Risk factors for mortality after the Norwood procedure


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Abstract

Objectives: Recent studies have suggested that survival following the Norwood procedure is influenced by anatomy and is worse for patients with hypoplastic left heart syndrome (HLHS), particularly aortic atresia (AA), as compared to other forms of functional single ventricle and systemic outflow tract obstruction. The current study was undertaken to evaluate our recent experience with the Norwood procedure and to evaluate potential predictors of operative and 1-year mortality. Methods: A retrospective study of risk factors for operative and 1-year mortality in 158 patients undergoing the Norwood procedure between January 1, 1998 and June 30, 2001. Results: HLHS was present in 102 patients (70 with AA) and other forms of functional single ventricle with systemic outflow tract obstruction in the remaining 56. Operative survival was 77% (122/158), 78% for patients with HLHS and 75% for patients with other diagnoses. Multivariable analysis identified birth weight (odds ratio (OR) 0.18/kg, 95% confidence limit (CL) 0.08–0.42, P < 0.001), associated cardiac anomalies (OR 4.45, 95% CL 1.50–13.2, P = 0.001), total support time (OR 1.02/min, 95% CL 1.01–1.03, P = 0.004), and extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) support (OR 17.8, 95% CL 4.40–71.0, P < 0.001) as predictors of operative mortality. The anatomic diagnosis (HLHS versus non-HLHS) was not a predictor of mortality, P = 0.6. The Kaplan–Meier survival estimate at 1 year was 66% (95% CL 58–73%) and was not different for patients with HLHS compared to non-HLHS, P = 0.5. For patients who have survived the Norwood procedure, survival to 1 year was 86% (95% CL 78–91%). Presence of an extra-cardiac anomaly or genetic syndrome (OR 2.70, 95% CL 0.98–7.41%, P = 0.05) and presence of an additional cardiac defect (OR 3.99, 95% CL 1.67–9.57, P = 0.002) were predictors of worse survival in the first year of life. Conclusions: The Norwood procedure is currently being applied to a heterogeneous group of patients. Operative and 1-year survival are equivalent for patients with HLHS and those with other cardiac defects. The presence of additional cardiac or extra-cardiac anomalies are predictors of poor outcome. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Hypoplastic left heart syndrome; Norwood procedure

1. Introduction

The Norwood procedure was introduced as first stage reconstructive surgery for patients with hypoplastic left heart syndrome (HLHS) and has subsequently been applied to many cardiac defects characterized by the presence of a functional single ventricle with systemic outflow tract obstruction [1]. Outcome following Norwood reconstruction has improved significantly secondary to modifications in the surgical technique, improved perioperative care, and improved anesthetic management [2,3]. Despite the continuing improvement in outcomes, the early survival for patients with functional single ventricle and systemic outflow tract obstruction is significantly poorer than that for other cardiac defects which require neonatal repair. A variety of factors have been suggested as possible predictors of operative mortality including anatomic diagnosis, aortic atresia (AA), additional cardiac defects, low birth weight, prematurity, associated non-cardiac anomalies and genetic syndromes, and recently post-natal diagnosis of the cardiac defect [3–10]. Recent studies also have suggested that the outcome following the Norwood procedure for HLHS, particularly AA, is worse than for other forms of single ventricle with systemic outflow tract obstruction [5,10]. In addition to the increased operative mortality, there is a...
persistent incidence of death; often sudden and unexplained, during the first year of life among patients who survive the initial hospitalization [11]. The current study was undertaken to evaluate our recent institutional experience with the Norwood procedure in patients with HLHS and other forms of functional single ventricle with systemic outflow tract obstruction and to evaluate potential predictors of operative and 1-year mortality.

