Anatomic subtype and survival after reconstructive operation for hypoplastic left heart syndrome

We conducted a retrospective study of 78 patients who underwent palliative reconstructive operation for hypoplastic left heart syndrome representing an entire consecutive experience between 1983 and 1991 to identify predictors of mortality that might enable more appropriate triage of patients to either reconstruction or transplantation. Twenty-nine patients had aortic atresia, mitral atresia; 18 had aortic stenosis, mitral stenosis; 20 had aortic atresia and mitral stenosis; and 11 had miscellaneous forms of hypoplastic left heart syndrome. There were 29 hospital deaths (37%). A worst preoperative pH \( p = 0.01 \) and immediate preoperative pH \( p = 0.03 \) less than the median were predictors of hospital mortality. The anatomic subgroup aortic atresia, mitral stenosis \( p = 0.06 \) had a possible increased hospital mortality. One patient was lost to follow-up. The Kaplan-Meier survival estimate among hospital survivors was 34% at 3 years and 25% at 5 years. The anatomic subgroup aortic atresia, mitral atresia \( p = 0.02 \) had a worse late outcome (11% 3-year survival) whereas the subgroup aortic stenosis, mitral stenosis \( p = 0.04; 76\% 3\text{-year survival} \) had a better late outcome. There were no other significant predictors of late survival other than immediate prerepair pH \( p = 0.05 \). Interpretation of this experience is complicated by the large number of different surgical techniques used for both first-stage neonatal reconstruction and the Fontan procedure plus introduction of the bidirectional Glenn shunt as an intermediate step midway through the experience. Nevertheless in this time frame and with the variety of techniques used, this experience demonstrates that patients with aortic atresia, mitral atresia, particularly those who have been very acidic in the neonatal period, are least likely to do well with the reconstructive approach to hypoplastic left heart syndrome and are the most appropriate subgroup to be directed to transplantation. Patients with aortic stenosis, mitral stenosis have an excellent late outcome with the reconstructive approach. (J THORAC CARDIOVASC SURG 1994;107:1121-8)

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In the past decade there have been remarkable improvements in the results of neonatal operations for many congenital heart anomalies. For example, there was a 1.7% early mortality rate among 171 neonates and young infants who underwent a prospective study of the arterial switch procedure at Boston Children's Hospital between 1989 and 1992.\(^1\) In the past 5 years introduction of the bidirectional Glenn shunt\(^2\) and fenestrated Fontan procedure\(^3\) for patients at high risk for a completed Fontan procedure has been associated with a reduction in the mortality rate of these procedures overall to less than 5% from a previous risk of greater than 20%.\(^4\) Although the outlook for children with hypoplastic left heart syndrome has undoubtedly improved in the 10 years since Norwood, Lang, and Hansen\(^5\) first reported successful application of palliative reconstructive operations for this anomaly, the advances have not been as spectacular as in other areas of congenital heart surgery.

In addition, Bailey and associates\(^6\) have in the same time frame demonstrated the feasibility of neonatal heart transplantation. Many institutions that have been frustrated by their continuing high mortality rates for the
reconstructive approach have adopted transplantation as a technically simpler alternative to multiple complex reconstructive procedures. However, increasing enthusiasm for transplantation has been tempered by the inevitable worsening shortage of donor hearts.

We hypothesized that there might be a subgroup of patients with hypoplastic left heart syndrome who have a worse outlook with the reconstructive approach. This subgroup would be more appropriately directed to heart transplantation and would therefore reap maximum advantage from the limited donor supply. In addition, with the higher-risk patients no longer facing reconstructive operations, the overall cost-effectiveness for this approach should improve. To test this hypothesis we undertook a comprehensive multivariate analysis of an unselected consecutive series of patients representing an entire personal experience.

Patients and methods

We conducted a retrospective study of 78 consecutive patients who underwent palliative reconstructive surgery for hypoplastic left heart syndrome between 1983 and 1991. More of the
procedures were undertaken in the early years of the series than in the latter years. Forty-seven percent of the first-stage procedures took place before 1986. All patients were less than 30 days of age at the time of operation. Of the 78 patients, 29 had aortic atresia with mitral atresia (37%), 18 had aortic stenosis with mitral stenosis (23%), 20 had aortic atresia with mitral stenosis (26%), and 11 had other variants (14%), mainly aortic stenosis with mitral atresia (Fig. 1). Six patients (8%) had an ascending aorta diameter of less than 2 mm, 18 (24%) had a diameter between 2 and 3 mm, and 27 (35%) had a diameter between 3 and 4 mm, with the remainder being 4 mm or greater (Fig. 2).

