Staged surgical management of hypoplastic left heart syndrome. A single-institution 12-year experience

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Abstract

Objective
This study sought to describe the 12-year experience with staged surgical management for hypoplastic left heart syndrome (HLHS) and identify the factors that influenced outcome.

Methods
Between December 1992 and June 2004, 333 patients with HLHS underwent a Norwood procedure (median age 4 days, range 0 to 217 days). A bidirectional Glenn (Stage II) was subsequently performed in 203 patients and 81 patients underwent a modified Fontan procedure (Stage III). Follow-up was complete (median interval 3.7 years, range 32 days to 11.3 years).

Results
Early mortality following the Norwood procedure was 29% (n=95); this decreased from 46% (first year) to 16% (last year; p<0.05). There were 49 inter-stage deaths, 27 prior to Stage II and 22 between Stages II and III. There was one early and 3 late deaths following Stage III. Actuarial survival (SEM) was 58% (3%) at 1 year and 50% (3%) at 5 and 10 years.

On multivariable analysis, five factors influenced early mortality following the Norwood procedure (p<0.05). Pulmonary blood flow supplied by a right ventricle to pulmonary artery (RV-PA) conduit; arch reconstruction with pulmonary homograft patch and increased operative weight improved early mortality. Increased periods of cardiopulmonary bypass and deep hypothermic circulatory arrest increased early mortality. Similar factors also influenced actuarial survival following the Norwood procedure.

Conclusion
This study identified an improvement in outcome following staged surgical management of HLHS, which was primarily attributable to changes in surgical technique. The RV-PA conduit, in particular, was associated with a marked and independent improvement in early and actuarial survival.

Measurements and abbreviations
HLHS, Hypoplastic left heart syndrome; RV-PA, right ventricle to pulmonary artery; RMBTS, right modified Blalock-Taussig shunt; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; BDG, bidirectional Glenn; EWMA, exponentially-weighted moving average.
Introduction

Hypoplastic left heart syndrome (HLHS) refers to the group of congenital cardiac abnormalities, characterised by severe stenosis or atresia of the mitral and aortic valves, diminutive ascending aorta and left ventricular hypoplasia.[1] The left ventricle is unable to support the systemic circulation, which is maintained by the right ventricle through a patent ductus arteriosus. HLHS accounts for 2.5% of congenital heart defects but is responsible for up to 25% of all deaths within the first week of life.[2]

Without surgical palliation, 95% of children die within the first month of life.[3]

In 1983, Norwood et al. reported the first successful surgical palliation of HLHS,[4] which involved a Norwood procedure followed by the Fontan procedure. In 1990, Bridges et al. described the bidirectional cavo-pulmonary anastomosis as an intermediate staging operation for the management of high-risk candidates for the Fontan procedure, such as patients with HLHS.[5] This three-stage surgical palliation remains the most common treatment for patients with HLHS.

There have been substantial improvements in outcome following surgical palliation for HLHS. This has been attributed to modifications in surgical technique and perioperative medical care, together with a better understanding of post-operative physiology.[6] One of the most important recent developments has been the right ventricle to pulmonary artery (RV-PA) conduit as an alternative source of pulmonary blood flow to the right modified Blalock-Taussig shunt (RMBTS).[7] The RV-PA conduit is reportedly associated with more stable post-operative haemodynamics,[8, 9, 10] superior ventricular function[11] and improved early survival.[10] The early survival following the Norwood procedure in contemporary series varies between 73 - 80%,[12, 13, 14] although an increasing number of centres have reported hospital survival rates greater than 90%.[10, 15, 16]

There has also been progressive improvement in early outcome following the subsequent stages of surgical palliation.[17] The introduction of the bidirectional cavo-pulmonary anastomosis as an interim staging procedure has improved survival following the modified Fontan procedure. Currently, early mortality following the Fontan procedure ranges between 2 - 7%.[18, 19] and does not appear to be influenced by the morphology of the single, functional ventricle.[19]