2. Methods

The cardiac surgery and cardiac intensive care unit databases of The Children’s Hospital of Philadelphia were reviewed to identify all patients undergoing the Norwood procedure between January 1, 1998 and June 30, 2001, as well as those with similar cardiac defects (functional single ventricle with systemic outflow tract obstruction) who did not undergo surgery. Anatomic diagnosis was based on review of echocardiography, operative findings, and autopsy reports. HLHS was defined as normal segmental anatomy (S,D,S), intact ventricular septum, aortic and mitral atresia or stenosis, and hypoplasia of the left ventricle (LV). Patients with double outlet right ventricle, mitral atresia or stenosis, and hypoplasia of the left ventricle were classiﬁed as unbalanced atriocerventricular canal defects (AVC) and single LV with transposition of the great arteries, were classiﬁed as non-HLHS (Table 1). Follow-up status was determined by review of the medical records and contact with the referring cardiologist. The study was approved by the Institutional Review Board at The Children’s Hospital of Philadelphia.

At our institution, patients with functional single ventricle and systemic outflow tract obstruction, including HLHS, undergo staged surgical reconstruction. Primary cardiac transplantation is not utilized. The Norwood procedure is performed in the neonatal period followed by superior cavopulmonary connection at approximately 6 months of age and a Fontan procedure at 18–24 months of age. Transplantation is reserved for patients who develop signiﬁcant ventricular dysfunction or AV valve regurgitation and who are not candidates for further reconstructive surgery. Thus, need for eventual transplantation is not considered failure of the newborn treatment protocol. The Norwood procedure was performed by four surgeons and several modifications were utilized during the study period. A standard Norwood operation was deﬁned as atrial septectomy, right modiﬁed Blalock–Taussig shunt, division of the main pulmonary artery with side-to-side anastomosis to the diminutive ascending aorta without aortic transection, and homograft patch augmentation of the ascending aorta and arch (Standard). In some patients, transection of both the aorta and pulmonary artery was performed with a side-to-side anastomosis of the proximal divided vessels. The distal ascending aorta and arch were augmented with a homograft patch and an end-to-end anastomosis performed between the distal aorta and the proximal great vessels (‘Double-Barrel’). A variety of other techniques were each utilized in a small number of patients including direct anastomosis of the divided main pulmonary artery to the aortic arch, with or without anterior patch augmentation; use of a homograft tube interposition graft to connect the main pulmonary artery to the aortic arch, and conversion to a Norwood type operation following previous coarctation repair (‘Other’). Repair of associated cardiac defects was performed as appropriate. Delayed sternal closure was not routinely utilized. Support with extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD) was utilized when the patient could not be separated from cardiopulmonary bypass (CPB) or during resuscitation following a cardiac arrest.

2.1. Statistical methods

Data were analyzed and compared for four groups of children: the entire cohort of children undergoing the Norwood procedure; the cohort of children who were operative survivors (survival to hospital discharge and at least 30 days post-operatively); the subgroup of children with HLHS; and in this subgroup, those with and without AA. Patient and operative variables were assessed as potential predictors of operative (hospital discharge and at least 30 days after surgery) and 1-year mortality (Table 2). Data are presented as medians and ranges.

Data analysis involved three phases. Phase I consisted of computation and evaluation of basic descriptive statistics (e.g. central tendency, variability, association) to assist with the data exploration and understanding. Phase II consisted of two separate logistic regressions with operative survival as the outcome interest (one for the whole cohort of patients and the other for patients with HLHS only). Finally, Phase III of data analysis consisted of four separate survival analyses, all with 1-year survival as the outcome of interest: one analysis for the entire cohort of patients; one for the patients who survived the initial operation; one for patients with HLHS only; and, finally, one analysis for the subgroup of patients with HLHS who survived the initial operation.

### Table 1: Cardiac defects other than HLHS

<table>
<thead>
<tr>
<th>Cardiac defect</th>
<th>n</th>
<th>Value</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unbalanced AVC</td>
<td>23/56</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Tricuspid atresia with TGA</td>
<td>5/56</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>TGA (S,L,L), DILV, coarctation</td>
<td>9/56</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>TGA (S,D,D) with hypoplastic LV</td>
<td>5/56</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>VSD with mitral atresia or stenosis</td>
<td>5/56</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9/56</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

*AVC, atriocerventric canal defect; TGA, transposition of the great arteries; DILV, double inlet left ventricle; VSD, ventricular septal defect.*
Table 2
Potential predictors of mortality

