Improved Survival of Patients Undergoing Palliation of Hypoplastic Left Heart Syndrome: Lessons Learned From 115 Consecutive Patients

James S. Tweddell, MD; George M. Hoffman, MD; Kathleen A. Mussatto, RN; Raymond T. Fedderly, MD; Stuart Berger, MD; Robert D.B. Jaquiss, MD; Nancy S. Ghanayem, MD; Stephanie J. Frisbee, MSc; S. Bert Litwin, MD

Background—Outcome of stage 1 palliation (S1P) for hypoplastic left heart syndrome (HLHS) has improved coincident with application of treatment strategies including continuous superior vena cava oximetry (SvO₂), phenoxybenzamine (POB), strategies to minimize the duration of deep hypothermic circulatory arrest (DHCA) and efforts to ameliorate the inflammatory response to cardiopulmonary bypass (CPB) using aprotinin and modified ultrafiltration.

Methods and Results—Analysis of a consecutive series of 115 patients undergoing S1P was done to identify the risk factors for mortality and the impact of new treatment strategies. For the current era, July 1996 to October 2001, hospital survival was 93% (75/81) compared with 53% (18/34) for the time period, January 1992 to June 1996, P<0.001. Survival to stage 2 palliation (S2P) was also significantly improved in the current era, 81% (66/81) versus 44% (15/34), P<0.01. Anti-inflammatory treatment strategies demonstrated improved survival by univariate analysis (P<0.001). Multivariate analysis identified continuous SvO₂ monitoring as a factor favoring S1P survival (P=0.02) and use of POB as a factor favoring survival to S2P (P=0.003). In the current era shorter duration of DHCA was associated with improved survival to S2P (P=0.02).

Conclusions—Improved survival following S1P can be achieved with strategies that allow for early identification of decreased systemic output and the use of afterload reduction to stabilize systemic vascular resistance and therefore the pulmonary to systemic flow ratio. Strategies to ameliorate the inflammatory response to CPB may decrease the degree and duration of postoperative support. Strategies to minimize duration of DHCA may improve intermediate survival and merit additional studies. (Circulation. 2002;106[suppl I]:I-82-I-89.)

Key Words: heart defects, congenital ▪ circulatory control ▪ cardiac output ▪ autonomic nervous system

Early survival following the Norwood procedure as stage 1 palliation (S1P) of hypoplastic left heart syndrome (HLHS) is complicated as a result of altered endothelial function, increased sympathetic tone and limited single ventricle reserve secondary to anatomic and operative factors. The period of increased risk encompasses not only the perioperative period but also the period of time before bidirectional cavopulmonary shunt, stage 2 palliation (S2P). Beginning in July of 1996, we began to identify improved survival of patients undergoing S1P of HLHS and its variants. Improved survival corresponded to the application of several new treatment strategies. This study was undertaken with a threefold purpose: first, to identify risk factors associated with mortality following palliation of HLHS; second, to determine which of the new treatment strategies was responsible for improved survival; and third, to determine if risk factors for early mortality following S1P and before S2P have changed in the current era.

Patients and Methods

Patients
From January 1992 through July 2001, 115 infants underwent S1P for HLHS or its variants at the Children’s Hospital of Wisconsin. Beginning in July of 1996, improved operative survival was noted for patients undergoing S1P (Figure 1). This improvement in survival corresponded to the application of several new treatment strategies, including: continuous SvO2 monitoring, initiated in July 1996 and employed in 74/115 subjects; modified ultrafiltration, initiated in September 1996 and used in 75/115 subjects; parenteral phenoxybenzamine (POB), initiated in December 1996 and used in 73/115 subjects; aprotinin (Bayer, Leverkusen, Germany) initiated in September 1997 and used in 65/115 subjects, modification of the operative technique, initiated in December 1997 and used in 63/115 subjects and a change in perfusion strategy allowing low-flow, continuous cerebral perfusion with minimal circulatory arrest time, initiated in September 2000 and used with 21/115 subjects. A prospective database containing data on all subjects undergoing S1P was reviewed; additional data were retrospectively obtained from...
Tweddell et al  Improving Survival Following Stage I Palliation  I-83

Figure 1. Hospital survival following stage 1 palliation by year. Hospital survival improved coincident with the application of new treatment strategies beginning in July of 1996 (arrow).

