (including the initial procedure) was at the discretion of institution physicians.

The primary objectives of the present study included defining overall survival for all 564 neonates after stage 1 single-ventricle palliation, defining end states after stage 1 single-ventricle palliation, and comparing the relative impact on survival between the hybrid procedure and Norwood operation. As an initial step, overall survival was compared among neonates who underwent NW-BT, NW-RVPA, or hybrid without adjusting for additional risk factors. Competing-risks methodology was then used to evaluate survival in the context of the various definitive end states after stage 1 palliation.

To adjust for the potential differences in characteristics among patients undergoing each of these operations, our analysis strategy incorporated 2 methods of risk adjustment, each of which was based on the competing-risks survival model. First, survival was evaluated among all 564 patients as part of a risk hazard analysis, specifically targeted at identifying whether procedure type was a risk factor. Then survival was evaluated between propensity-matched subsets. Neonates undergoing a stage 1 hybrid procedure were matched to neonates who underwent NW-BT and also to neonates who underwent NW-RVPA. The secondary objectives of this study were aimed at identifying risk factors for death other than the type of stage 1 palliation, including morphologic, demographic, and center-related factors.

Data Acquisition and Follow-up

Participation in the study and submission of patient information were voluntary and confidential. The CHSS Data Center and all participating institutions obtained Ethics Board approval, and parental consent was obtained for all neonates before enrollment. The Data Center contacted the

institution and a parent or guardian of each patient annually to ascertain details of clinical history and subsequent investigations and interventions. Admission, diagnostic, and surgical information was abstracted from institutional medical records, echocardiogram reports, and surgical reports as described previously.¹¹ The median duration of follow-up for all neonates from the date of the initial procedure was 2.2 years (range, 1 day to 8.3 years). For survivors, the median duration of follow-up was 3.9 years (range, 1 day to 8.3 years), and data were complete for 79% of the patients within 1 year of the last annual follow-up. For the surviving patients who did not have data within 1 year of the last annual follow-up (21%), the median duration of follow-up was 3.3 years (range, 15 days to 7.7 years).

Statistical Analysis and Presentation

Demographic, diagnostic, and procedural information before stage 1 palliation were included as baseline variables and handled as described previously.¹¹ Measurements of cardiac dimensions were standardized as *z*-scores on the basis of published normative data, if available, or otherwise indexed to height or body surface area (BSA).¹² Missing values were estimated using multiple imputation,¹³ and final variable selection was guided by bootstrap resampling (Appendix E1).¹⁴ Continuous variables were compared with the Kruskal-Wallis test, using Wilcoxon rank scores or Student's *t* test. Frequencies for categorical variables were compared using a χ^2 test of independence or Fisher's exact test as appropriate. Data are summarized as mean $\pm$ standard deviation (SD); as equivalent 15th, 50th (median), and 85th percentiles; or as frequency and percentage. Data analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

Survival analysis. Survival was first evaluated from the date of stage 1 surgery to the date of death, with neonates otherwise censored at the last-known date of life (ie, overall survival). Survival was then evaluated in the context of mutually exclusive end states (competing risks).

Although definitive palliation for the majority of neonates after stage 1 palliation includes staged reconstruction culminating with the Fontan/Kreutzer (Fontan) operation, a minority of neonates undergo an alternative definitive repair, including transplantation or biventricular repair. As such, there are multiple events "competing" with the event of interest (death), each of which is associated with a unique hazard function that potentially influences the hazard for death.¹⁵ In addition, the hazard for death after definitive repair (ie, Fontan, transplantation, or biventricular repair) is associated with an inherent hazard that is unrelated to stage 1 palliation. To adjust for the associated hazard functions related to these alternative end states, we evaluated survival in the context of competing risks, such that neonates were censored at a definitive repair operation, defined based on the separation of systemic and pulmonary circulation.¹⁶ By doing so, our analysis leads to a more accurate estimate of the proportion of patients who actually experience the event of interest.¹⁷

Kaplan-Meier estimates of time to event were constructed and then used to create parametric, multiphase hazard models for transition to various end states¹⁸ (for additional details, see <http://www.lerner.ccf.org/qhs/software/hazard/>). Using these parametric models, univariate and multivariable risk hazard analyses were conducted for all 564 neonates, neonates in the propensity-matched hybrid-NW-BT subset, and neonates in the propensity-matched hybrid-NW-RVPA subset (see Appendix E1 for further details).

Propensity-score matching. Propensity-score matching was used to adjust for potential differences among neonates who underwent NW-BT, NW-RVPA, and hybrid procedures (Appendix E1).¹⁹ Each propensity score incorporated demographic, morphological, and functional baseline characteristics into a multivariable logistic regression model that provided the probability of a given patient belonging to one group versus the other group.^{19,20} Two separate propensity scores were generated to match neonates between hybrid and NW-BT and between hybrid and NW-RVPA (Figure E2). Subsequently, survival was evaluated between each matched subset using parametric methods. Additional information

regarding statistical techniques and patient characteristics before and after propensity matching (Table E3) is provided in the Appendix E1.

Center and era effect on survival. To adjust for estimated center volume and distribution of procedures per center, variables tested as independent risk factors for death included the (1) total number of reported procedures per center, (2) absolute number of reported procedure type per center, (3) percentage of reported procedure type per center, and (4) individual centers. The potential "era effect" was evaluated as a continuous variable using the date of operation and by stratifying era into 3 categories: 2005 to 2007, 2008 to 2011, and 2012 to 2014.

RESULTS

Compared with the neonates who underwent NW-BT or NW-RVPA, those who underwent a hybrid procedure were significantly older at stage 1, had lower birth weight, had a higher prevalence of important baseline right ventricle dysfunction, and tended to exhibit an increased prevalence of significant baseline tricuspid valve regurgitation (Table 1). They also had a lower prevalence of aortic atresia and mitral valve atresia.

Survival

Overall survival. The overall mean unadjusted survival for all 564 patients, irrespective of final end state, was 65% $\pm$ 2% at 4 years. The unadjusted 4-year survival was significantly better after NW-RVPA (73% $\pm$ 3%; *P* < .001) compared with NW-BT (61% $\pm$ 3%) and hybrid (60% $\pm$ 5%) procedures (Figure 1).

Competing risks: Survival without definitive repair. Independent of time, 183 children underwent a Fontan operation, 34 received a heart transplant, and 18 underwent biventricular repair. In addition, 176 children died before definitive repair could be performed. By 6 years, 7% $\pm$ 2% of patients had undergone transplantation; 4% $\pm$ 1% had transitioned to biventricular repair; 50% $\pm$ 3% had undergone a Fontan operation; 32% $\pm$ 2% died before undergoing Fontan, transplantation, or biventricular repair; and 7% $\pm$ 2% were alive at last follow-up without reaching a definitive end state (Figure 2). Risk factors for death included initial procedure type, smaller ascending aorta, aortic valve atresia, and lower birth weight (Table 2). In a multivariable risk-adjusted comparison, 4-year survival without having achieved a definitive repair remained significantly better after NW-RVPA (76% $\pm$ 2%; *P* = .001) compared with NW-BT (60% $\pm$ 4%) and hybrid (61% $\pm$ 4%) (Figure 3).