Patient variables
- Anatomic diagnosis (HLHS versus non-HLHS)
- Aortic atresia (for HLHS subgroup, yes or no)
- Age at admission for Norwood procedure
- Prenatal diagnosis (yes or no)
- Presence of a genetic syndrome or major extra-cardiac anomaly (yes or no)
- Presence of additional cardiac defects (other than LSVC or interrupted IVC)
- Prematurity (<37 weeks gestational age)
- Birth weight (kg)

Operative variables
- Age at surgery (days)
- Surgeon
- Weight at surgery (kg)
- Shunt size (3.0, 3.5, or 4.0 mm)
- Total support time (CPB time + DHCA time)
- CPB time (min)
- DHCA time (min)
- Myocardial ischemia time (min)
- Type of Norwood Reconstruction (standard, ‘Double-Barrel’, or other)
- Delayed sternal closure (yes or no)
- Need for post-operative ECMO or VAD support

a HLHS, hypoplastic left heart syndrome; LSVC, left superior vena cava; IVC, inferior vena cava; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

One-year survival estimates were obtained from the Kaplan–Meier model. For survival analysis, the date of birth was considered as time zero. Logistic models were tested for fit using traditional chi-square goodness-of-fit statistics with log likelihood and Wald tests serving as the basis for model comparisons. Similarly, Cox proportional hazard models were tested using chi-square goodness-of-fit statistics and groups were compared using the log–rank test for equality of functions. Results are expressed as odds ratio (OR) with 95% confidence limits (CL). All hypotheses were tested at the \( \alpha = 0.01 \) level. The experiment-wise error rate was held constant at the \( \alpha = 0.05 \) level using Westfall and Young’s method for correlated endpoints [12]. Data were analyzed using STATA 7.0 (Stata Corporation 2000, College Station, TX, USA).

The area under the receiver operating characteristic (ROC) curve is a measure of the predictive accuracy of the logistic model at different points of sensitivity and specificity (or 1 – specificity). The curve is generated by calculating the proportion of deaths predicted by the model among those who died as compared with the proportion of deaths predicted by the model among those who survived for different threshold values. Threshold values used in these ROC curves are determined by the predicted probabilities of death for each case in the logistic model. Thus, the area under the curve represents the probability that a randomly chosen predicted probability value from the survivor group. The more a logistic model can distinguish between these groups, the closer the area under the ROC curve will be to one [13].

3. Results
Between January 1, 1998 and June 30, 2001, 158 infants underwent the Norwood procedure at The Children’s Hospital of Philadelphia. During the same time period, 11 children with suitable cardiac anatomy were admitted and did not undergo surgery because of multiple congenital anomalies or severe neurologic injury from a pre-hospital arrest. There were 98 males and 60 females. The median birth weight was 3075 g (range 1200–4625, \( n = 156 \)). Twenty-six children (16%) were born prematurely (gestational age <37 weeks, range 28–36 weeks). A prenatal diagnosis of congenital heart disease had been made in 80 of the children (51%). HLHS was present in 102 patients (70 with AA) and other diagnoses in 56 patients (Table 2). Significant associated cardiac lesions, excluding persistent left superior vena cava and interrupted inferior vena cava, were present in 33 children (21%) (Table 3). Significant extra-cardiac anomalies or genetic syndromes were present in 23 patients (15%) (Table 3). The median age at admission to our institution for the Norwood procedure was 1 day (range 1–145). Five patients underwent surgery prior to the Norwood procedure including atrial septectomy (2), coarctation repair (2), and coarctation repair with pulmonary artery banding (1). During the study period, no other children underwent coarctation repair and pulmonary artery banding. The median age at the Norwood procedure was 5 days (range 1–156). Sixteen children (10%) were 14 days of age or greater at the time of surgery. The median weight at surgery was 3.04 kg (range 1.2–5.7). Thirty-seven children weighed 2.5 kg or less at the time of surgery (23%). Weight less than or equal to 2.5 kg at the time of surgery and/or an associated anomaly (cardiac or extra-cardiac) was present in 73 patients (46%). A Standard Norwood procedure was performed in 115 patients, a ‘Double-Barrel’ procedure in 28 patients, and ‘Other’ types in 15 patients. The median total support time (CPB time + deep hypothermic circulatory arrest (DHCA) time) was 88 min (range 60–295). The median CPB time alone was 43 min (range 37–233). The median DHCA time was 44 min (range 1–116). The median myocardial ischemia time was 45 min (range 20–125). Delayed sternal closure was utilized in 38 patients (24%). ECMO or VAD support was utilized in 18 patients (11%).

