Original research article

Long-term results of children operated for hypoplastic left heart syndrome in Children's Heart Centre

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A R T I C L E   I N F O

Article history:
Received 31 March 2014
Received in revised form 28 July 2014
Accepted 31 July 2014
Available online 28 August 2014

KEYWORDS
Hypoplastic left heart syndrome
Staged palliation
Children
Long-term follow up

A B S T R A C T

Introduction: Hypoplastic left heart syndrome (HLHS), one of the most serious congenital heart defects, can be surgically paliated using 3 subsequent stages. Long-term results of this approach are reviewed in this study.

Methods: Fifty-two consecutive patients (pts.) operated for HLHS from 1999 to 2012 were evaluated retrospectively.

Results: Norwood stage I operation was performed at the median age of 6.5 days with a total mortality of 19%. Significant risk factor for death was lower weight at surgery (Cox proportional risk per 1 g increase 0.997, CI 0.995–0.999, P < 0.001). Between stages I and II, 15 catheter/surgical reintervention had to be carried out in 13 pts. (aortic arch narrowing in 10/13). Forty-two pts. underwent stage II operation at the median age of 6.8 months with a total mortality of 4.8% and 18 subsequent reinterventions in 13 patients. Finally, 26 patients aged median 3.9 years underwent stage III operation (total cavopulmonary connection) with a total mortality of 8%. The probability of survival at 1/5/10 years of age was 77/77/71%. At long-term follow up (median 7.8 years) 37 of the 38 surviving patients are in NYHA functional class I or II.

Conclusions: Despite a highly centralized care, surgical treatment of HLHS is still associated with a significant mortality and morbidity. Long-term survivals, however, have an acceptable functional status during childhood corresponding to other groups of patients after surgical palliation for functionally single ventricle.

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http://dx.doi.org/10.1016/j.crvasa.2014.07.006
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Introduction

Hypoplastic left heart syndrome (HLHS) represents one of the most serious complex congenital heart defects (CHD), 100% fatal in its natural course. The only therapeutic option for these children is a staged surgical palliation or heart transplantation. If surgery is contraindicated, or parents refuse surgical treatment, comfort care is offered with inevitable death. Before establishing the nationwide prenatal detection program of CHD in the Czech republic the prevalence of HLHS was 0.21/1000 live births (3.42% of all the CHD). Male gender prevails [1].

Anatomy of the HLHS refers to abnormal development of the left ventricle, aortic and mitral valves in various combinations from atresia to stenosis and aortic arch hypoplasia (Fig. 1). Associated cardiac defects have been reported, such as bicuspid pulmonary valve, cleft of the tricuspid valve, dysplasia of the tricuspid or pulmonary valves, less frequently, total or partial anomalous pulmonary venous return, atresia of the coronary sinus and interruption of the aortic arch [2,3]. Postnatal survival of newborns with HLHS depends on open fetal shunts – foramen ovale and ductus arteriosus.

The first successful surgical treatment of children with HLHS was reported by Norwood et al. in 1980 [4,5]. Since then, development of surgical techniques, cardiopulmonary bypass, and postoperative care improved survival [6,7]. A number of studies have been carried out to analyze the risk factors affecting surgical result [8]. Current surgical strategy comprises of 3 stages. Neonates undergo stage I (Norwood) operation, connecting the right ventricle to both the systemic and pulmonary circulations. Neo-aorta is constructed using the pulmonary trunc and pulmonary flow is established by a vascular prosthesis [9,10]. Stage II operation, bi-directional cavopulmonary anastomosis (BCPA), is performed usually by 4 months of age. In this stage, superior vena cava is anastomosed to the right pulmonary artery and the vascular prosthesis is taken down. The procedure reduces volume load to the systemic right ventricle. The final stage III, total cavopulmonary connection (TCPC) is completed by connecting the inferior vena cava to the right pulmonary artery with use of a Gore-tex tunnel. The systemic and pulmonary circulation work in series, with the right ventricle as the only single driving force. This stage is usually performed around the age of 2–4 years and a weight over 10 kg. In patients with lower capacity of the pulmonary vascular bed or elevated end-diastolic pressure in the right ventricle, a fenestration between the systemic venous tunnel and the pulmonary venous atrium is created. An obligatory right-to-left shunt through the fenestration maintains satisfactory cardiac output at the expense of a slight systemic desaturation. The staged palliative correction is only feasible if normal resistance and capacity of the pulmonary vascular bed have been proved.