Propensity-matched survival: Hybrid (n = 88) and NW-BT (n = 88). Propensity-matching between neonates who underwent a stage 1 hybrid or NW-BT procedure resulted in 88 matched pairs (20 variables; c-statistic, 0.76). Survival at 4 years was similar for the hybrid and NW-BT groups (62% $\pm$ 5% vs 57% $\pm$ 5%; *P* = .58) (Figure 4, A). Among propensity-matched neonates, additional risk factors for death included a smaller ascending aorta and lower birth weight (Table 2).

TABLE 1. Selected characteristics stratified by stage 1 operation

Characteristic	NW-BT (n = 232)		NW-RVPA (n = 222)		Hybrid (n = 110)		P value
	n	Mean $\pm$ SD or n (%)	n	Mean $\pm$ SD or n (%)	n	Mean $\pm$ SD or n (%)	
General							
Male	232	147 (63%)	222	145 (65%)	110	68 (62%)	.81
Age at stage 1, d	232	8 $\pm$ 6	222	6 $\pm$ 4	110	12 $\pm$ 16	<.0001
Birth weight, kg	231	3.2 $\pm$ 0.52	217	3.15 $\pm$ 0.47	109	2.9 $\pm$ 0.63	.0004
Birth weight <2.5 kg	231	15 (6%)	217	15 (7%)	109	24 (22%)	<.0001
BSA at birth, m ²	222	0.21 $\pm$ 0.02	201	0.21 $\pm$ 0.02	104	0.2 $\pm$ 0.03	.0011
Institutional diagnosis							
HLHS	232	220 (94%)	222	208 (94%)	110	99 (90%)	.24
Primary aortic valve obstruction*	232	4 (2%)	222	6 (3%)	110	5 (4%)	.32
Primary aortic arch obstruction†	232	4 (2%)	222	3 (1%)	110	4 (4%)	.41
Not listed	232	4 (2%)	222	5 (2%)	110	2 (2%)	.92
Associated lesions							
Aortic arch coarctation	227	80 (35%)	217	63 (29%)	108	31 (29%)	.29
Interrupted aortic arch	232	2 (1%)	222	6 (3%)	110	3 (3%)	.30
Anatomic							
Ascending aorta, cm	187	0.37 $\pm$ 0.2	166	0.33 $\pm$ 0.2	86	0.36 $\pm$ 0.2	.084
Aortic valve atresia	220	100 (45%)	207	124 (60%)	100	39 (39%)	.0006
Mitral valve atresia	214	93 (43%)	205	94 (46%)	102	32 (31%)	.046
TR ($\geq$ moderate)	221	17 (8%)	216	21 (10%)	100	16 (16%)	.071
RV dysfunction ($\geq$ moderate)	215	6 (3%)	213	2 (1%)	102	6 (6%)	.04
Preoperative							
Respiratory failure w/intubation	232	42 (18%)	222	56 (25%)	110	25 (23%)	.18
Identifiable genetic syndrome	232	10 (4%)	222	4 (2%)	110	6 (6%)	.17
CNS: seizure, bleed, stroke	232	4 (2%)	222	5 (2%)	110	6 (6%)	.12
Outcomes/end states‡							
Total deaths	232	89 (38%)	222	59 (27%)	110	44 (40%)	.011
Fontan operation	232	76 (33%)	222	83 (37%)	110	24 (22%)	.017
Total transplant	232	7 (3%)	222	13 (6%)	110	16 (15%)	.0002
Total biventricular repair	232	1 (1%)	222	8 (4%)	110	9 (8%)	<.0001

Values for baseline morphologic and demographic and procedural characteristics for all 564 neonates stratified by NW-BT (n = 232), NW-RVPA (n = 222), and a hybrid procedure (n = 110). P values were determined using the Kruskal-Wallis test, using Wilcoxon rank scores or Student's *t* test (continuous variables), and the χ^2 test of independence or Fisher's exact test (categorical variables) and indicate whether a significant difference exists among the 3 groups. *NW-BT*, Norwood operation with modified Blalock-Taussig shunt; *NW-RVPA*, Norwood operation with right ventricle-to-pulmonary artery conduit; *SD*, standard deviation; *BSA*, body surface area; *HLHS*, hypoplastic left heart syndrome; *TR*, tricuspid valve regurgitation; *RV*, right ventricle; *CNS*, preoperative stroke, seizure or central nervous system/intracranial hemorrhage. *Includes aortic valve stenosis, hypoplasia, or atresia as primary diagnosis. †Includes aortic arch coarctation, hypoplasia, or interrupted aortic arch as the primary diagnosis. ‡P values for outcomes and end states are based on a crude comparison and do not take time to event into consideration.

Propensity-matched survival: Hybrid (n = 81) and NW-RVPA (n = 81). Propensity matching between neonates who underwent a stage 1 hybrid or NW-RVPA procedure resulted in 81 matched pairs (17 variables; c-statistic, 0.77). Survival at 4 years was significantly better in the NW-RVPA group compared with the hybrid group (75% $\pm$ 5% vs 59% $\pm$ 5%; *P* = .008) (Figure 4, B). Additional risk factors for death in these patients included a lower birth weight and smaller left ventricular outflow tract (Table 2).

Impact of Low Birth Weight on Survival

For the entire cohort, as well as for the matched-pair comparisons, lower birth weight had a strong association with poor survival. Incremental changes in birth weight were associated with a larger change in the magnitude of survival relative to additional risk factors for death. There

was also a nonlinear relationship between birth weight and survival. For all patients, an approximate threshold of 2.0 to 2.5 kg was associated with increased decrements in survival (Figure 5, A). In addition, there was a significant interaction between birth weight and hybrid procedures, such that the magnitude of decrement of survival was not as large for neonates with lower birth weight who underwent a hybrid procedure compared with those who underwent NW-BT or NW-RVPA (Figure 5, B). This finding suggests that hybrid procedures may offer a modest survival advantage over NW-RVPA at birth weight $<\sim$ 2.0 kg and over NW-BT at birth weight $<\sim$ 3.0 kg. Of note, among all significant risk factors for death, only birth weight demonstrated a significant interaction with hybrid procedures. Furthermore, birth weight was the sole risk factor in the final multivariable model to exhibit a nonlinear association with survival.