3.1. Operative mortality
The overall operative mortality was 36 patients (23%). Hospital survival for patients with HLHS was 78% (80/102) and for non-HLHS patients was 75% (42/56). Among the sub-group of patients with HLHS, survival for patients with AA was 74% (52/70) and for patients with aortic stenosis was 87% (28/32). Hospital survival for patients weighing
Other (4)
Biliary atresia (1)
CHARGE Syndrome (1)
Craniosynostosis (1)
Cleft palate (1)
Jacobsen Syndrome (1)
Malrotation (1)

Associated major extra-cardiac anomalies or genetic syndromes

Associated cardiac lesions (n = 33)*
- Interrupted aortic arch (4)
- Moderate–severe tricuspid regurgitation or AV valve regurgitation (9)
- Total anomalous pulmonary venous return (3)
- Partial anomalous pulmonary venous return (3)
- Intact atrial septum or restrictive atrial septal defect (6)
- Anomalous origin of the right subclavian artery from the descending aorta (6)
- Anomalous origin of either subclavian artery from the pulmonary artery (2)
- Complete heart block (1)
- Sinus node dysfunction (1)

Associated major extra-cardiac anomalies or genetic syndromes (n = 23)
- Chromosomal abnormalities/trisomy (5)
- Ellis-van Creveld Syndrome (1)
- Meningomyelocele (1)
- Congenital diaphragmatic hernia (1)
- Duodenal atresia (2)
- Oral–Digital–Facial Syndrome (1)
- Omphalocele (1)
- Recto–vaginal fistula (1)
- Malrotation (1)
- Jacobsen Syndrome (1)
- Cleft palate (1)
- Craniosynostosis (1)
- CHARGE Syndrome (1)
- Biliary atresia (1)
- Other (4)

* More than one additional lesion was present in two children.

2.5 kg or less at the time of surgery was 62% (23/37), compared to 82% (99/121) for patients who weighed greater than 2.5 kg. Hospital survival for patients with low weight at the time of surgery (<2.5 kg) and/or an associated anomaly (cardiac or extra-cardiac) was 73% (53/73) compared to 88% (75/85) for patients weighing greater than 2.5 kg with no associated anomaly. Since January 1, 2000, mortality for this low-risk group has been 8% (3/38). Prenatal diagnosis of congenital heart disease did not alter hospital survival which was 77% (62/80) for patients with a prenatal diagnosis of congenital heart disease, compared to 77% (60/78) for those with a post-natal diagnosis.

3.2. Logistic regression models

In the multivariable analysis for the entire cohort, the only characteristics which were associated with an increased risk of operative death were lower birth weight, longer total support time, and ECMO or VAD support (Table 2). Birth weight and weight at surgery was similar for the cohort; however, inclusion of birth weight resulted in a better fit of the model. Anatomic diagnosis (HLHS versus non-HLHS) was not a predictor of mortality (P = 0.6). The area under the ROC curve yielded a predictive accuracy of 87%. In the multivariable analysis for the HLHS patients alone (n = 102), the only characteristics which increased the risk of operative death were lower birth weight, longer total support time, and ECMO or VAD support (Table 4). The presence of AA was not a predictor of operative death (P = 0.3). The area under the ROC curve yielded a predictive accuracy of 89%.

