Survival After Reconstructive Surgery for Hypoplastic Left Heart Syndrome
A 15-Year Experience From a Single Institution

William T. Mahle, MD; Thomas L. Spray, MD; Gil Wernovsky, MD; J. William Gaynor, MD; Bernard J. Clark III, MD

Background—There are limited data regarding the long-term survival of patients who have undergone reconstructive surgery for hypoplastic left heart syndrome (HLHS). We reviewed the 15-year experience at our institution to examine survival in the context of continued improvements in early operative results.

Methods and Results—Between 1984 and 1999, 840 patients underwent stage I surgery for HLHS. From review of medical records and direct patient contact, survival status was determined. The 1-, 2-, 5-, 10-, and 15-year survival for the entire cohort was 51%, 43%, 40%, 39%, and 39%, respectively. Late death occurred in 14 of the 291 patients discharged to home after the Fontan procedure, although only 1 patient has died beyond 5 years of age. Heart transplantation after stage I reconstruction was performed in 5 patients. Later era of stage I surgery was associated with significantly improved survival ($P<0.001$). Three-year survival for patients undergoing stage I reconstruction from 1995 to 1998 was 66% versus 28% for those patients undergoing surgery from 1984 to 1988. Age >14 days at stage I and weight <2.5 kg at stage I were also associated with higher mortality ($P=0.004$ and $P=0.01$, respectively). Other variables, including anatomic subtype, heterotaxia, and age at subsequent staging procedures, were not associated with survival.

Conclusions—Over the 15-year course of this study, early- and intermediate-term survival for patients with HLHS undergoing staged palliation increased significantly. Late death and the need for cardiac transplantation were uncommon. (Circulation. 2000;102[suppl III]:III-136-III-141.)

Key Words: surgery ■ mortality ■ heart defects, congenital ■ survival

Hypoplastic left heart syndrome (HLHS) is the fourth most common lesion requiring neonatal open heart surgery and is the most common anomaly resulting in death from congenital heart disease within the first year of life.1,2 Without surgical intervention, this lesion is uniformly lethal.3 In 1980, Norwood et al4 reported successful reconstructive surgery for HLHS. In the intervening years, there has been significant improvement in survival at the time of the stage I procedure. Several institutions have reported operative survival for the stage I procedure between 68% and 77%.5–7 There has also been a reduction in operative mortality with subsequent staging procedures.8,9 Modifications in the Fontan operation, such as fenestration of the Fontan baffle, and the introduction of intermediate staging with a bidirectional cavopulmonary anastomosis (BCPA) have contributed to this improved survival.8,9 Although these reported series have documented improved early survival, less is known about longer-term survival after reconstructive surgery for HLHS. Experience with patients who have undergone the Fontan procedure for other lesions suggests that there is a continued risk of later mortality.10,11 Diminished ventricular function appears to be a major factor in “late deaths.”10,11 Some investigators have suggested that the risk of late ventricular failure may be even greater in those patients with a single right ventricle.12

Because early surgical efforts with staged reconstruction for HLHS were performed at our institution, we reviewed our experience to describe the long-term survival for this population and to analyze the risk factors for mortality and failure. We sought to interpret the results from this historical cohort in light of continued improvements in early survival.

Methods

Study Design
We reviewed the surgical database at The Children’s Hospital of Philadelphia to identify all patients who underwent stage I reconstruction for HLHS between January 1, 1984, and January 1, 1999. The diagnosis of HLHS was based on angiographic or 2D echocardiographic evidence of a diminutive ascending aorta, aortic atresia or stenosis, and a hypoplastic left ventricle. The study included patients with variants of HLHS, such as unbalanced common atrioventricular canal and double-outlet right ventricle with mitral atresia and arch

Correspondence to Bernard J. Clark III, MD, The Children’s Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104, E-mail clark@email.chop.edu
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hypoplasia. Those patients with a single left ventricle and aortic arch obstruction who underwent stage I reconstruction were not included.

