Two-Year Survival and Mental and Psychomotor Outcomes After the Norwood Procedure

An Analysis of the Modified Blalock-Taussig Shunt and Right Ventricle–to–Pulmonary Artery Shunt Surgical Eras

Joseph Atallah, MD; Irina A. Dinu, PhD; Ari R. Joffe, MD; Charlene M.T. Robertson, MD; Reg S. Sauve, MD; John D. Dyck, MD; David B. Ross, MD; Ivan M. Rebeyka, MD; and the Western Canadian Complex Pediatric Therapies Follow-Up Group

***Background*—**The Norwood procedure for stage 1 palliation of hypoplastic left heart syndrome is performed with either the modified Blalock-Taussig (MBTS) or the right ventricle–to–pulmonary artery (RVPA) shunt. In our institution, surgical practice changed from use of the MBTS to use of the RVPA shunt in 2002. We analyzed survival and mental and psychomotor outcomes of the 2 consecutive surgical eras.

***Methods and Results*—**Between September 1996 and July 2005, 94 neonates with hypoplastic left heart syndrome underwent the Norwood procedure. Patients were recruited as neonates and followed up prospectively. Health, mental, and psychomotor outcomes (Bayley Scales of Infant Development-II) were assessed at 2 years. The study subjects were from the Norwood-MBTS era (n=62; 1996 to 2002) or the Norwood-RVPA era (n=32; 2002 to 2005). In the MBTS era, early and 2-year mortality rates were 23% (14/62) and 52% (32/62); the mean (SD) mental and psychomotor developmental indices were 79 (18) and 67 (19). In the RVPA era, early and 2-year mortality rates were 6% (2/32) and 19% (6/32); the mean (SD) mental and psychomotor developmental indices were 85 (18) and 78 (18). The 2-year mortality rate ($P=0.002$) and the psychomotor developmental index ($P=0.029$) were improved in the more recent surgical era. On multivariable Cox regression analysis, postoperative highest serum lactate independently predicted 2-year mortality in the MBTS and RVPA eras.

***Conclusions*—**Analysis of 2 consecutive surgical eras of hypoplastic left heart syndrome patients undergoing the Norwood procedure showed a significant improvement in 2-year survival and psychomotor development in the more recent era. Adverse neurodevelopmental outcome in this patient population remains a concern. **(*Circulation*. 2008;118:1410-1418.)**

Key Words: heart defects, congenital ■ pediatrics ■ mortality ■ prognosis

The Norwood procedure for palliation of hypoplastic left heart syndrome (HLHS) was first described in 1980,[1] and it has since undergone several modifications that have led to improved patient mortality and morbidity. Nevertheless, hemodynamic instability and postoperative death remain concerns. Unpredictable variability in pulmonary vascular resistance leading to overcirculation and coronary insufficiency is thought to be an important factor in the death of patients who have undergone the Norwood procedure with the modified Blalock-Taussig shunt (MBTS). More recently, the right ventricle–to–pulmonary artery (RVPA) shunt modification of the Norwood procedure was revived.[2] This modification offers the advantage of separating the effects of changes in pulmonary vascular resistance from the systemic circulation while providing adequate pulmonary blood flow. This may lead to better survival rates. In 2003, Sano et al[3] reported their positive experience with the RVPA shunt modification of the Norwood procedure. Since then, several centers have adopted the new technique; however, reports in the literature are conflicting as to the surgical and interstage survival differences.[4–10] To the best of our knowledge, there are no reports in the literature comparing neurodevelopmental outcome between the MBTS and RVPA

Received September 24, 2007; accepted July 25, 2008.

From the Department of Pediatrics (J.A., A.R.J., C.M.T.R., J.D.D., I.M.R.), School of Public Health (I.A.D.), and Department of Surgery (D.B.R., I.M.R.), University of Alberta, Edmonton, Alberta, Canada; Pediatric Rehabilitation Outcomes Evaluation and Research Unit (C.M.T.R.), Glenrose Rehabilitation Hospital, Edmonton, Alberta, Canada; and Department of Pediatrics (R.S.S.), University of Calgary, Calgary, Alberta, Canada.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.741579/DC1.

Correspondence to Ari Joffe, MD, FRCP(C), Department of Pediatrics, 3A3.07 Stollery Children's Hospital, 8440 112 St, Edmonton, Alberta, Canada T6G 2B7. E-mail ajoffe@cha.ab.ca

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.107.741579**

modifications of the Norwood procedure. We report our experience, with analysis of 2 consecutive surgical periods separately and evaluation of survival and mental and psychomotor outcomes at 2 years of age for each of the 2 study periods.

Clinical Perspective p 1418

Methods

The present cohort study is part of a prospective interprovincial, inception-cohort outcomes follow-up project conducted in 4 provinces in Western Canada. As described previously,[11,12] infants ≤6 weeks of age were identified at the time of complex cardiac surgery and were followed up prospectively. In the present study, we included all patients with the diagnosis of HLHS or its variants who had undergone the Norwood procedure between September 1996 and July 2005. All surgeries were performed at the Stollery Children's Hospital, Edmonton, Alberta, Canada. Predetermined demographic, preoperative, intraoperative, and postoperative variables were collected prospectively.[11,12] Long-term follow-up was discussed with parents or guardians once survival was probable, and with their written consent, contact was made with their respective follow-up clinics at the tertiary site of origin.