3.3. Follow-up

For the 108 patients born prior to June 30, 2000, follow-up to death or at least 1-year of age is complete for 102 of 108 patients (94%). For the remaining six patients, a median of 337 days follow-up is available (range 84–358). For the 50 patients born after June 30, 2000, complete follow-up to death or till July 1, 2001 is available for 38 of the 50 patients (76%). For the remaining 12 patients, a median of 208 days of follow-up is available (range 20–308). A superior cavo-pulmonary connection has been performed in 92 of the 123 patients who survived the initial operation. Ninety were performed during the first year of life at a median age of 190 days (range 119–308). Two patients underwent an unstaged Fontan procedure at greater than 1 year of age. Orthotopic cardiac transplantation was performed during the first year following the Norwood procedure in three patients.

There were 15 deaths during the first year of life among the 122 children (12%) who survived the Norwood procedure; 11 occurred prior to the superior cavopulmonary connection, one at the time of the superior cavopulmonary connection at another institution, and three following superior cavopulmonary connection. Among the 11 deaths prior to superior cavopulmonary connection; eight were sudden unexplained cardiac deaths, one was secondary to respiratory syncitial viral infection, one occurred during readmission for shunt revision, and one was secondary to a cerebrovascular accident following cardiac catheterization. Among the three deaths following superior cavopulmonary connection; two were sudden unexplained deaths and one occurred during readmission for take-down of the superior cavopulmonary connection.

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>0.18/kg</td>
<td>0.08–0.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Additional cardiac anomaly</td>
<td>4.45</td>
<td>1.50–13.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Total support time</td>
<td>1.02/min</td>
<td>1.01–1.03</td>
<td>0.004</td>
</tr>
<tr>
<td>ECMO or VAD support</td>
<td>17.8</td>
<td>4.40–71.0</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>0.20/kg</td>
<td>0.07–0.58</td>
<td>0.003</td>
</tr>
<tr>
<td>Total support time</td>
<td>1.02/min</td>
<td>1.00–1.03</td>
<td>0.02</td>
</tr>
<tr>
<td>ECMO or VAD support</td>
<td>25.5</td>
<td>4.75–137</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.
3.4. Survival analysis

For the entire cohort, the Kaplan–Meier survival estimate at 1 year was 66% (95% CL 58–73%) (Fig. 1). Survival at 1 year was not different for patients with HLHS (64%, 95% CL 54–73%) compared to non-HLHS (68%, 95% CL 54–79%), $P = 0.6$ (Fig. 2). In the multivariable analysis, the characteristics which predicted mortality in the first year of life for the entire cohort were lower birth weight, an associated cardiac anomaly, an extra-cardiac anomaly or genetic syndrome, longer total support time, and ECMO or VAD support (Table 5). Among the HLHS cohort, characteristics which predicted 1-year mortality were similar; lower birth weight, an extra-cardiac anomaly, longer total support time, and ECMO or VAD support (Table 5). In the univariable analysis, there was lower survival at 1 year for patients with AA (57%, 95% CL 44–68%), compared to those without AA (81%, 95% CL 62–91%), $P = 0.05$. However, in the multivariable analysis, AA was not a predictor of mortality ($P = 0.3$). Survival to 1 year of age was significantly greater for patients weighing $\geq 2.5$ kg at the time of the Norwood procedure without an associated anomaly (cardiac and/or extra-cardiac) (82%, 95% CL 71–89%), compared to the survival of patients with weight $\leq 2.5$ kg and/or an associated anomaly (cardiac and/or extra-cardiac) (48%, 95% CL 35–59%), $P = 0.0003$ (Fig. 3).

For patients who survived the Norwood procedure, survival to 1 year was 86% (95% CL 78–91%). The only characteristic which predicted 1-year mortality in the early survivors were an additional cardiac defect (OR 3.99, 95% CL 1.67–9.57, $P = 0.002$) or an extra-cardiac anomaly or genetic syndrome (OR 2.70, 95% CL 0.98–7.41%, $P = 0.05$). Anatomic diagnosis was not a predictor of 1-year mortality. For the HLHS patients who survived the initial surgery, survival to 1 year was 83% (95% CL 72–90%) and 92% (95% CL 76–97%) for non-HLHS patients, $P = 0.2$. The only predictor of mortality during the first year of life for the HLHS patients who survived the initial procedure was an extra-cardiac anomaly or genetic syndrome (OR 5.27, 95% CL 1.12–24.7, $P = 0.035$).