Due to the progress of the ultrasound diagnostics and teaching programs for gynecologists, prenatal detection of the HLHS at the early stages of pregnancy have exceeded 90% in his country [11]. Number of fetuses diagnosed with HLHS and the number of patients operated at our institution is shown in Fig. 2. At our center, the program of surgical care for patients with HLHS was established in 1999. Retrospective analysis of the results is subject of this paper.

Patients and methods

Since the beginning of the program, we employed semi-selective operability criteria (Table 1), to eliminate unfavorable effects of specific anatomic and functional findings on the result of staged palliative surgery [8]. Fifty-two pts. (44 boys, 8 girls) out of a total of 65 newborns admitted with diagnosis of HLHS underwent stage I palliation from January 1999 to the end of 2012. Stage I surgery was performed at the age of 3–17 (median 6.5) days in patients weighing from 2.4 to 4.3 (median 3.2) kg. Delayed sternal closure was used routinely to prevent low cardiac output caused by tissue edema and cardiac pseudo-tamponade. Only 17/52 (33%) newborns were diagnosed prenatally reflecting the fact, that most prenatally

Fig. 1 – Echocardiography of hypoplastic left heart syndrome. Apical four chamber view, (RA – right atrium, LA – left atrium, RV – right ventricle, LV – left ventricle) (with permission of [2]).

Fig. 2 – Number of fetuses diagnosed with HLHS to number of newborns operated for HLHS.
detected fetuses with HLHS undergo pregnancy termination in our country. Anatomic subtypes of HLHS included combination of aortic atresia with mitral stenosis in 25 newborns, aortic stenosis with mitral stenosis in 20 and aortic and mitral atresia in 7 newborns. Thirty-eight spontaneously breathing neonates with a balanced pulmonary and systemic flows required standard care and only prostaglandin infusion before surgery. Fourteen neonates required intensive care due to unstable hemodynamics, with symptoms of low cardiac output and organ hypoperfusion or pulmonary congestion. These patients were treated with inotropic support, correction of metabolic acidosis and/or demand mechanical ventilation on the top of the prostaglandin infusion. All unstable patients requiring intensive care were born at regional hospitals and passed through a period of an acute heart failure and significant desaturation. Balloon atrioseptostomy was required in 2 newborns with a restrictive inter-atrial communication.

Besides the patients operated in this period, additional 13 newborns were diagnosed with HLHS, of which in 6 newborns parents refused operation, and 7 had associated cardiac defects that contraindicated the surgery or did not meet the semiselective criteria of operability.

For the retrospective analysis we reviewed the medical database of the Children’s Heart Centre, including demographic data, surgery and cardiopulmonary by-pass reports, records from hospitalization, postoperative course, and outpatient clinic reports. Non-obligatory surgical or catheter re-interventions were defined as those that were not part of the 3-stage surgical palliation of HLHS.

### Statistical analysis

The statistical analysis was performed using the SigmaStat 3.5 (SPSS Inc.) software. Actuarial survival was determined by the Kaplan–Meier estimate and proportional hazard was calculated using the univariate Cox analysis. P values <0.05 were considered significant.