Early Childhood Assessments

Outcome assessments were completed when the children were between 18 and 24 months of age. History and physical measurements were obtained as described previously.[11,12] The family socioeconomic status was determined with the Blishen Index.[13] Maternal education was indicated by years of schooling. Pediatricians experienced in neurodevelopmental follow-up examined each child for evidence of cerebral palsy[14] or visual impairment, defined as corrected visual acuity in the better eye of <20/60.[11,12] Hearing was evaluated by experienced certified pediatric audiologists in soundproof environments as described previously.[11,12] Sensorineural hearing impairment was defined as responses in the better ear of >40 dB at any frequency from 250 to 4000 Hz. Five certified pediatric psychologists and psychometrists administered the Bayley Scales of Infant Development-II[15] in their respective referral institutions. The Bayley Scales of Infant Development-II is a widely accepted standardized outcome measure used in neonatal follow-up clinics that yields separate mental developmental index (MDI) and psychomotor developmental index (PDI) standardized scores with a mean of 100 and SD of 15. Developmental indices of <70 (2 SD below the mean) indicated mental or psychomotor delay. Within a normative sample, 2.27% of children have scores <70.

Variables

Demographic, preoperative, intraoperative, postoperative, and overall variables used in the study are listed in Table 1.

Outcomes

The primary outcomes of interest were (1) mortality (early, interim, and 2-year) and (2) mental and motor development. Early mortality was defined as death that occurred within 30 days of the Norwood procedure or at any time in the hospital if the patient was never discharged. Interim mortality was defined as death that occurred after the above-defined early mortality period and before the bidirectional cavopulmonary anastomosis surgical procedure. Two-year mortality included all deaths that occurred between the Norwood procedure and the 2-year birth date, inclusive. Secondary outcomes included morbidity, defined by the health and growth variables listed in Table 2.

Statistical Analysis

Continuous variables are presented as mean (SD) and were analyzed with the Student *t* test. Categorical variables are presented as counts and percentages and were analyzed with Fisher exact test. Actuarial survival analysis was performed with Kaplan-Meier estimates with log-rank comparison of cumulative survival by study era. Mortality and mental and psychomotor development were analyzed for the 2 study groups separately. To screen for variables associated with early and 2-year mortality, we used univariate logistic and Cox regression analysis, respectively, and included all relevant variables from Table 1. Multivariable logistic and Cox regression analysis included variables that were significant at $P \leq 0.10$ in the corresponding univariate analysis. To screen for variables associated with MDI and PDI, we used univariate logistic regression models and included all relevant variables from Table 1. Multiple linear regression models consisted of variables found to be significant at $P \leq 0.10$ in the univariate analysis, after screening for multicollinearity. Regression model results are reported as hazard ratios or effect sizes with confidence intervals and 2-sided *P* values. Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Description of Cohort

Ninety-four patients with HLHS or its variants underwent the Norwood procedure between September 1996 and July 2005. Patients with additional significant cardiac diagnoses included 1 with total anomalous pulmonary venous drainage and 1 with double-outlet right ventricle in the MBTS group, as well as 2 with unbalanced atrioventricular septal defects in the RVPA group. Complete follow-up data were available for all patients. The 2 study groups are from 2 consecutive surgical eras. The first was from September 1996 to September 2002 and included 62 patients having the Norwood procedure performed with the MBTS (MBTS era). The second was from October 2002 to July 2005 and included 32 patients having the Norwood procedure modified with the use of the RVPA shunt (RVPA era). Other significant changes that took place during the transition of surgical eras were (1) the use of regional cerebral perfusion and (2) the home monitoring program (as described by Ghanayem et al[16]).

Group Comparison

The demographic, preoperative, operative, postoperative, and overall variables compared between the MBTS and RVPA eras are shown in Table 1. Noncardiac diagnoses are listed in Table I in the online-only Data Supplement.

Primary Outcomes

Mortality

Early mortality was 23% (14/62) for the MBTS era and 6% (2/32) for the RVPA era ($P=0.079$). Interim mortality was 21% (13/62) for the MBTS era and 13% (4/32) for the RVPA era ($P=0.403$). Mortality by 2 years of age was 52% (32/62) for the MBTS era and 19% (6/32) for the RVPA era ($P=0.002$). Kaplan-Meier estimates of survival time after the Norwood surgery show significantly better survival at 2 years of age for the RVPA era than for the MBTS era ($P=0.003$; Figure 1).

For early mortality, multiple logistic regression analysis was performed only for the MBTS era, adjusted for variables

Table 1. Descriptive Variables of 94 Patients After the Norwood Procedure: Comparison of the MBTS and RVPA Shunt Modification Eras

