Factors influencing early outcome of Norwood procedure for hypoplastic left heart syndrome

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Abstract

Objective: The operative outcome of the Norwood procedure for hypoplastic left heart syndrome is still not satisfactory. Conflicting reports concern factors associated with early Norwood procedure mortality and the reasons for the instability after surgery are not sufficiently understood. The purpose of this study was to determine some perioperative factors influencing early (30 days) outcome.

Methods: We retrospectively analyzed a group of 30 consecutive children with hypoplastic left heart syndrome (aged 5±39 days) who underwent Norwood procedure in 1997 and 1998. The following factors were considered and statistically analyzed: operative age, birth weight, operative weight, serum level of bilirubin, aminotransferases, creatinine, urea, arterial blood gasses, anatomic subgroups, ascending aorta and arch size, systemic to pulmonary modified right Blalock±Taussig shunt size, cardiopulmonary circulatory arrest time, cardiopulmonary bypass time, and delayed chest closure. Eighteen patients underwent hemi-Fontan procedure with one late death and the modified Fontan operation was performed in 16 of them (one late death).

Results: The early mortality was 37%. Seven deaths (64%) occurred during the first 24 h after operation. There was a significant difference between survivals and non-survivals in: birth weight ($P = 0.047$), operative age ($P = 0.016$), preoperative serum level of bilirubin ($P = 0.044$), and cardiopulmonary circulatory arrest time ($P = 0.006$). The other assessed factors were not found to be predictors of early mortality. All 16 survivals followed up are in New York Heart Association class I or II.

Conclusions: Anatomic and functional status of the patient, as well as procedural factors are related to Norwood operation early mortality. High mortality in hypoplastic left heart syndrome after stage I surgery indicates the necessity of assessing all factors which may determine further improvement in the outcome. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Cardiac surgery; Hypoplastic left heart syndrome; Norwood procedure; Single ventricle; Fontan operation

1. Introduction

The hypoplastic left heart syndrome (HLHS) comprises about 2% of congenital heart defects and is the most frequent cause of cardiac death in the first week of life [1]. There have been major advances in the surgical management of the defect in the form of staged palliative surgery or transplantation [2]. Palliative surgery of the hypoplastic left heart syndrome, whereby both pulmonary and systemic circulation are restored, was first described by Norwood in 1983 [3,4]. Careful ventilatory and pharmacological modulation of the ratio of pulmonary to systemic vascular resistance is a crucial part of the perioperative management. The purpose of this study is to present of our experience in consecutive 30 newborns with HLHS who underwent the Norwood operation in 1997 and 1998. Some demographic, diagnostic, and procedure-related parameters were evaluated retrospectively in these patients and we analyzed the effect of these factors on the course of the disease immediately after the operation. We also presented mid-term results after stage II (hemi-Fontan) and stage III (modified Fontan) procedures.

2. Materials and methods

2.1. Stage I palliation

From January 1997 to January 1999 30 consecutive patients underwent stage first palliation for HLHS at our Department. After the diagnosis all patients underwent the Norwood procedure using pulmonary homograft augmentation of the aortic arch.

Each patient had a detailed examination with anteroposterior (A-P) chest X-rays, electrocardiography and two dimensional and color flow Doppler transthoracic
echocardiography for non-invasive evaluation of the cardiac anatomy according to the standard criteria before surgery. Potential surgical risk factors in the perioperative period were evaluated. These included: operative age, birth weight, sex, operative weight, serum level of bilirubin, aspartate aminotransferase (AspAT), alanine aminotransferase (AlAT), creatinine, urea, pH, partial arterial oxygen tension (pO2), partial arterial carbon dioxide tension (pCO2), base excess (BE), bicarbonate concentration (HCO3), arterial oxygen saturation, anatomic subgroups, ascending aorta and arch size, delayed chest closure, systemic to pulmonary modified right Blalock–Taussig shunt size, cardiopulmonary circulatory arrest time (CCAT) and cardio-pulmonary bypass time (CBT) (Tables 1 and 2). Hepatic injury was defined by serum aspartate aminotransferase exceeding 120 U/l and alanine aminotransferase exceeding 40 U/l, while renal injury was defined by serum creatinine exceeding 88 μmol/l.

All the patients were stabilized before operation by intravenous infusion of prostaglandin (PGE1) (0.01–0.1 μg/kg per min), evaluation and correction of pH and blood gasses to maintain the acid-base and fluid-electrolyte balance, inotropes and ventilation as required.

