Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia

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Objective: This study was undertaken to determine the demographic, anatomic, institutional, and surgical risk factors associated with outcomes after the Norwood operation.

Methods: A total of 710 of 985 neonates with critical aortic stenosis or atresia enrolled in a prospective 29-institution study between 1994 and 2000 underwent the Norwood operation. Admission echocardiograms were independently reviewed for 64% of neonates. Competing risks analyses were constructed for outcomes after Norwood operation and after cavopulmonary shunt. Incremental risk factors for outcome events were sought.

Results: Overall survival after the Norwood operation were 72%, 60%, and 54% at 1 month, 1 year, and 5 years, respectively. According to competing risks analysis, 97% of neonates reached a subsequent transition state by 18 months after Norwood operation, consisting of death (37%), cavopulmonary shunt (58%), or other state (2%, cardiac transplantation, biventricular repair, or Fontan operation). Risk factors for death occurring before subsequent transition included patient-specific variables (lower birth weight, smaller ascending aorta, older age at Norwood operation), institutional variables (institutions enrolling ≤10 neonates, two institutions enrolling ≥40 neonates), and procedural variables (shunt originating from aorta, longer circulatory arrest time, and management of the ascending aorta). Of neonates undergoing cavopulmonary shunt, 91% had reached a subsequent transition state by 6 years after cavopulmonary shunt, consisting of Fontan operation (79%), death (9%), or cardiac transplantation (3%). Risk factors for death occurring before subsequent transition included younger age at cavopulmonary shunt and need for right atrioventricular valve repair.

Conclusions: Competing risks analysis defines the prevalence of the various outcomes after Norwood operation and predicts improved outcomes with successful modification of controllable risk factors.

Hypoplastic left heart syndrome (HLHS) remains the most common congenital cardiac lesion causing death within the first year after birth.1 The vital anatomic component of classic HLHS is underdevelopment of the left ventricle-aorta complex, resulting in critical aortic valve stenosis (AVS) or aortic valve atresia (AVA) and a variable degree of hypoplasia of other left-sided heart structures.2 Since the early 1980s, when Norwood and coworkers3-4 popularized surgical palliation of HLHS, the prognosis for infants born with this lesion has dramatically improved from certain early death to an appreciable prospect of survival.

Previous reports from the Congenital Heart Surgeons Society (CHSS) on neonates with AVA or AVS have compared the selection of initial therapeutic approaches and their outcomes for each group.5-7 Treatment options for neonates with AVA and for those with AVS not amenable to biventricular repair include staged
surgical palliation and orthotopic cardiac transplantation. Staged surgical palliation has become the preferred option rather than cardiac transplantation in most institutions because of low donor organ supply, waiting list attrition, unknown long-term graft function and survival, necessity for chronic immunosuppressive therapy, and improvements in results after staged palliation.

Many reports address the outcomes for neonates with HLHS undergoing the Norwood operation and often incorporate variants of HLHS that are known to carry a better prognosis than classic HLHS. Few have analyzed outcomes at each stage of palliation in the same cohort of patients, and none have used competing risks methodology. Although interstage attrition after the Norwood operation is an acknowledged problem, few reports have attempted to elucidate risk factors for death occurring after hospital discharge but before subsequent stages. Because of these considerations, we constructed a competing risks analysis with data from a multi-institutional, longitudinal study to determine the prevalence of the various outcomes after the Norwood operation, to demonstrate the changes in risk with time associated with these outcomes, and to elucidate the demographic, anatomic, institutional, and surgical risk factors associated with each outcome.

Patients and Methods
Between January 1994 and December 2000, a total of 710 neonates underwent staged surgical palliation via the Norwood operation. This group was extracted from a pool of 985 neonates with critical left ventricular outflow tract obstruction (AVS, n = 422) or AVA (n = 563) entered into simultaneous prospective studies. The neonates were managed at 29 member institutions of the CHSS. Institutional enrolment ranged from 1 to 155 neonates, with 9 institutions enrolling more than 40 neonates and 18 enrolling 10 or fewer. Participation in the study and submission of patient information was voluntary and confidential. Consent from each family was obtained consistent with individual institutional policy. Ethics approval for the CHSS Data Center is obtained annually from the institutional review board of the Hospital for Sick Children in Toronto.

Study Population
Neonates younger than 30 days at the time of admission to a participating institution were eligible for inclusion. Morphologic criteria for entry included concordant atrioventricular and ventriculoarterial connections and either AVA or critical AVS. The surgical criterion for inclusion in this analysis was a Norwood operation. AVA was considered to be the absence of blood flow across the aortic valve, as determined by color Doppler echocardiography. AVS was considered to be important left ventricular outflow tract obstruction or hypoplasia, with demonstrated patency of the aortic valve and either moderately or severely reduced left ventricular function at admission or presence of duct-dependent systemic perfusion.