Surgical Technique

The Norwood procedure was performed using deep hypothermic circulatory arrest (DHCA). Circulatory arrest was established after reaching a bladder temperature of 18°C, and duration of cooling was always greater than 30 minutes. Before July of 1996, patients underwent the Norwood procedure as described by Pigott and colleagues.1 A single period of DHCA was used for the entire reconstruction with the exception of the systemic to pulmonary artery shunt, which was constructed during the rewarming phase. From July of 1996 until November of 1997, arterial cannulation was achieved by direct cannulation of the ductus arteriosus, this allowed us to transect the pulmonary artery above the sinotubular junction before establishing circulatory arrest as described by Fraser and Mee.2 Beginning in December of 1997, arch reconstruction was modified. The proximal descending thoracic aorta was mobilized during cooling, including division of the first 2 sets of intercostal branches. The aortic isthmus was ligated and all residual ductal tissue was resected from the descending thoracic aorta. Routinely, this involved resection to within 2 mm of the first intercostal branch. The posterior one-half of the circumference of the proximal descending aorta was then anastomosed to the posterior edge of an arteriotomy made in the undersurface of the aortic arch opposite the origin of the innominate artery. The arteriotomy in the aortic arch was then extended down the anterior surface of the ascending aorta to the kissing point between the aorta and main pulmonary artery. An incision was made in the pulmonary root adjacent to the ascending aorta. The ascending aorta, incised to a point 2 to 3 mm cephalad to the sinus of Valsalva, was anastomosed to the main pulmonary artery or at below the level of the sinus of Valsalva of the pulmonary valve using running 7–0 polypropylene suture (Ethicon, Somerville, NJ). The goal of placement of the ascending aorta to pulmonary artery anastomosis deep within the pulmonary root is both to enlarge the anastomosis and to avoid distortion (and therefore coronary insufficiency) of the tripartite connection of a diminutive ascending aorta, pulmonary root and distal neoaascending aorta. The anastomosis between the descending aorta and the ascending aorta, augmented anteriorly with a distal pulmonary homograft and this single patch was also used to augment the ascending aorta and complete the Damus-Kaye-Stansel (DKS) connection. The technique of reconstruction of the aortic arch and construction of the DKS connection is shown in Figure 2. Twenty-one patients were managed with an effort to minimize the duration of DHCA through the use of continuous cerebral perfusion via a Gore-Tex graft (W. L. Gore and Associates, Flagstaff, AZ), anastomosed to the innominate artery and destined to become the proximal portion of the systemic to pulmonary artery shunt. Based on the work of Pigula and colleagues, flow to the innominate artery was maintained at 30 to 40 mL/kg/min.3,4

Aprotinin administration was initiated before the skin incision. A loading dose of 1.7 × 10^6 kallikrein inactivator units (KIU)/m^2 was given intravenously. 1.7 × 10^6 KIU/m^2 was placed in the extracorporeal circuit and during the procedure a continuous infusion, 4.0 × 10^5 KIU/m^2/h was administered until the patient was transferred from the operating room.

Postoperative Management

Nasotracheal intubation was used for maintenance of the airway. An autoregulating infant warmer was used to maintain normothermia. The sternum was routinely opened and patients underwent delayed sternal closure on postoperative day 2 to 5. All patients were maintained on neuromuscular blockade for the first 12 hours and continuous narcotic infusion (fentanyl 5 to 10 mcg/kg/h) until chest closure. Before July of 1996, postoperative management relied on indirect assessment of cardiac output and circulatory balance. Peripheral pulses, capillary refill time, urine output, and arterial blood gases were used to assess the adequacy of cardiac output. Inotropes were used routinely and included milrinone, dopamine and epinephrine. Preload was optimized by observing the response to judicious fluid administration. Additional afterload reduction was attempted with nitroprusside. Pulse oximetry was used as a guide to circulatory balance and to assess measures to raise the pulmonary vascular resistance. Limitation of FiO2 and intentional hyperventilation were induced if the arterial saturation (SaO2) was greater than 80%.4

Continuous assessment of superior vena cava oxygen saturation was initiated in July of 1996 using a French oximeter catheter (Abbott Laboratories, North Chicago, IL) and was used as an approximation of mixed venous saturation (SvO2).5 Postoperative management then centered on maximizing SvO2 and circulatory balance was estimated using the Fick equation. The identification of a baseline elevation of systemic vascular resistance (SVR) compound by further episodes of acute elevation of SvO2, led to the routine use of POB for control.
of SVR and sympathetic output in the early postoperative period. Strategies of continuous SvO₂ monitoring and phenoxybenzamine for afterload reduction have been previously described.6