An estimate of the insult experienced before the neonatal first-stage reconstructive procedure was obtained by retrieving the worst pH recorded before the operation (usually from the referral hospital or transport team) and worst creatinine value. A measure of the success of the preoperative resuscitation with prostaglandin E1 and other measures as previously described was obtained from the immediate prerepair pH and creatinine value. The presence of right ventricular dysfunction or tricuspid regurgitation was assessed from preoperative echocardiographic reports.

Various techniques were applied for the first-stage reconstruction in the neonatal period. The neoaorta was constructed by a number of different methods. Twenty-eight patients (36%) had direct anastomosis of the proximal divided main pulmonary artery to the side of the ascending aorta with a generous gusset of cryopreserved aortic or pulmonary homograft arterial wall as previously described. 9 (12%) received a tube graft of aortic or pulmonary homograft with the ascending aorta implanted end to side into the neoaorta or left as a branch of the aortic arch, 29 (37%) received a synthetic tube graft, and other forms of reconstruction were used in 12 (15%). A central shunt was placed in 10 patients (13%) and a modified right Blalock shunt in 68 (87%). The Blalock shunts were all 4 mm tube grafts because this series predates the introduction of the 3.5 mm shunt, which is currently our shunt of preference. In addition to collecting information regarding the method of reconstruction as described herein, the circulatory arrest time and total pump time were recorded.

All surviving patients but one were reviewed or contacted over a 3-month period ending August 1991. Follow-up information included status at the time of follow-up or the cause of death, as well as the occurrence of any postoperative complications.

**Results**

There were 29 hospital deaths (37%). Causes of hospital deaths are listed in Table I. Six patients were thought to have died as a result of technical difficulties in achieving adequate coronary blood flow retrograde through the tiny ascending aorta. This was manifest as arrhythmias, global hypokinesis, or discoloration of the myocardium with or without ST changes on the electrocardiogram. The severity of the preoperative insult was thought to be a contributing factor to deaths from sepsis, renal failure, and hepatic failure in a number of cases. There were three deaths attributed to multorgan failure caused by the preoperative insult. One patient died with a ruptured pseudoaneurysm of a pulmonary homograft patch in the setting of sepsis and multorgan failure. Among three patients who died with persistent postoperative metabolic acidosis and who had elevated arterial oxygen levels, two were found at autopsy to have distal arch obstruction. Two patients died of persistent hypoxia caused by inadequate shunt flow. The two patients who were receiving cardiac massage at the time of transport to the operating room died early as did the two premature neonates who weighed less than 1900 gm.

The anatomic subgroup aortic atresia with mitral stenosis (p = 0.06) appeared to be possibly at increased risk of hospital mortality (55%) relative to aortic atresia with mitral atresia (31%) or aortic stenosis with mitral stenosis (28%). By logistic regression analysis, the presence of a worse preoperative pH less than the median (p = 0.01) and an immediate prerepair pH less than the median (p = 0.03) were both predictors of hospital mortality. Neonates whose worst preoperative pH and immediate prerepair pH were less than the median had a 71% hospital mortality rate, those whose worst pH was less than the median but were resuscitated successfully to have an immediate preoperative pH greater than the median had a hospital mortality rate of 43%, and those whose worst pH and immediate preoperative pH were greater than the median had no hospital mortality. The use of a synthetic tube graft was a possible risk factor (p = 0.08) for hospital mortality relative to use of a homograft as either a gusset or a tube. The preoperative presence of tricuspid regurgitation (p = 0.26) and right ventricular dysfunction (p = 0.8) and a worst preoperative creatinine value less than the median (p = 0.87) were not predictors of hospital mortality. This was also true for age at operation, year of operation, and diameter of the ascending aorta.

### Table I. Causes of hospital mortality in hypoplastic left heart syndrome, 1983 to 1991 (n = 78)

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Coronary</td>
<td>6</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Sudden/unknown</td>
<td>2</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2</td>
</tr>
<tr>
<td>Emergency operation</td>
<td>2</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2</td>
</tr>
<tr>
<td>Aortic arch obstruction</td>
<td>2</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Excessive shunt flow</td>
<td>1</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
</tr>
</tbody>
</table>