Norwood Operation
Aortic reconstruction was performed with classic patch aortoplasty in 80%, with the Brawn-Mee modification (distal aortic transection and arch reconstruction without prosthetic material) in 9%, with transection of the ascending aorta with reimplantation into the neoaoorta in 9%, and with a modified technique consisting of pulmonary artery-arch anastomosis without proximal or distal aortic transection in 2%. The systemic-pulmonary arterial shunt most commonly originated from the innominate artery (84%), followed by the subclavian artery (7%), aorta (6%), and carotid artery (2%). Mean shunt diameter indexed to body weight was 1.15 ± 0.22 mm/kg. A 3.5-mm shunt was most commonly used (64%). A classic Blalock-Taussig shunt was used in 1% of the neonates. Median age at the Norwood operation was 6 days (range <1-140 days), and median weight was 3.2 kg (range 1.5-5.2 kg).

Data Collection
Copies of medical records, including admission, diagnostic, and procedure reports, were requested for initial and subsequent assessments, admissions, or procedures and abstracted into a database by the Data Center and members of the CHSS. Detailed morphologic data were obtained by reviewing initial (before important intervention) echocardiographic videotape recordings from participating institutions. The protocol for this independent, blinded review has been described previously elsewhere. Among the study population, initial echocardiograms were made available for 76% of neonates with AVS and for 57% of those with AVA.

Follow-up
The physician, family, or guardian of each child not known to have died has been contacted yearly since cohort inception to ascertain clinical status and any intervening problems or procedures. However, contact by the Data Center is dependent on institutional review board and parental consent at each institution, limiting potential follow-up. The most recent cross-sectional follow-up was conducted between May and August 2001 and was 76% complete. If cross-sectional follow-up data from 2000 are included for the 183 children without 2001 follow-up, 91% had cross-sectional follow-up data within 1 year of this analysis.

Data Analysis
Goals of this analysis include defining the prevalence of various outcomes after the Norwood operation and determining the risk factors associated with each outcome. All analyses were performed with SAS statistical software (version 8; SAS Institute, Inc, Cary, NC). Data are given as frequency, median with range, or mean ± SD as appropriate.

Missing data. The number of nonmissing values is given for descriptive statistics. If weight, height, or body surface area was not reported, informative imputation was based on available patient characteristics and standard percentile growth charts, assuming that the patient’s height and weight percentiles were concordant. If ascending aortic diameter was not available from echocardiographic review, values obtained from the operative record were used (n = 114). Inclusion of surgical values did not significantly affect the mean aortic diameter in either the AVA group (2.4 ± 0.9 mm vs. 2.5 ± 0.9 mm for echocardiography only, P = .20) or the AVS group (5.3 ± 1.8 mm vs. 5.4 ± 1.8 mm for
echocardiography only, $P = .44$). Missing value indicator variables were created for missing continuous variables (eg, echocardiographic variables and circulatory arrest time), and the mean value of available information was imputed (noninformative imputation). In multivariable analyses, the relevant missing value indicator variables were carried to adjust for the possibility that patients with a given missing value may be different with respect to outcome from those in whom the value is not missing.

**Competing risks after the Norwood operation.** The following mutually exclusive states after the Norwood operation were designated: death, cavopulmonary shunt (CPS), other state (cardiac transplantation; BVR, biventricular repair consisting of Damus-Kaye-Stansel aortopulmonary connection, baffling of left ventricular outflow to neoaorta, and Rastelli-type connection from right ventricle to pulmonary artery.  

<table>
<thead>
<tr>
<th>State</th>
<th>No further procedures</th>
<th>HTX</th>
<th>CPS</th>
<th>BVR</th>
<th>Fontan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwood</td>
<td>59</td>
<td>11</td>
<td>11</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>n=710</td>
<td>(261 died)</td>
<td>(2 died)</td>
<td>(28 died)</td>
<td>(2 died)</td>
<td>(1 died)</td>
</tr>
<tr>
<td>Fontan</td>
<td>119</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>n=142</td>
<td>(5 died)</td>
<td>(1 died)</td>
<td>(1 died)</td>
<td>(3 died)</td>
<td>(8 died)</td>
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<tr>
<td>HTX</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=3</td>
<td>(3 died)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Flow chart illustrating subsequent procedures for 710 neonates with AVA or AVS who underwent Norwood operation. Prevalences of death after each procedure are indicated within parentheses. HTX, Cardiac transplantation; BVR, biventricular repair consisting of Damus-Kaye-Stansel aortopulmonary connection, baffling of left ventricular outflow to neoaorta, and Rastelli-type connection from right ventricle to pulmonary artery.

Competing risks after CPS. A second competing risks of events analysis was constructed to illustrate outcomes after CPS. The following mutually exclusive states were designated: death, Fontan operation, cardiac transplantation, and survival without transition to subsequent state. Risk factors for rate of transition to these states were determined as described earlier with incorporation of additional variables applicable to this stage of palliation (Appendix Table 2).