### Results

#### Stage I operation

Modified Norwood operation was performed in 52 newborns using a reconstruction of heart outflow via the pulmonary artery root anastomosis to ascending aorta and with augmentation of the aortic arch with pulmonary artery homograft in 45 patients (Fig. 3). Seven patients, with sufficient dimension of the ascending aorta, were operated using the Damus–Kaye–Stansel procedure (direct anastomosis of the main pulmonary artery to the ascending aorta). Pulmonary blood flow was established by a modified Blalock–Taussig (BT) anastomosis in 28 patients and the Sano shunt, right ventricle-to-pulmonary artery conduit, in 24 patients. Associated procedures were tricuspid valve repair in 2 patients and re-creation of BT shunt because of its inadequacy in 2 patients. Overall mortality after the stage I palliation was 19% (10/52 pts). Hospital mortality was 13.5% (7/52 pts). Three of 5 patients who died early failed the cardiopulmonary by-pass weaning (2 of them despite of a prolonged mechanical circulatory support using the same circuit). Two further patients died early after surgery, 1 from myocardial ischemia and right ventricular dysfunction without a chance of surgical re-intervention and 1 from malignant arrhythmia (junctional ectopic tachycardia) refractory to antiarrhythmic therapy. Most of the patients had complicated postoperative course (Table 3). During hospitalization, there were 2 late post-operative deaths for mediastinitis, sepsis and persistent chylothorax, metabolic deterioration with adrenocortical insufficiency. Between stage I and II palliation, 2 patients died from an impaired function of the systemic right ventricle and 1 patient died suddenly at home.

Lower weight at surgery was the only significant risk factor identified for the stage I palliation. The risk of death decreased by 0.3% (0.1–0.5%) per 1 g of body weight (Table 2). Fetal diagnosis of HLHS did not lead to a statistically significant decrease of mortality, 17 newborns/3 deaths (18%) compared to 35 newborns/7 deaths (20%).

Between stage I and II palliation, 13 patients underwent a total of 15 surgical and catheter re-interventions for significant residual findings. The most frequent re-intervention was balloon angioplasty for significant narrowing of the aortic arch in 10 patients at median age of 4.5 months (45 days–13.6 months) after stage I operation. Four patients required another BT shunt for hypoxemia or small size of pulmonary artery size at 2.9–13.7 (median 7) months after stage I operation. One patient required a blade atrial septostomy and subsequent

<table>
<thead>
<tr>
<th>Table 1 - Semi-selective operability criteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta &gt; 2 mm</td>
</tr>
<tr>
<td>Tricuspid valve regurgitation &lt; severe</td>
</tr>
<tr>
<td>No pulmonary vein hypoplasia or total anomalous pulmonary veinous drainage</td>
</tr>
<tr>
<td>No severe liver, renal failure or sepsis – not responsible to therapy</td>
</tr>
<tr>
<td>Absence of significant extracardiac congenital defects or chromosomal anomalies</td>
</tr>
</tbody>
</table>

![Fig. 3 – Norwood operation. Excision of interatrial septum, construction of “neoaorta” using aorta, pulmonary trunk and homograft patch. Pulmonary flow is established by a vascular prosthesis (Gore tex) with permission from archive of prof. T. Tláskal M.D.](image)
surgical septectomy for restrictive inter-atrial communication at 20th day after surgery, and after 4 months, respectively.

**Stage II operation**

Bidirectional cavopulmonary anastomosis (BCPA, Fig. 4) was performed in 42 patients at the age of 2.1–22 (median 6.8) months. Associated surgical procedures were augmentation of the aortic arch in 8 patients, tricuspid regurgitation repair in 6 patients, augmentation or repair of stenotic right pulmonary artery in 5 patients and left pulmonary artery in 2 patients. In 6 cases, we kept the original source of pulmonary flow (BT or Sano shunt). Hospital mortality after the stage II was 4.8% (2/42 pts.). Both patients died early and suffered from heart failure due to severe tricuspid regurgitation already before the surgery. The postoperative course was uncomplicated in surviving patients.

Between stage II and III palliation, 13 patients underwent a total of 18 re-interventions (10 catheter and 8 surgical) for significant residual lesions. The most common procedures were transcatheter occlusion of cavo-caval collaterals in 5 patients. Three patients underwent reoperation for significant tricuspid valve insufficiency – valve replacement in 2 patients and annuloplasty using Carpentier Edwards ring in 1 patient. There were no late inter-stage deaths.