Survival status was determined by direct patient contact, when possible, or by confirmation by the referring cardiologist. Determination of patient status was carried out between January 1, 1999, and May 1, 1999. All patients were classified as (1) expired, (2) known living as of January 1, 1999, or (3) lost to follow-up. For those patients who were lost to follow-up, we recorded the date of their last evaluation by the referring cardiologist. Patients who underwent heart transplant subsequent to the stage I procedure were also identified. “Interstage” attrition was defined as death that occurred after hospital discharge for stage I palliation but before the Fontan procedure. Hospital deaths related to the BCPA were not considered interstage attrition. A late death was defined as mortality after hospital discharge that followed the Fontan procedure. For the patients with interstage mortality or late death, we reviewed available medical records to characterize the cause of death. Hospital deaths were considered as any deaths during the hospital stay after stage I. BCPA, or Fontan surgery, regardless of duration.

Pertinent variables were obtained by retrospective review of the medical records; these are listed in Table 1. Anatomic subtype of HLHS was categorized in the following manner: (1) aortic atresia/mitral atresia, (2) aortic atresia/mitral stenosis, (3) aortic stenosis/mitral stenosis, or (4) other variants.

Statistics
The data are presented as mean ± SD or median and range, as appropriate. In the analysis of outcome, time to death or transplantation was the variable of interest. Time zero is the date of birth. Patients who were lost to follow-up were censored at the time of the last evaluation by the referring cardiologist. Survival estimates were obtained by means of the Kaplan-Meier method; subgroups were compared with the use of the log-rank test. The impact of the year of surgery on survival was evaluated by dividing the study period into 4 eras. The first era, 1984 to 1989, represents our early experience with stage I palliation before the routine use of the BCPA. The following 10-year period is divided into 3 eras: 1990 to 1993, 1994 to 1995, and 1996 to 1998.

Results
Patient Population
Between January 1, 1984, and January 1, 1999, 840 patients with HLHS underwent stage I surgery at our institution.

Figure 1. Distribution of patients by anatomic diagnosis. AA/MA indicates aortic atresia/mitral atresia; AA/MS, aortic atresia/mitral stenosis; and AS/MS, aortic stenosis/mitral stenosis.

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Figure 2. Non-risk-adjusted survival with 70% confidence limits.

There were 547 males (65.1%) and 293 females (34.9%). As of the follow-up period, there were 309 survivors (36.8%), 5 patients who had undergone orthotopic heart transplantation (0.6%), and 51 patients who were lost to follow-up (6.1%). There were 475 nonsurvivors (56.6%). The median age at the time of stage I surgery was 6 days (range 0 to 218 days). There were 150 patients (17.9%) who underwent stage I surgery after 14 days of age. The median weight at stage I surgery was 3.2 kg (range 1.4 to 5.8 kg). The lowest weight of a hospital survivor of stage I surgery was 1.5 kg. The Fontan procedure was performed in 337 patients at a median age of 19.5 months (range 4.1 to 110.1 months). The surgical approach to the Fontan procedure underwent considerable modification over the 15-year study period. A variety of techniques were used, including atro pulmonary anastomosis in 6 patients (1.8%), atro pulmonary tube graft in 1 (0.3%), lateral tunnel without fenestration in 92 (27.3%), lateral tunnel with partial exclusion of hepatic veins in 33 (9.8%), lateral tunnel with fenestration in 200 (59.3%), extracardiac conduit without fenestration in 1 (0.3%), and extracardiac conduit with fenestration in 4 (1.2%). Intermediate staging with BCPA was introduced in 1989. The BCPA was performed in 343 patients at a median age of 6.6 months (range 2.7 to 50.1 months). Of the 343 patients who underwent intermediate staging, a hemi-Fontan procedure was performed in 333 (97.1%), and bidirectional Glenn’s operation was performed in 10 patients (2.9%).

The anatomic classifications for the 840 study patients are shown in Figure 1. There were 151 patients (18%) with

<table>
<thead>
<tr>
<th>TABLE 1. Variables Analyzed for Association With Mortality</th>
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<tbody>
<tr>
<td><strong>Patient- and Procedure-Related Variables</strong></td>
</tr>
<tr>
<td>Anatomic subtype</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Weight at stage I surgery</td>
</tr>
<tr>
<td>Age at surgery*</td>
</tr>
<tr>
<td>Year of stage I surgery</td>
</tr>
<tr>
<td>Intermediate staging (BCPA)</td>
</tr>
<tr>
<td>Heterotaxia</td>
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<tr>
<td>Fontan surgical technique</td>
</tr>
</tbody>
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*For each staging procedure.