**Competing risks after the Fontan operation.** Survival after the Fontan operation was examined. Because of the small number of terminal events, survival free of cardiac transplantation was considered. Risk factors were sought from Fontan-specific variables (Appendix Table 2).

### Results

Overall survivals to last follow-up after Norwood palliation were 72% at 1 month, 63% at 6 months, 60% at 1 year, and 54% at 5 years.

### Competing Risks After Norwood Operation

Outcomes occurring after the Norwood operation are shown in time-independent fashion in Figure 1. Neonates transitioned to two major competing states: death ($n = 261$) and CPS ($n = 377$). Smaller numbers underwent direct transition to cardiac transplantation ($n = 8$), biventricular repair ($n = 4$), and Fontan operation ($n = 1$). Fifty-nine infants remain alive without transition to one of these states.

Transition to any of these states was time related, and the rate at which each transition occurred varies with interval from the Norwood operation (Figure 2, A). Early after the Norwood operation, there was a single rapidly declining hazard phase for death occurring before transition to a subsequent state. Within 3 months, rate of transition to CPS began to predominate, and it peaked just beyond 6 months. There was a low, continuous risk of undergoing other operations, mainly cardiac transplantation.

With these transition rates used simultaneously, time-dependent prevalence of each state was calculated by the competing risks analysis (Figure 2, B). Six months after the Norwood operation, prevalence in various states included CPS (31%), death before a subsequent transition (37%), and other state (1%). The remaining 31% were surviving in the initial state. Between 6 months and 1 year after the Nor-
wood operation, prevalence of death before subsequent transition did not appreciably change; however, prevalence of CPS increased to 57%.

Risk factors for post-Norwood mortality. Incremental risk factors for increased time-related death after the Norwood operation but before transition to any other state included patient-specific factors (lower birth weight, older age at Norwood, and smaller size of ascending aorta), surgical factors (shunt origin from neoaorta and longer circulatory arrest time), and institutional factors (institutions enrolling fewer than 10 neonates and 2 institutions enrolling more than 40 neonates; Table 1). The effects on survival of birth weight, age at Norwood operation, aortic origin of the shunt, and circulatory arrest time are shown in Appendix Figure 1. When institutions were excluded from risk factor selection, the technique of transecting and reimplanting the ascending aorta into the neoaorta was associated with increased survival in neonates with a small ascending aorta. Solving the multivariable equation while adjusting for other risk factors suggested a survival benefit for neonates with an ascending aorta measuring 3 mm or less if the ascending aorta was transected and reimplanted into the neoaorta (Figure 3).

Of 512 patients surviving to be discharged from the hospital, 63 (12%) died in the interim between discharge and subsequent staging. The absence of a constant or late

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate* (±SE)</th>
<th>P value</th>
<th>Reliability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Including institution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower birth weight (per 1-kg increment)</td>
<td>0.44 ± 0.14</td>
<td>.01</td>
<td>53</td>
</tr>
<tr>
<td>Older age at operation (per 1-wk increment)</td>
<td>0.091 ± 0.035</td>
<td>.01</td>
<td>83</td>
</tr>
<tr>
<td>Longer total circulatory arrest time† (per 10-min increment)</td>
<td>0.0012 ± 0.00031 &lt; .001</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Smaller ascending aortic dimension‡ (per 1-mm increment)</td>
<td>0.49 ± 0.13 &lt; .001</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Shunt originating from aorta</td>
<td>0.51 ± 0.23</td>
<td>.03</td>
<td>52</td>
</tr>
<tr>
<td>Institution enrolling ≤10 neonates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institution H</td>
<td>1.01 ± 0.30</td>
<td>&lt; .001</td>
<td>79</td>
</tr>
<tr>
<td>Institution I</td>
<td>0.48 ± 0.22</td>
<td>.03</td>
<td>43</td>
</tr>
<tr>
<td>Excluding institution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower birth weight (per 1-kg increment)</td>
<td>0.42 ± 0.14</td>
<td>.01</td>
<td>71</td>
</tr>
<tr>
<td>Older age at operation (per 1-wk increment)</td>
<td>0.12 ± 0.036</td>
<td>.01</td>
<td>89</td>
</tr>
<tr>
<td>Longer total circulatory arrest time† (per 10-min increment)</td>
<td>0.0013 ± 0.00031 &lt; .001</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>Smaller ascending aortic dimension‡ (per 1-mm increment)</td>
<td>0.64 ± 0.13 &lt; .001</td>
<td>89</td>
<td></td>
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<tr>
<td>Nonreimplantation of ascending aorta into neoaorta</td>
<td>1.68 ± 0.86</td>
<td>.05</td>
<td>39</td>
</tr>
<tr>
<td>Interaction term between ascending aortic diameter and nonreimplantation</td>
<td>1.48 ± .99</td>
<td>.14</td>
<td>—</td>
</tr>
<tr>
<td>Shunt origin from aorta</td>
<td>0.35 ± 0.24</td>
<td>.13</td>
<td>55</td>
</tr>
</tbody>
</table>

*For a single early hazard phase adjusted for missing arch reconstruction technique in the model excluding institution.
†Entered after square transformation.
‡Entered after logarithmic transformation.