There is limited information to describe the medium and long-term outcome of surgical palliation for patients with HLHS.[12, 14, 20, 21] This study was undertaken to describe our 12-year single-institution experience with the surgical palliation of HLHS. We sought to identify those anatomic and technical factors that influenced outcome following the modified Norwood procedure.
Methods
Between December 1992 and June 2004, 366 consecutive patients underwent a modified Norwood procedure at the Diana Princess of Wales Children's Hospital, Birmingham, UK. Three hundred and thirty-three patients had HLHS. Thirty-three patients with functionally single ventricle anatomy of left ventricular morphology underwent a modified Norwood procedure and were not included in this study.

Patient population
The diagnosis of HLHS was based on detailed two-dimensional echocardiography. The majority of patients had classical HLHS (n=290, 87%). The remaining 43 patients had a HLHS variant (Table 1A), characterised by left ventricular hypoplasia and systemic outflow tract obstruction. There were 219 males (66%) and 114 females.

Table 1A  Primary cardiac anatomy

<table>
<thead>
<tr>
<th>Primary cardiac anatomy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical hypoplastic left heart syndrome</td>
<td>290</td>
<td>87%</td>
</tr>
<tr>
<td>Variants of hypoplastic left heart syndrome</td>
<td>43</td>
<td>13%</td>
</tr>
<tr>
<td>Unbalanced atrio-ventricular septal defect</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Double-outlet right ventricle with mitral atresia</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Critical aortic stenosis with hypoplastic left ventricle</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Double-inlet, double-outlet right ventricle</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Mitral atresia with aortic arch hypoplasia</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The median diameter of the ascending aorta was 3.0 mm (range 1.0 to 10.0 mm), and was ≤2.0 mm in 82 patients (25%). The majority of patients had evidence of a discrete coarctation ridge (n=252, 75%). Fifty-four patients (16.2%) had additional cardiac abnormalities (Table 1B). Fourteen patients (4.2%) were premature (gestational age ≤36 weeks) and 18 patients (5.4%) were diagnosed with extra-cardiac abnormalities, including major structural or genetic abnormalities (Table 1C).

Table 1B  Additional cardiac abnormalities

<table>
<thead>
<tr>
<th>Additional cardiac abnormalities</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arch abnormalities</td>
<td>16</td>
<td>4.8%</td>
</tr>
<tr>
<td>Interrupted aortic arch (type A)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Interrupted aortic arch (type B)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Interrupted aortic arch (Type C)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Right subclavian artery arising from descending thoracic aorta</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Abnormal systemic venous drainage</td>
<td>31</td>
<td>9.3%</td>
</tr>
<tr>
<td>Bilateral superior vena cava</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Azygos or hemiazygos continuation of inferior vena cava</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Left atrial isomerism</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Abnormal pulmonary venous drainage</td>
<td>5</td>
<td>1.5%</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous drainage</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Partial anomalous pulmonary venous drainage</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous obstruction</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Congenital heart block</td>
<td>2</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
### Table 1C  Associated genetic anomalies and major structural abnormalities

<table>
<thead>
<tr>
<th>Genetic anomalies</th>
<th>7</th>
<th>2.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turners syndrome</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Di George syndrome</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other chromosomal micro-deletion</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Major structural abnormalities</td>
<td>14</td>
<td>4.2%</td>
</tr>
<tr>
<td>Congenital hydrocephalus</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Microcephaly</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Agenesis of corpus callosum</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tracheo-oesophageal fistula</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Congenital bronchomalacia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bilateral renal dysplasia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Choanal atresia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Perinatal (pre-operative) necrotising enterocolitis</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Most patients were initially stabilised with medical management. Seven patients (2.1%) had a surgical procedure (atrial septectomy, n=4; coarctation repair, n=2; open aortic valvotomy, n=2) and 4 patients (1.2%) had balloon atrial septostomy prior to the Norwood procedure.