**Data Collection and Statistics**

In addition to new treatment strategies listed above, the following variables were included: date of operation, age, weight, diagnostic group, use of pre-operative mechanical ventilation, or inotropic support, ascending aorta size, indexed shunt size (cross-sectional area of the shunt in square millimeters divided by patient weight in kilograms), cardiopulmonary bypass (CPB) time, and deep hypothermic circulatory arrest (DHCA) duration. Ascending aortic size was measured from the preoperative echocardiogram and was taken as the internal diameter of the proximal ascending aorta above the sinotubular junction. End-points studied include S1P hospital survival and survival to bidirectional cavopulmonary shunt (S2P).

Statistical analysis was completed using SPSS Advanced Models™ 9.0 (SPSS, Inc, Chicago, IL) and STATA software (College Station, TX). Analysis of risk factors for mortality was completed using ANOVA techniques for continuous variables and chi² for categorical variables. Multivariate analysis, using stepwise logistic regression and Cox proportional hazards regression analysis, was performed to determine factors related to outcome, either alone or in combination. Actuarial survival analysis was performed using Kaplan-Meier methods with log-rank comparison of cumulative survival by treatment group. Data are reported as mean ± standard deviation for continuous variables and count with percent for categorical variables. Median values are included where appropriate.

**Results**

Follow-up was obtained through October 1, 2001 for 100% of the subjects. Mean length of follow-up for survivors was 40±29 months with a range of 2.6 to 112 months. Sixty-five percent of the sample was male. The mean age at operation for the group was 7.3±7.9 days with a median age of 5 days. Sixty-six percent of the subjects were less than 1 week of age at operation, 24% were 1 to 2 weeks old and 10% were greater than 2 weeks of age. Average weight at operation was 3.2±0.6 kg. Hypoplastic left heart syndrome (situs solitus, d-looped ventricles with an intact ventricular septum) was present in 77% (88/115) of the patients including aortic atresia with mitral atresia or stenosis in 57% (65/115) and severe aortic and mitral stenosis in 20% (23/115). Hypoplasia of the left heart with a ventricular septal defect was present in 7% (8/115). Other complex cardiac anatomy with outflow obstruction from a single ventricle and aortic arch obstruction/coarctation was present in 16% (19/115), including 7% (8/115) with a single left ventricle and 2 additional patients with aortic atresia. Ascending aorta diameter averaged 3.3±1.7 mm with a range of 1 to 8 mm. Before surgery, 89 patients (77%) required mechanical ventilation and 62 patients (54%) required preoperative inotropic support. Cardiopulmonary bypass time averaged 124±48 minute, Deep hypothermic circulatory arrest was utilized for a mean time of 56±25 minutes. In the most recent twenty-one subjects, the use of low-flow, continuous cerebral perfusion with minimal circulatory arrest during the procedure was employed. For these subjects, the mean DHCA and CPB times were 10±5.4 and 151±48 minutes respectively, significantly different from the group in which this technique was not utilized (DHCA 66±13 minute, P<0.001; CPB 124±48 minute, P<0.005). All 21 patients in which continuous cerebral perfusion was used survived S1P and are alive at last follow-up. Gore-Tex grafts ranging in size from 3 to 5 mm in diameter were utilized to construct the aorto-pulmonary shunt. Ninety percent of the patients received grafts that were either 3.5 or 4 mm in diameter. The indexed shunt size (cross sectional

### TABLE 1. Impact of Risk Factors on S1P Survival and Survival to S2P

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>S1P Survival</th>
<th>Survival to S2P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td>Patient and operative risk factors</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Earlier year of op</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>Younger age</td>
<td>0.49</td>
<td>0.25</td>
</tr>
<tr>
<td>Lower weight</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Diag. cat. (AA worse)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Smaller asc ao</td>
<td>0.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Preop vent</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Preop ino</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Larger shunt size</td>
<td>0.71</td>
<td>0.21</td>
</tr>
<tr>
<td>Longer CPB</td>
<td>0.007</td>
<td>0.29</td>
</tr>
<tr>
<td>Longer DHCA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

area of the graft divided by the patient’s weight) averaged 3.44±0.52 mm²/kg. Mean length of hospital stay for all subjects surviving to discharge was 35±21 days, with a median of 30 days.