4. Discussion

The current study demonstrates that the Norwood procedure is being applied to a heterogeneous patient population and outcomes continue to improve. The overall hospital survival was 77%, despite a patient population with either

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CL</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire cohort ($n = 158$)</strong></td>
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<td></td>
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<tr>
<td>Extra-cardiac anomaly or genetic syndrome</td>
<td>2.50</td>
<td>1.27–4.89</td>
<td>0.008</td>
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<tr>
<td>Additional cardiac defect</td>
<td>3.24</td>
<td>1.82–5.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.51/kg</td>
<td>0.34–0.77</td>
<td>0.001</td>
</tr>
<tr>
<td>Total support time</td>
<td>1.01/min</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECMO or VAD support</td>
<td>5.89</td>
<td>2.95–11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HLHS cohort ($n = 102$)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Additional cardiac defect</td>
<td>3.08</td>
<td>1.54–6.18</td>
<td>0.002</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.44/kg</td>
<td>0.25–0.78</td>
<td>0.005</td>
</tr>
<tr>
<td>Total support time</td>
<td>1.01/min</td>
<td>1.00–1.01</td>
<td>0.008</td>
</tr>
<tr>
<td>ECMO or VAD support</td>
<td>4.99</td>
<td>2.37–10.5</td>
<td>&lt;0.001</td>
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</table>
The early and late outcomes for children presenting with functional single ventricle and systemic outflow tract obstruction, including HLHS, have improved significantly since the introduction of the Norwood procedure. Mahle et al. [2] reported outcomes of 840 patients who underwent the Norwood procedure for HLHS between 1984 and 1999. The overall 1-year survival was 51%, however, there was a significant improvement in the mortality associated with the Norwood procedure in recent years. Later year of surgery was associated with significantly improved survival. Operative survival for the period 1995–1998 was 71.4%. Anatomic subtype was not a risk factor for death. Clancy et al. [8] assessed pre-operative predictors of operative mortality in a large group of neonates with congenital heart disease. Patients with functional single ventricle and systemic outflow tract obstruction had an increased operative mortality (26%), compared to other defects. Predictors of mortality in this group included presence of a genetic syndrome, decreased Apgar score, and increased age at hospital admission.

Many factors are likely responsible for the improvement in operative survival following the Norwood procedure including improved surgical techniques, improved perioperative management, and improved anesthetic techniques. Despite the improving outcome, early survival for these children is still significantly lower than for other forms of heart disease, which require neonatal surgical intervention. Factors which have been identified in multiple studies as potential predictors of mortality include low weight; presence of associated extra-cardiac defects or chromosomal abnormalities; presence of additional cardiac defects such as obstructed pulmonary venous drainage, total anomalous pulmonary venous connection, anomalous origin of the right subclavian artery; as well as operative factors such as prolonged CPB time [3–10]. Unlike the current study, some studies have suggested that the cardiac diagnosis remains a risk factor with less favorable outcomes for patients with HLHS as compared to other cardiac defects. Daebritz et al. [5] compared the results of the Norwood operation for patients with HLHS and those with other malformations in 194 patients who underwent surgery between 1990 and 1998. One hundred thirty-one patients had HLHS and 63 patients had other defects. In this study, the operative mortality was significantly greater for patients with HLHS (37%) compared to those with other defects (19%). One-year survival was also significantly lower for patients with HLHS (51%) compared to patients with other defects (71%). There was no difference in survival between the anatomic subgroups in the HLHS patients.

Low weight at the time of surgery has been identified as a predictor of mortality [3,4]. In 1999, Weinstein reported outcome following the Norwood procedure for 67 patients weighing ≤2.5 kg at the time of surgery between 1990 and 1997 with an operative mortality of 51% [4]. No variable could be correlated with increased mortality, although there was a trend toward increased mortality with decreased CPB time and decreased ventricular function. The hospital survival for low weight infants of 62% in the current study suggests that the prognosis may be improving.