<table>
<thead>
<tr>
<th>TABLE 2. Causes of Interstage and Late Deaths</th>
<th>Interstage (n=75)</th>
<th>Late (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis, n</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Arch obstruction, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Viral respiratory illness, n</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Sudden death, n</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Refractory pleural effusions, n</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ventricular failure, n</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other causes, n</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Unknown, n</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>
Orthotopic heart transplantation after initial surgical palliation was performed in 5 patients at a median age of 1.3 years (range 1.1 to 2.2 years). In all 5 patients, the indication for transplantation was right ventricular failure. Two of the patients who had undergone transplantation were alive as of January 1, 1999. Three remaining patients died after transplantation.

**Risk Factors for Mortality**

The risk factors for death at any time after stage I surgery are shown in Table 3. Later era of stage I surgery was associated with significantly improved survival ($P<0.001$). The survival for the different eras is shown in Figure 3. Hospital survival for the surgical staging procedures is shown in Table 4. The hospital survival for stage I surgery increased from 56.2% from 1984 to 1989 to 71.3% from 1995 to 1998 ($P<0.001$). The hospital survival after stage I surgery in 1998 was 77.4%. Mortality for the Fontan procedure decreased significantly as well over the course of the study. There were no hospital deaths at the time of the BCPA and Fontan procedures among the patients who underwent stage I surgery in the most recent era, 1995 to 1998.

To understand the effect of era on early and late mortality, we analyzed mortality before 120 days of life and mortality beyond 120 days of life. Mortality before 120 days is related primarily to stage I hospital deaths and early complications of stage I surgery. Mortality after 120 days is related to a variety of factors, including the surgical deaths at the time of the BCPA and Fontan procedure as well as interstage and late deaths. This analysis demonstrated an ~2-fold reduction in early mortality (<120 days) over the course of the study (Figure 4). Survival beyond 120 days improved even more dramatically in the more recent eras (odds ratio 16.1). One factor that contributed to the improved survival beyond 120 days was the introduction of the BCPA. Analyzing the impact of the BCPA is difficult because it was introduced in 1989, and intermediate staging became routine thereafter. To gain some insight into the impact of the BCPA on survival, we analyzed survival beyond 120 days for those patients who underwent stage I surgery between 1987 and 1989, the year before and 1 year after its introduction. Figure 5 shows a significant reduction in mortality for patients who underwent a BCPA during this period.

**Additional Risk Factors for Mortality of Failure**

In addition to the year of surgery, age >14 days at the time of stage I surgery and weight <2.5 kg at stage I were associated with increased mortality. Age at the time of the BCPA or Fontan procedure was not associated with survival. The high degree of association between era and type of Fontan procedure prevented us from determining the impact of modified Fontan technique and survival. Multivariate analysis demonstrated no significant association between anatomic subtype and survival, nor was the presence of heterotaxia a risk factor for mortality.

**Discussion**

The management of the neonate with HLHS remains controversial. Although alternative strategies such as transplantation...
have been advocated, staged reconstructive surgery continues to gain increased acceptance. Nonetheless, there are remaining questions regarding the appropriateness of staged reconstruction. In addition to the relatively high operative mortality associated with stage I surgery, the long-term outcome of these patients remains unknown. The present study attempts to address these concerns by reporting the results for 840 patients who have undergone staged reconstruction for HLHS. The present study found that although the 10-year survival in the entire cohort was <50%, early survival has dramatically improved over the 15-year time period of the present study. Moreover, late death and the need for transplantation are uncommon after staged reconstruction regardless of the year of stage I surgery.