#### Norwood procedure

The Norwood procedure was performed at a median age of 4 days (range 0 to 217 days). The majority (n=265, 80%) were operated within the first 7 days and only thirteen (3.9%) were operated at >30 days of age. The median weight at operation was 3.1 kg (range 1.7 to 6.6 kg), and 48 patients (14%) were ≤2.5 kg.

All operations were performed by one of three surgeons using deep hypothermic cardiopulmonary bypass (CPB) with periods of circulatory arrest for arch reconstruction. Antegrade cerebral perfusion, introduced in September 2002, was used during arch reconstruction in patients whose head and neck vessels were able to accommodate an arterial cannula. Myocardial protection was provided using a single dose of cold crystalloid cardioplegia (30 ml·kg⁻¹), administered prior to circulatory arrest. The median duration of CPB, aortic cross-clamp and deep hypothermic circulatory arrest was 71 min (range 17 to 323 min), 51 min (range 0 to 109 min) and 55 min (range 0 to 121 min), respectively.

The main pulmonary artery was divided at the level of the bifurcation and the distal pulmonary arteries were repaired with direct suture (n=97, 29%) or a patch (n=236, 71%). An atrial septectomy was performed during circulatory arrest, usually through the venous cannulation site. The arch was reconstructed using one of two established techniques; the original technique involved arch reconstruction without the use of additional patch material (n=129, 39%);[22, 23] the second technique, used exclusively since April 1999, involved arch reconstruction with a pulmonary homograft patch (n=204, 61%).[24]

Pulmonary blood flow was established using a RMBTS (n=258, 77%) or RV-PA conduit (n=73, 22%). Two patients (0.6%) with an anomalous right subclavian artery arising from the descending thoracic aorta had a 3 mm shunt between either the proximal main pulmonary artery or the aortic arch and the right pulmonary artery. The RMBTS was formed by anastomosing a polytetrafluoroethylene (PTFE) tube conduit (GORE-TEX®, WL Gore & Associates (UK) Ltd. Livingston, Scotland) between the innominate artery and the upper border of the right pulmonary artery. The median size of this shunt was 3.5 mm (range 3 to 5 mm) and the mean (SD) shunt size indexed to body weight was 1.07 (0.18) mm·kg⁻¹. The
RV-PA conduit was introduced in March 2002 and involved a PTFE tube conduit that passed to the left of the neo-aorta \((n=17)\).[7, 24] More recently, this technique was modified so that the conduit passed to the right of the neo-aorta \((n=56)\). The median size of the RV-PA conduit was 5 mm (range 4 to 5 mm) and mean (SD) indexed shunt size was 1.65 (0.30) mm·kg\(^{-1}\).

Delayed sternal closure was employed in virtually all patients. Inotropic support usually comprised dobutamine \((10 \, \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) or milrinone \((0.3 - 0.7 \, \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) plus epinephrine \((0 - 0.3 \, \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})\) as required. Mechanical ventilation using pressure-regulated neonatal ventilators was adjusted to maintain arterial oxygen saturations of 70 - 80% and arterial carbon dioxide tension between 35 - 45 mmHg. Inspired carbon dioxide and nitrogen were not utilised to manipulate the pulmonary vascular resistance. Patients were discharged from hospital on aspirin \((5 \, \text{mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1})\) and oral diuretic therapy. Patients with impaired right ventricular function or clinically important systemic atrio-ventricular valvar regurgitation also received an angiotensin converting enzyme inhibitor (Captopril).

Stage II and Stage III procedures

Cardiovascular function was assessed by echocardiography and elective cardiac catheterisation prior to the bidirectional Glenn (BDG; Stage II) and modified Fontan procedure (Stage III). Thirty-seven patients required cardiological intervention prior to Stage II, primarily for neo-aortic arch obstruction \((n=34)\).[25] Thirty-six patients also required cardiological intervention prior to Stage III. The majority \((n=27)\) had balloon dilatation of the pulmonary arteries with or without stent insertion. Twelve patients had balloon dilatation of residual \((n=5)\) or previously untreated \((n=7)\) neo-aortic arch obstruction.