Variables	MBTS: 1996–2002 (n=62)	RVPA: 2002–2005 (n=32)	*P**
Demographic			
Gestational age, wk	38.8 (1.7)	39.4 (1.4)	0.093
Birth weight, kg	3.2 (0.6)	3.4 (0.5)	0.063
Male sex, n (%)	33 (53)	21 (66)	0.278
Socioeconomic status† (n=56)	46 (16)	41 (9)	0.164
Guardianship (both parents; n=56), n (%)	26 (87)	24 (92)	0.675
Primary language (English; n=56), n (%)	22 (73)	23 (89)	0.192
Mother's education, y (n=56)	14.5 (3.7)	13.5 (1.8)	0.144
Preoperative			
Prenatal diagnosis, n (%)	19 (31)	20 (63)	0.004
Aortic atresia, n (%)	16 (26)	7 (22)	0.802
Highest serum lactate, mmol/L	3.5 (3.2)	4.7 (4.6)	0.159
Lowest arterial pH	7.2 (0.15)	7.2 (0.10)	0.338
Lowest Pa_{O_2}	33 (14)	31 (6)	0.470
Lowest base deficit, mmol/L	−6.8 (6.5)	−7.1 (4.4)	0.828
Highest dopamine used, $\mu g \cdot kg^{-1} \cdot min^{-1}$	5.4 (5.2)	3.6 (5.3)	0.107
Ventilation time, d	7.5 (6.5)	8.8 (8.2)	0.382
Convulsions, n (%)	2 (3)	2 (6)	0.603
CPR, n (%)	3 (5)	1 (3)	0.999
ECLS, n (%)	3 (5)	0	0.549
Operative			
Age, d	11.1 (18.4)	10.9 (8.4)	0.978
Age >14 d, n (%)	6 (10)	7 (22)	0.123
Weight, kg	3.3 (0.6)	3.6 (0.6)	0.034
Weight <2.5 kg, n (%)	5 (8)	2 (6)	0.999
Year of surgery (SD)	1999 (1.8)	2003 (0.9)	<0.001
CPB, min	134 (75)	117 (32)	0.212
ACC, min	48 (15)	35 (13)	<0.001
DHCA, min	42 (20)	24 (14)	<0.001
RCP use, n (%)	13 (21)	32 (100)	<0.001
Re-CPB, n (%)	30 (48)	1 (4)	<0.001
Postoperative			
Highest serum lactate, mmol/L (d1)	9.0 (5.6)	7.5 (3.7)	0.201
Lowest arterial pH (d1)	7.3 (0.09)	7.3 (0.06)	0.746
Lowest Pa_{O_2} (d1)	32 (9)	30 (3)	0.385
Lowest base deficit, mmol/L (d1)	−0.8 (5.4)	−2.4 (3.1)	0.086
Highest dopamine used, $\mu g \cdot kg^{-1} \cdot min^{-1}$ (d1)	8.6 (5.5)	4.9 (4.1)	0.001
Highest serum lactate, mmol/L (d2–5)	5.6 (6.4)	3.2 (2.5)	0.016
Lowest arterial pH (d2–5)	7.3 (0.1)	7.3 (0.1)	0.127
Lowest Pa_{O_2} (d2–5)	33 (5)	33 (3)	0.729
Lowest base deficit, mmol/L (d2–5)	−1.5 (5)	−0.75 (3)	0.372
Highest dopamine used, $\mu g \cdot kg^{-1} \cdot min^{-1}$ (d2–5)	8.9 (6)	3.4 (4.9)	<0.001
Convulsions, n (%)	7 (12)	4 (13)	0.999
CPR, n (%)	13 (23)	2 (3)	0.079
ECLS, n (%)	10 (16)	1 (3)	0.091
Open sternum, d	6.6 (8.8)	5.9 (2.2)	0.628

(*Continued*)

Table 1. Continued

Variables	MBTS: 1996–2002 (n=62)	RVPA: 2002–2005 (n=32)	*P**
Overall			
Ventilation time, d	17.8 (14.9)	14.7 (7.3)	0.183
Hospitalization, d	37.4 (24.1)	43.4 (30.4)	0.295
Convulsions, n (%)	8 (13)	5 (16)	0.758
CPR, n (%)	16 (26)	3 (9)	0.102
Home monitoring program, n (%)	0	13 (41)	<0.001
Age at BCPA, mo	7.7 (2.1)	5.6 (1.5)	<0.001

CPR indicates cardiopulmonary resuscitation; ECLS, extracorporeal life support; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp time; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; Re-CPB, repeat cardiopulmonary bypass; BCPA, bidirectional cavopulmonary anastomosis; d1, postoperative day 1; and d2–5, postoperative days 2 to 5.

Values are mean (SD) or n (%) where indicated.

*Significance with Student *t* test, Fisher exact test.

†See Blishen.[13]

listed in Table 1 (see online-only Data Supplement Table II for univariate analysis). Highest lactate on postoperative days 2 to 5 (odds ratio 1.14, 95% confidence interval 1.03 to 1.27, $P=0.016$) and male sex (odds ratio 0.23, 95% confidence interval 0.05 to 1.07, $P=0.062$) were associated with early mortality. When the multiple logistic regression was repeated with the exclusion of postoperative variables, only male sex was associated with early mortality. Multiple regression analysis for early mortality was not performed for the RVPA era, because the outcome consisted of only 2 deaths.

For mortality by 2 years of age, multivariable Cox regression analysis was performed for the MBTS era and the RVPA era separately and adjusted for variables listed in Table 1 (see

Table 2. Neurodevelopmental, Growth, and Health Outcomes of 30 Norwood-MBTS and 26 Norwood-RVPA Surgical-Era Patients at 2 Years of Age

	MBTS: 1996–2002 (n=30)	RVPA: 2002–2005 (n=26)	*P**
MDI	79 (18)	85 (18)	0.248
PDI	67 (19)	78 (18)	0.029
MDI <70, n (%)	9 (30)	6 (23)	0.763
PDI <70, n (%)	18 (60)	8 (31)	0.035
Epilepsy, n (%)	0	0	N/A
Cerebral palsy, n (%)	0	1 (4)†	0.464
Vision loss, n (%)	1 (3)‡	0	0.999
SNHL, n (%)	1 (3)§	6 (23)‖	0.039
Height <3rd percentile, n (%)	6 (20)	3 (12)	0.481
Weight <3rd percentile, n (%)	5 (17)	7 (27)	0.515
Microcephaly, n (%)	2 (7)	0	0.386
Supplementary diet, n (%)	8 (26)	6 (23)	0.812
Gastrostomy, n (%)	8 (26)	3 (13)	0.241
Supplemental oxygen, n (%)	3 (10)	0	0.240
Chronic pulmonary medications, n (%)	6 (20)	4 (16)	0.741
Chronic cardiac medications, n (%)	26 (88)	25 (96)	0.358
No. of noncardiac hospitalizations	1.4 (1.9)	1.5 (1.8)	0.842
No. of cardiac hospitalizations	2.1 (0.43)	1.9 (0.63)	0.146

SNHL indicates sensorineural hearing loss (all bilateral).

Values are mean (SD) or n (%) where indicated.

*Significance with Student *t* test, Fisher exact test.

†Left hemiparetic ambulatory cerebral palsy associated with presurgical right cerebral infarction; also SNHL.