All 30 patients underwent the Norwood procedure. The surgical technique remained constant over the time of analysis. Cardiopulmonary bypass was established by cannulation of the proximal main pulmonary artery and right atrium. The branch right and left pulmonary arteries were occluded and systemic cooling was begun. After bypass has been established, the arch of the aorta was mobilized. The circulation was arrested at a rectal temperature of 20°C and

### Table 1

Differences between early (30 days) survivals and non-survivals in continuous variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-survivals</th>
<th>Survivals</th>
<th>P value</th>
<th>Mann–Whitney’s test</th>
<th>Multiple logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>16.7</td>
<td>12.9</td>
<td>0.016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2957.7</td>
<td>3409.4</td>
<td>0.047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative weight (g)</td>
<td>3263.3</td>
<td>3452.4</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascendent aortic size (mm)</td>
<td>3.4</td>
<td>3.8</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic arch size (mm)</td>
<td>3.7</td>
<td>4.6</td>
<td>0.077</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCAT (min)</td>
<td>59.4</td>
<td>52.4</td>
<td>0.006</td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td>CBT (min)</td>
<td>76.3</td>
<td>64.6</td>
<td>0.076</td>
<td>0.056</td>
<td></td>
</tr>
<tr>
<td>Mean pO2 (mmHg)</td>
<td>38.4</td>
<td>38.2</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial saturation (%)</td>
<td>70.8</td>
<td>68.6</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39</td>
<td>7.38</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean pCO2 (mmHg)</td>
<td>39.7</td>
<td>39.3</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>-1.4</td>
<td>-1.4</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>7.5</td>
<td>6.8</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>92.2</td>
<td>85.3</td>
<td>0.80</td>
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<tr>
<td>Bilirubin (μmol/l)</td>
<td>180.2</td>
<td>113.3</td>
<td>0.044</td>
<td></td>
<td></td>
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<tr>
<td>AspAT (U/l)</td>
<td>374.0</td>
<td>280.0</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AlAT (U/l)</td>
<td>139.0</td>
<td>178.0</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HCO3 (mmol/l)</td>
<td>20.2</td>
<td>17.9</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CCAT, cardiopulmonary circulatory arrest time; CBT, cardio-pulmonary bypass time; pO2, arterial oxygen partial tension; pCO2, arterial carbon dioxide partial tension; HCO3, bicarbonate concentration.

### Table 2

Differences between early (30 days) survivals and non-survivals in categorical variables (one-dimensional analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>P-value Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Shunt</td>
<td>3.5 mm</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>4.0 mm</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>Closed</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td></td>
</tr>
<tr>
<td>AspAT</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>AlAT</td>
<td>Normal</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>Normal</td>
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<tr>
<td></td>
<td>Increased</td>
<td>0.60</td>
</tr>
<tr>
<td>pH</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>1.00</td>
</tr>
<tr>
<td>pCO2</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>0.45</td>
</tr>
<tr>
<td>HCO3</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Base excess</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Hepatic injury</td>
<td>Yes</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

* AspAT, aspartate aminotransferase; AlAT, alanine aminotransferase; pCO2, arterial carbon dioxide partial tension; HCO3, bicarbonate concentration.
the branch vessels of the aortic arch were occluded. The standard procedure involved transecting the pulmonary artery proximal to the bifurcation and closing the distal pulmonary artery using a small patch of homograft. The ductus arteriosus was ligated and the ascending, transverse and descending aorta were reconstructed with pulmonary artery homograft augmentation. The proximal pulmonary artery was then anastomosed to the ascending aorta. The primum atrial septum was excised, creating a large interatrial communication. A systemic to pulmonary modified right Blalock–Taussig shunt from the innominate artery to the right pulmonary artery using a polytetrafluoroethylene (PTFE) tube (3.5–4 mm) was created to supply the pulmonary blood flow. After bypass discontinuation, a right atrial monitoring catheter was placed to measure the central venous pressure.

After stage I patients were initially managed with dopamine and sodium nitroprusside as required. Sodium nitroprusside was used when needed to lower vascular resistance (1–4 μg/kg per min.) and dopamine to improve ventricular function (2–5 μg/kg per min). Mechanical ventilation was performed using volume regulated neonatal ventilators in as low an inspired oxygen concentration as possible to maintain an adequate arterial tension of oxygen (pO₂ = 25–45 mmHg) and haemodynamic parameters.

2.2. Stage II and III procedures

Eighteen of thirty patients underwent establishment of hemi-Fontan circulation. During cardiopulmonary bypass and hypothermic circulatory arrest the superior vena cava (SVC) was anastomosed side to side to the confluence of the pulmonary artery with Homograft augmentation. The polytetrafluoroethylene patch was used to close the junction of the atrium with the SVC. The systemic to pulmonary shunt was ligated.

The modified Fontan operation was carried out in 16 out of 18 children. During the cardiopulmonary bypass and circulatory arrest the blood from the inferior vena cava was directed to the superior vena cava-pulmonary artery anastomosis, using lateral tunnel technique with a fenestrated (3–4 mm) polytetrafluoroethylene baffle.