Survival Data
Seventy-four (64%) of the 115 subjects were alive at the time of last follow-up on October 1, 2001. Kaplan-Meier actuarial survival analysis for the entire group demonstrates 68±4.5% survival to age 6 months, 66±4.5% to 1 year, 65±4.7% to 2 years, and 61±5.5% to 5 years. There were 22 deaths in the group occurring within thirty days of the Norwood procedure or within the primary hospitalization for an early survival rate of 81% for the entire cohort. Twelve deaths (13%) occurred in the 93 hospital survivors during the interval between hospital discharge following S1P and before S2P. Seventy-five subjects have undergone S2P at a mean age of 6±2.9 months (median=5.2 months). The entire cohort (115 subjects) thus demonstrated a 70% survival rate to S2P.

Morbidity Related to New Treatment Strategies
One patient required chest exploration for bleeding following removal of an SVO₂ catheter. No thrombotic complications occurred as a result of oximetric catheter use; specifically no patient developed superior vena cava thrombosis. Among the 63 patients who underwent the Norwood procedure using the modified operative technique, intervention for recurrent arch obstruction was required in 19 (30%). Thromboses of the systemic to pulmonary artery shunt occurred in 2 of 65 patients (3%) receiving aprotinin with one early death.

Risk Factors for S1P
By univariate analysis, patient and operative factors negatively impacting S1P survival included earlier year of operation, smaller ascending aortic diameter and longer duration of DHCA. Improved S1P survival was associated with use of all of the new treatment strategies with the exception of continuous cerebral perfusion. Stepwise logistic regression analysis identified use of SVO₂ monitoring with improved outcome following S1P. Table 1 summarizes the results of univariate and multivariate analysis of S1P survival.

Risk Factors for Survival to S2P
By univariate analysis patient and operative factors negatively impacting survival to S2P included earlier year of operation, lower weight, the presence of aortic atresia, smaller ascending aortic diameter, larger shunt size and longer duration of DHCA. All new treatment strategies were associated with increased survival to S2P. Stepwise logistic regression analysis identified lower weight and smaller ascending aortic diameter as risk factors for mortality before S2P. POB use was associated with improved survival to S2P. Table 1 summarizes the results of univariate and multivariate analysis of survival to S2P palliation.

Comparison of Early and Recent Eras
Based on a significant shift in management strategy beginning in July 1996 that involved techniques targeting reduction of SVR, optimizing systemic oxygen delivery and reduction of the systemic inflammatory response in contrast to manipulation of pulmonary vascular resistance, the group was divided into 2 eras group A (January 1992 through June 1996, n=34) and group B (July 1996 through August 2001, n=81). Survival to hospital discharge was significantly better for the more recent era, group B (93% versus 53%, P<0.001), as was survival to bidirectional cavopulmonary anastomosis or second stage palliation (81% versus 44%, P<0.01). Early survival was particularly improved with actuarial survival analysis demonstrating 100% (81/81, CI 96% to 100%) survival to postoperative day 10 for the more recent group versus 62% (21/34, CI 44% to 78%, P<0.001) in the historical group. Long-term survival is also significantly better in group B with actuarial survival to 5 years of age at 72% (60/83, CI 61% to 83%) versus 41% (14/41, CI 20% to 51%, P<0.001) (Figure 3).

The groups were compared for statistically significant differences in both categorical and continuous variables in the dataset. No statistically significant differences were found between group A and group B for the following variables: gender, diagnostic category, preoperative mechanical ventilation, preoperative inotropic support, age and size at S1P, ascending aorta diameter, indexed shunt size, cardiopulmonary bypass times or length of stay for hospital survivors. In group B, circulatory arrest time was significantly shorter (49±26 versus 73±7 minute, P<0.001). In 21/81 group B patients, continuous cerebral perfusion was utilized with minimal circulatory arrest duration (mean 10±5.4 minute). With these subjects excluded, circulatory arrest time remains significantly shorter in group B (62±13 versus 73±7 minute, P<0.001). Age at BDCPS (5.2±2 versus 8±1.6 months, P<0.001) was significantly lower in group B. These results are summarized in Table 2. It should be noted that 2 survivors in group B were not discharged to home between S1P and S2P. In-hospital management was maintained for social reasons in 1 and the need for continuous infusion of milrinone.
TABLE 2. Patient Characteristics, Group A versus Group B