‡Cortical visual impairment due to ischemic insult.

§Sloping, mild to severe high-frequency SNHL, amplified.

‖One child with flat, profound SNHL, planned cochlear implant; 1 child with flat, profound SNHL, amplified (also cerebral palsy); 3 children with mild to moderate high-frequency SNHL, amplified; and 1 child with mild to moderate high-frequency SNHL, planned amplification.

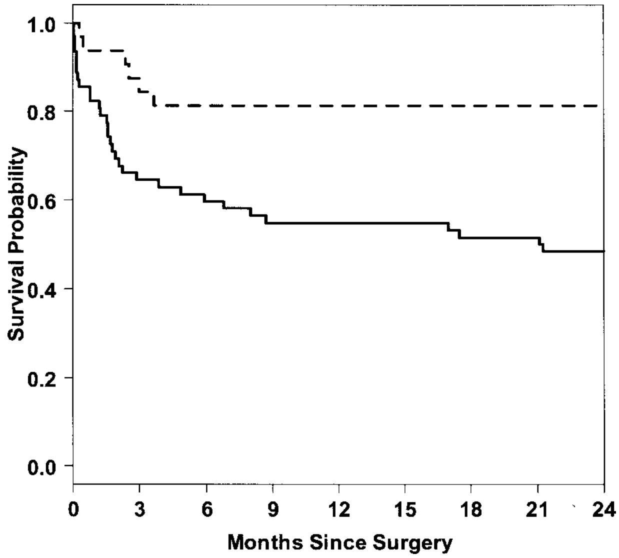

Figure 1. Kaplan-Meier estimates of survival time after Norwood surgery during the RVPA (interrupted line) and MBTS (continuous line) eras (P=0.003).

online-only Data Supplement Table III for univariate analysis). The results are shown in Table 3.

Mental and Psychomotor Outcomes

Survivors were assessed with the Bayley Scales of Infant Development-II at 21.4 (4.2) and 21.9 (4.5) months in the RVPA and MBTS eras, respectively (P=0.695). The mean MDI scores in the RVPA and MBTS eras were not statistically significantly different (Table 2). The mean PDI scores were significantly higher and the incidence of psychomotor delay (score <70) was significantly lower in the RVPA era (Table 2; Figure 2).

Multiple linear regression analysis, performed for the MBTS era and the RVPA era separately, included variables found to be significantly related to mental and psychomotor scores ($P \leq 0.10$) in the univariate logistic regression analysis (online-only Data Supplement Table IV). The results are shown in Table 4.

Secondary Outcomes

Overall, no difference was found in the growth and health outcomes as listed in Table 4, except for sensorineural hearing loss, which occurred more often in patients in the RVPA era. Six patients (5 with RVPA shunt) required amplification (Table 2).

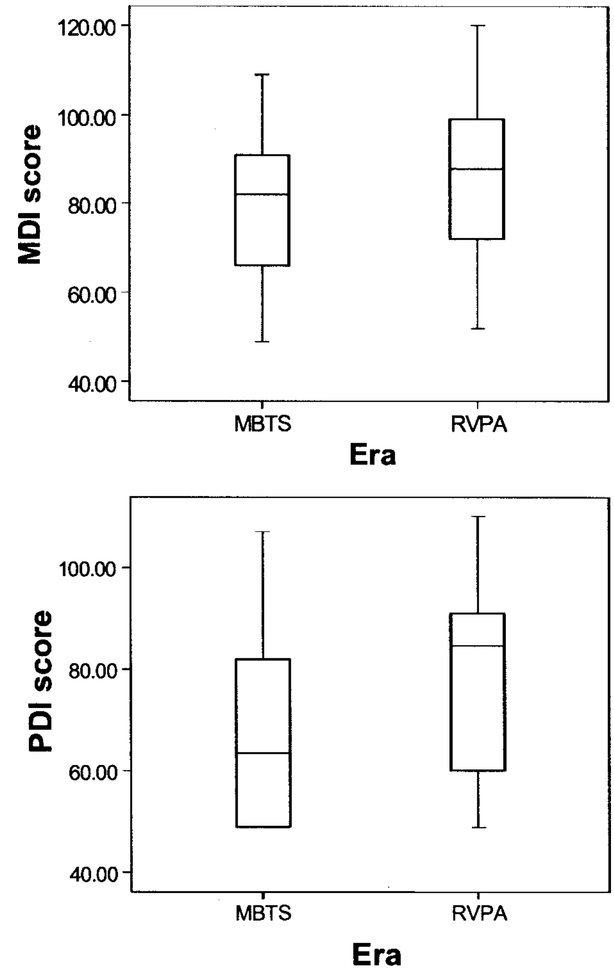

Figure 2. Boxplots of MDI and PDI scores for the MBTS and RVPA eras.

Discussion

The incidence of HLHS is 1 in 4000 to 6000 live births. A natural history study reported a 95% mortality rate in the first month of life for unoperated HLHS.[17] The past 2 decades have been witness to improvements in the care of the patient with HLHS. Advances have allowed marked improvement in the survival of these infants, and attention has shifted to their neurodevelopmental outcome. To the best of our knowledge, this is the first report describing the 2-year general and

Table 3. Multivariable Cox Regression Analysis Results for Mortality by 2 Years of Age in 62 Norwood-MBTS and 32 Norwood-RVPA Surgical-Era Patients

	MBTS 1996–2002		RVPA 2002–2005	
Postoperative Variable (Days 2 to 5)	HR (95% CI)	P	HR (95% CI)	P
Highest serum lactate, mmol/L	1.06 (1.03–1.09)	<0.001	1.52 (1.12–2.07)	0.007
Lowest base deficit, mmol/L	0.95 (0.93–0.98)	0.001	...	...

HR indicates hazard ratio; CI, confidence interval.