Two hundred and three patients underwent a BDG at a median age of 4.9 months (range 27 days to 22.8 months) and median interval of 4.7 months (range 18 days to 22.6 months) following the Norwood procedure. Concomitant surgical procedures were performed in 84 patients \((41\%)\), including pulmonary artery patch augmentation \((n=76)\), patch augmentation of the neo-aortic arch \((n=7)\), atrio-ventricular valve annuloplasty \((n=4)\), atrial septectomy \((n=1)\), and insertion of a permanent pacemaker \((n=1)\).

Eighty-one patients underwent the modified Fontan procedure at a median age of 4.4 years (range 2.2 to 6.6 years) and median interval of 4.0 years (range 1.9 to 6.1 years) following Stage II. The modified Fontan procedure was performed using a lateral atrial tunnel \((n=7, 8.6\%)\) or an extracardiac conduit \((n=74, 91.4\%)\) and was fenestrated in 57 patients \((70\%)\).[19] Concomitant surgical procedures were performed in 27 patients \((33\%)\), including pulmonary artery patch augmentation \((n=24)\), atrio-ventricular valve annuloplasty \((n=1)\), surgical occlusion of the native aortic valve \((n=1)\), and insertion of a permanent pacemaker \((n=1)\). All patients were warfarinised post-operatively, with a target international normalised ratio of 2.0 - 3.0.[19]

Data analysis

This retrospective study involved a review of hospital records, operation notes and cardiac catheter data. All patients have been followed up since discharge by a paediatric cardiologist. Follow-up was complete with a median interval of 3.7 years (range 32 days to 11.3 years).

Data has been examined by analysis of variance with SPSS for Windows (version 12, SPSS Inc, Chicago, IL, USA). Continuous variables are expressed as mean (SD) or median (range) and comparative univariable analyses have been made using the T-test, Mann–Whitney U-test or Wilcoxon signed rank test. Binominal or ordinal data are expressed as percentage and comparative univariable analyses have been made using the \(\chi^2\) test, two-sided Fisher exact test or binomial logistic regression. A probability value, \(p<0.05\), was taken to represent a statistically significant difference between groups.

An estimate of early mortality (in-patient or 30-day) was calculated using a running estimate, in which equal weight was apportioned to each case, or an exponentially-weighted moving average (EWMA), in which previous observations were systematically down-weighted by 5% per case.[26] Using this EMWA, the experience with the fourteenth previous patient carried about half the weight of the last patient seen. The 95% confidence intervals (CI) for each estimate were calculated.[27]
The early mortality and actuarial survival following the Norwood procedure, BDG and modified Fontan procedure were evaluated with a series of morphologic, preoperative and operative variables using univariable and multivariable analyses. Univariable analyses of early outcome measures were made using the $\chi^2$ test, two-sided Fisher exact test and binomial logistic regression. Variables with a probability value, $p \leq 0.1$, were included in a stepwise logistic regression model. Results of these analyses have been expressed as odds ratios (OR; 95% CI) for variables with a probability value, $p < 0.05$. Actuarial survival was estimated using the Kaplan–Meier product limit method. These results have been expressed as probability estimate (SEM). Univariable analyses of actuarial outcome measures have been made using the log-rank test. Variables with a probability value, $p \leq 0.1$ were included in a stepwise Cox regression analysis. Results of these analyses have been expressed as likelihood-ratios (LR; 95% CI) for variables with a probability value, $p < 0.05$. 
Results

At the time of follow-up, there were 183 survivors (55%) and 150 deaths (45%). Two patients had undergone orthotopic heart transplantation (0.6%). The actuarial survival (SEM) was 58% (3%) at 1 year, 54% (3%) at 3 years and 50% (3%) at 5 and 10 years (figure 1).

