Impact of preoperative treatment strategies on the early perioperative outcome in neonates with hypoplastic left heart syndrome

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Supplemental material is available online.

Objective: This study was undertaken to determine the impact of specific intensive care procedures on preoperative hemodynamics, incidence of preoperative organ dysfunction, and in-hospital mortality among neonates with hypoplastic left heart syndrome with pulmonary overcirculation and to assess the influence of the change in preoperative management on early postoperative outcome.

Methods: In this retrospective evaluation of 72 neonates with classic hypoplastic left heart syndrome and severe pulmonary overcirculation with different preoperative management strategies from 1992 to 1995 and from 1996 to 2000, univariate and multivariate analyses of risk factors were performed with stepwise logistic regression.

Results: Among patients with ventilatory and inotropic support from admission until surgery, degree of metabolic acidosis (lowest recorded and prerepair pH values) was significantly higher than among patients who received systemic vasodilators without ventilation before surgery. Preoperative organ dysfunction occurred in 19 of 72 patients (26%), predominantly before 1996; the most significant was hepatic failure in 13 (68%). Lowest recorded and prerepair pH values did not predict the development of organ dysfunction, whereas inotropic medication, lack of afterload reduction, and especially ventilatory support correlated significantly with organ injury. In-hospital mortality decreased from 65% (13/20) to 13% (6/46) from the first to the second period. According to multivariate analysis, ventilatory support and organ dysfunction were significantly related to in-hospital mortality.

Conclusion: In neonates with hypoplastic left heart syndrome, systemic afterload reduction can avoid preoperative artificial respiration, identified as a significant risk factor for the development of preoperative dysfunction of end organs and in-hospital mortality.

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Since the first report of Norwood and coworkers[1] about the staged reconstructive surgery for hypoplastic left heart syndrome (HLHS), modifications and refinements in surgical technique and postoperative care have slowly improved in-hospital survival after the first stage of surgical palliation from low figures to a range from 68% to 93%.[2-4] Mortality seemed mainly related to surgical or postoperative risk factors, with only a few aspects concerning the preoperative period considered in the literature. Among these, severe preoperative metabolic acidosis and lack of prenatal diagnosis were identified as risk factors for an adverse outcome.[5-8] Metabolic acidosis reflects an excessive

Abbreviations and Acronyms
HLHS = hypoplastic left heart syndrome
$\dot{Q}p$ = pulmonary perfusion
$\dot{Q}s$ = systemic perfusion

maldistribution of cardiac output, with significant preference of the pulmonary blood flow and concomitant critical reduction of systemic flow, possibly contributing to severe end-organ damage (eg, liver injury) or right ventricular dysfunction.[6,9-12]

Only a few authors have issued some details of their preoperative management,[13,14] and we are unaware of any systematic analysis of the influence of various treatment options on patient condition at the time of surgery and on postoperative outcome.[15-17] Therefore the aim of our study in infants with HLHS and pulmonary hyperperfusion was to assess the impact of some specific intensive care procedures (mechanical ventilation, vasoactive substances) on the incidence of preoperative organ dysfunction and hospital mortality and to determine whether our experience with a modification of preoperative management contributed to an improved early postoperative outcome.

Patients and Methods

Patients

We reviewed the cases of 126 consecutive infants who were admitted for stage I reconstruction for all forms of HLHS from September 1992 to July 2000. In this study, we enrolled only neonates with classic HLHS (aortic and mitral atresia or stenosis, diminutive ascending aorta, and severe hypoplasia of the left ventricle) with pulmonary hyperperfusion, as determined by a ratio of pulmonary perfusion ($\dot{Q}p$) to systemic perfusion ($\dot{Q}s$) greater than 2. Nine infants had no pulmonary overcirculation ($\dot{Q}p/Qs < 2$) because of restrictive atrial communications, total anomalous pulmonary venous drainage, and left-sided hypoplasia of the pulmonary veins. Patients with other forms of functionally univentricular heart (n = 13), significant coarctation and thus reduced reverse flow to the coronary arteries (n = 4), or incomplete hemodynamic data (n = 16), and infants enrolled in another study protocol (n = 9) were excluded. Finally, 3 patients with major noncardiac congenital defects or severe prematurity were not enrolled.