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S1P survival</td>
<td>53% (18/34)</td>
<td>93% (75/81)**</td>
</tr>
<tr>
<td>Survival to S2P</td>
<td>44% (15/34)</td>
<td>81% (66/81)*</td>
</tr>
<tr>
<td>Gender</td>
<td>71% Male (24/34)</td>
<td>63% Male (51/81)</td>
</tr>
<tr>
<td>Diagnostic category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA/MA and/or MS</td>
<td>56% (19/34)</td>
<td>57% (46/81)</td>
</tr>
<tr>
<td>AS/MS</td>
<td>29% (10/34)</td>
<td>16% (13/81)</td>
</tr>
<tr>
<td>HLHS with VSD</td>
<td>3% (1/34)</td>
<td>9% (7/81)</td>
</tr>
<tr>
<td>Other variant</td>
<td>12% (4/34)</td>
<td>18% (15/81)</td>
</tr>
<tr>
<td>Ascending aortic dia.</td>
<td>3.4±1.8 mm</td>
<td>3.3±1.6 mm</td>
</tr>
<tr>
<td>Preop vent</td>
<td>79% (27/34)</td>
<td>77% (62/81)</td>
</tr>
<tr>
<td>Preop ino</td>
<td>59% (20/34)</td>
<td>52% (42/81)</td>
</tr>
<tr>
<td>Age at operation</td>
<td>6.5±7.1 days</td>
<td>7.6±8.3 days</td>
</tr>
<tr>
<td>Weight</td>
<td>3.3±0.7 kg</td>
<td>3.2±0.5 kg</td>
</tr>
<tr>
<td>CPB time</td>
<td>Mean=118±48 min</td>
<td>Mean=133±49 min</td>
</tr>
<tr>
<td></td>
<td>Median=103 min</td>
<td>Median=114 min</td>
</tr>
<tr>
<td>DHCA time</td>
<td>Mean=73±7.4 min</td>
<td>Mean=49±26 min**</td>
</tr>
<tr>
<td></td>
<td>Median=73 min</td>
<td>Median=56 min</td>
</tr>
<tr>
<td>Total support time (CPB)</td>
<td>Mean=191±49 min</td>
<td>Mean=182±54 min</td>
</tr>
<tr>
<td></td>
<td>Median=181 min</td>
<td>Median=166 min</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>Mean=35±11 days</td>
<td>Mean=36±23 days</td>
</tr>
<tr>
<td></td>
<td>Median=34.5 days</td>
<td>Median=30 days</td>
</tr>
<tr>
<td>Shunt size</td>
<td>3.55±0.4 mm²/kg</td>
<td>3.38±0.5 mm²/kg</td>
</tr>
<tr>
<td>Age at S2P</td>
<td>8±1.6 months</td>
<td>5.2±2 months**</td>
</tr>
</tbody>
</table>

*P<0.01. **P<0.001.

Secondary to important tricuspid insufficiency in another. Both patients survived S2P and are currently at home.

Similar analyses to those previously described with the whole sample were undertaken to analyze risk factors for survival within the 2 surgical eras, group A and group B. In group A, for hospital survival after S1P, the need for preoperative mechanical ventilation (P=0.05), younger age (P=0.03), and smaller ascending aorta (P=0.001) all proved significant in univariate analysis. In multivariate analysis, longer duration of CPB (P=0.05) was identified as a risk factor for mortality prior to discharge following S1P. For survival to S2P in group A, younger age (P=0.02), smaller ascending aorta (P<0.001), and lower weight at S1P (P=0.02) were significant in univariate analysis. Younger age (P=0.03) and smaller ascending aorta (P=0.02) remained significant in multivariate analysis as well as longer duration of CPB (P=0.004). In group B, for hospital survival after S1P, none of the previously identified risk factors proved significant in either univariate or multivariate analyses. For survival to S2P in group B, only longer duration of DHCA proved significant in both univariate (P=0.002) and multivariate (P=0.02) analyses. Table 3 and 4 summarize the comparison of risk factors for survival between the 2 surgical eras.