Early mortality and actuarial survival with a Norwood circulation

The early mortality following the Norwood procedure was 29% (n=95). The estimates of early mortality over the study period are illustrated in figure 2. Between December 1992 and December 1995, the running estimate (95% CI) declined from 100% (21% to 100%) to 30% (20% to 41%). The running estimate remained relatively constant thereafter, and was 29% (24% to 34%) in June 2004 (figure 2A). The EMWA showed a similar trend; the estimated early mortality (95% CI) declined from 100% (21% to 100%) in December 1992 to 17% (6% to 38%) in September 1995. The EMWA also identified continued improvement in early outcome, such that estimated early mortality was 10% (3% to 30%) in June 2004 (figure 2B).

There were 27 inter-stage deaths prior to Stage II, at a median interval of 70 days following the Norwood procedure (range 31 days to 8 months). Actuarial inter-stage mortality (SEM) was 7.9% (1.8%) at 3 months and 15% (3%) at 6 months. Overall actuarial survival (SEM) with a Norwood circulation was 66% (3%) at 3 months and 61% (3%) at 6 months following the Norwood procedure (figure 3A).

Multivariable analysis identified five factors (OR; 95% CI), which were independently associated with early mortality following the Norwood procedure (Table 2A). An RV-PA conduit (0.2; 0.1 to 0.5) and increased weight at operation (0.8 per 250g increase; 0.7 to 0.9) reduced the risk of early mortality. Arch reconstruction without the use of additional material (2.0; 1.1 to 3.7); increased duration of cardiopulmonary bypass (1.6 per 15 min increase; 1.3 to 1.9); and increased duration of deep hypothermic circulatory arrest (1.4 per 15 min increase; 1.1 to 1.8) increased the risk of early mortality.

Table 2A  Logistic regression analyses for early mortality following Norwood procedure

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariable</th>
<th>Multivariable OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of ascending aorta (per mm increase)</td>
<td>p=0.02</td>
<td></td>
</tr>
<tr>
<td>Preoperative ventricular function</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Height at operation (per quartile increase)</td>
<td>p=0.005</td>
<td></td>
</tr>
<tr>
<td>Weight at operation (per 250g increase)</td>
<td>p=0.001</td>
<td>0.8 (0.7 to 0.9; p&lt;0.001)</td>
</tr>
<tr>
<td>Body surface area at operation (per dm² increase)</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>Pulmonary blood flow (RV-PA conduit v RMBTS)</td>
<td>p=0.01</td>
<td>0.2 (0.1 to 0.5; p=0.001)</td>
</tr>
<tr>
<td>Arch reconstruction (No additional material v patch augmentation)</td>
<td>p=0.08</td>
<td>2.0 (1.1 – 3.8; p=0.02)</td>
</tr>
<tr>
<td>Surgeon</td>
<td>p&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Year of operation</td>
<td>p=0.01</td>
<td></td>
</tr>
<tr>
<td>Duration CPB (per 15 minute increase)</td>
<td>p=0.03</td>
<td>1.6 (1.3 – 1.9; p&lt;0.001)</td>
</tr>
<tr>
<td>Duration DHCA (per 15 minute increase)</td>
<td>p&lt;0.001</td>
<td>1.4 (1.1 – 1.8; p&lt;0.05)</td>
</tr>
<tr>
<td>Duration of cardiopulmonary support (per 15 minute increase)</td>
<td>p=0.001</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable analysis identified five factors (LR; 95% CI), which were independently associated with actuarial survival following the Norwood procedure (Table 2B). An RV-PA conduit (0.3; 0.2 to 0.6) and an increased weight at operation (0.9 per 250g increase; 0.8 to 0.9) reduced the risk of mortality. Female gender (1.7; 1.2 to 2.4) and increasingly prolonged cardiopulmonary bypass (1.4 per 15 min increase; 1.2 to 1.5) and deep hypothermic circulatory arrest (1.3 per 15 min increase; 1.1 to 1.5) increased the risk.
Table 2B  Logistic regression analyses for actuarial survival with Norwood circulation