FIGURE 1. Unadjusted survival for all 564 patients by type of stage 1 procedure. Unadjusted, overall, 4-year survival, irrespective of final end state, for all 564 neonates after stage 1 palliation for NW-BT (n = 232; blue curve), NW-RVPA (n = 222; green), and hybrid procedures (n = 110; red curve). Each symbol represents an event (death) positioned on the vertical axis by the Kaplan-Meier estimator. Vertical bars are the confidence limits equivalent to ± 1 standard error. Solid lines are parametric estimates enclosed within dashed 68% confidence bands equivalent to ± 1 standard error. Numbers in parentheses are the number of children at risk at the associated time. NW-RVPA, Norwood operation with a right ventricle-to-pulmonary artery conduit; NW-BT, Norwood operation with modified Blalock-Taussig shunt.

For each propensity-matched subset, birth weight remained a significant risk factor for death, again demonstrating worse survival at an approximate threshold

FIGURE 2. Transition to various competing end states for all 564 neonates after stage 1 palliation. All neonates began alive immediately after stage 1 (time 0) and thereafter remained in this state (black curve) or entered 1 of 4 mutually exclusive end states: transition to Fontan operation (blue curve), heart transplantation (green curve), conversion to biventricular repair (purple curve), or death without definitive repair (red curve). At any point in time the sum of proportions of patients in each end state must be 100%. Solid lines represent continuous parametric estimates, enclosed within dashed 68% confidence bands equivalent to ± 1 standard error; circles represent nonparametric point estimates with corresponding confidence bar equivalent to ± 1 standard error. HTx, Heart transplantation; BVR, biventricular repair.

TABLE 2. Incremental risk factors for death

Risk factor	Parameter estimate	P value	Reliability, %
All 564 neonates			
Early-phase risk factors			
NW-RVPA	−0.85	.001	71
Hybrid procedure*	1.6	.025	—
Birth weight (inverse transformation), kg†	7.7	<.001	67
Ascending aorta index, cm/m ²	−0.29	.039	89
Aortic valve atresia	0.45	.044	58
Interaction, procedure and birth weight‡	−5.0	.01	—
Constant phase risk factors			
Mitral valve z-score	−0.09	.099	40
Matched hybrid and NW-BT neonates (n = 176)			
Early phase risk factors			
Hybrid procedure*	−0.63	.53	43
Birth weight (inverse transformation), kg†	3.3	.002	60
Ascending aorta index, cm/m ²	−2.6	.01	47
Matched hybrid and NW-RVPA neonates (n = 162)			
Early-phase risk factors			
NW-RVPA	−2.4	.02	70
Birth weight (inverse transformation), kg†	3.6	.001	66
Smaller LVOT diameter z-score	−1.8	.05	74

Incremental risk factors for the time-related risk of death without Fontan operation, transplantation, or biventricular repair (competing-events concept) for all 564 neonates after stage 1 palliation, 176 propensity-matched neonates after a hybrid procedure (n = 88) and NW-BT (n = 88), and 162 propensity-matched neonates after a hybrid procedure (n = 81) and NW-RVPA (n = 81). Reliability was determined by bootstrap resampling (n = 500). NW-RVPA, Norwood operations with right ventricle to pulmonary artery conduit; NW-BT, Norwood operation with modified Blalock-Taussig shunt; LVOT, left ventricular outflow tract. *The hybrid procedure variable was manually included in the final multivariable model to determine the impact of hybrid procedures on survival relative to NW-BT and NW-RVPA. †The inverse transformation of birth weight was used to improve linearity; therefore, the parameter estimate indicates that as the inverse of birth weight increases (or birth weight decreases), the risk of death increases. ‡A significant interaction was associated with procedure type and birth weight such that there was a disproportionate impact on survival for hybrid procedures resulting in improved survival at lower birth weights. Parameter estimates were determined from multiphase risk hazard analysis and represent the magnitude of a risk factor for death. The parameter estimate for each variable is related to the hazard function, and the polarity of the estimate (negative or positive) describes decreased (negative) or increased (positive) association with each hazard phase (instantaneous risk of an event). In a multivariable hazard analysis, the overall influence on the hazard function is described by the total effect of each estimate in the model.

of 2.5 kg. Therefore, neonates with lower birth weight are at increased risk of death despite having otherwise similar characteristics before stage 1 palliation. This finding further emphasizes the important influence of birth weight on survival for patients undergoing single-ventricle palliation.

Center and Era Effect on Survival

Among 14 centers that enrolled ≥ 10 patients, 3 were identified as a significant risk factor for death and 1 was

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FIGURE 3. Risk-adjusted survival for all 564 patients by type of stage 1 procedure. Risk-adjusted 4-year survival censored at the time of transition to a Fontan operation, transplantation, or biventricular repair for 564 neonates after NW-RVPA (green curve), NW-BT (blue curve), and hybrid procedures (red curve). Solid lines are continuous parametric estimates enclosed within dashed 68% confidence bands equivalent to ± 1 standard error. Each curve represents the predicted, risk-adjusted survival for a hypothetical patient based on the index procedure performed. All other risk factors are held constant at their median or mean values. Median value for risk factors: birth weight, 3 kg; ascending aorta index, 1.8 cm/m²; aortic valve atresia, 0.48; mitral valve z-score, -15. NW-RVPA, Norwood operation with right ventricle-to-pulmonary artery conduit; NW-BT, Norwood operation with modified Blalock-Taussig shunt.

associated with significantly reduced mortality in an unadjusted univariate analysis (Table E4). However, in risk-adjusted comparisons, for both the multivariable and propensity-matched analyses, none of the center-specific variables was identified as an independent risk factor for death, including the individual center, the absolute enrolled volume or procedure type per center, the percentage of specific procedures performed at a given center, and the era of operation.

DISCUSSION

In this multicenter study of patients with critical LVOTO undergoing stage 1 single-ventricle palliation, in neonates with lower birth weight, hybrid procedures tended to be associated with improved survival compared with Norwood operations. Although our analysis of baseline characteristics suggests that hybrid procedures may be selected for stage 1 palliation in higher-risk neonates, these procedures might not be a lower-risk alternative for all patients. In all neonates except those of lower birth weight, in whom hybrid procedures tended to be associated with a modest survival advantage, NW-RVPA was associated with the best overall survival.