The medical histories of patients, preoperative laboratory data, echocardiographic results, operative, anesthesiological and perfusion reports and ICU histories for all patients were retrospectively reviewed. Early mortality was defined as mortality within 30 days. Follow up was complete for all patients. Survival curve for overall mortality was estimated using the Kaplan–Meier method. Statistical analysis for early mortality was performed using: descriptive statistics, Mann–Whitney’s test, and Fisher’s exact test. The multidimensional analysis was performed by estimating the multiple logistic regression model using stepwise procedure. All data were accepted as statistically significant when P-values were smaller than significance level 0.05.

3. Results

3.1. Stage I palliation

There were nine girls aged from 5 to 39 days (mean 13.5 days), weighing from 1280 to 3870 g (mean 3153.6 g) and 21 boys aged from 5 to 35 days (mean 14.8 days), weighing from 1700 to 4270 g (mean 3435.4 g). The majority (27) were term infants (more than 37 weeks of gestational age), only three infants had congenital heart disease detected in utero, and 15 had mothers with poor obstetric histories. Seven out of 11 early deaths (64%) occurred within 24 h after surgery. Four others died 31, 42, 47, and 59 h after the operation. All 11 deaths (37%) were associated with decreased ventricular function and low cardiac output. One late death occurred 3 months after the Norwood procedure (because of sepsis and multiorgan dysfunction).

The mean age at operation was 14.3 days; in survivors 12.9 days, and 16.7 days in infants who subsequently died. The average birth weight was 3409.4 g among survivors vs. 2957.7 g among those who died. There was a significant difference in operative age (P = 0.016, univariate analysis) and birth weight (P = 0.047, univariate analysis; P = 0.038, multidimensional analysis) between survivals and non-survivals (Table 1). There was no significant difference in the body weight at the operation (P = 0.32).

There was no significant difference in the mean preoperative pH, bicarbonate concentration, mean arterial carbon dioxide tension and mean arterial oxygen tension between survivors and non-survivals (Table 1).

Fourteen patients had preoperative renal and fourteen hepatic injury. The only significant difference between survivals and non-survivals was noted in the mean preoperative serum level of bilirubin (113.3 vs. 180.2 μmol/l) (P = 0.044) (Tables 1 and 2). There were no found significant difference between survivals and non-survivals regarding incidence of hepatic or renal injury (Table 2).

Intracardiac anatomy and subsequent early survival of the patients are illustrated in Fig. 1. In echocardiography all...
patients had an interatrial communication and patent arterial duct. There were 16 (53%) patients with aortic stenosis and mitral atresia, eight (27%) infants with aortic and mitral atresia, three (10%) with aortic and mitral stenosis, and three (10%) with aortic atresia and mitral stenosis. The mean diameter of the ascending aorta was 3.64 mm (range from 1.7 to 9.6 mm) and aortic arch 4.5 mm (range from 3 to 7 mm). There was no significant difference in aortic arch and ascending aorta diameter between survivals and non-survivals. Associated cardiac anomalies included ventricular septal defects in three patients, and partial anomalous pulmonary venous return in one infant. Seven infants had restrictive atrial communication; one had double outlet right ventricle, seven had coarctation of the aorta.

Twenty patients had 4 mm shunts, ten patients had 3.5 mm shunts. Five of the seven patients who died within 24 h after surgery had 4 mm shunts; two had a 3.5 mm shunt. The mean circulatory arrest time was 52.4 min (range from 41 to 67 min) in survivals and 59.4 min (range from 50 to 65 min) in non-survivals. There was a statistically significant difference between these two groups (\( P = 0.006 \) (Table 1). In the multi-variate logistic regression \( P \)-value is borderline. If we accept significance level 0.10 instead of the usual 0.05 the affect of CBT and CCAT on early mortality is important. The latter is possible since the number of patients is small and it is relatively ‘difficult’ to reject null hypothesis in such a case.

Because of the myocardial distension and haemodynamic lability, five patients had delayed sternal closure (the sternal wound was closed using a PTFE patch). Two children died within 24 h after operation and the others had a successful closure within 3 days. Sodium nitroprusside was used in 15 (50%) children for 1–5 days (mean 2.3 days) and dopamine in 23 (77%) children for 1–9 days (mean 3.6 days).

The mean duration of postoperative mechanical ventilation was 121.5 h with a range of 16–1008 h. The mean duration of stay in the intensive care unit for survivals was 40.9 days with a range of 5–285 days.