*RV, Right ventricular.*
Of 49 patients who survived first-stage palliation, 30 died during the follow-up period. The Kaplan-Meier (product limit) survival estimate was 25% at 5 years. Survival with censoring at the time of a second procedure of any sort, including a bidirectional Glenn shunt or non-fenestrated or fenestrated Fontan procedure, was 41% at 2 years. Late survival was analyzed both by log rank and stepwise Cox regression (proportional hazards model). Anatomic subgroup was a significant predictor of late mortality ($p = 0.03$) for hospital survivors. The subgroup aortic atresia with mitral atresia ($p = 0.02$) had a significantly worse late outcome whereas the subgroup aortic stenosis with mitral stenosis ($p = 0.04$) had a significantly better late outcome. Three-year survival of patients with aortic atresia with mitral atresia was 11%, for those with aortic atresia with mitral stenosis 25%, and for those with aortic stenosis with mitral stenosis 76% (Fig. 3). These differences held true when the analysis was repeated with survival censored at the next procedure.

In the log rank analysis there were no other predictors of late survival other than the immediate prerepair pH ($p = 0.05$), but this did not remain in the multivariate Cox model once anatomic subgroup was included. Other nonsignificant variables were the type of operation including type of shunt and neoaortic reconstruction ($p = 0.22$), age at operation ($p = 0.48$), and date of operation ($p = 0.31$). There was a trend toward worse late outcome if the ascending aorta was particularly small though this did not come close to achieving statistical significance ($p = 0.2$; Fig. 4). Analysis of survival by log rank test including early and late mortality (Fig. 5) suggested a trend toward improved survival in the subgroup aortic stenosis with mitral stenosis ($p = 0.12$).

**Discussion**

It is important to emphasize that the series described represents a complete consecutive experience and encompasses a personal learning curve and many modifications of surgical technique. Some of these modifications such as the use of a synthetic tube graft were found to carry an
increased risk and are no longer used. The introduction of the bidirectional Glenn shunt and fenestrated Fontan procedure has had a dramatic impact on the results of operations for other forms of complex single ventricle. They were introduced relatively late in this series and will have an important influence on later results. For example, after the introduction of the bidirectional Glenn shunt in July 1988 within this series, which extends to August 1991, 11 children received the bidirectional Glenn shunt and 6 children underwent Fontan procedures with no deaths. Perhaps the unselected nature of this series and inclusion of patients who underwent surgical procedures subsequently proved to be high-risk have unmasked patient-related risk factors that have not been identified by similar reviews at other centers.

The findings of the study emphasize the importance of aggressive and complete resuscitation before the operation as we previously reported for the neonatal repair of interrupted aortic arch and in our previous report of first-stage management of hypoplastic left heart syndrome. Analysis of late survival revealed that the immediate prerepair pH was a predictor of late mortality \((p = 0.05)\). Immediate prerepair pH also had an important impact on hospital mortality. Patients whose worst pH and immediate preoperative pH were greater than the median had no hospital mortality. This finding is of particular relevance for those physicians counseling parents when hypoplastic left heart syndrome has been detected prenatally by ultrasound. Careful supervision of the pregnancy and delivery should allow acidosis in these children to be avoided completely, thereby improving their outlook substantially.

Despite marked improvements in the outlook for children who survived to the point of undergoing a bidirectional Glenn shunt or fenestrated Fontan procedure, there was a persistently high mortality for the first-stage procedure including the first weeks after hospital discharge throughout this experience. More recently, however, the results of first-stage palliation have improved somewhat. This may be related to the introduction of the 3.5 mm shunt, which is now our shunt of first choice in neonates of average size, and a low threshold for leaving the sternum open in the first 2 to 3 days after operation. A similar improvement has recently been reported by Iannettoni and associates. This is in contrast to biventricular reparative procedures such as the neonatal arterial switch procedure, which in our experience, even in the time frame of the current report, carried a less than 2% mortality rate. It seems that the child with a single ventricle who has a shunt-dependent pulmonary circulation is inherently less hemodynamically stable than the child who does not have continuing runoff to the lungs during diastole. This may be a result of lower coronary perfusion pressure and difficulty in distributing blood appropriately between the systemic and pulmonary vascular beds. Nevertheless, previous attempts to derive pulmonary blood flow directly from the ventricle were not successful and almost certainly would result in late impairment of ventricular function.