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Actuarial survival</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable LR</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Gender (female v male)</td>
<td>p&lt;0.01</td>
<td>1.7 (1.2 to 2.4; p&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Size of main pulmonary artery</td>
<td>p=0.05</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Height at operation (per quartile increase)</td>
<td>p&lt;0.05</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Weight at operation (per 250g increase)</td>
<td>p&lt;0.01</td>
<td>0.9 (0.8 to 0.9; p=0.001)</td>
<td></td>
</tr>
<tr>
<td>Body surface area at operation (per dm² increase)</td>
<td>p&lt;0.005</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pulmonary blood flow (RV-PA conduit v RMBTS)</td>
<td>p&lt;0.05</td>
<td>0.3 (0.2 to 0.6; p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Surgeon</td>
<td>p&lt;0.05</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Year of operation</td>
<td>p&lt;0.005</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Duration CPB (per 15 minute increase)</td>
<td>p&lt;0.001</td>
<td>1.4 (1.2 to 1.5; p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Duration DHCA (per 15 minute increase)</td>
<td>p&lt;0.001</td>
<td>1.3 (1.1 to 1.5; p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Duration of cardiopulmonary support (per 15 minute increase)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

On univariable analysis, female gender was the only factor that adversely influenced actuarial inter-stage survival following the Norwood procedure (LR 3.5; 95% CI 1.7 to 7.0; p<0.001).

Early mortality and actuarial survival following stage II and III

Early mortality following Stage II was 3.9% (n=8). Between May 1993 and October 1996, the running estimate (95% CI) of early mortality increased from 0% (0% to 79%) to 10% (5% to 22%). It subsequently declined to 4% (2% to 8%) at the end of the study (figure 4). There were 13 late deaths prior to Stage III at a median interval of 18 months following the BDG (range 51 days to 3.6 years). Four patients (2.0%) required takedown of the BDG and restoration of the Norwood circulation; all subsequently died. Two patients underwent orthotopic heart transplantation 2.2 and 2.9 years following Stage II. The actuarial survival (SEM) with a BDG was 90% (2%) at 1 year, 85% (3%) at 3 years and 83% (3%) at 5 years following Stage II (figure 3B).

Univariable analysis identified a progressive improvement in early mortality over the study period (p<0.01). No factors were associated with survival following Stage II on univariable analysis.

There was one early death following Stage III and one further patient required acute takedown of the Fontan circulation and reformation of the BDG. There were 3 late deaths at 69 days, 9.4 months and 1.4 years following Stage III. The actuarial survival (SEM) with a Fontan circulation was 96% (2%) at 1 year and 94% (3%) at 3, 5 and 7 years following Stage III (figure 3C). Univariable analysis did not identify any factors independently associated with survival following Stage III.
Discussion

The management of HLHS continues to present one of the greatest challenges in congenital heart surgery. The optimal surgical management for these patients remains controversial. Alternative strategies, such as neonatal orthotopic heart transplantation, have been advocated. However, staged surgical palliation has gained increasing acceptance as the primary treatment option for these patients. Nevertheless, the Norwood procedure for HLHS is associated with an operative mortality that is substantially higher than that associated with other congenital cardiac defects requiring neonatal repair. Furthermore, the long-term outcome following staged surgical palliation has not been clearly defined.

This study has reported a series of 333 patients following staged surgical palliation for HLHS. This represents our entire, unselected experience with the surgical management of HLHS, since its inception in December 1992. Five and 10-year survival following Norwood procedure were 50%. These figures are consistent with previous reports in which the five-year survival ranged between 40 - 59%.

We have demonstrated a marked improvement in outcome following the Norwood procedure over the study period. Many authors have reported a similar improvement in outcome over time. Several reasons have been postulated to explain this ‘era effect’, including increasing antenatal diagnosis, improved perioperative medical management and modifications in surgical technique. In our experience, the improvements in early mortality were primarily attributable to modifications in surgical technique. Aortic arch reconstruction with a pulmonary homograft patch and, more recently, the use of an RV-PA conduit were independently associated with an improvement in early mortality.