### 3.2. Stage II and III procedures

Four infants underwent cardiac interventions between the first and second stages (balloon dilatation of a recurrent aortic coarctation). Eighteen children underwent hemi-Fontan procedure at an average age of 7.3 months (range from 6 to 10 months) with one late death (sudden death at home from an unknown cause). The mean age of 16 children in whom modified Fontan procedure was carried out was 18.3 months (range 13–22 months). One patient died 12 months after this operation with severe right ventricular dysfunction. One child is currently awaiting the Fontan procedure. All 15 stage III Fontan survivals are followed up and are doing well. Thirteen of them are at present in New York Heart Association (NYHA) functional class I. Two of them are in NYHA class II.

As shown in Fig. 2, survival for the entire group of 30 patients of the whole study period, including hospital deaths and subsequent operative procedures (hemi-Fontan and modified Fontan), was 63 % at 1 month, 60% at 1 year and 53% at 3 years.

### 4. Discussion

The hypoplastic left heart syndrome is the fourth most common congenital cardiac defect diagnosed in the first year of life [5]. Without treatment, HLHS is fatal and more than 95% of children die in the first month of life [6]. In the past two decades the outlook for these children has improved and nowadays there are two surgical options available: cardiac transplantation [7], and staged reconstructive palliation [3,4,8]. Despite the progress in treatment and understanding of the anatomy and physiology of HLHS, the outcome in this anomaly is still not satisfactory and high mortality after the procedure is still a challenge for surgeons and intensive care unit staff.

Cardiac transplantation – the alternative way of treatment for HLHS – is restricted by the limited availability of suitable donor hearts and by adverse side-effects of long-term immunosuppression [9–11]. The post-operative course after the Norwood procedure is characterized by haemodynamic instability. Early death is associated with alternation in the pulmonary-to-systemic flow ratio and low cardiac output, but understanding of the reasons of the high post-procedural mortality is still incomplete. Many risk factors for early mortality after the Norwood procedure have been reported as significant, but controversy still exists.

In our study the early postoperative mortality was 37%, which is similar to the recently reported data [6,12–15]. We have observed a higher mortality in children with lower birth weight. There was however no significant difference in the body weight at the operation between our 30-day survivals and non-survivals (Table 1). Although some
studies have shown that poor preoperative conditions, e.g. lower preoperative pH [16] and renal or hepatic injury [17], are risk factors for operative mortality, in our study operative survival was not found to be associated with preoperative organ damage. Only the preoperative serum level of bilirubin was significantly higher in non-survivals than in survivals ($P = 0.04$), and neither the preoperative serum level of aminotransferases (aspartate and alanine aminotransferase) nor the serum levels of urea and creatinine were not found to be predictors of early mortality (Tables 1 and 2). Some referred authors [12,18] maintain that infants with severe organ disease can still be candidates for surgical intervention, if renal or hepatic dysfunction is at least partially normalized. Furthermore, in patients in whom surgery was delayed to allow for resolution of renal or hepatic insufficiency, better outcome than in children operated without renal or hepatic injury have been observed [14].

This observation may be associated with age at operation (maturity of the child), but there is no consensus of opinion that this factor can affect short-term survival. [9,12,14,18]. In our study, survivals were significantly younger than non-survivals ($P = 0.016$). Although these data could have important implications for the timing of the surgical intervention, above all for those centers which perform the Norwood procedure only when a suitable donor heart is not available, controversy concerning the age at operation is widespread [12,14,18].

The previous analysis found longer cardiopulmonary bypass time (CBT) and circulatory arrest time (CCAT) to be significant risk factors for hospital mortality [9,18]. Some authors [9] have observed a decreasing need for inotropic drugs in the group with shorter circulatory arrest time. The shorter time of ischemia in children who survive is probably the main reason of the improved right ventricular function, but many investigators suggest that the extended CBT may be the consequence of a poor haemodynamic situation during the initial weaning from bypass, and therefore associated with higher mortality [18].

The controversy over the affect of anatomic subtype on survival still persists. In our study neither the anatomic subgroup nor the ascending aorta and aortic arch diameter were not found to be associated with an increased risk of death (Table 1). This is similar to the reports by Iannettoni et al. [12], as well as Kern et al. [18], who found that anatomic subtype was not predictive of survival. In contrast, Forbess et al. [16], in the analysis of their 10 years’ experience, have revealed improved operative survival rates in patients with mitral stenosis and aortic stenosis. A smaller ascending aorta diameter triggers technical difficulties, but does not change the haemodynamic conditions after the operation. These data suggest that the anatomic subtype and aortic size are not contraindications for this surgical approach.

The staged strategy allows for the survival of newborns with HLHS and gives them a chance for a satisfactory development and quality of life. The highest mortality is observed in post-stage I patients, but these children make good candidates for the hemi-Fontan and Fontan procedures, and the results are quite good.

References