**Discussion**

Beginning in July of 1996, we altered our approach to the care of patients undergoing the Norwood procedure for HLHS. The purpose of this study was to review our entire experience with the Norwood procedure for HLHS, to determine the risk factors for mortality and to determine if new treatment strategies had an impact on survival. Finally, we hoped to determine if risk factors for survival had changed in the current era when nearly all of the patients have received the new treatment strategies. Improvements in outcome of patients with HLHS requiring complex, palliative neonatal surgery lags behind that of other lesions. Furthermore, the period of vulnerability extends beyond the initial hospitalization, with mortality before S2P nearly equaling the operative mortality. The patient following S1P and before S2P remains with in-parallel circulation with shunt dependent pulmonary blood flow. The result is continued arterial hypoxemia and an inconsistent relationship between systemic and pulmonary blood flow. The single ventricle must perform the work of both the systemic and pulmonary circuits despite a low diastolic pressure that results in altered coronary blood flow. In addition, reflex sympathetic responses to stress will result in an increase in the SVR that may reduce systemic perfusion by increasing the pulmonary to systemic flow ratio. We have shown that physiologic differences identified in the early postoperative period, such as differences in anaerobic threshold, predicted interstage mortality. Although it is unclear how these types of biologic differences impact the patient following hospital discharge, given the persistence of an at risk circulatory anatomy we felt it was important to use both S1P survival as well as survival to S2P as end-points.

In the past, the clinician caring for the patient following S1P had little objective data with which to guide management. Indirect assessment of cardiac output and systemic oxygen delivery was the rule. Peripheral pulse volume, capillary refill, urine output, arterial blood gas analysis, systemic and atrial pressures were used to assess the cardiac output.

TABLE 3. Risk Factor Analysis for Hospital Survival after S1P, Group A vs. Group B

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op mech Vent</td>
<td>0.05 0.98 0.68 0.80</td>
<td></td>
</tr>
<tr>
<td>Pre-op ino</td>
<td>0.68 0.70 0.45 0.59</td>
<td></td>
</tr>
<tr>
<td>Younger age</td>
<td>0.03 0.10 0.75 0.96</td>
<td></td>
</tr>
<tr>
<td>Smaller asc Ao</td>
<td>0.001 0.23 0.45 0.25</td>
<td></td>
</tr>
<tr>
<td>Lower weight</td>
<td>0.11 0.70 0.96 0.21</td>
<td></td>
</tr>
<tr>
<td>Longer CPB</td>
<td>0.26 0.05 0.39 0.29</td>
<td></td>
</tr>
<tr>
<td>Longer DHCA</td>
<td>0.40 0.95 0.49 0.44</td>
<td></td>
</tr>
<tr>
<td>Larger shunt</td>
<td>0.29 0.80 0.68 0.29</td>
<td></td>
</tr>
</tbody>
</table>

**Asc=ascending, Ao=aorta, CPB=cardiopulmonary bypass time, DHCA=deep hypothermic circulatory arrest duration.**
output. The pulmonary to systemic flow ratio (Qp/Qs) was estimated from the arterial saturation, requiring assumptions about both systemic cardiac output and pulmonary venous saturation. The result was an approach that targeted arterial saturations between 70 and 80%. Beginning in July of 1996, we began routine placement of 4 Fr. oximetric catheters in the superior vena cava of patients undergoing S1P. We identified multiple episodes of abrupt decrease in systemic venous saturation that were associated initially, with only very subtle changes in arterial saturation or blood pressure. The use of continuous SvO₂ monitoring allowed for early identification of decreased cardiac output and correction before development of oxygen delivery dependent oxygen consumption, anaerobic metabolism. Furthermore, SvO₂ monitoring more precisely estimated the Qp/Qs with fewer assumptions than earlier models.

Experience with continuous SvO₂ monitoring revealed that most patients following S1P have elevated SVR. In addition, the acute episodes of systemic venous desaturation were because of abrupt increases in SVR, rather than a decrease in pulmonary vascular resistance (PVR). These episodes of SVR elevation did not result in a dramatic increase in arterial blood pressure because of the potential for increased Qp/Qs through the systemic to pulmonary artery shunt. The episodes appeared to be a result of excessive vasodilatation and must be used with caution. In addition to strategies that target systemic oxygen delivery we have added several strategies to ameliorate the inflammatory response to CPB. We have added routine use of aprotinin, a serine protease inhibitor that has been shown to have broad anti-inflammatory effects on patients undergoing procedures involving CPB. Specifically, many of the inflammatory cascades involve serine proteases. Aprotinin inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response, including inhibition of factor XII, bradykinin, anaphylatoxins as well as activation of leukocytes and platelets. The use of aprotinin is associated with decreased capillary leak and improved myocardial recovery. Aprotinin inhibits kallikrein and plasmin, resulting in suppression of multiple inflammatory cascades involve serine proteases. Aprotinin inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response, including inhibition of factor XII, bradykinin, anaphylatoxins as well as activation of leukocytes and platelets. The use of aprotinin is associated with decreased capillary leak and improved myocardial recovery.