Between 1984 and 1988, the operative mortality for stage I surgery exceeded 40%. It is important to recall, however, that this time period represents some of the earliest experience with stage I palliation. Many technical modifications were undertaken during the initial 5-year period. Arch reconstruction was performed with various materials, including Dacron, pericardium, and aortic homograft, before the routine use of pulmonary homograft. A central aortopulmonary shunt was used in many patients to avoid left pulmonary artery hypoplasia, although this was later abandoned for technical reasons. In addition, our understanding of the complex balance between systemic and pulmonary flow in the postoperative state evolved over several years. Novel techniques, such as the use of hypoxemia and hypercarbia to balance the systemic/pulmonary flow ratio, were introduced. As the present study and reports from several other centers demonstrate, survival for stage I surgery is significantly higher in the current era. From 1995 to 1998, 71.3% of patients survived to hospital discharge after stage I surgery. It is important to recognize that these survival data are unadjusted and include all patients with HLHS who underwent stage I surgery. Our own experience and that reported from other centers suggests that early survival is significantly higher for those patients who do not have associated risks, such as genetic anomalies, low birth weight, and low Apgar scores.6,14

Subsequent staging surgery also evolved considerably over the study period. In 1989, we began routine intermediate staging with the BCPA. The theoretical advantage of the BCPA is that it reduces the volume load on the single ventricle, thereby preserving ventricular function. In addition, the BCPA is thought to improve preoperative status before the Fontan procedure by optimizing the mass/volume ratio of the single ventricle.15 Hospital mortality for the Fontan procedure decreased considerably over the course of the present study. There were no deaths after the Fontan procedure in the most recent era. The routine fenestration of the Fontan baffle and advances in perfusion techniques, such as the use of modified ultrafiltration, may also have contributed to decreased operative mortality.9

Improved operative results for patients with HLHS are well recognized. Less attention has been paid to deaths not associated with staging surgery. The present study found that interstage attrition contributes significantly to mortality after staged reconstruction. Previous authors have also noted a significant risk of death within the first 6 months after stage I surgery. Bove and Lloyd6 described 8 nonoperative deaths in a group of 62 hospital survivors of stage I surgery. Ishino et al7 reported 6 nonoperative deaths among 82 hospital survivors of modified stage I surgery. There are several factors that contribute to interstage deaths. These include the risk for late surgical complications, such as arch obstruction or obstruction of the aortopulmonary shunt. In addition, there appears to be a significant risk for sudden-death events, the
majority of which occur within the first 6 months of life. The mechanisms of sudden death after reconstructive surgery are incompletely understood. Previous authors have demonstrated diminished coronary flow reserve and abnormal coronary artery flow patterns in patients with HLHS, which may be a risk factor for myocardial ischemia.16,17 Detailed analysis of the risk factors for unexpected death is ongoing.

Although the improved survival for all 3 operative stages has been well documented in recent years, little is known about the longer-term survival for patients with HLHS. Such data are only now becoming available. Bove and Lloyd6 reported 58% 5-year survival for patients undergoing staged palliation between January 1990 and August 1995. Forbes et al8 described the 10-year experience with palliative surgery HLHS at their institution. Unfortunately, in the latter study, there were only 14 survivors aged >5 years. In the present study, we report 5-year actuarial survival of 40% and 10-year survival of 39%. The present study included 61 patients aged >10 years at the time of follow-up. Perhaps of greatest importance is the finding there were very few deaths among patients discharged to home after the Fontan procedure. Moreover, the majority of these late deaths occurred within the first year after Fontan surgery. The one patient who expired at 9 years of age died of noncardiac causes. It is also important to point out that there have been relatively few patients who have undergone cardiac transplantation after “failed” palliative surgery.

Although data regarding longer-term survival in patients with HLHS are limited, there are several reports on long-term survival in patients with other forms of single ventricle who have undergone the Fontan procedure. Mair et al18 recently reported a 25-year follow-up for patients with tricuspid atresia who have undergone the Fontan procedure. Their study suggests that there is a continued risk for late death after the Fontan procedure. The 20-year survival for operative survivors was 81%. Importantly, late survival was significantly improved for patients who underwent the Fontan procedure in the more recent era. The most common causes of late death in this cohort were sudden death and ventricular failure. Gentles et al11 reported on 500 patients who had undergone Fontan surgery. The overall 10-year survival after Fontan surgery was 71.4%. They found a slow but continuing hazard phase extending to 10 years. Early survival after Fontan surgery was greater in more recent eras, although the risk for late failure was not significantly improved. In this study, Gentles and colleagues found a slow but continuing hazard phase extending to 10 years. At present, follow-up information for patients who have undergone the Fontan procedure for lesions other than HLHS at our institution is not available. However, compared the published results from other institutions, our data would suggest that the risk of late failure after palliation for HLHS is relatively low.