Previously reported analyses comparing outcomes among hybrid procedures and Norwood operations are limited to single-center reviews or do not distinguish between the source of pulmonary blood flow used for the Norwood operations.^{3,9,10,21-23} Our analysis shows that

A

B

FIGURE 4. Survival for propensity-matched neonates. The 4-year survival censored at the time of transition to a Fontan operation, transplantation, or biventricular repair for (A) 88 propensity-matched neonates after NW-BT (blue curve) and 88 propensity-matched neonates after a hybrid procedure (red curve), and (B) 81 propensity-matched neonates after NW-RVPA (green curve) and 81 propensity-matched neonates after a hybrid procedure (red curve). A, Independent of time, there were at total of 36 deaths after NW-BT and 27 deaths after a hybrid procedure before definitive repair. B, The difference in survival between NW-RVPA and NW-BT was related predominantly to an increased early (<1-year) hazard (PE = 0.95; $P = .008$). Thereafter, there was a constant hazard that demonstrated similar low rates of attrition between groups (PE = -1.2; $P = .98$). Independent of time, there were at total of 18 deaths after NW-RVPA and 29 deaths after hybrid procedures before definitive repair. Each circle represents a death positioned on the vertical axis by the Kaplan-Meier estimator. Vertical bars are the confidence limits equivalent to ± 1 standard error. Solid lines are parametric estimates (PE) enclosed within dashed 68% confidence bands equivalent to ± 1 standard error. Numbers in parentheses are the number of patients at risk at the associated time. PE values were determined from multiphase risk hazard analysis and represent the magnitude of hybrid as a risk factor for death. NW-BT, Norwood operation with a modified Blalock-Taussig shunt; NW-RVPA, Norwood operation with a right ventricle-to-pulmonary artery conduit.

among all neonates, survival after the hybrid procedure was similar to that after NW-BT but significantly worse than that after NW-RVPA. A plausible explanation for the early differences in survival may be attributed to the various

FIGURE 5. Impact of birth weight on survival overall and stratified by stage 1 procedure. A, Risk-adjusted nomogram depicting the overall impact of birth weight on survival and (B) the impact of birth weight on survival stratified by stage 1 procedure. Survival is censored at the time of transition to a Fontan operation, transplantation, or biventricular repair. The estimated 4-year survival (vertical axis) is plotted against birth weight (horizontal axis). A, For all patients, birth weight had a nonlinear association with survival, such that at birth weight ~2.0 to 2.5 kg there was a substantial decline in survival (solid black line). B, The estimated 4-year survival plotted against birth weights, stratified by NW-BT ($n = 232$; blue curve), NW-RVPA ($n = 222$; green curve), and hybrid procedure ($n = 110$; red curve) truncated to fit the range of birth weights for each group. There was a significant interaction between birth weight and hybrid procedures, such that birth weight had a disproportionate impact on survival for hybrid relative to NW-BT and NW-RVPA. Solid lines are parametric estimate enclosed within dashed 68% confidence bands equivalent to ± 1 standard error. Risk factors other than birth weight, and procedure for (B), were held constant at their median or mean value. Risk factors (median value): hybrid, 0.2; NW-RVPA conduit, 0.39; ascending aorta index, 1.8 cm/m²; atretic aortic valve, 0.48; mitral valve z-score, -15; years, 4. NW-RVPA, Norwood operation with right ventricle-to-pulmonary artery conduit; NW-BT, Norwood operation with modified Blalock-Taussig shunt.

patterns of coronary artery perfusion associated with each operation.²⁴

Normally, coronary artery perfusion is greatest during diastole. Following NW-BT, however, the lower resistance

of the pulmonary circulation compared with the systemic circulation results in continuous forward flow through the BT shunt.²⁵⁻²⁷ The preferential blood flow through the BT shunt, away from the systemic and coronary vascular bed (“diastolic runoff”), is associated with coronary artery insufficiency and decreased myocardial flow reserve and perfusion.^{2,24,26,27} In contrast, the physiology after NW-RVPA eliminates the possibility of diastolic runoff away from the coronary circulation and thus potentially results in better myocardial perfusion.²⁸ A key finding of the Pediatric Heart Network Single Ventricle Reconstruction Trial was the better early (<1 year) transplantation-free survival after NW-RVPA compared with NW-BT (74% vs 64%).² The fundamental difference in coronary artery perfusion between NW-BT and NW-RVPA has been speculated to be an important factor contributing to the early difference in survival between these 2 groups.^{2,26} The physiology after the hybrid procedure is similar to that after NW-BT, in that there is associated diastolic runoff. Although causality cannot be determined from our results, or from previous reports, it is reasonable to suggest that the similar survival observed after hybrid procedures and NW-BT, and the difference in survival between hybrid procedures and NW-RVPA, are related, at least in part, to the physiology of coronary perfusion for each strategy.

Although there are some similarities in outcomes between our present analysis and the Single Ventricle Reconstruction Trial, there are several important methodological differences. For example, our study was not an intention-to-treat analysis, did not randomize patients, included patients who underwent a stage 1 hybrid procedure, and evaluated different endpoints. As such, we have intentionally avoided drawing specific comparisons between our results and those of the Single Ventricle Reconstruction Trial. However, a recent CHSS publication comparing propensity-matched patients undergoing NW-BT and NW-RVPA demonstrated transplantation-free survival similar to that found in the Single Ventricle Reconstruction Trial, supporting the proposition that coronary perfusion may account for the differences in early survival.²⁹

In our cohort, the neonates who underwent a stage 1 hybrid procedure had significantly lower birth weight compared with those who underwent a Norwood operation, which likely represents a bias when selecting the type of stage 1 procedure. Previous studies, including the Single Ventricle Reconstruction Trial, have identified birth weight <2.5 kg as associated with an increased risk of death after Norwood operations.^{2,30} Similarly, our study found lower birth weight to be a strong risk factor for death, with an approximate threshold for reduced survival of 2.5 kg, irrespective of stage 1 procedure. Importantly, we found that hybrid procedures mitigated some the risk associated with low birth weight, resulting in a trend toward improved survival for neonates of lower birth weight.

Although the threshold for improved survival after hybrid procedures appears to occur at approximately 2.0 kg for NW-RVPA and 3.0 kg for NW-BT, the confidence intervals for each procedure converge at the lower end of the birth weight spectrum. As such, a distinct birth weight associated with improved survival after hybrid procedures relative to NW-BT or NW-RVPA cannot be defined with statistical certainty. Nonetheless, the significant interaction between hybrid procedures and birth weight does provide statistical evidence indicating that the decrease in survival for neonates at the lower end of the birth weight spectrum is less after a hybrid procedure than after NW-BT or NW-RVPA; that is, neonates of lower birth weight who underwent a hybrid procedure exhibited a nonproportional decrease in survival compared with those who underwent NW-BT or NW-RVPA. Therefore, it is reasonable to speculate that as the number of neonates of low birth weight continues to increase, the distinction among the survival curves will become more apparent with subsequent analysis.