The use of afterload reduction has resulted in greatly simplified postoperative management specifically, control of SVR results in pharmacologic stabilization of Qp/Qs. Although, most afterload reducing agents including POB result in reduction of both PVR and SVR, potentially adversely impacting the Qp/Qs, the shunt acts as a fixed resistor. With the net PVR controlled by the shunt and the stable afterload reduction resulting in a relatively fixed SVR, the Qp/Qs is stabilized and can fluctuate only slightly. With a Qp/Qs that is fixed pharmacologically, medical gas manipulation of PVR is unnecessary and ineffective. Specifically, deliberate induction of hypoxemia and hypercapnea are unnecessary. Higher arterial saturations achieved with POB are well tolerated and are not indicative of an elevated Qp/Qs or a reduction in SvO₂. In fact, a higher SaO₂ is a unique determinant of a higher SvO₂. We have shown that POB prevents systemic desaturation at high arterial saturations. Higher arterial saturation increases myocardial oxygen delivery and may result in better cardiac function further contributing to improved systemic oxygen delivery. We speculate that higher arterial saturations may result in improved neurologic recovery following DHCA. Limiting FiO₂ can also result in pulmonary venous desaturation; the targeted SaO₂ will be achieved but without an alteration in Qp/Qs. Pulmonary venous desaturation would result in reduction of systemic oxygen delivery, which has been demonstrated in both preoperative patients with HLHS and the patient following S1P. Although manipulation of PVR and SVR with hypercapnea may improve systemic oxygen delivery postoperatively, no clinical study has shown that limiting FiO₂ results in improved systemic oxygen delivery in the patient following S1P. Also noteworthy is the finding that shunt size, within the range used in this study, did not have an impact on early survival. This suggests that a strategy of afterload reduction may limit the impact of shunt size on early mortality. POB is a powerful long acting vasodilator, although used successfully in this series; POB can result in excessive vasodilatation and must be used with caution.

In addition to strategies that target systemic oxygen delivery we have added several strategies to ameliorate the inflammatory response to CPB. We have added routine use of aprotinin, a serine protease inhibitor that has been shown to have broad anti-inflammatory effects on patients undergoing procedures involving CPB. Specifically, many of the inflammatory cascades involve serine proteases. Aprotinin inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response, including inhibition of factor XII, bradykinin, anaphylatoxins as well as activation of leukocytes and platelets. The use of aprotinin is associated with decreased capillary leak and improved myocardial recovery. Aprotinin has also been shown to result in more rapid recovery of cerebral energy metabolism following DHCA in animal models and is associated with a decrease in neurologic complications of patients undergoing coronary artery bypass grafting. Aprotinin will prolong the activated clotting time and an alternative method to determine adequacy of heparinization during CPB is necessary. We have not identified important thrombotic complications as a result of aprotinin use and use it routinely even in patients with diminutive ascending aortas. We have also used modified ultrafiltration in patients following weaning from CPB. Modified ultrafiltration results in removal of proinflammatory cytokines and reduction of fluid accumulation. Strategies to counter the inflammatory response to CPB resulting in less total body water and improved myocardial and pulmonary function, hasten weaning from mechanical

### TABLE 4. Risk Factor Analysis for survival to S2P, Group A vs. Group B

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op mech Vent</td>
<td>0.10</td>
<td>0.31</td>
</tr>
<tr>
<td>Pre-op ino</td>
<td>0.20</td>
<td>0.66</td>
</tr>
<tr>
<td>Younger age</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Smaller asc Ao</td>
<td>&lt;0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>Lower weight</td>
<td>0.02</td>
<td>0.54</td>
</tr>
<tr>
<td>Longer CPB</td>
<td>0.30</td>
<td>0.96</td>
</tr>
<tr>
<td>Longer DHCA</td>
<td>0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>Larger shunt</td>
<td>0.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Asc = ascending, Ao = aorta, CPB = cardiopulmonary bypass time, DHCA = deep hypothermic circulatory arrest duration.
ventilation and diminish inotropic support requirements. Further, limiting the inflammatory response to CPB results in decreased sympathetic tone and as noted above, elevated SVR is particularly detrimental to the single ventricle patient with parallel circulation. Although the anti-inflammatory strategies were highly significant in the univariate analysis, multivariate analysis did not identify these strategies as significant. Despite a potential positive impact of an anti-inflammatory strategy, we have not yet tested whether delayed sternal closure or narcotic sedation, both associated with morbidity, could be eliminated or more selectively applied in the postoperative period.