The data regarding the risk for late failure after Fontan surgery for HLHS are germane to the debate concerning the relative merits of transplantation versus staged palliation. Several institutions have advocated a strategy of transplantation as primary therapy for neonates with HLHS. The potential advantages of transplantation include the benefit of 2-ventricle circulation and the need for a single surgical procedure. The operative mortality for infant heart transplantation has been reported to be as low as 9%,19 although a recent multi-institutional study reported an operative mortality of 17%.10 In addition, there can be up to 25% mortality for those patients awaiting transplantation. In a multi-institutional experience, Jacobs et al20 compared outcomes with staged reconstruction and heart transplantation for neonates with aortic atresia. Their study demonstrated superior 3-year survival for patients managed with a transplantation protocol. The survival for patients managed at 4 “low-risk” institutions, however, did not differ between the 2 management strategies. Because this report was limited to 3-year survival, it is not known how these strategies will compare over the long term. One factor that contributes to late mortality after transplantation is graft vasculopathy. Razzouk et al21 reported their experience with transplantation for HLHS and described a 70% 7-year survival after transplant. Of the 129 operative survivors, there were 22 late deaths, and graft vasculopathy was detected 8 patients. Graft vasculopathy increases the risk of sudden death and is an indication for retransplantation. In light of the continued risk for graft vasculopathy and acute rejection after heart transplantation, staged palliation may provide better long-term survival than transplantation.

Analysis of additional variables demonstrated that stage I surgery at an older age was a risk factor for mortality. Lannettini et al22 have also found older age to be a risk factor for stage I death. It is believed that patients who are older at stage I surgery are more prone to pulmonary hypertensive crises in the postoperative period. In addition, the prolonged volume load on the single right ventricle before stage I surgery may have a negative impact on ventricular function. Low birth weight was also found to be a risk factor for mortality. There are several factors that may contribute to increase mortality in the low–birth-weight infant, such as elevated pulmonary vascular resistance and the increased risk of postoperative complications, such as necrotizing enterocolitis. A recent report of outcome for low–birth-weight infants undergoing stage I surgery from our institution suggested that there was no clear advantage in delaying surgery to achieve an arbitrary weight.23

There was no association between anatomic subtype and mortality. A previous publication has suggested that early and intermediate mortality is significantly higher for those patients with aortic atresia.24 The authors suggested that stratification to a transplantation protocol might be more appropriate for patients with aortic atresia. However, reports from several other institutions, including an earlier report from our own, have not identified aortic atresia as a risk factor for mortality.22,25 Last, although heterotaxia is relatively uncommon in patients with HLHS, it has previously been reported to be a risk factor for mortality after the Fontan procedure.10,11 We found no association between heterotaxia and outcome.

Study Limitations

The retrospective cohort study design and the close association of some variables with era prevented us from determining the causality of some risk factors. For example, the impact of the fenestrated Fontan procedure on survival is
difficult to determine in light of the continued improvement in survival with each successive era. In addition, complete data regarding known risk factors for mortality, such as genetic anomalies and Apgar scores, were not available for many patients and, hence, were not included in the analysis. A further limitation to the present study is that a number of patients were lost to follow-up, although this number is relatively small (6.1%).

Conclusions
Survival for patients undergoing staged palliation for HLHS has increased significantly since the introduction of reconstructive surgery in the early 1980s. Continued efforts to reduce even further the mortality associated with stage I surgery are ongoing. Evaluation of this historical cohort demonstrates that late death and ventricular failure necessitating cardiac transplantation are uncommon. Continued surveillance of this unique group of patients will be necessary to understand the natural history of HLHS after staged reconstruction.

References
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