**Stage III operation**

The final surgical palliation, total cavo-pulmonary connection (TCPc), using Gore-tex tube (16–20 mm) as extra-anatomic tunnel, was accomplished in 26 patients aged 2.3–6.3 (median 3.9) years weighing 10.5–22.0 kg (median 14.4) kg. TCPc had to be taken down in 1 patient because of an unacceptably high systemic venous pressure. Fenestration was created in 13 patients (52%). Associated surgical procedures were augmentation or plasty of the pulmonary arteries in 7 patients, and tricuspid valve annuloplasty (1 using annuloplasty ring) in 2 patients. Two patients received a pacemaker: 1 patient for 3rd degree atrio-ventricular block and another patient to resynchronize the right ventricle in the setting of complete right bundle branch block and severe right ventricle dysfunction. In

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**Table 2 – Univariate Cox analysis of risk factors for mortality after stage I.**

<table>
<thead>
<tr>
<th>Considerable risk factors</th>
<th>Proport. hazard</th>
<th>5% CL</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal diagnosis</td>
<td>1.4844</td>
<td>0.3542</td>
<td>6.2199</td>
</tr>
<tr>
<td>Weight at operation (g)</td>
<td>0.9970</td>
<td>0.9951</td>
<td>0.9990</td>
</tr>
<tr>
<td>Age at operation (days)</td>
<td>0.9399</td>
<td>0.7129</td>
<td>1.2391</td>
</tr>
<tr>
<td>Tricuspid insufficiency</td>
<td>2.0959</td>
<td>0.8541</td>
<td>5.1432</td>
</tr>
<tr>
<td>Restrictive inter-atrial communication</td>
<td>0.8668</td>
<td>0.1748</td>
<td>4.2987</td>
</tr>
<tr>
<td>Ascending aorta diameter (mm)</td>
<td>1.0060</td>
<td>0.6653</td>
<td>1.5213</td>
</tr>
<tr>
<td>Right ventricular function</td>
<td>1.4947E-05</td>
<td>1.6473E-295</td>
<td>1.3562E+285</td>
</tr>
<tr>
<td>Pre-operative circulatory instability</td>
<td>1.4376</td>
<td>0.3438</td>
<td>6.0123</td>
</tr>
<tr>
<td>Multiorgan failure before surgery</td>
<td>2.2367</td>
<td>0.5338</td>
<td>9.3723</td>
</tr>
<tr>
<td>Surgeon</td>
<td>0.7611</td>
<td>0.2227</td>
<td>2.6011</td>
</tr>
<tr>
<td>Cardiopulmonary by-pass time (min)</td>
<td>1.0243</td>
<td>0.9966</td>
<td>1.0528</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>1.0111</td>
<td>0.9646</td>
<td>1.0598</td>
</tr>
<tr>
<td>Vascular prosthesis – BT/Sano shunt</td>
<td>0.9231</td>
<td>0.2309</td>
<td>3.6903</td>
</tr>
<tr>
<td>Stage I – type of the operation – Norw/DKS</td>
<td>1.3729E-05</td>
<td>3.9887E-231</td>
<td>4.7254E+220</td>
</tr>
</tbody>
</table>


* P < 0.001.

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**Table 3 – Postoperative course – data.**

<table>
<thead>
<tr>
<th>C.I.C.U stay</th>
<th>Median 9 (5–38) days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropic support</td>
<td>Median 6 (3–23) days</td>
</tr>
<tr>
<td>Artificial ventilation</td>
<td>Median 7 (4–36) days</td>
</tr>
<tr>
<td>Delayed sternal closure</td>
<td>median 4 (1–14) days</td>
</tr>
</tbody>
</table>

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**Fig. 4 – Bidirectional cavopulmonary anastomosis (BCPA). Superior vena cava is anastomosed to the right pulmonary artery and vascular prosthesis is taken down (with permission from archive of prof. T. Tláskal M.D.).**
1 patient, mediastinitis was successfully treated. There were no hospital deaths. Late mortality was 7.7% (2/25 pts.). These 2 patients suffered from right ventricular dysfunction and moderate to severe tricuspid insufficiency. One of them also was treated for exudative enteropathy, and required a reoperation with tricuspid valve annuloplasty and subsequent pacemaker implantation for advanced 2nd degree atrio-ventricular block. The other died on the waiting list for heart transplantation. After the stage III palliation the fenestration was closed by a catheter technique in 5/13 patients and surgically in one patient along with the resection of the atrial septum because of an intra-atrial restriction. In 1 patient a mechanical valve was implanted into the neo-aortic position for a significant insufficiency.