Table 4. Multiple Linear Regression Analysis Results for MDI and PDI Scores of Survivors in the Norwood-MBTS (n=30) and Norwood-RVPA (n=26) Eras

	MBTS 1996–2002				RVPA 2002–2005			
	MDI		PDI		MDI		PDI	
Variables	Effect Size (95% CI)	P	Effect Size (95% CI)	P	Effect Size (95% CI)	P	Effect Size (95% CI)	P
Demographic								
Sex (male)	...	...	−14.29 (−27.48 to −1.10)	0.035	...	...	...	...
Socioeconomic status†	0.49 (0.12, 0.85)	0.011	...	...	...	...	...	...
Preoperative								
Lowest Pa_{O_2}, mm Hg	...	...	...	...	1.22 (0.22 to 2.24)	0.024	...	...
Ventilation time, d	...	...	...	...	−2.11 (−3.10 to −1.12)	0.001	...	...
Operative								
DHCA, min	...	...	...	...	−0.53 (−1.02 to −0.03)	0.039	...	...
Overall								
Hospitalization, wk	−14.76 (−26.42 to −3.11)	0.015	...	...	...	...	−16.78 (−26.92 to −6.64)	0.002
CPR	...	...	...	...	...	...	−28.94 (−50.59 to −7.28)	0.011

DHCA indicates deep hypothermic circulatory arrest; CPR, cardiopulmonary resuscitation; and CI, confidence interval.
†See Blishen.[13]

neurodevelopmental outcomes of infants with HLHS undergoing the MBTS and RVPA modifications of the Norwood procedure. We found a pattern of improvement in intraoperative management and improved early postoperative variables in the RVPA era, which likely reflects a more stable hemodynamic status. Several other authors have reported on the favorable hemodynamics of the RVPA modification of the Norwood procedure compared with the MBTS.[18–23] Moreover, we showed significant differences in mortality and psychomotor developmental outcome between the 2 surgical eras.

Early Mortality

We found a trend to lower early mortality in the more recent RVPA surgical era; however, the present study was not powered to show this difference as statistically significant. Pizarro et al[4] and Griselli et al[8] reported a similar decrease in early mortality. On the other hand, other series identified no difference in early mortality between the MBTS and RVPA groups.[5,7,10] In the late 1990s, reports on early mortality after the Norwood-MBTS ranged from 7% to 29%.[24–27] A more recent study reported a 21% early mortality, with noncardiac abnormalities and birth weight <2.5 kg identified as risk factors.[28] In the present study, multiple logistic regression analysis showed that postoperative serum lactate and male sex were independent predictors of early mortality in the MBTS era. Cheung et al[29] previously identified postoperative lactate as a predictor of early mortality after neonatal surgery.

Interim Mortality

The difference in interim mortality did not reach statistical significance. Most comparative reports of interim death demonstrate a decreased incidence in the RVPA patient population compared with the MBTS population.[4–6] Previous reports analyzing patients undergoing the Norwood-MBTS in the 1990s reported interim mortality rates of 13%[24] and 15%.[25] Overall, interim mortality appears to be declining. It is still not negligible, however, and remains an important clinical concern. The benefit of the home surveillance program in decreasing interim mortality documented by others[16] could not be confirmed in the present study cohort.

Two-Year Mortality

We found a significantly lower mortality rate by 2 years of age in the RVPA era. In the late 1990s, MBTS mortality rates were reported at 28%[24] and 34%.[27] Sano et al,[30] in a multi-institutional study, reported a 37% 2-year mortality rate for an RVPA cohort. Two recent studies reported similar MBTS versus RVPA late mortality rates of 32% versus 30%[5] and 31% versus 27%,[10] respectively. In the present study, multivariable Cox regression analysis identified postoperative serum lactate and base deficit as statistically significant predictors of mortality by 2 years of age in the MBTS era. In the RVPA era, a higher postoperative serum lactate was the only independent predictor of mortality by 2 years of age.

Bidirectional Cavopulmonary Anastomosis

The bidirectional cavopulmonary anastomosis procedure was performed at a younger age in the RVPA era. This earlier timing has been observed by others[5,7,10] and is thought to be due to earlier cyanosis.[7] Another study showed no difference in the timing of the bidirectional cavopulmonary anastomosis between the MBTS and RVPA groups.[31] The earlier timing of bidirectional cavopulmonary anastomosis may also be related to a gradual change in the medico-surgical practice toward earlier relief of the right ventricular volume overload and shortening of the high-risk interim period. There has been some theoretical concern about poor growth of the pulmonary arteries after RVPA; however, recent studies showed that the RVPA conduit provided better growth of the pulmonary arteries than the MBTS.[31,32]

Mental and Psychomotor Outcomes

Some infants undergoing complex surgery for congenital heart disease have an abnormal neurodevelopmental outcome when evaluated at as early as 1 or 2 years of life.[11,33–35] Mahle et al[36] evaluated 115 of 138 eligible surgically palliated school-aged and adolescent children with HLHS using mailed questionnaires. They found that performance correlated with the incidence of preoperative seizures and cumulative duration of cardiopulmonary bypass. Standardized neurocognitive evaluation was performed on 28 of 34 patients, who were eligible if they lived within a local geographic region and if English was their primary language used at home. Eighteen percent (5/28) had IQ scores in the mentally retarded range. Other studies have reported the significant risk for adverse neurodevelopmental outcome in HLHS patients.[37–40] One study showed the duration of DHCA to be inversely associated with performance IQ in a small cohort of 14 patients.[39] For children after Norwood MBTS surgery, a strong correlation has been found between the MDI at 18 to 24 months of age and full-scale intelligence scores at 5 years of age.[41]