The immature organ systems of neonates make them especially susceptible to the adverse effects of CPB and DHCA or regional cerebral perfusion.³¹ The significant deleterious effects associated with exposure to CBP during the fragile neonatal period appear to be exacerbated among those of lower birth weight and contribute to the early morbidity and mortality after Norwood operations.^{3,4,32} Conversely, by virtue of delaying exposure to CPB and extensive surgical reconstruction, hybrid procedures achieve the key elements of initial palliation with a theoretically less destabilizing intervention compared with Norwood operations.^{3,5-7} Given these considerations, it is reasonable to speculate that the improved survival in neonates of lower birth weight after hybrid procedures, particularly among very-low-birth-weight neonates, may be related to the avoidance of the detrimental effects associated with CPB in the neonatal period. However, for neonates without higher-risk characteristics, such as low birth weight, the perceived advantages of the less-invasive hybrid procedure might not be associated with improved survival relative to NW-RVPA.

Although hybrid procedures provide the theoretical advantage of avoiding CPB in neonates, patients who undergo a stage 1 hybrid procedure are more susceptible to complications related to diminished retrograde aortic arch flow secondary to arch obstruction. Specifically, retrograde aortic arch obstruction can jeopardize coronary artery and cerebral perfusion.³³ Despite the fact that our present analysis did not identify a specific relationship between aortic arch obstruction and hybrid procedures, it is reasonable to assume, based on previous analyses, that the increased early attrition after hybrid may be related in part to the effects of retrograde aortic arch obstruction.³³

Neonates who undergo a stage 1 hybrid procedure may be perceived as a higher-risk population than those who

undergo a stage 1 Norwood operation.^{5,8,23,34} Karamlou et al²³ recently reported that among the 100 institutions enrolling patients into the Society of Thoracic Surgeons Congenital Heart Surgery Database, only 13% of patients underwent a hybrid procedure as initial palliation for hypoplastic left heart syndrome.²³ Furthermore, the unadjusted in-hospital mortality was higher after hybrid procedures compared with after Norwood operations (29.7% vs 15.7%; $P < .0001$).²³ An important caveat, however, is that their data demonstrated a selection bias favoring the use of hybrid procedures in neonates with more potential risk factors.²³ Similarly, in our series, only 20% of neonates underwent a stage 1 hybrid procedure, suggesting that most institutions are not using hybrid strategies for stage 1 palliation. In addition, the baseline characteristics of the neonates in our series may indicate that hybrid procedures are being used in patients with greater comorbidities.

Our analysis attempted to account for the differences in baseline characteristics among patients using both risk-adjusted and propensity-matched survival analyses. Risk factors commonly associated with poor outcomes, including aortic atresia, smaller ascending aorta, and lower birth weight,^{10,35,36} are consistent with the findings of our risk-adjusted analysis. It is important to note that our risk-adjusted analysis did not identify other commonly reported risk factors, such as prematurity and genetic syndromes, as predictors of poor survival. One possible explanation for this finding is that because low birth weight was the among the most robust and strongest predictor of death in our analysis, any correlation between birth weight and other important clinical variables may have overshadowed these variables, rendering them nonsignificant in our risk-adjusted analysis. However, important high-risk comorbidities, including genetic/nonsyndromic abnormalities and circulatory collapse with associated metabolic acidosis and the need for preoperative mechanical ventilation,^{5,8,34} were adjusted for by propensity score matching.

Our present analysis did not identify a significant relationship between enrolled surgical volume and death. Although this is a discrepancy compared with a recent study demonstrating that both surgeon and center volume are associated with outcomes after complex congenital heart operations,³⁷ it is not without precedent. A previous CHSS analysis evaluated the volume–outcome relationship among 4 distinct subsets of patients, including infants with interrupted aortic arch, those with pulmonary atresia with an intact ventricular septum, those with transposition of the great arteries (TGA), and those who underwent a Norwood operation. Only in infants undergoing an arterial switch operation for TGA was a higher institutional volume found to be associated with improved outcomes.³⁸ Possible explanations for the discrepancy in these findings are related to the use of an administrative database versus a clinical database and to the decreased enrollment among

CHSS cohorts.^{31,38} In addition, because our present study was not an intention-to-treat analysis, we based our inclusion criteria on the initial operation rather than on the institutional diagnosis; however, for the majority of patients the institutional diagnosis was hypoplastic left heart syndrome. Furthermore, given that there was no difference in the number of non-hypoplastic left heart syndrome diagnoses, this was unlikely to have influenced our present analysis.

Our study was subject to intrinsic limitations associated with all observational studies. Although risk-adjusted parametric survival analysis and propensity-matching methodologies are validated statistical techniques, they are limited by data quality and availability and cannot adjust for unrecognized or unmeasured factors. Pertaining to our study, major limitations included (1) a limited ability to identify the impact of center-specific factors on outcomes, (2) the decreased or absent enrollment in certain CHSS institutions, and (3) the heterogeneity of procedures performed among the enrolled centers. Given that submission of data to CHSS cohorts is voluntary, center volume, procedural distribution, and era of operation can only be estimated based on enrollment. Similarly, the lack of enrollment in certain CHSS institutions is an important limitation, and likely contributed to the heterogeneity of procedures performed among the various institutions. Again, this is an intrinsic limitation of any study based on voluntary enrollment and cannot be accounted for despite our comprehensive statistical strategy. The decreased or absent enrollment in certain CHSS institutions was documented in the recent Society of Thoracic Surgeons Congenital Heart Surgery Database–CHSS database linkage experience, which demonstrated that institutions involved in the CHSS LVOTO cohort study enrolled 34% of eligible patients.³⁹ However, despite the low enrollment, a crude comparison found similar discharge mortality in CHSS-enrolled and nonenrolled patients (16% vs 15%). Therefore, despite the potential limitations associated with low enrollment, it is reasonable to suggest that our data are generalizable, and that our results are representative of the experience of CHSS member-surgeons.

Hybrid procedures are associated with significant differences in procedural techniques, clinical indications, intended objectives (ie, staged palliation, transplantation, or biventricular repair), and institutional preference and availability. Similarly, the choice of palliative strategy/pathway is likely associated with a number of complex patient, center, and clinical factors. Although clinical reports were thoroughly reviewed, physician intent was not always discernible and, thus was not incorporated into our analysis. Furthermore, because hybrid procedures avoid CPB and circulatory arrest in the neonatal period, there is the theoretical advantage of limited neurologic insult; as such, the overall benefit of hybrid strategies, or lack thereof,

cannot be fully evaluated until sufficient data exist to explore long-term functional and developmental outcomes. Nonetheless, the CHSS understands the importance of identifying the contemporary clinical applications of stage 1 hybrid procedures and is currently obtaining data to investigate this important question.

Despite these limitations, it is reassuring that our results are consistent for both the risk hazard and propensity-matched analyses. Our use of a multilevel statistical approach that incorporated competing-risks methodology and multiple risk-adjustment strategies allows for important inferences to be obtained from the aggregate of our results.