Figure 2. Competing risks analysis of outcomes after Norwood operation in 710 neonates with AVS or AVA. All patients began alive at Norwood operation and thereafter could transition to one of three mutually exclusive outcomes: death, CPS, and other outcomes (including cardiac transplantation, biventricular repair, and Fontan operation). Solid lines represent parametric point estimates; dashed lines enclose 70% confidence interval. At each point in time, sum of percentages of neonates in all categories is 100%. A, Competing hazard functions for each outcome. B, Proportion of neonates (expressed as percentage of total) in each of four categories at any given time after undergoing Norwood operation.
Phase of hazard for death occurring before subsequent operation indicates that the risk factors defined previously were applicable both to hospital mortality and interval mortality before subsequent staging. To confirm this observation, the multivariable equation was solved on the condition of hospital discharge to predict the occurrence of interval mortality. The observed time-related prevalence of interval mortality was accurately predicted by the current parametric model (Figure 4).

**CPS as an intermediate stage.** A total of 377 infants underwent CPS at a median age of 6 months (range 1-28 months) as an intermediate stage to Fontan completion. Factors associated with earlier CPS included two patientspecific factors (lower birth weight and smaller z score of mitral valve diameter) and two procedural variables (lower post-Norwood oxygen saturation and smaller shunt size indexed to body weight; Table 2). Impact of shunt size on transition to CPS was greatest for lower weight neonates (Figure 5). The effect of post-Norwood oxygen saturation on transition to CPS is illustrated in Figure 6. Two institutions were predictive of earlier CPS, and two institutions were predictive of later CPS (Table 2).

**Prediction of outcomes for various levels of risk.** To illustrate the difference in outcomes for patients undergoing the Norwood operation affected by various patient and procedural characteristics, the multivariable equations for the major transitions were solved. The resulting competing risks curves demonstrate the difference in predicted outcomes for neonates having characteristics consistent with the upper and lower 25th risk percentiles (Figure 7).

**Competing Risks After CPS**  
Death after CPS but before undergoing subsequent stages occurred in 28 infants (Figure 1). Of 349 survivors of CPS,
progressed to the Fontan operation. Cardiac transplantation was performed in 8 children after CPS. No transition to a subsequent state has occurred in 142 children. Examination of the competing hazard functions for these states reveals a rapidly declining early phase for death occurring before subsequent state (Figure 8, A). Between 9 months and 18 months after CPS, a rapid increase in the rate of transition to the Fontan operation occurred, with subsequent slow decline during the next 4 years. On the basis of these hazard functions, the time-related prevalences of these states after CPS were determined (Figure 8, B).

Risk factors for post-CPS mortality. Incremental risk factors for time-related death after CPS included younger age at CPS and repair of right atrioventricular valve insufficiency at CPS (Table 3). The magnitude of the effect of age at CPS on mortality increased with decreasing age (Figure 9). No institution was identified as significant predictor.

Conversion to Fontan circulation. Fontan operation was performed at a median age of 2 years (range 1-6 years). Incremental factors associated with transition to Fontan operation are listed in Table 4.
Outcome After Fontan Operation

Five children died after the Fontan operation, and 3 have required cardiac transplantation. Survival free of cardiac transplantation after the Fontan operation was 96% at 2 years (Appendix Figure 2). Because of the small numbers of deaths and transplants, risk factors for these events could not be determined.

Discussion

Principal Findings

The prognosis of neonates born with HLHS has dramatically improved relative to its dismal natural history. However, the competing risks analysis reported here confirms that mortality associated with staged surgical palliation of neonates with HLHS remains heavily concentrated around
the time of the Norwood operation. Outcomes beyond conversion to CPS are excellent. The analysis reveals that patient, institutional, and procedural factors influence both goals of early palliation: survival and successful transition to subsequent intermediate and final states.

The overall post-Norwood survivals reported in this multi-institutional study are comparable to those in two earlier multi-institutional reports and several reports by high-volume centers. Our early mortality data are also similar to those reported by the Society of Thoracic Surgeons National Congenital Heart Surgery Database, in which the operative mortality for 187 neonates undergoing the Norwood operation between 1994 and 1997 was 27%.22

A number of reports from individual institutions have examined post-Norwood mortality and its associated risk factors. Several of these studies have shown significant improvement in survival with time. Mahle and colleagues from the Children’s Hospital of Philadelphia reported the outcomes of 840 infants undergoing the Norwood operation between 1984 and 1999 in the largest single institutional series published to date. Their center had improvements in hospital and 3-year survivals between 1984 to 1998 (56% and 28%, respectively) and 1995 to 1998 (71% and 66%, respectively). We did not demonstrate whether age at Norwood operation to be a significant factor associated with post-Norwood survival, signifying no trend toward improved survival during the study’s 6-year span.