**Long-term follow-up**

Thirty-eight of the 52 patients are currently followed-up for 7.3 months to 14.3 (median 7.8) years. The probability of survival at 1/5/10 years of age was 77%/77%/71% (Fig. 5). The overall mortality of our group was 27% (14/52 pts.). Summary of staged operations, subsequent re-interventions for residual findings and deaths is shown in Fig. 6. Types and numbers of non-obligatory re-interventions are summarized in Table 4. Probability of the freedom from non-obligatory re-interventions is shown in Fig. 7. 37/38 surviving patients (97%) are in New York Heart Association (NYHA) functional class I and II and only 1 patient (3%) is in the NYHA class III. Neurological impairment is observed in 7 patients (18%): 2 patients are currently on an antiepileptic medication, one patient with autistic behavioral findings is attending special school for autistic children. Five patients with dyslexia attend special elementary school for children with learning disabilities.

**Discussion**

The treatment of children with the HLHS has undergone a considerable progress over the years. Refinement of surgical techniques and accumulation of peri-operative care experience have reduced mortality [12]. Application of semi-selective operability criteria helps to maintain mortality at an acceptable level [13].

The most critical period is the stage I operation associated with the highest mortality, as also confirmed by our study. In accordance with other reports [8,14] we also proved low birth weight as a significant risk factor for mortality after the stage I. The early postoperative period is often accompanied by significant cardiopulmonary instability. For this reason, we have been routinely using delayed sternal closure, to prevent low cardiac output caused by tissue edema and cardiac pseudo-tamponade [15].

Introduction of the Sano shunt in our patients did not lead to reduction of total mortality after the stage I surgery. Absence of a mortality benefit has also been reported in the literature [16,17]. Better acute hemodynamic stability and better growth of the pulmonary arteries due to the pulsatile flow have, however, been described with the Sano shunt [16,17].
Prenatal detection of CHD in the Czech Republic is highly successful (estimated >90% for HLHS) [11]. In the majority of early diagnosed HLHS the parents decide to terminate the pregnancy. In the last 12 years, this has been the case in 87% of fetuses with this diagnosis (V. Tomek, unpublished data). Thus predominantly prenatally undiagnosed newborns with HLHS are coming to surgery at our institution, which may be accompanied by increased preoperative morbidity. In case of prenatal diagnosis and a pro-treatment decision, fetuses with HLHS are transported in utero to the University Hospital Motol, Prague, where optimum postpartum care, including a subsequent surgical treatment is provided. Such management is likely to positively affect the pre-operative patients’ condition, prevent ductal closure and decrease morbidity [18]. However, we did not prove a positive impact of the fetal diagnosis on mortality in our series.

Inter-stage catheter or surgical re-interventions for significant residual findings are common in patients with HLHS. Early detection of the residua, along with an effective intervention may ultimately affect the overall mortality. Close follow-up of the patients, especially during the first year of life, was focused on the right ventricle and tricuspid valve function, aortic arch development and pulmonary artery branches growth.

Despite the recent advances in the treatment of children with HLHS, their neuro-developmental outcome remains a major concern. Behavioral and cognitive problems occur more frequently than in other CHD as few studies show [19,20], probably as a consequence of fetal and neonatal pathological hemodynamics and complicated surgical procedures. Major neuro-developmental impairment was found in 26% and minor neurologic dysfunction in 43% of the patients with HLHS. Magnetic resonance imaging revealed cerebral abnormalities, mostly ischemic changes of different degrees, in 82% of the patients [21]. Major neurologic dysfunction was found in 19% of our patients ranging from autism to epilepsy. We also have registered light forms of the attention deficit hyperactivity disorder (ADHD) and learning disorders.

### Conclusions
Staged surgical palliation is the only treatment offering chance for life to children with HLHS. It is, however, still associated with a significant mortality and morbidity. Long-term survivors have an acceptable functional status during childhood comparable to other groups of patients after the surgical palliation for functionally single ventricle.

### Conflict of interest
None declared.

### Funding
The authors were supported by Ministry of Health, Czech Republic – conceptual development of research organization, University Hospital Motol, Prague, Czech Republic 00064203.

### Ethical statement
For this purely retrospective descriptical study not influencing patient management an informed consent has not been obtained in accordance with the institutional ethical guidelines.

### References