In this current observational study of neonates with critical LVOTO undergoing single-ventricle palliation, NW-RVPA was associated with the best survival to a definitive surgical end state. Although lower birth weight was identified as an important risk factor for death for the entire cohort, the detrimental impact of low birth weight was mitigated, to some degree, for patients who underwent a hybrid procedure. As such, hybrid alternatives appear to provide a survival advantage for neonates with very low birth weight.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: congenital heart disease, single ventricle, critical left ventricular outflow tract obstruction, hypoplastic left heart syndrome, hybrid, Norwood

APPENDIX E1. STATISTICAL METHODS

Parametric Risk Hazard Analysis

Kaplan-Meier (KM) estimates of time to event were constructed and then used to create parametric multiphase models defining transition to various end states. These models use shaping parameters (mathematical equations) that capture various phases of risk, each of which can be independently subjected to risk hazard regression analysis.^{E1} (For additional details, see <http://www.lerner.ccf.org/qhs/software/hazard>.) These parametric models are tested for adequate fit of the underlying data by plotting observed KM estimates (expected) versus the predicted parametric events over time. Therefore, the unadjusted (baseline) parametric model closely matches the KM survival estimates.

After establishing the basic structure of the parametric model, incremental risk factors associated with a defined endpoint can be explored via risk hazard analysis. This process is similar to that of identifying significant variables in other types of regression equations and is described in detail below. Advantages of parametric approaches include (1) analysis of all events of an entire follow-up period without the need for artificially imposed cutoffs, (2) the combined analysis of multiple patients and procedural characteristics, and (3) the ability to efficiently plot data for increased interpretation of results. For example, Figure 1 represents unadjusted survival stratified by each procedure type (ie, closely follows KM survival estimates). Alternatively, Figure 3 represents survival adjusted for additional important variables (identified in Table 2). The advantage of the parametric regression approach is the ability to graph survival while adjusting for multiple covariables. Although the more traditional Cox regression model is able to identify associated risk factors for death, this approach is limited by the inability to graphically represent survival with incorporated risk factors.

The advantage of using a fully parametric model that allows for identification of multiple phases of risk has been well documented.^{E2} Specifically, the importance as it pertains to our study is related to the timing of maximum hazard for death after stage 1 palliation. It was previously demonstrated that the hazard for death is greatest in the early postoperative period.^{E3} Subsequently, as time progresses after stage 1 palliation, there is a lower rate of attrition and thus a change in hazard for death. The use of a multiphase approach allows us to define the time at which the hazard begins to change. This offers an advantage when comparing survival among procedures types, in that we are able to specify when the difference in survival occurs between groups (ie, early vs late). Although multivariable analysis is possible with traditional Cox regression analysis, Cox regression assumes that each risk factor is associated with a constant hazard throughout follow-up, which we know is not always the case. An alternative approach would

be to stratify groups of interest using the standard KM survival estimates; however, multivariable analyses cannot be conducted via the KM approach and thus cannot adjust for baseline characteristics.

Risk Hazard Analysis

Each parametric hazard function can be subjected to risk hazard analysis. Selected variables extracted from clinical reports are incorporated into this process. To minimize the risk of model overdetermination, continuous variables with excessive missing values (>75%) and categorical or ordinal variables with at least 5 associated events were excluded (unless deemed necessary for analysis). For all other variables, informative imputation (multiple imputation) based on available data was used to replace missing values. Missing values were estimated by 5-fold multiple imputation using Markov chain Monte Carlo.^{E4} Relevant missing-value indicator variables were created and included in multivariable analyses to adjust for possible bias introduced by missing data. Missing-value indicator variables were entered into final multivariable models. In the current analysis, none of the missing-value indicator variables was found to have a significant *P* value, and thus each variable remained in the final model. For continuous variables, various mathematic transformations were tested for optimal calibration of the relationship to risk, and the significance of various interaction terms was explored. The multivariable models were solved in a competing end states format for multiple combinations of risk factors to explore the magnitude of effect of these factors and to predict outcomes for patients with given characteristics.

Variable selection was guided by bootstrap bagging ($n = 500$; threshold for inclusion, $P = .10$).^{E5,*} Variables selected in at least ~50% of resamples or their clusters were considered reliable for inclusion. A *P* value < .06 was considered significant for final variable retention. To create the final risk-adjusted model, parametric hazard analysis was performed on bootstrap-proven variables from each of the 5 imputed datasets to yield regression coefficients and their variance-covariance matrices. These 5 sets of estimates were then combined to determine the final regression coefficients and *P* values.^{E4} A *P* value < .05 was considered significant; however, important variables of interest (ie, procedure type and institutional variables) with a *P* value > .05 were sometimes included to determine the relative impact on survival. The parameter estimate for each variable is related to the hazard function, and the polarity of the estimate (negative or positive)

*Many variables that reach statistical significance in clinical regression analyses are poorly reliable, in that they are not statistically significant when tested in other similar datasets. Bootstrap resampling (bagging) tests the “generalizability” of a variable to the wider study population by describing both its significance and its reliability.

describes decreased (negative) or increased (positive) association with each hazard phase (instantaneous risk of an event). In a multivariable hazard analysis, the overall influence on the hazard function is described by the total effect of each estimate in the model.

Propensity-Score Matching

Propensity-score matching was used to adjust for potential differences in baseline characteristics.^{E6} This process comprised the following steps:

1. All baseline demographic, morphologic, and clinical parameters were incorporated into a bootstrap regression model. These parameters included variables reflective of preoperative clinical status, including identifiable genetic syndromes, nonsyndromic anomalies, evidence of metabolic acidosis, respiratory failure, and cerebral hemorrhage or stroke.
2. Variables that met the bootstrap criteria were subsequently incorporated into a logistic regression equation, modeling the probability of any given neonate belonging to the hybrid versus NW-BT groups and the hybrid versus NW-RVPA groups.
3. This parsimonious model was then augmented with important clinical variables as described previously, and adequate propensity-matching was based on the c-statistic. The c-statistic is a measure of how well the propensity score is able to control for confounders. A score

between 0.65 and 0.85 is associated with an adequate match.

4. Neonates were then matched with a 1:1 greedy-matching algorithm between each group based on propensity scores.^{E7}
5. The difference between the 2 groups before and after propensity-score matching was compared using the standardized differences for mean values of important baseline characteristics (Figure E2), and post-propensity-matching summary statistics for each group (Table E3).^{E8}

E-References

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FIGURE E1. Institutional enrollment for all 564 neonates in the critical left ventricular outflow tract cohort at the time of analysis of stratified stage 1 palliation strategy. *NW-BT*, Norwood operation with modified Blalock-Taussig shunt (blue bars); *NW-RVPA*, Norwood operation with right ventricle-to-pulmonary artery conduit (green bars). Red bars, hybrid procedure.