We found increasing age at Norwood operation to be a risk factor for mortality in a continuous manner. Mahle and associates found that age older than 14 days was a risk factor, and Bove and Lloyd described increased risk for neonates older than 30 days. The potential for a neonate to undergo the Norwood operation days after birth is at least partially dependent on his or her postnatal clinical status. Tworetzky and colleagues correlated improved clinical status and significantly younger age at operation with perinatal diagnosis. These observations emphasize the importance of early perinatal optimization of the neonate with the goal of early, but not emergency, Norwood operation.

Several groups have described the increased risk posed by low birth weight. Weinstein and coworkers reported an early mortality of 49% for 67 neonates smaller than 2.5 kg, compared with an overall early mortality of 26% at their institution. Delaying staged surgical reconstruction for the prospect of increasing neonatal weight is offset by the risk imposed by older age at operation. Although cardiac transplantation represents an alternative therapy for these neonates, there have been mixed reports regarding low birth weight as a risk factor for cardiac transplantation. A previous CHSS study found lower birth weight to be a risk factor for infants with AVA entered into a transplant protocol, whereas a report from Razzouk and colleagues at Loma Linda on a larger group of patients with HLHS did not find low birth weight to be a risk factor. At present, low birth weight is an immutable patient-specific factor for which no optimal solution is known.

There have been differing reports regarding the impact of ascending aortic size on survival. Our data show an association between smaller ascending aortic size and post-Norwood mortality. The most important implication of the small ascending aorta involves compromise of coronary blood flow. Anatomic subtype has also been purported to be a risk factor. Although neonates with AVA had significantly smaller ascending aortas than those with AVS, neither AVA nor AVS emerged as significant risk factors. These data suggest that antegrade coronary flow potentially resulting from patency of the left-sided valves does not diminish the impact of the tiny ascending aorta. Technical modifications aimed at creating a durable, maximally patent coronary connection are expected to benefit neonates with a diminutive (<3 mm) ascending aorta.

Diastolic coronary blood flow has been shown to be impaired after the Norwood operation. A systemic-pulmonary shunt originating from the aorta may reduce coronary perfusion to a greater degree than a more distal shunt by further reducing neoaortic diastolic blood pressure and increasing competing flow to the pulmonary arteries. That this phenomenon would not be well tolerated in the post-Norwood period is supported by previous reports of reduced baseline and maximal coronary blood flows, particularly in the setting of volume loading. Shunt origin from the aorta as a risk factor for mortality has important implications in neonates with anomalous origin of the right subclavian artery. Because the carotid artery is often not suitable for shunt origin, alternate surgical technique is necessary in these neonates to decrease the risk conferred by aortic shunt origin.

Use of total circulatory arrest has been implicated in reducing neurodevelopmental outcomes of children who undergo staged palliation for HLHS. Although our study did not assess neurologic outcomes, we found that increasing circulatory arrest time was associated with higher mortality after the Norwood operation. These findings illustrate the importance of minimizing the exposure of the neonate to ischemia. Although we observed no survival benefit associated with use of modified perfusion techniques, further data are needed to support the inference that modified regional perfusion could result in both survival and neurodevelopmental benefits.

Unexpected death after discharge from the surgical institution has been reported to range in prevalence from 4% to 15%. Factors linked to interstage attrition by previous authors include perioperative arrhythmia, earlier date of operation, and atresia of the aortic and mitral valves. We found a 12% mortality before CPS for hospital survivors of the Norwood operation. Our model accurately predicted the occurrence of these deaths, indicating that the same set of...
risk factors explain post-Norwood deaths whether they oc-
cur before or after hospital discharge. This finding is not
surprising when one considers that impaired coronary per-
fusion or extremes of pulmonary blood flow accounted for
63% of deaths in a large postmortem series of Norwood nonsurvivors.33 Although not specifically examined as a risk
factor in our study, obstruction at the site of distal aortic arch reconstruction may also contribute to post-Norwood
attrition. Nonetheless, the frequency of these deaths is of
concern and indicates a need to improve the postdischarge
evaluation and home management of these infants. Close
echocardiographic surveillance of the central circulation in
the neonatal period was not reported, and thus inability to
close atrial or ventricular septal defects was not considered
a risk factor. The number of days between discharge and
death may be a rough proxy for home care quality. This
factor was not accounted for in the competing risks model.