Of concern is the persistent incidence of death during the first year of life among patients who survived the initial hospitalization. In the current study, 12% of the survivors of the initial procedure died prior to 1 year of age, most before superior cavopulmonary connection. These deaths are usually sudden and often unexplained. Mahle et al. [11] evaluated the incidence of unexpected death among 536 patients with HLHS who survived the Norwood procedure. Unexpected death occurred in 4.1% of this large group of patients (22/536) at a median age of 79 days. A multivariable analysis demonstrated that perioperative arrhythmias and earlier era of surgical procedure were associated with an increased risk for unexpected death. No anatomic subtypes were found to be risk factors for death. In the current study, most of the late deaths occurred prior to the superior cavopulmonary connection; while mortality for this procedure is itself very low, 1/92 (1.1%). Multiple factors may be responsible for the unexplained deaths, including coronary insufficiency, arrhythmia, ventricular dysfunction, residual arch obstruction, pulmonary artery distortion, restrictive atrial septal defect, and inadequate pulmonary blood flow. However, in the current study, the only predictor of mortality in the first year of life for those who survived the Norwood procedure was the presence of associated anomalies (either cardiac or extra-cardiac). There was no difference in 1-year survival between patients with HLHS and other cardiac defects, however, there was a trend toward poorer survival for patients with AA as is reported in other
studies. In the current study, AA was not a predictor of mortality in the multivariable analysis suggesting it is linked to other risk factors such as lower birth weight or associated anomalies. Patients with AA may be at risk for sudden death, secondary to the lack of antegrade aortic flow and abnormal coronary artery flow patterns. Some studies have suggested that patients with smaller ascending aortas have a worse outcome [6,7]. As operative survival continues to improve, it is important to identify patients at increased risk for death after hospital discharge and determine if modification of the treatment protocol can improve survival.

Associated cardiac defects have also been identified as risk factors for both operative and 1-year mortality in other studies as well [3–10]. Unfortunately, not every study reports the same defects. In the current study, associated cardiac defects included interrupted aortic arch, anomalies of pulmonary venous connection, obstruction to pulmonary venous drainage, anomalous origin of a subclavian artery, and atroventricular valvar regurgitation. All of these have been implicated in other studies as predictors of mortality. The finding that additional cardiac defects are risk factors for both operative and 1-year mortality suggests that cardiac transplantation could be a better treatment strategy for some of these patients. However, many of these patients, particularly those with obstruction to pulmonary venous drainage, are difficult to stabilize medically while awaiting transplantation. Because of the increasing scarcity of appropriate donor organs as well as the mortality and morbidity while waiting for an organ, it is not clear that a strategy of primary transplantation would result in an improved outcome. Interestingly, associated extra-cardiac anomalies and genetic syndromes were predictors of 1 year of survival but were not associated with increased operative mortality. Thus, even though these patients may survive the initial procedure, the mid-term outcome is less favorable. Changing surgical treatment protocols are unlikely to improve outcome for this subgroup of patients, as they do not alter the underlying syndrome.

There are several limitations to this study. The retrospective nature precludes identification of risk factors not entered into the model. The presence of an associated cardiac defect was a predictor of both operative and 1-year mortality, however, the number of patients with each defect is small and it is not possible to evaluate the impact of each defect individually. In addition, there is a trend toward worse outcomes for patients with AA, however, data on the actual size of ascending aorta is not available.

In conclusion, the Norwood procedure is currently being applied to a heterogeneous group of patients with variable results in certain subgroups. The early survival for patients undergoing the Norwood procedure continues to improve, especially for patients of normal birth weight without associated anomalies. There is no difference in operative or 1-year survival for patients with HLHS, compared to those with other forms of functional single ventricle and systemic outflow tract obstruction. Much of the mortality risk, both operative and during the first year, is due to patient-related, rather than procedure-related variables, over which the medical and surgical teams have little control. The outcome for low birth weight infants has improved, but low weight remains a risk factor for mortality. In low-risk patients (i.e. those weighing >2.5 kg without additional cardiac or non-cardiac anomalies), the early risk of surgery is 8%, which is similar to other forms of critical heart disease requiring newborn surgical management. As operative survival following the Norwood procedure continues to improve, it is difficult to justify either non-intervention or primary transplantation. Inter-stage mortality remains a concern. The most important predictors of a poor outcome in the first year of life for patients who survive the initial hospitalization are the presence of additional cardiac or extracardiac defects. Additional studies are necessary to determine if changes in management strategy or patient selection may reduce this risk.