In the present study cohort, MDI scores and the incidence of mental delay did not improve in the recent surgical era. Linear regression analysis identified a lower socioeconomic status and prolonged hospitalization at the time of the Norwood procedure as independent predictors of lower mental scores in the MBTS era. In the RVPA era, lower PaO_2 and longer ventilation time (days) before the Norwood procedure, as well as longer DHCA time during the Norwood procedure, were independent predictors of lower mental scores. Robertson et al[11] previously identified preoperative ventilation as a significant predictor of neurodevelopmental outcome after neonatal open heart surgery. Longer hospitalization was identified previously as an independent predictor of lower full-scale IQ scores in a cohort of school-aged HLHS patients who had undergone either the Norwood procedure or heart transplantation.[42]

The present results showed a significant improvement in PDI scores and a lower incidence of psychomotor delay in the RVPA era. Linear regression analysis identified only male sex as an independent predictor of lower psychomotor scores in the MBTS era. In the RVPA era, longer overall hospitalization and the need for cardiopulmonary resuscitation at any time before or after the Norwood procedure were independent predictors of a lower psychomotor score.

The use of regional cerebral perfusion was not a significant predictor of MDI or PDI scores in the MBTS era. Regional cerebral perfusion was used, however, in all patients in the RVPA era and thus could not be analyzed as a predictor. A recent retrospective study[43] and a recent randomized clinical trial[44] compared the neurodevelopmental outcome of patients undergoing the Norwood procedure with and without low-flow regional cerebral perfusion and showed no difference in the Bayley Scales of Infant Development-II scores when assessed at 1 year of age.

Sensorineural hearing loss occurred more commonly in the RVPA era. This degree of hearing loss, even if amplified, may have reduced the MDI scores among RVPA survivors. The cause of the hearing loss remains unknown.[45] An unexpectedly high prevalence of sensorineural hearing loss has been reported previously among children with congenital heart defects.[46]

The results of the present study must be interpreted in the context of its nonrandomized study design and the use of a single surgical center and consecutive surgical eras. The inception cohort size limited the statistical power of the study. Nevertheless, the study included a large number of variables, and there was no loss to follow-up. We cannot determine whether the finding of improved outcomes in the RVPA era is a cause-effect relationship attributable to the change in surgical shunt technique only, because many known or unidentified changes in practice over the years may account for the findings.

Conclusions

An analysis of 2 consecutive surgical eras showed that HLHS patients undergoing the Norwood procedure have experienced significant improvement in their survival to 2 years of age and in their psychomotor developmental outcome without any significant adverse change in general health or mental outcome. Survival and developmental outcome predictors varied between the 2 surgical eras and included modifiable and nonmodifiable variables. Further research in this field is needed, because adverse neurodevelopmental outcome in this patient population remains a concern.

Acknowledgments

We would like to thank the families of these children for their active participation in the developmental sites across Western Canada and their commitment to this project. We sincerely thank the research coordinators and psychologists who made this research possible. We acknowledge the contributions of the Western Canadian Complex Pediatric Therapies Follow-Up Group: Dr D. Moddemann, Winnipeg, Manitoba, Canada; Dr P. Blakley, Saskatoon, Saskatchewan, Canada; and Dr A. Ninan, Regina, Saskatchewan, Canada.

Sources of Funding

Financial support was initially provided by the Glenrose Rehabilitation Hospital Research Trust Fund, with ongoing operational funding from The Registry and Follow-up of Complex Pediatric Therapies Project, Alberta Health and Wellness.

Disclosures

None.

References

1. Norwood WI, Kirklin JK, Sanders SP. Hypoplastic left heart syndrome: experience with palliative surgery. *Am J Cardiol*. 1980;45:87–91.
2. Kishimoto H, Kawahira Y, Kawata H, Miura T, Iwai S, Mori T. The modified Norwood palliation on a beating heart. *J Thorac Cardiovasc Surg*. 1999;118:1130–1132.
3. Sano S, Ishino K, Kawada M, Arai S, Kasahara S, Asai T, Masuda Z, Takeuchi M, Ohtsuki S. Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 2003;126:504–509.
4. Pizarro C, Mroczek T, Malec E, Norwood WI. Right ventricle to pulmonary artery conduit reduces interim mortality after stage 1 Norwood for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2004; 78:1959–1963.
5. Tabbutt S, Dominguez TE, Ravishankar C, Marino BS, Gruber PJ, Wernovsky G, Gaynor JW, Nicolson SC, Spray TL. Outcomes after the stage I reconstruction comparing the right ventricular to pulmonary artery conduit with the modified Blalock Taussig shunt. *Ann Thorac Surg*. 2005;80:1582–1590.