Reconstruction of the aortic arch represents one of the central tenets of the Norwood procedure. It relieves the systemic outflow tract obstruction and establishes unobstructed systemic and coronary blood flow from the right ventricle. In 1986, Jonas et al. described a modified Norwood procedure, in which the aortic arch was reconstructed using a pulmonary homograft patch. The patch extended from the ascending aorta at the level at which the main pulmonary artery was transected, throughout the arch concavity into the descending thoracic aorta distal to the duct insertion. This technique has been adopted as the standard method of arch reconstruction for HLHS.

In 1995, we described an alternative technique for arch reconstruction that did not use any patch material. By using only native tissue, this technique avoided potential risks associated with a pulmonary homograft patch, such as failure of normal arch development, patch degeneration and the risk of rupture or false aneurysm formation following balloon dilatation of any residual coarctation. In a subsequent series of 120 neonates with HLHS, we reported that arch reconstruction without additional material was possible in 85% of cases. However, in the remaining 15%, arch reconstruction was supplemented with a pulmonary homograft patch in order to avoid excessive tension on the arch or its branch arteries or prevent arch distortion. Furthermore, this technique did not address the problem of a diminutive ascending aorta.

We have since adopted a more reproducible method of arch reconstruction with a pulmonary homograft patch, which could be applied to all patients irrespective of arch morphology. This technique preserves the continuity of the aortic arch and may prevent arch distortion. In addition, it has enabled more aggressive augmentation of the ascending aorta. The pulmonary homograft patch is extended proximally into the aortic root and below the level of the transected end of the main pulmonary artery, as reported by Jonas et al. Consequently, this technique may improve coronary perfusion in patients who are otherwise at risk of myocardial ischaemia. In the present study, multivariable analysis demonstrated arch reconstruction with a pulmonary homograft patch reduced early mortality by half. A similar advantage was not apparent when actuarial survival was analysed.

During the Norwood procedure, pulmonary blood flow is usually established using a RMBTS, although central shunts have also been described. Increasing experience with the Norwood procedure has resulted in the use of smaller shunts, which optimise the systemic to pulmonary blood flow ratio at ≤1, therefore preventing excessive pulmonary blood flow. In general, we used a 3.5 mm shunt in patients who weighed ≥2.5 kg and a 3 mm shunt in patients who weighed <2.5 kg. Nevertheless,
maldistribution of the cardiac output was implicated as a major cause of early death in our own experience.[23]

The RV-PA conduit was initially described as the source of pulmonary blood flow by Norwood et al. [32] and subsequently developed by Kishimoto et al.[34] and Sano et al.[7] The principle advantage of the RV-PA conduit is that it abolishes the diastolic ‘runoff’ from the systemic to the pulmonary circulation, which characterises the RMBTS. This raises diastolic pressure and increases coronary perfusion pressure.[7] Abolishing diastolic ‘runoff’ may also ensure a more stable balance between the systemic and pulmonary circulations, such that systemic and coronary blood flow are less influenced by fluctuations in pulmonary vascular resistance.[8]

A number of authors have reported improved early post-operative haemodynamics associated with the RV-PA conduit compared with the RMBTS.[7, 8, 10] Hughes et al. reported the RV-PA conduit was associated with better early post-operative right ventricular function.[11] Pizarro et al. also suggested that the RV-PA conduit might have a beneficial impact on early and midterm outcome following the Norwood procedure.[10, 35] In the present study, multivariable analysis demonstrated that the modified Norwood procedure with an RV-PA conduit was associated with a substantial improvement in early mortality and actuarial survival.