Although the 5-year survival of 25% for hospital survivors is disappointing, the outlook for the subgroup with aortic stenosis and mitral stenosis is remarkably good, namely 76% to 3 years. When one contrasts this latter result with the results of surgical or catheter valvotomy for neonates considered to have critical aortic valve stenosis rather than hypoplastic left heart syndrome, the outcome is remarkably similar for the two different procedures. It is reasonable to infer that extension of the sin-
gle-ventricle palliative approach further into the spectrum previously labeled aortic valve stenosis would result in an overall improvement for the two groups considered together; that is to say, if there is doubt whether to proceed with a biventricular or Norwood approach, it is preferable from the point of view of 3-year survival to adopt the Norwood approach. It is important to make this decision early in the neonatal period. The approach of doing a valvotomy and, if the child becomes ventilator-dependent because of high left-sided diastolic pressures because of inadequacy of the structures of the left side of the heart, subsequently proceeding to a Norwood approach is unlikely to be successful. Exposure of the child’s lungs to high pulmonary artery pressures for at least 1 month in our experience and as recently reported by Iannettoni and associates results in an extremely high mortality with the Norwood approach. We have found the measurement of structures of the left side of the heart by echocardiography with scoring for anatomic risk factors as described by Rhodes and colleagues to be helpful in making the decision to proceed with a biventricular (valvotomy) or Norwood approach.

Probably the most important implications of this study relate to the issue of heart transplantation for hypoplastic left heart syndrome. Bailey and associates have described encouraging results for cardiac transplantation during the neonatal period and in early infancy. However, as other groups have adopted this approach the inevitable shortage of donor hearts has been exacerbated. It seems unlikely that there will ever be an adequate number of donor hearts if transplantation is applied to all patients with hypoplastic left heart syndrome and other forms of single ventricle presenting in the neonatal period and carrying an equally bad prognosis. The current series suggests that it should be possible to triage patients to optimize the benefits of the limited supply of donor hearts.

Those institutions that have focused on either reconstruction or transplantation should continue to refine their particular approach. However, physicians at referral centers should be aware that patients with aortic atresia and mitral atresia, particularly those who have been significantly acidotic, are least likely to do well with the reconstructive approach and are the most appropriate patients to be referred for transplantation. On the other hand, patients with aortic stenosis and mitral stenosis, particularly those in whom the diagnosis was made prenatally or at birth, may have a greater chance of a successful long-term outcome with a reconstructive approach rather than competing for the limited number of donor hearts.

Just as the decision regarding valvotomy or a Norwood procedure needs to be made early in the neonatal period because of the deleterious effects of high pulmonary artery pressure and the resulting greatly increased risk for the Norwood approach, the decision regarding transplantation or a Norwood procedure should be made early in the neonatal period. If the child waits several weeks for a donor heart and subsequently undergoes palliative reconstruction because of lack of a suitable donor heart, the Norwood procedure is less likely to be successful.

We gratefully acknowledge the contributions of Laura Young, who assisted with follow-up and prepared the manuscript and figures.

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Discussion

Dr. Christo I. Tchervenkov (Montreal, Quebec, Canada). In previous discussions involving complex cardiac lesions, we have often focused on the surgical treatment for the severe end of the spectrum. I would like to direct my discussion and questions toward the favorable end of the spectrum of hypoplastic left heart syndrome, for several reasons.

At the Montreal Children's Hospital we have had experience in the past several years with several patients referred to us for a stage I palliation for hypoplastic left heart syndrome. Careful assessment of these patients has revealed hypoplasia of the mitral and aortic valves, with hypoplasia of the left ventricle, ascending aorta, and aortic arch. Most important, the flow in the ascending aorta has always been antegrade through the ventricular cavity, with the rest of the systemic circulation supported by the patent ductus arteriosus. In these four patients we have performed extensive arch reconstruction and augmentation of the ascending aorta down to the sinuses of the aortic valve and closed the atrial septal defect. All four patients have survived the operation, initially with very high left atrial pressures settling to about 14 or 15 mm Hg by 24 hours.

My first question to Dr. Jonas is this: Because it is preferable to have a biventricular repair, has he encountered in his series patients who might have retrospectively been able to undergo primary biventricular repair? Second, are there patients who on subsequent analysis have had a dramatic development of the left ventricle in the case of aortic stenosis/mitral stenosis in whom he has undertaken takedown of the Norwood operation to do a biventricular repair? Third, could the improved survival in the aortic stenosis/mitral stenosis group be explained by contribution to the systemic cardiac output by the diminutive left ventricle?