FIGURE E2. Mirrored histograms and covariable balance plots for determining adequacy of propensity matching. (Top) Mirrored histograms of the distribution of propensity scores for (A) neonates who underwent a stage 1 Norwood operation with modified Blalock-Taussig shunt (NW-BT; blue) versus neonates who underwent a hybrid procedure (red) and for (B) neonates who underwent a stage 1 Norwood operation with right ventricle-to-pulmonary artery conduit (NW-RVPA; green) versus neonates who underwent a hybrid procedure (red). The colored areas represent matched neonate pairs of NW-BT ($n = 88$) and hybrid ($n = 88$) and matched pairs of NW-RVPA ($n = 81$) and hybrid ($n = 81$). (Bottom) Covariable balance plots for selected variables between (A) NW-BT and hybrid and (B) NW-RVPA and hybrid. Values on the horizontal axis represent percent standardized difference between each group. Triangles indicate standardized difference before matching; squares, standardized difference after matching. *Op BSA*, Body surface area at stage 1; *BW*, birth weight; *BSA*, body surface area; *TV*, size of tricuspid valve annulus; *MV atr*, mitral valve atresia; *Arch*, transverse arch size/coarctation; *AoV atr*, aortic valve atresia; *Acid*, preoperative metabolic acidosis; *AI*, aortic valve insufficiency; *Asc.Ao*, ascending aorta diameter; *BPA min*, minimum branch pulmonary artery size; *Genetic*, any identifiable genetic syndrome; *RVOT*, right ventricle outflow tract size/stenosis; *AoV ann*, aortic valve annulus diameter; *RV dys*, important right ventricle dysfunction; *LVOT*, minimum diameter of smallest measurement of the left ventricular outflow tract; *Brain*, any preoperative seizure, stroke, or cerebral bleed; *MV*, mitral valve annulus; *TR*, important tricuspid valve regurgitation; *Op age*, age at stage 1.

TABLE E1. Participating CHSS member institutions

Alfred I. duPont Hospital for Children, Wilmington, Del
All Children's Hospital, St Petersburg, Fla
Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Ill
Children's Hospital of Alabama, Birmingham, Ala
Children's Hospital of Michigan, Detroit, Mich
Children's Hospital of Pittsburgh, Pittsburgh, Pa
Children's Mercy Hospitals and Clinics, Kansas City, Mo
Children's National Heart Institute Children's National Medical Center, Washington, DC
Children's Hospital of Wisconsin, Milwaukee, Wisc
Cincinnati Children's Hospital, Cincinnati, Ohio
C. S. Mott Children's Hospital, Ann Arbor, Mich
Inova Fairfax Hospital for Children, Falls Church, Va
Kosair Children's Hospital, Louisville, Ky
Lucile Packard Children's Hospital Stanford, Palo Alto, Calif
Milton Hershey Medical Center, Hershey, Pa
Primary Children's Medical Center, Salt Lake City, Utah
Rady Children's Hospital, San Diego, Calif
Riley Hospital for Children, Indianapolis, Ind
St. Louis Children's Hospital, St. Louis, Mo
The Children's Heart Clinic of Minnesota, Minneapolis, Minn
The Hospital for Sick Children, Toronto, Ontario, Canada

TABLE E2. Operative details and reported indications for hybrid procedures

	n (%)
Operative details	
Number of institutions	11 (52)
Bilateral pulmonary artery banding*	106 (95)
Ductal stent	76 (69)
PDA maintained with prostaglandin infusion	35 (32)
Atrial septostomy/stenting at time of procedure	11 (10)
Reverse BT shunt†	18 (16)
Initial hybrid converted to Norwood operation	26 (24)
Reported indications	
Norwood considered too high risk	54 (49)
Prematurity or low birth weight	16 (15)
Hemodynamic instability or organ malperfusion	12 (11)
Restrictive/absent ASD	3 (3)
High-risk indication not stated	23 (20)
Salvage procedure	20 (18)
Bridge to transplantation‡	11 (10)
Single-ventricle to biventricle deferral strategy§	9 (8)
Parental request	7 (6)
Institution routine	2 (2)
Indication not stated	7 (6)

PDA, Patent ductus arteriosus; BT, Blalock-Taussig; ASD, atrial septal defect.

*Four patients underwent pulmonary artery banding in 2 stages. †Reverse BT shunt designates a procedure in which a shunt was placed from the main pulmonary artery to innominate artery to prevent retrograde aortic arch malperfusion after ductal stenting. ‡Nine of 11 patients where the intended strategy was transplantation went on to transplantation. §Six of 9 patients where the intended strategy for the hybrid procedure was to defer single-ventricle versus biventricular decision process underwent a biventricular repair.

TABLE E3. Baseline characteristics after propensity-score matching

Variable	Hybrid (n = 88)		NW-BT (n = 88)		P value
	No. available	Mean ± SD or n (%)	No. available	Mean ± SD or n (%)	
Age at operation, d*	88	9 ± 9	88	9.6 ± 8	.14
BSA at operation, m ² *	85	0.2 ± 0.02	87	0.2 ± 0.02	.86
Birth weight	87	3.03 ± 0.54	88	3.02 ± 0.53	.66
Birth weight <2.5 kg	88	12 (14%)	88	12 (14%)	1
Unrestrictive VSD*	44	6 (14%)	56	12 (21%)	.31
Small/restrictive ASD*	57	26 (46%)	63	23 (37%)	.31
Minimum LVOT z-score*	81	−19.2 ± 10.4	86	−18.42 ± 11	.51
Ascending aorta, cm	68	0.36 ± 0.17	72	0.36 ± 0.16	.96
Transverse arch index, cm/m ² *	51	1.8 ± 0.55	37	1.87 ± 0.62	.96
EFE (any level)*	24	20 (83%)	20	19 (95%)	.22
Aortic insufficiency (any degree)*	71	15 (21%)	75	18 (24%)	.68
Aortic atresia*	80	31 (39%)	83	32 (39%)	.98
Aortic arch coarctation*	86	26 (30%)	86	28 (33%)	.74
Functional left ventricle atresia*	42	17 (40%)	35	11 (31%)	.41
Mitral valve annulus z-score*	62	−14.32 ± 7.9	59	−15.1 ± 7.1	.49
Mitral valve atresia*	83	29 (35%)	82	28 (34%)	.91
Tricuspid valve annulus z-score*	41	−1.17 ± 2.04	23	−1.38 ± 2	.61
Grade of tricuspid regurgitation*,†	78	9 (12%)	85	10 (12%)	.96
Grade RV dysfunction*,†	81	4 (5%)	83	3 (4%)	.72
Minimum branch PA z-score*	21	−0.46 ± 1.62	52	−0.52 ± 1.72	.86
Any nonsyndromic anomaly*	88	29 (33%)	88	30 (34%)	.87
Identifiable genetic syndrome	88	5 (6%)	88	7 (8%)	.55
Preoperative metabolic acidosis*	88	16 (18%)	88	19 (22%)	.57
Respiratory failure requiring mechanical ventilation	88	16 (18%)	88	19 (22%)	.57
CNS: seizure, bleed, stroke*	88	4 (5%)	88	3 (4%)	.7
Total deaths	88	29 (33%)	88	35 (40%)	.32
Total Fontan operations	88	22 (25%)	88	29 (33%)	.24
Total transplantation	88	12 (13%)	88	3 (3%)	.012
Total biventricular repair	88	7 (8%)	88	0	.014