Competing Risks
Use of competing risks analysis allowed us to evaluate the
efficiency with which survivors of the Norwood operation
can be transitioned to the intermediate state of CPS. Al-
though optimal timing of CPS in this population remains
elusive, our data reveal that younger age is a risk factor for
CPS mortality. One might consider that younger age at CPS
is simply a marker for poorer progress after the Norwood
operation, because we have demonstrated that survivors
among neonates at increased risk for death also transition
more rapidly to CPS. However, we found that postoperative
oxygen saturation and indexed shunt size, which in addition
to total cardiac output are related to the quantity of pulmo-
nary blood flow, are predictors of the transition to CPS.
Conversely, we did not find shunt size to be a factor asso-
ciated with post-Norwood mortality. One might infer from
these data that a larger shunt size indexed to body weight
(1.15-1.25 mm/kg) and higher post-Norwood oxygen satu-
ratio (70%-80%) predict older age and therefore increased
survival at CPS. However, further studies are needed to
determine whether the survival benefit at CPS for older
infants is offset by the deleterious effects of the longer
duration of shunt-dependent physiology.

Study Limitations
The multi-institutional nature of this study and its large
cohort of patients provide a broad view of the status of
staged surgical palliation for neonates with critical AVS or
AVA. Although a comprehensive set of variables was used,
missing data points are a potential weakness of the study.
With currently available data, we could not explore the
hemodynamic status of infants before subsequent staging.
Incorporation of such data could allow determination of the
optimal age for performing CPS and Fontan completion.
Also, a combined analysis of outcomes after the Norwood
operation and after cardiac transplantation could potentially
define factors that would direct neonates toward the more
beneficial pathway.

Conclusions
We have shown that patient, institutional, and procedural
variables affect outcomes after the Norwood operation. So-
lution of the competing risks model for various levels of risk
demonstrates that successful modification of these risk fac-
tors predicts better survival and more efficient transition to
subsequent stages, which may lead to better outcomes for a
larger proportion of neonates with HLHS undergoing the
Norwood operation.

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tribution to the study. We acknowledge the assistance of the personnel
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References
1. Gillum RF. Epidemiology of congenital heart disease in the United
2. Lev M. Pathologic anatomy and interrelationship of hypoplasia of the
3. Norwood WI, Lang P, Castaneda AR. Experience with operations for
hypoplastic left heart syndrome. J Thorac Cardiovasc Surg. 1981;82:
511-9.
4. Norwood WI, Lang P, Hansen DD. Physiologic repair of aortic atre-
5. Lofland GK, McCrindle BW, Williams WG, Blackstone EH, Tcher-
venkov CI, Sittiwangkul R, et al. Critical aortic stenosis in the neo-
nate: a multi-institutional study of management, outcomes, and risk
6. Jacobs ML, Blackstone EH, Bailey LL. Intermediate survival in neo-
nates with aortic atresia: a multi-institutional study. J Thorac Cardio-
balloon valvotomy equivalent in neonatal critical aortic stenosis?
8. Daebritz SH, Noller GD, Zurakowski D, Khalil PN, Lang P, del Nido
PJ, et al. Results of Norwood stage I operation: comparison of hypoplas-
ic left heart syndrome with other malformations. J Thorac Cardiovasc
Ten-year institutional experience with palliative surgery for hypoplas-
ic left heart syndrome: risk factors related to stage I mortality.
10. Mahle WT, Spray TL, Gaynor JW, Clark BJ. Unexpected death after
reconstructive surgery for hypoplastic left heart syndrome. Ann Thor-
11. Bu’Lock FA, Stumper O, Jagtap R, Silove ED, De Giovanni JV,
Wright JG, et al. Surgery for infants with a hypoplastic systemic
ventricle with or without outflow obstruction: early results with a modified
12. Fraser CD, Mee RB. Modified Norwood procedure for hypoplastic left
Primary repair of interrupted aortic arch and severe aortic stenosis in
23. Forbess JM, Cook N, Serraf A, Burke RP, Mayer JE, Jonas RA. Anomalous pulmonary venous drainage (No.). AVA (No.) 710 0 454 (64%)
Critical AVS (No.) 710 0 449 (63%)
Mild 200 (50%)
Mild 131 (33%)
Mild 58 (17%)
Tricuspid regurgitation (No.) 389 321
None 200 (50%)
Tricuspid regurgitation (No.) 389 321
None 200 (50%)
Mild 131 (33%)
Mild 58 (17%)
Any endocardial fibroelastosis (No.) 254 456 143 (56%)
Persistent left superior vena cava (No.) 710 0 51 (7%) Anomalous pulmonary venous drainage (No.) 710 0 25 (4%)
Coronary artery anomaly (No.) 710 0 46 (6%)
Tricuspid valve abnormality (No.) 710 0 17 (2%)
Pulmonary valve abnormality (No.) 710 0 20 (3%)
Procedural characteristics (Norwood operation) Age at surgery(d, median and range) 709 1 6 (<1-140)
Weight at surgery (kg, median and range) 501 209 3.2 (1.5-5.2) 
Lowest cooling temperature (°C, mean ± SD) 495 215 (18) 0.22
Atrial septectomy (No.) 684 261 (37%)
Distal aorta transected (No.) 691 206 (31%)
Absolute shunt diameter (mm) 679 31
3.5 mm 15 (20%)
3.0 mm 53 (8%)
4.0 mm 193 (28%)
Additional shunt indexed to body weight (mm/kg, mean ± SD) 481 225 (11.5 ± 0.22)
Shunt origin (No.) 680 30
Aorta 41 (6%)