To further delineate the impact of new treatment strategies on outcome we analyzed operative and patient risk factors in 2 eras. We chose as a dividing point July of 1996, which corresponded with the application of continuous SvO₂ monitoring and shortly preceded the introduction of POB, the 2 factors with the largest impact on patient outcome. Looking at the 2 eras, we identified patient related variables, specifically lower weight, smaller ascending aorta and younger age, as risk factors for survival to S2P among patients operated on early in the experience. The only operative factor of importance was the longer duration of CPB. In the most recent era, patient related variables did not reach significance. This suggests that new treatment strategies eliminated previously identified patient related risk factors for survival to S2P.

Multivariate analysis identified longer duration of DHCA as a factor predicting mortality before S2P in the current era. It is conceivable that a longer duration of DHCA results in a patient less able to withstand the rigors of the interstage period. Alternatively, a longer duration of DHCA could simply be a marker of important anatomic differences necessitating a longer time to complete reconstruction and it is, in fact, these anatomic differences that are predictors of worse survival. Strategies to limit duration of DHCA have been employed only recently (September 2000) and the strategy of continuous cerebral perfusion did not reach statistical significance when entered as a separate categorical variable. However, it is noteworthy that although used in only 21 patients, the strategy of continuous cerebral perfusion has thus far been associated with uniform S1P survival and 100% survival to S2P. Whether this improvement in survival will persist with recruitment of additional patients remains to be seen but suggests a survival advantage that persists beyond the perioperative period.

The risk factors selected for analysis in this study were those identified in previous studies both at the Children’s Hospital of Wisconsin and at other institutions as important in patients undergoing staged palliation of HLHS. It should be noted that all of the new treatment strategies with the exception of continuous cerebral perfusion were introduced over a 12-month period. This temporal relationship introduces collinearity to the multivariate analyses that may confound the identification of individual treatment strategies as important. The result is that factors identified in the multivariate analysis may not be the only important contributors to improved survival. Indeed the inclusion of any single treatment strategy with the exclusion of the others identified that strategy as highly correlated with improved results. Nevertheless, the identification of SvO₂ and POB as important contributors to improved early survival after S1P is consistent with the overwhelming clinical impression. Finally, we felt it was important to look not only at S1P survival but to include the other period of greatest vulnerability specifically, survival to S2P, to fully evaluate new strategies for postoperative management. In that regard the data reported in this study are unique and important, as they address factors that correlated with improved survival during the entire period of greatest vulnerability.

Conclusion

Improved early and intermediate survival following S1P can be achieved with strategies that allow for early identification of decreased systemic output and the use of long acting afterload reduction that stabilizes systemic vascular resistance and therefore the pulmonary to systemic flow ratio. Strategies to ameliorate the inflammatory response to CPB may be of benefit in minimizing the duration and degree of postoperative support. The use of strategies that limit the duration of DHCA appear to have a positive impact on survival and merit additional studies. In our experience new treatment strategies have minimized the impact of the patients’ preoperative condition and the impact of anatomic variables specifically, low weight and small ascending aortic size. Although significant institutional biases exist, a multi-institutional study to systematically review perioperative management issues may shed light on the contribution of individual treatment strategies and allow further refinement of patient care in this complex population.

References


Improved Survival of Patients Undergoing Palliation of Hypoplastic Left Heart Syndrome: Lessons Learned From 115 Consecutive Patients
James S. Tweddell, George M. Hoffman, Kathleen A. Mussatto, Raymond T. Fedderly, Stuart Berger, Robert D. B. Jaquiss, Nancy S. Ghanayem, Stephanie J. Frisbee and S. Bert Litwin

Circulation. 2002;106:I-82-I-89
doi: 10.1161/01.cir.0000032878.55215.bd
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/12_suppl_1/I-82

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/