Variable	Hybrid (n = 81)		NW-RVPA (n = 81)		P value
	No. available	Mean ± SD or n (%)	No. available	Mean ± SD or n (%)	
Age at operation, d*	81	8 ± 6	81	7 ± 6	.87
BSA at procedure, m ² *	78	0.2 ± 0.02	77	0.2 ± 0.02	.96
Birth weight	81	3.02 ± 0.55	78	3.03 ± 0.52	.94
Birth weight <2.5 kg	81	12 (15%)	81	10 (12%)	.65
Unrestrictive VSD*	42	6 (14%)	59	12 (20%)	.43
Small/restrictive ASD*	51	25 (49%)	55	21 (38%)	.26
Ascending aorta index, cm/m ² *	61	1.84 ± 0.9	58	1.81 ± 0.96	.54
Minimum LVOT z-score	75	−19.27 ± 10.7	72	−19.45 ± 10.6	.96
Transvers aortic arch*	44	1.78 ± 0.51	41	1.76 ± 0.51	.87
EFE (any level)	23	20 (87)	20	17 (85)	.85
AI (any degree)	65	13 (20)	65	11 (17)	.65
Aortic atresia*	73	32 (44%)	75	33 (44%)	.98
Aortic arch coarctation*	73	30 (41%)	78	30 (38%)	.74
Functional left ventricle atresia	39	16 (41)	48	19 (40)	.89
Mitral valve annulus z-score*	54	−15 ± 8	48	−15 ± 8	.73
Mitral valve atresia*	75	26 (35%)	75	28 (37%)	.73
Tricuspid valve annulus z-score*	38	−1.4 ± 2.3	7	−0.9 ± 1.3	.49
Grade of tricuspid regurgitation*,†	71	7 (10%)	78	6 (8%)	.64
Grade RV dysfunction*,†	74	3 (4%)	78	0	.11
Pulmonary valve z-score*	41	1.2 ± 1.3	11	0.8 ± 1.4	.26
Any nonsyndromic anomaly*	81	23 (28%)	81	29 (36%)	.31
Identifiable genetic syndrome	81	4 (5%)	81	4 (5%)	1

(Continued)

TABLE E3. Continued

Hybrid and NW-RVPA	Hybrid (n = 81)		NW-RVPA (n = 81)		
Preoperative metabolic acidosis*	81	10 (12%)	81	10 (12%)	1
Respiratory failure requiring mechanical ventilation*	81	18 (22%)	81	22 (27%)	.47
CNS: seizure, bleed, stroke	81	4 (5%)	81	4 (5%)	1
Total deaths	81	31 (38%)	81	17 (21%)	.016
Total Fontan operations	81	22 (27%)	81	27 (33%)	.39
Total transplantation	81	9 (11%)	81	6 (7%)	.42
Total biventricular repair	81	6 (7%)	81	6 (7%)	1

Baseline characteristics, number available, and values for variables after propensity matching for neonates who underwent a stage 1 NW-BT and neonates who underwent a hybrid procedure and for neonates who underwent a stage 1 NW-RVPA and neonates who underwent a hybrid procedure. *SD*, Standard deviation; *NW-BT*, Norwood operation with a modified Blalock-Taussig shunt; *BSA*, body surface area; *VSD*, ventricular septal defect; *ASD*, atrial septal defect; *LVOT*, left ventricular outflow tract; *EFE*, endocardial fibroelastosis; *RV*, right ventricle; *PA*, pulmonary artery; *CNS*, central nervous system; *NW-RVPA*, Norwood operation with a right ventricle-to-pulmonary artery conduit; *AI*, aortic insufficiency. *Designates variables used to generate the propensity scores. Each propensity score was then used to match neonates with similar baseline characteristics from each respective group. †Reported values are for right ventricular dysfunction and tricuspid regurgitation. A total of 176 neonates who underwent NW-BT (n = 88) or a stage 1 hybrid procedure (n = 88) were matched with a propensity score generated from 20 variables (c-statistic, 0.76). A total of 162 neonates who underwent NW-RVPA (n = 81) or a stage 1 hybrid procedure (n = 81) were matched with a propensity score generated from 17 variables (c-statistic, 0.77). The c-statistic is a measure of how well the propensity score is able to control for confounders. A score between 0.65 and 0.85 is associated with an adequate match.

TABLE E4. Center-specific and era of operation risk factors

Risk factor	Parameter estimate	P value
Individual institutions with ≥10 enrolled patients		
Univariate analysis		
Institution A	0.45	.37
Institution B*	0.73	.034
Institution D	−1.82	.085
Institution E	−0.15	.732
Institution F	0.46	.072
Institution G	0.91	.22
Institution H	−15.1	.98
Institution I*	0.55	.016
Institution K	−0.45	.28
Institution M	0.31	.18
Institution N*	0.61	.054
Institution P	−0.98	.72
Institution Q*	−1.2	.024
Institution T	0.35	.16
Multivariable analysis		
Institution B†	0.51	.16
Institution I†	0.34	.15
Institution N†	0.16	.66
Institution Q†	−0.87	.099
Procedural volume and era of operation		
Total procedures per center	0.01	.11
% of total procedures performed per center as hybrids	0.005	.98
Absolute number of hybrids performed per center	0.007	.29
% of total procedures performed per center as NW-RVPA	−0.005	.26
Absolute number of NW-RVPA performed per center	−0.004	.54
% of total procedures performed per center as NW-BT	0.004	.30
Absolute number of NW-BT performed per center	0.012	.031
Era of operation	0.036	.37

Center-specific volume and era of operation were risk factors for death. The volume of operations at each center was based on enrolled patients and tested as the total enrolled volume per center, the percentage of each procedure performed at each center (based on enrolled volume), and the absolute number of each procedure performed at each center (based on enrolled volume). Era of operation was entered into the final multivariable model and tested as a continuous variable calculated from the date of operation to the current date at the time of analysis. *NW-RVPA*, Norwood operation with a right ventricle-to-pulmonary artery conduit; *NW-BT*, Norwood operation with a modified Blalock-Taussig shunt. *Denotes institutions that were found to have a significant association (either positive or negative) with survival. †All institutions found to have a significant association with survival were entered into the final multivariable as a risk factor. Therefore, the *P* value and parameter estimate represent each institution as risk factors in the otherwise parsimonious multivariable model.