(Continued on next page)
Appendix TABLE 1. Cont’d

<table>
<thead>
<tr>
<th>Variable</th>
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<td>Total circulatory arrest time (min, mean ± SD)</td>
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<td>49 ± 16</td>
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Discussion

Dr James S. Tweddell (Milwaukee, Wis). It is an honor to discuss this outstanding and well-presented contribution by Ashburn and colleagues. This multi-institutional analysis of patients undergoing Norwood palliation of HLHS has confirmed important patient risk factors and identified important procedural variables. Further, Ashburn and colleagues have shown that these risk factors persist into the interstage period. This is an important contribution. In our experience the period of greatest risk is now that between the Norwood procedure and subsequent stage II palliation.

I have the following questions for Dr Ashburn:

1. The period covered by the study is one that has seen dramatic improvement in the outcome of patients undergoing the Norwood procedure. In our own program we have experienced something of a sea change in the management of this group of patients. From 1994 to the present, looking at only 108 true hypoplasts, or the anatomic category presented here, our survival at 1 month was 83%. But if we look at the 78 patients operated on in our program from 1996 to the present, which includes the uniform use of venous oxygen saturation monitoring and afterload reduction with β-blockade, we have a 1-month survival of 96% with subsequent survivals to 1 and 5 years of 79% and 77%.

2. In the study presented today, 102 deaths occurred within 48 hours of the Norwood procedure. This represents 14% of the study population. Since the application of venous oxygen saturation monitoring and the use of afterload reduction, we have had no deaths within 48 hours.

3. Did you look at any postoperative management variables in their analysis, specifically, the use of an open sternum strategy, sedation and paralysis, ventilator management, medical gas manipulation, vasodilators, or inotropes? The contributions of these factors might have shed as much or more light on the outcome than the factors chosen for analysis.

4. We have also been concerned with the small ascending aorta and agree that the tripartite connection of the diminutive ascending aorta, pulmonary root and the neo-ascending aorta may result in distortion or kinking, resulting in coronary insufficiency. We have dealt with this by cutting back on the pulmonary root and ascending aorta and placing that connection at or below the sinotubular junction of the pulmonary valve and away from the connection of the neo-ascending aorta and the pulmonary root. Was this or a similar strategy used in any of the patients in the study? Would you care to conjecture on the impact of this operative approach on outcome?

5. This study is unique in that several strategies for arch reconstruction were used. Did you gain any insight into the

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<td>31</td>
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</tr>
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<td>(59%)</td>
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<td>Fontan operation</td>
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<tr>
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<td>175</td>
<td>24</td>
<td>26 (15%)</td>
</tr>
<tr>
<td>Right</td>
<td>29</td>
<td>17</td>
<td>(17%)</td>
</tr>
<tr>
<td>Left</td>
<td>27</td>
<td>16</td>
<td>(16%)</td>
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</table>
impact of these arch reconstruction strategies on the development of recurrent or residual arch obstruction?

6. Finally, could you expand on the choice of competing risk analysis and the advantage of this type of analysis relative to other forms of multivariable analysis?

Dr Ashburn. We certainly are aware of the excellent results being presented from your institution, as well as from a number of other institutions, with particular improvement in recent years. Regarding improvement through time in the outcomes of these children, we did not find date of operation to be a statistically significant predictor of survival between 1994 and 2000. I noticed that you included in your breakdown 1996 to the present, and it may be that in the last 2 years since our study ended that the rate of improvement, considering new technology such as what your group has introduced, has made a difference in recent outcomes. Certainly, compared across decades of time there have been dramatic improvements reported in the literature, and one hopes that further improvement will continue.

We did not incorporate postoperative variables, such as hemodynamic, inotrope, blood gas, or ventilator management variables, into the analysis. I cannot comment on the impact of those factors on outcomes.

Appendix Figure 1. Risk-adjusted percent survival after the Norwood operation before transition to a subsequent state stratified by birth weight (A), age at operation (B), aortic or nonaortic origin of systemic-pulmonary shunt (C), and total circulatory arrest time (D). Solid lines represent parametric point estimates; dashed lines enclose 70% confidence interval.