6. Cua CL, Thiagarajan RR, Taeed R, Hoffman TM, Lai L, Hayes J, Laussen PC, Feltes TF. Improved interstage mortality with the modified Norwood procedure: a meta-analysis. *Ann Thorac Surg*. 2005;80:44–49.
7. Cua CL, Thiagarajan RR, Gauvreau K, Lai L, Costello JM, Wessel DL, Del Nido PJ, Mayer JE Jr, Newburger JW, Laussen PC. Early postoperative outcomes in a series of infants with hypoplastic left heart syndrome undergoing stage I palliation operation with either modified Blalock-Taussig shunt or right ventricle to pulmonary artery conduit. *Pediatr Crit Care Med*. 2006;7:238–244.
8. Griselli M, McGuirk SP, Stumper O, Clarke AJ, Miller P, Dhillon R, Wright JG, de Giovanni JV, Barron DJ, Brawn WJ. Influence of surgical strategies on outcome after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2006;131:418–426.
9. McGuirk SP, Griselli M, Stumper OF, Rumball EM, Miller P, Dhillon R, de Giovanni JV, Wright JG, Barron DJ, Brawn WJ. Staged surgical management of hypoplastic left heart syndrome: a single institution 12 year experience. *Heart*. 2006;92:364–370.
10. Ballweg JA, Dominguez TE, Ravishankar C, Kreutzer J, Marino BS, Bird GL, Gruber PJ, Wernovsky G, Gaynor JW, Nicolson SC, Spray TL, Tabbutt S. A contemporary comparison of the effect of shunt type in hypoplastic left heart syndrome on the hemodynamics and outcome at stage 2 reconstruction. *J Thorac Cardiovasc Surg*. 2007;134:297–303.
11. Robertson CM, Joffe AR, Sauve RS, Rebeyka IM, Phillipos EZ, Dyck JD, Harder JR. Outcomes from an interprovincial program of newborn open heart surgery. *J Pediatr*. 2004;144:86–92.
12. Freed DH, Robertson CM, Sauve RS, Joffe AR, Rebeyka IM, Ross DB, Dyck JD. Intermediate-term outcomes of the arterial switch operation for transposition of great arteries in neonates: alive but well? *J Thorac Cardiovasc Surg*. 2006;132:845–852.
13. Blishen BR. The 1981socioeconomic index for occupations in Canada. *Can Rev Soc Anthropol*. 1987;24:465–488.
14. Bax MC. Terminology and classification of cerebral palsy. *Dev Med Child Neurol*. 1964;11:295–297.
15. Bayley N. *Manual: Bayley Scales of Infant Development.* 2nd ed. San Antonio, Tex: Psychological Corp; 1993.
16. Ghanayem NS, Hoffman GM, Mussatto KA, Cava JR, Frommelt PC, Rudd NA, Steltzer MM, Bevandic SM, Frisbee SS, Jaquiss RD, Litwin SB, Tweddell JS. Home surveillance program prevents interstage mortality after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2003;126:1367–1377.
17. Report of the New England Regional Infant Cardiac Program. *Pediatrics*. 1980;65:375–461.
18. Malec E, Januszewska K, Kolcz J, Mroczek T. Right ventricle-to-pulmonary artery shunt versus modified Blalock-Taussig shunt in the Norwood procedure for hypoplastic left heart syndrome: influence on early and late haemodynamic status. *Eur J Cardiothorac Surg*. 2003;23:728–733.
19. Mahle WT, Cuadrado AR, Tam VK. Early experience with a modified Norwood procedure using right ventricle to pulmonary artery conduit. *Ann Thorac Surg*. 2003;76:1084–1088.
20. Azakie A, Martinez D, Sapru A, Fineman J, Teitel D, Karl TR. Impact of right ventricle to pulmonary artery conduit on outcome of the modified Norwood procedure. *Ann Thorac Surg*. 2004;77:1727–1733.
21. Pizarro C, Malec E, Maher KO, Januszewska K, Gidding SS, Murdison KA, Baffa JM, Norwood WI. Right ventricle to pulmonary artery conduit improves outcome after stage I Norwood for hypoplastic left heart syndrome. *Circulation*. 2003;108(suppl 1):II-155–II-160.
22. Maher KO, Pizarro C, Gidding SS, Januszewska K, Malec E, Norwood WI Jr, Murphy JD. Hemodynamic profile after the Norwood procedure with right ventricle to pulmonary artery conduit. *Circulation*. 2003;108:782–784.
23. Mair R, Tulzer G, Sames E, Gitter R, Lechner E, Steiner J, Hofer A, Geiselseder G, Gross C. Right ventricular to pulmonary artery conduit instead of modified Blalock-Taussig shunt improves postoperative hemodynamics in newborns after the Norwood operation. *J Thorac Cardiovasc Surg*. 2003;126:1378–1384.
24. Tweddell JS, Hoffman GM, Mussatto KA, Fedderly RT, Berger S, Jaquiss RD, Ghanayem NS, Frisbee SJ, Litwin SB. Improved survival of patients undergoing palliation of hypoplastic left heart syndrome: lessons learned from 115 consecutive patients. *Circulation*. 2002;106(suppl I):I-82–I-89.
25. Azakie T, Merklinger SL, McCrindle BW, Van Arsdell GS, Lee KJ, Benson LN, Coles JG, Williams WG. Evolving strategies and improving outcomes of the modified Norwood procedure: a 10-year single-institution experience. *Ann Thorac Surg*. 2001;72:1349–1353.
26. Gaynor JW, Mahle WT, Cohen MI, Ittenbach RF, DeCampli WM, Steven JM, Nicolson SC, Spray TL. Risk factors for mortality after the Norwood procedure. *Eur J Cardiothorac Surg*. 2002;22:82–89.
27. Mahle WT, Spray TL, Wernovsky G, Gaynor JW, Clark BJ III. Survival after reconstructive surgery for hypoplastic left heart syndrome: a 15-year experience from a single institution. *Circulation.* 2000;102(suppl III):III-136–III-141.
28. Stasik CN, Gelehrter S, Goldberg CS, Bove EL, Devaney EJ, Ohye RG. Current outcomes and risk factors for the Norwood procedure. *J Thorac Cardiovasc Surg*. 2006;131:412–417.
29. Cheung PY, Chui N, Joffe AR, Rebeyka IM, Robertson CM. Postoperative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: a cohort follow-up to 18 months. *J Thorac Cardiovasc Surg*. 2005;130:837–843.
30. Sano S, Ishino K, Kado H, Shiokawa Y, Sakamoto K, Yokota M, Kawada M. Outcome of right ventricle-to-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome: a multi-institutional study. *Ann Thorac Surg*. 2004;78:1951–1957.
31. Januszewska K, Kolcz J, Mroczek T, Procelewska M, Malec E. Right ventricle-to-pulmonary artery shunt and modified Blalock-Taussig shunt in preparation to hemi-Fontan procedure in children with hypoplastic left heart syndrome. *Eur J Cardiothorac Surg*. 2005;27:956–961.
32. Rumball EM, McGuirk SP, Stumper O, Laker SJ, de Giovanni JV, Wright JG, Barron DJ, Brawn WJ. The RV-PA conduit stimulates better growth of the pulmonary arteries in hypoplastic left heart syndrome. *Eur J Cardiothorac Surg*. 2005;27:801–806.
33. Wernovsky G, Shillingford AJ, Gaynor JW. Central nervous system outcomes in children with complex congenital heart disease. *Curr Opin Cardiol*. 2005;20:94–99.
34. Dittrich H, Buhrer C, Grimmer I, Dittrich S, Abdul-Khaliq H, Lange PE. Neurodevelopment at 1 year of age in infants with congenital heart disease. *Heart*. 2003;89:436–441.
35. Robertson DR, Justo RN, Burke CJ, Pohlner PG, Graham PL, Colditz PB. Perioperative predictors of developmental outcome following cardiac surgery in infancy. *Cardiol Young*. 2004;14:389–395.
36. Mahle WT, Clancy RR, Moss EM, Gerdes M, Jobes DR, Wernovsky G. Neurodevelopmental outcome and lifestyle assessment in school-aged and adolescent children with hypoplastic left heart syndrome. *Pediatrics*. 2000;105:1082–1089.
37. Wernovsky G, Stiles KM, Gauvreau K, Gentles TL, duPlessis AJ, Bellinger DC, Walsh AZ, Burnett J, Jonas RA, Mayer JE Jr, Newburger JW. Cognitive development after the Fontan operation. *Circulation*. 2000;102:883–889.
38. Rogers BT, Msall ME, Buck GM, Lyon NR, Norris MK, Roland JM, Gingell RL, Cleveland DC, Pieroni DR. Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. *J Pediatr*. 1995;126:496–498.
39. Kern JH, Hinton VJ, Nereo NE, Hayes CJ, Gersony WM. Early developmental outcome after the Norwood procedure for hypoplastic left heart syndrome. *Pediatrics*. 1998;102:1148–1152.
40. Goldberg CS, Schwartz EM, Brunberg JA, Mosca RS, Bove EL, Schork MA, Stetz SP, Cheatham JP, Kulik TJ. Neurodevelopmental outcome of patients after the Fontan operation: a comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions. *J Pediatr*. 2000;137:646–652.
41. Creighton DE, Robertson CM, Sauve RS, Moddemann DM, Alton GY, Nettel-Aguirre A, Ross DB, Rebeyka IM. Neurocognitive, functional, and health outcomes at 5 years of age for children after complex cardiac surgery at 6 weeks of age or younger. *Pediatrics*. 2007;120:e478–e486.
42. Mahle WT, Visconti KJ, Freier MC, Kanne SM, Hamilton WG, Sharkey AM, Chinnock RE, Jenkins KJ, Isquith PK, Burns TG, Jenkins PC. Relationship of surgical approach to neurodevelopmental outcomes in hypoplastic left heart syndrome. *Pediatrics*. 2006;117:e90–e97.
43. Visconti KJ, Rimmer D, Gauvreau K, del Nido P, Mayer JE Jr, Hagino I, Pigula FA. Regional low-flow perfusion versus circulatory arrest in neonates: one-year neurodevelopmental outcome. *Ann Thorac Surg*. 2006;82:2207–2211.