Several other factors have been identified as risk factors for mortality following the Norwood procedure, including prematurity;[12, 13, 20] anatomical subtype;[20, 23, 36] additional cardiac defects, associated extra-cardiac defects or chromosomal abnormalities;[14] and lower weight at operation.[21] In the present study, lower weight at operation was identified as an independent risk factor for early mortality and actuarial survival following the Norwood procedure. This finding is consistent with previous reports.[12, 13] Nevertheless, the outlook for these patients appears to have improved somewhat[13] and the introduction of the RV-PA conduit may further improve the outcome for these high-risk patients.[7]

This study also identified longer CPB and DHCA times as independent risk factors for early mortality and actuarial survival following the Norwood procedure, in keeping with previous reports.[13, 37] This probably reflects the increased risk associated with longer and more complex procedures. We also identified female gender as an independent risk factor for actuarial survival, although the importance of this finding is unclear.

Despite improvements in early outcome following the Norwood procedure, there is a continued attrition prior to Stage II. In the current study, the actuarial inter-stage mortality was 15% at 6 months following the Norwood procedure. This is consistent with previous reports in which inter-stage mortality has ranged between 9 – 16%.[6, 12, 13, 15] The cause of inter-stage mortality has not been fully elucidated and a substantial proportion remains sudden and unexpected.[38] Nevertheless, Ghanayem et al. reported complete inter-stage survival following the introduction of a ‘home surveillance program’ that enabled at-risk patients to be identified and treated aggressively.[39]

Early outcome following subsequent stages of surgical palliation has improved over time.[17] The introduction of the superior cavo-pulmonary anastomosis as an intermediate operation (Stage II) has been associated with improved overall survival for patients with HLHS.[17] This study has identified that the BDG is associated with a low operative mortality in this high-risk population. Nevertheless, we identified a continued attrition of patients between Stage II and Stage III. The actuarial inter-stage mortality was 9% at 3 years following Stage II, which is higher than previously reported.[17, 40] The reason for this increased risk is not clear, but may be a consequence of differences in the timing of Stage III. Most North American units complete the Fontan circulation by two years of age. In contrast, we perform the modified Fontan procedure when patients develop progressive cyanosis or exertional dyspnoea, which is generally when they are four to five years of age.[19] There is currently no data to confirm the optimal timing for Stage III.

The early mortality following the modified Fontan procedure in the current era ranges between 2 – 7%. [18, 19] This study has shown that comparable results can be achieved in patients with HLHS. This group has traditionally been regarded as high-risk for the Fontan procedure, primarily because the morphologic right ventricle must support the Fontan circulation.[18] However, this study corroborates
more recent reports, which demonstrated equivalent survival following the modified Fontan procedure in patients with a single functional ventricle of left or right ventricular morphology.[19]

**Study limitations**

The retrospective design of this study precluded the assessment of risk factors not entered in the model. Complete data on known risk factors for mortality, such as antenatal diagnosis and primary cardiac anatomy, were not available for many patients and were not included in the analysis. We also identified a high level of correlation between some of the variables, which may have confounded the multivariable analysis and prevented us from identifying independent associations between variables and the outcome measures. Finally, the duration of follow-up is limited.

**Conclusion**

This study has reported the 12-year survival for patients undergoing staged palliation for HLHS. This study has demonstrated a marked improvement in survival for these patients, which was primarily attributable to changes in surgical technique. The introduction of the RV-PA conduit to supply pulmonary blood flow, in particular, was associated with a marked improvement in survival following the Norwood procedure. It remains to be seen whether these encouraging results are reflected in improved longer-term outcome for these patients.
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Competing Interests

None declared

Figure Legends

FIGURE 1
Actuarial survival following staged surgical management of hypoplastic left heart syndrome

FIGURE 2
Serial estimates of early mortality with 95% CI. A, Running estimate; B, EWMA with 5% down-weighting per case.

FIGURE 3
Actuarial survival following the three stages of surgical management. A, With Norwood circulation; B, With BDG; C, With Fontan circulation.

FIGURE 4
Running estimate of early mortality with 95% CI
References


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Staged surgical management of hypoplastic left heart syndrome: a single-institution 12-year experience

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