Appendix Figure 2. Survival free of cardiac transplantation after Fontan operation. Numbers in parentheses represent patients remaining at risk at each time point.

In a subsequent review and subanalysis, 77 infants were found to require reintervention for recurrent or residual distal aortic arch obstruction. According to the Kaplan-Meier method, the freedoms from reintervention for arch obstruction were 96%, 87%, and 84% at 3 months, 6 months, and 1 year, respectively. In a preliminary
analysis, the technique of arch reconstruction did not arise as a risk factor for reintervention for recurrent arch obstruction. Although reintervention for recurrent coarctation was not shown to have a statistically significant impact on the overall survival after the Norwood operation, we believe that this issue requires further study.

The study revealed a strong logarithmic association of ascending aortic size with post-Norwood mortality. The technique of aortopulmonary anastomosis most commonly used in our population was the classic patch aortoplasty, in which the arch and ascending aorta are opened and connected to the neoaoorta with an extensive patch. We do not have data on the cutback modification that you describe. However, I think the study shows that technical modifications that result in less kinking and distortion, as you suggest, and a more durable, patent coronary connection can be expected to improve survival of neonates with an ascending aorta smaller than 3 mm.

Regarding the competing risks analysis methodology, perhaps the biggest advantage is that it allows us to see what is happening to the overall group of patients at any given point in time. Use of competing risks also gives a more accurate representation of the prevalences of outcome events. It is really the time relatedness of how these events occur that is of interest. It’s not uncommon to see raw mortality figures represented in an article, but we try to take that a step further and not only represent the mortality but explain the timing of the mortality and how it relates to other transitions that these patients may undergo. For instance, birth weight is a significant risk factor for death after the Norwood operation. By competing risks analysis, we also discovered that birth weight is a predictor of rate of transition to CPS. Those are the types of relationships that wouldn’t come out of a different type of analysis.

Dr Thomas L. Spray (Philadelphia, Pa). The virtue of the multi-institutional CHSS studies is the fact that they give you a snapshot, if you will, of practice across a broad range of different institutions. But one of the disadvantages is the fact that a few institutions can significantly skew the data. For example, I wonder how many institutions there were that used the reimplantation strategy for the small ascending aorta. If you took a few institutions that used that strategy with very good results, would that skew the data to suggest that reimplantation was in fact favorable, when in fact other institutions—maybe many more institutions—where reimplantation wasn’t used as a technique contributed many more patients with slightly worse outcomes? For example, if you took what I would call low-risk institutions for the standard reconstruction and compared those with the institutions that used reimplantation strategies, would you still find that reimplantation decreased the risk of early death?

In addition, I also wonder how you measured the ascending aortic diameter. It depends a lot on whether there is an independent observer looking at all patients to measure the diameter by echocardiography or whether it’s a surgical measurement in the operating room and whether it’s an estimate by the surgeon or by probing or whatever. The difference between 1 mm and 2 mm (100%) may be pretty subjective by estimation in the operating room.

Dr Ashburn. The morphologic variables were obtained by an independent blinded echocardiographic tape review. In the case of ascending aortic dimension, echocardiographic review values were preferentially used and account for 82% of the measurements. Where echocardiographic values were not available, ascending aortic dimension was obtained from the operative record, and such cases account for 18% of the measurements. Inclusion of operative values did not result in a statistically significant change in the mean values for either AVS or AVA when compared with echocardiographic values alone.

With regard to your question about ascending aortic reimplantation, eight institutions enrolled neonates in whom this technical modification was used. We did not perform risk adjustment for individual institutions, nor did we compare institutional outcomes with one another, so I cannot comment on the possible differential impact of ascending aortic management on the survivals at high-risk and low-risk institutions.

Dr Christian P. R. Brizard (Melbourne, Australia). I was surprised to hear that you found that young age for the CPS was a risk factor for death after CPS. In our institution we have been able to significantly reduce the attrition rate in the waiting period for the CPS by bringing forward the CPS to 3 months of age, with no increase in the mortality or morbidity of the CPS procedure. How do you explain your result? Also, from your statistical analysis, can you extrapolate to determine what would be the optimal age for the CPS?

Dr Ashburn. Your second question is of great interest to us, and we had hoped that we could answer it from this analysis. Unfortunately, we have not been able to put that analysis together at this point. I might add that incorporating hemodynamic data from the pre-CPS catheterization into such an analysis could be important in quantifying the time dependence of deleterious effects of shunt-dependent single-ventricle physiology in these neonates.

With respect to why younger age at CPS increases risk, I think that it goes back to the risk factors for that transition. In our study the patients who were at risk for undergoing an earlier CPS also tended to be the patients who were at high risk for death after the Norwood operation. So those high-risk neonates who survived the Norwood operation but fared poorly were also more likely to do poorly at the time of CPS.