Among the remaining 72 infants (49 male and 23 female), two groups were distinguished according to the period of treatment: 23 patients were treated between 1992 and 1995, representing our early experience, and 49 patients were treated between 1996 and 2000. All but 6 neonates with severe hepatic or renal damage or severely depressed myocardial function underwent Norwood operation and comprise the surgical cohort (n = 66). The groups did not differ with respect to anatomic subgroups of HLHS (mitral atresia with aortic atresia; mitral stenosis with aortic atresia; mitral stenosis with aortic stenosis; mitral atresia with aortic stenosis and ventricular septal defect) and birth weight (3363 ± 352 g vs 3323 ± 629g), and surgery was performed at a similar median age (8 days vs 6 days), although with a wider range in the first group (3-80 days vs 1-37 days).

So that we could better understand the effect of preoperative ventilation on the degree of metabolic acidosis and pulmonary overcirculation, we formed three subgroups (Table E1). Nineteen patients (subgroup 1) received ventilatory support before or soon after admission until operation, with inotropes and vasodilators as needed. Subgroup 2 included 13 patients who received ventilation for reasons of transport security for less than 24 hours; most were subsequently treated with sodium nitroprusside for systemic vasodilation. Subgroup 3 included 40 patients who received systemic afterload reduction from the time of diagnosis or admission but without mechanical ventilation at any time before surgery.

Preoperative Evaluation

Ratio of pulmonary to systemic blood flow. Soon after admission, arterial and central venous lines were placed for pressure and blood gas monitoring, allowing calculations of $\dot{Q}p/Qs$ by the Fick equation.[18] In patients with HLHS physiology, aortic and pulmonary arterial saturations are identical. Pulmonary vein oxygen saturation was assumed to be 100% in patients receiving mechanical ventilation with an inspired oxygen fraction of 30% or greater (n = 5) and to be 95% in patients with or without ventilation with an inspired oxygen fraction less than 30% (n = 27). $\dot{Q}p/Qs$ greater than 2 was considered to indicate pulmonary overcirculation.

Right ventricular dysfunction. Right ventricular function was evaluated by 2-dimensional echocardiography after admission and the day before surgery. We formed two functional categories: (1) normal if the function was considered normal or mildly depressed and (2) abnormal if it was moderately or severely depressed. Similarly, the degree of tricuspid regurgitation was classified as absent if it was either absent or mild and present if it was moderate or severe. Because both echocardiograms were evaluated before the operation, the interpreting cardiologist was blinded to the final outcome.

Organ dysfunction. Organ dysfunction was considered to be evident according to the following criteria. Severe hepatic dysfunction was indicated by high hepatic enzyme levels (aspartate aminotransferase >200 U/L, lactate dehydrogenase >1500 U/L), reduced concentrations of coagulation factors (factors II and V <30%), and increased conjugated bilirubin (>0.5 mg/dL). In the case of lethal outcome, histologic examination of a liver specimen was performed with parental consent. Severe renal injury was indicated by serum creatinine greater than 200 μmol/L. Necrotizing enterocolitis and seizures were included in the diagnosis of organ dysfunction.

Preoperative Management

Between 1992 and 1995, mechanical ventilation was considered the most useful tool to support the neonate with cardiorespiratory exhaustion. We tried to perform a slight hypoventilation to obtain a permissive hypercapnea (tidal volume <8-10 mL/kg, positive end-expiratory pressure level 3-5 mm Hg, targeted arterial P_{CO_2}

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35-50 mm Hg) and used continuous sedation with fentanyl and midazolam to avoid the hyperventilation often triggered by metabolic acidosis. As a consequence of the lack of endogenous catecholamines, inotropic support (epinephrine 0.06 ± 0.02 μg/[kg/min], dopamine 3.8 ± 0.9 μg/[kg/min]) was necessary in most cases to compensate for low blood pressures. Supplemental carbon dioxide and subatmospheric oxygen were not applied. All patients were treated with prostaglandin E_1 (0.017 μg/[kg/min]). Parenteral nutrition was most common, because oral or gastric tube feeding seemed unfavorable.

Since 1996, we have pursued a new preoperative treatment protocol designed to achieve a more favorable ratio between systemic and pulmonary vascular resistances. Mainly it is started in the referring hospital. Whenever feasible, no inotropic or ventilatory support is applied, and patients are extubated as soon as possible after admission. Afterload reduction is obtained by continuous infusion of sodium nitroprusside (2.1 ± 0.8 μg/[kg/min]) titrated clinically to achieve adequate urinary output and stable nonacidotic blood gas values. Prostaglandin E_1 is administered at a reduced dosage (0.005 μg/[kg/min]). Oral sedatives are given if necessary. Oral or gastric tube feeding until surgery has been possible for almost all patients.