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References

into the coronaries proximal to the takeoff of the shunt. In essence, this technique is similar to the standard Norwood operation that puts the coronary at the same risk of stenosis. One has to decide where exactly to implant the aorta and a circumferential suture line is necessary in a very diminutive ascending aorta. I think if one prefers this technique, there is no real disadvantage but I am not sure there is a real advantage either.

My own personal prejudice is that in very tiny patients, a central shunt may be a better option than a modified Blalock–Taussig shunt using a 3 mm central shunt in a 1.2–1.5 kg baby.

**Dr. Jalali** (Brisbane, Australia): When we looked into our own results in Brisbane with a success rate of about 72%, there were a number of patients who had pre-operative pulmonary insufficiency of more than mild degree, mild to moderate. Have you encountered that problem, has it been an issue in your group, and how did you handle those patients, please?

**Dr. Spray**: Pre-operative pulmonary insufficiency has not been common above a mild degree; when a patient has excessive pulmonary blood flow pre-operatively, sometimes functional pulmonary insufficiency will occur but this has not really been a problem late after the Norwood operation. I can only remember two patients in our overall experience with staged reconstruction who have required pulmonary valve surgery after staged reconstruction. Therefore, pulmonary insufficiency of the neoaorta seems to be quite rare. Tricuspid regurgitation is relatively common but rarely requires surgical intervention. When tricuspid regurgitation does require intervention, it is usually present at birth and reflects anatomic abnormalities of the tricuspid valve or the papillary muscles. It is possible that patients with severe tricuspid regurgitation at presentation are better served by cardiac transplantation.

**Dr. S. Sano** (Okayama, Japan): I presented my new technique in Toronto and then have some comment about death after Norwood. And I think most of the presentation you do and Edward Bove do are very much similar. You have a huge experience of Norwood, and I think the mortality is higher in a low birth weight baby, small baby, and also a small ascending aorta, like aortic atresia. These are due to the coronary perfusion, malperfusion. So I think my technique of RV–PA shunt is useful to these low birth weight babies, especially small babies, and those with aortic atresia with very tiny ascending aortas. What do you think of the RV–PA shunt?

**Dr. Spray**: I am intrigued by the use of an RV to PA shunt. While there are advantages to antegrade flow into the pulmonary arteries, it is also associated with pulmonary insufficiency and requires an incision in the right ventricle, which is the systemic ventricle. I believe many surgeons still have some concerns about making an incision in the systemic ventricle, however, when one reflects on your results, it is hard to say that RV function has been significantly altered. It would be valuable to see long term data of function of the right ventricular free wall.

I am intrigued that use of this technique may be beneficial in the very small patient. Obviously, when one is operating on a 1.2 kg baby, shunt selection is difficult and antegrade flow may be more easily accomplished with your technique.

**Dr. Sano**: I have done six patients out of 18 less than 2.5 kg. I lost one. And the post-operative management is very much the same of the patient with like a 3.1 kg baby. This is completely different.

**Dr. Spray**: One interesting thing to me is the fact that the mortality after the Norwood operation has fundamentally changed over the last 5 years. The timing of mortality has also changed. Mortality usually doesn’t occur in the first few days of after surgery now, but still occurs in the first 6 weeks after the Norwood operation and may be from other associated abnormalities. Sudden cardiovascular collapse is rarely the cause of mortality, while it used to be the most common sequence of events early after the first stage reconstruction. I do not know how much of the early mortality was ischemia in the past and how much ischemia contributes to the later mortality that we see today. I would love to be able to do PET scan on every one of these infants and look at coronary blood flow and perfusion, however, we have not been able to accomplish that yet in our own institution.

**Dr. Sano**: In these 2 years I had no early deaths, no late deaths, no sudden deaths at all.