Dr. Edward L. Bove (Ann Arbor, Mich.). At the University of Michigan we have also been actively pursuing staged reconstructive operations for neonates with hypoplastic left heart syndrome for a number of years. Our results are remarkably similar to those achieved at Children's Hospital in Boston in some ways, but not in all. From 1986 to 1992, 103 patients underwent first-stage palliation with the techniques essentially described by Norwood. Throughout this time period, our approach has remained essentially constant and has consisted of atrial septectomy and augmentation of the ascending aorta, transverse arch, and proximal descending aorta with homograft tissue. Limited pulmonary blood flow is provided by the insertion of a 4 mm or 3.5 mm shunt from the innominate artery to the central pulmonary artery confluence adjacent to the ligated ductus arteriosus. Our hospital survival for this entire series is 63%, exactly as reported by Dr. Jonas. However, survival has clearly improved during the latter years of this experience, with 83% of patients (44/53) undergoing operation between 1990 and 1992 surviving compared with 42% (21/50) between 1986 and 1989, a highly significant difference.

Although we have not yet completed a detailed analysis, such as the elegant one reported by Dr. Jonas, of all the potential risk factors, one has been clear among our more recent patients, namely, that older age is a strong risk factor for hospital death. Only four patients over the age of 3 weeks underwent first-stage palliation, with no survivors. In contrast, of 49 patients under the age of 3 weeks, 44 survived hospitalization for a 90% survival in the latter years of our experience.

Although age was not a predictor in Dr. Jonas' series, I would like to ask him what his experience has been, if any, with patients older than 3 or 4 weeks. Additionally, as this experience has grown, has there been any preoperative selection among the patients reported here? Specifically, were any patients refused operation during this time frame on the basis of certain preoperative risk factors?

Dr. Jonas. I would like to thank the discussants for their comments. Dr. Bove, regarding our hospital mortality, there were years when we were encouraged and thought that we had really solved this problem. During the first 2 years of the series, the hospital mortality rate was less than 20%, but this did not improve, and in fact it deteriorated with further experience. When we compared the mortality risk for hypoplastic left heart syndrome with the risk for other forms of single ventricle with subaortic stenosis, that is, children who had Damus-Kaye-Stansel type procedures, we found that the hospital mortality for that group was also substantial. So perhaps the concept of a single ventricle reconstructive operation that leaves the child with a systemic-pulmonary arterial shunt-dependent circulation carries with it an inherent mortality risk. Until we can fundamentally change that approach, we may be left with a high mortality. Although your current mortality rate of 20% is outstanding for hypoplastic left heart syndrome, I do believe that it will be difficult to improve it to the mortality level of less than 5% that we are seeing for corrective operations.

Regarding the age of the patients, we did not find that age influenced outcome. I cannot tell you specifically the risk for patients older than a month. There are very few such patients in our series.

Regarding patients who were refused surgery, there were five patients who did not undergo an operation during this period. This was either for associated chromosomal problems, very low birth weight, or infants who had had severe acidotic insults. Dr. Tchervenkov raises the interesting question of how one deals with patients who stray into the border zone between aortic stenosis, mitral stenosis, hypoplastic left heart syndrome, and critical neonatal aortic valve stenosis. We used to use an end-diastolic volume of 20 ml/m2 as a cutoff point below which we would direct children into a pathway suitable for hypoplastic left heart syndrome and above which we would attempt a valvotomy. We found that adequate left ventricular growth rarely occurred in children who were ventilator-dependent for more
than a few days after a valvotomy. Ventilator dependence was often due to poor compliance with a high end-diastolic pressure. We have not seen any children after a Norwood-type operation in whom the ventricle has grown sufficiently for us to consider a biventricular repair.

Currently, to determine whether or not to use a single ventricle-type approach in the child with aortic stenosis and a small left ventricle, we use the “Rhodes factors,” which were published in Circulation in 1991 (Circulation 1991;84:2325-35). Left ventricular length less than 80% of the long-axis dimension of the heart, an ascending aortic diameter of less than about 6 to 7 mm, mitral valve area, and left ventricular mass are the four major predictors of successful outcome with a biventricular aortic valvotomy approach.

Regarding the final question of whether children with aortic stenosis/mitral stenosis have a better outcome because of some contribution from the left ventricle, I have certainly speculated that the reason these children survived the Fontan operation early in our experience was related to the Fontan technique that we were using in 1985 and 1986. We placed an oblique baffle and although children with aortic atresia/mitral atresia would have severe problems with pulmonary venous obstruction because of bulging of the baffle into the pulmonary venous pathway, that was not a fatal event for children with a patent mitral valve. They could get forward flow into the left ventricle and from there into the coronary arteries. Certainly some of these children several years after the Fontan operation have quite impressive-looking left ventricles; they are not big enough to sustain the child per se, but I suspect such ventricles do contribute to systemic output.