Surgical and Postoperative Management

The first stage of the reconstructive procedure for HLHS is essentially as previously described.[15,17] A 3.0-, 3.5- or 4.0-mm IMPRA shunt (C. R. Bard, Inc, Murray Hill, NJ) was placed between the right subclavian artery and the proximal right pulmonary artery. During the study period, there were no significant changes in circuit design and conduct of cardiopulmonary bypass. The postoperative management with mechanical ventilation (tidal volume <8-10 mL/kg, arterial P_{CO_2} 35-50 mm Hg), inotropic support (epinephrine, dopamine), and afterload reduction (nitroprusside) did not change essentially during the study periods.

Data Collection and Analysis

Patient data were compiled by reviewing medical files, operative reports, and echocardiographic results. Data are presented as mean ± SD or median and range as appropriate. The analysis was conducted both for the time groups and for the therapeutic subgroups.[1-3]

Preoperative factors (prenatal diagnosis, lowest recorded and prerepair arterial pH values, presence of ventricular dysfunction or tricuspid insufficiency), preoperative treatment (mechanical ventilation, use of vasodilators and inotropic support), and surgical data or factors (age at operation, era of operation 1992-1995 vs 1996-2000, diameter of ascending aorta, shunt size normalized as cross-sectional area divided by patient body weight, duration of deep hypothermic circulatory arrest) were evaluated for impact on persisting organ dysfunction at the time of surgery and for the probability of in-hospital death (Table E2).

Continuous variables were dichotomized at either the median (age, prerepair pH, normalized shunt size, deep hypothermic circulatory arrest duration) or the 10th percentile (lowest recorded pH) to create categoric variables. The relevances of potential risk factors were determined with χ^2 or Fisher exact tests. Variables found to be significant by univariate analysis were entered into multivariate analysis with stepwise logistic regression. Odds ratios are presented with 95% confidence intervals. For situations in which the 95% confidence interval does not contain the value 1, the corresponding test for odds ratio 1 is significant to the 5% level. The Cochran-Armitage trend test, which is specifically designed to analyze trends with time, was used to determine whether there was a linear trend in in-hospital mortality year by year. This test should rule out a major influence of the effect of continuously increasing human experience.

The Kruskal-Wallis *H* test was used to confirm the same distribution of anatomic subtypes of HLHS within the two experience periods. For comparison between time groups or among therapeutic subgroups, the nonparametric *t* test or Wilcoxon rank test was applied. Statistical analysis was performed with Systat 10 software (SPSS Inc, Chicago, Ill).

Results

Organ Dysfunction

Preoperative organ dysfunction occurred in 10 of 23 patients (43%) between 1992 and 1995 and in 9 of 49 (18%) between 1996 and 2000. Only 1 case of organ dysfunction (4%) was observed among the last 15 patients, when the new treatment protocol was routinely applied immediately after diagnosis in the referring hospitals. Fourteen of the 19 affected patients showed signs of organ dysfunction at admission.

Among the 19 patients with organ dysfunction (Table E3), circulatory shock resulted in hepatic failure in 13 (68%). Seven of these 13 patients (54%) showed some improvement in hepatic function test results and underwent cardiac surgery, whereas 6 (3 in each group) had irreversible hepatic failure and died without operation. The postmortem analysis of 4 liver specimens revealed widespread centrilobular necrosis and congestion caused by microthrombi in the small liver veins. Three of the 7 patients who underwent surgery died of excessive nonsurgical bleeding in the early postoperative period. Because their coagulation factor II and V levels were still significantly decreased immediately before the operation, the bleeding may have been related to an inappropriate postoperative synthesis of these factors. All patients with hepatic failure also had reduced renal function. Five of the 19 patients with organ dysfunction (26%) had necrotizing enterocolitis develop; 3 required bowel resection before cardiac surgery. Preoperative seizures were observed in 1 infant (5%).

The risk factors for preoperative organ dysfunction are shown in Table 1. Preoperative ventilatory support, inotropic medication, and lack of systemic vasodilation were correlated significantly with organ injury. Ventilatory support was used in 18 of the 19 infants who had organ injury, inotropic medication in 15, and no afterload reduction in 6. For the other risk factors, especially the lowest recorded

TABLE 1. Univariate risk factor analysis: Preoperative organ dysfunction

Risk factor	Odds ratio	95% Confidence interval
Absence of prenatal diagnosis	2.3	0.7-8.9
Age at admission (<median)	1.6	0.3-7.9
Lowest recorded plasma pH (<10th percentile)	1.9	0.1-4.4
No systemic vasodilation	5.7	2.3-10.5
Ventilatory support	14.5*	2.3-154.5
Inotropic support	6.4	1.8-23.8
Prerepair plasma pH (<median)	2.4	0.1-4.9
Preoperative $\dot{Q}p/\dot{Q}s$ (<median)	2.1	0.4-4.7

Number of patients with organ dysfunction, 19; number without, 53. All confidence intervals that do not include the value 1 indicate significant results. Variables found to be significant by univariate analysis were entered into multivariate analysis with stepwise logistic regression. *Significant by multivariate analysis ($P < .05$).

pH, no significant association with preoperative organ dysfunction was seen.