44. Goldberg CS, Bove EL, Devaney EJ, Mollen E, Schwartz E, Tindall S, Nowak C, Charpie J, Brown MB, Kulik TJ, Ohye RG. A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. *J Thorac Cardiovasc Surg*. 2007;133:880–887.
45. Borg E. Perinatal asphyxia, hypoxia, ischemia and hearing loss: an overview. *Scand Audiol*. 1997;26:77–91.
46. Couture E, Riley P, Rohlicek C, Julien S, Zavalkoff B. Hearing loss in children with congenital heart defects. *Paediatr Child Health*. 2003; 8(Suppl B):29B–30B. Abstract.

CLINICAL PERSPECTIVE

The outcomes of patients with hypoplastic left heart syndrome treated with the Norwood procedure over 2 consecutive surgical eras (1996 to 2002 and 2002 to 2005) were evaluated. Survival in the early postoperative period and at 2 years of age demonstrated improvement. Neurodevelopmental outcomes at 2 years of age (mental and psychomotor developmental indices) showed improvement in the more recent era, with psychomotor delay decreasing by half. For these outcomes, we have identified independent predictors, including modifiable variables, that may be important in guiding clinical care management. For survival outcome at 2 years of age, postoperative lactate was identified as an independent predictor, which supports the longstanding clinical practice aimed at optimizing patient hemodynamic status. For neurodevelopmental outcomes, the identified independent negative predictors included prolonged hospitalization and preoperative ventilation. We also identified other independent outcome predictors that may play an important role in parental counseling on anticipated neurodevelopmental outcome. Such findings may allow the clinician to tailor parent counseling by considering specific patient characteristics, such as the need for cardiopulmonary resuscitation, as well as sex and the family's socioeconomic status. Finally, early intervention and close multidisciplinary follow-up are instrumental for these children at risk for adverse neurodevelopmental outcomes.

Circulation

Two-Year Survival and Mental and Psychomotor Outcomes After the Norwood Procedure: An Analysis of the Modified Blalock-Taussig Shunt and Right Ventricle–to–Pulmonary Artery Shunt Surgical Eras

Joseph Atallah, Irina A. Dinu, Ari R. Joffe, Charlene M.T. Robertson, Reg S. Sauve, John D. Dyck, David B. Ross, Ivan M. Rebeyka and the Western Canadian Complex Pediatric Therapies Follow-Up Group

Circulation. 2008;118:1410-1418; originally published online September 15, 2008;
doi: 10.1161/CIRCULATIONAHA.107.741579
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539