Preoperative Management in Subgroups

The influence of the type of preoperative management (subgroups 1-3) on the arterial pH (lowest and immediate preoperative pH values) is illustrated in Figure 1. All patients with ventilatory support on admission (subgroups 1 and 2) showed a significantly higher degree of metabolic acidosis than did patients who did not receive ventilatory support at any time before surgery (lowest recorded pH 7.08 ± 0.22, $P = .0024$, and 7.24 ± 0.13, $P = .048$, vs 7.34 ± 0.06). At the time of surgery, the arterial pH was significantly lower in patients still receiving ventilatory support (subgroup 1) than in patients with exclusive vasodilator therapy (subgroup 3, 7.38 ± 0.08 vs 7.45 ± 0.07, $P = .023$). Five of 19 patients who had ventilation until surgery required an emergency stage I operation within 48 hours because of unstable hemodynamics and persistent metabolic acidosis.

In-Hospital Mortality

Sixty-six of 72 patients underwent first-stage surgery, with an in-hospital mortality of 28.8%. Thirteen of 20 infants operated on between 1992 and 1995 (65%) died, whereas only 6 of 46 patients operated on since 1996 (13%) died. Statistical analysis specifically designed to analyze trends with time showed no significant trend in in-hospital mortality in either time period; however, a very strong time effect was seen when both periods were analyzed together.

Preoperative factors. Preoperative factors that correlated significantly with adverse outcome included absence of prenatal diagnosis of HLHS and the lowest preoperatively recorded pH, as well as low pH immediately before surgery (Table 2). Patients with end-organ dysfunction and also with right ventricular dysfunction were less likely to survive than patients without any organ damage. Among therapeutic features, ventilatory and inotropic support at any time before surgery and lack of systemic vasodilation were associated with significantly increased mortality. In the multivariate analysis, ventilatory support and preoperative organ dysfunction were significantly related to in-hospital mortality. In-hospital survival was 89% among patients without mechanical ventilation at any time before surgery (subgroup 3) and differed significantly from that among patients supported by mechanical ventilation, independent of time of application of ventilation (subgroup 1, 26% [$P = 0.007$], and subgroup 2, 72% [$P = 0.032$]).

Additional surgical risk factors. Some potential surgical risk factors in this analysis, such as presence of aortic atresia, diameter of the ascending aorta, and shunt size, were not significantly related to in-hospital mortality. Era of operation and duration of deep hypothermic circulatory arrest were associated with significantly increased mortality (Table 2).

Comparison of periods. Postoperative mortality between 1993 and 1995 (13/20, 65%) was caused by excessive shunt flow (n = 4), bleeding complications (n = 3), and right ventricular dysfunction (n = 3). Another 2 patients died of

TABLE 2. Univariate risk factor analysis: In-hospital mortality

Risk factor	Odds ratio	95% Confidence interval
Absence of prenatal diagnosis	10.5	1.8-17.9
Lowest recorded plasma pH (<10th percentile)	3.2	1.1-14.1
Ventilatory support	9.7*	2.9-23.6
No systemic vasodilation	5.6	1.2-9.6
Inotropic support	8.1	2.3-27.7
Prerepair plasma pH (<median)	8.3	1.8-15.2
Presence of aortic atresia	0.6	0.3-1.7
Diameter of ascending aorta (<median)	1.6	0.3-1.8
Ventricular dysfunction	14.6	3.9-54.4
Tricuspid insufficiency	1.9	0.6-6.1
Age at operation (<median)	2.4	0.8-7.7
Organ dysfunction	11.8*	1.9-19.3
Deep hypothermic circulatory arrest time (<median)	4.4	3.8-5.9
Era of operation	6.5	1.1-9.9
Shunt size (indexed)	1.5	0.3-1.8

Number of in-hospital deaths, 19; number of survivors, 47. All confidence intervals that do not include the value 1 indicate significant results. Variables found to be significant by univariate analysis were entered into multivariate analysis with stepwise logistic regression. *Significant by multivariate analysis ($P < .05$).

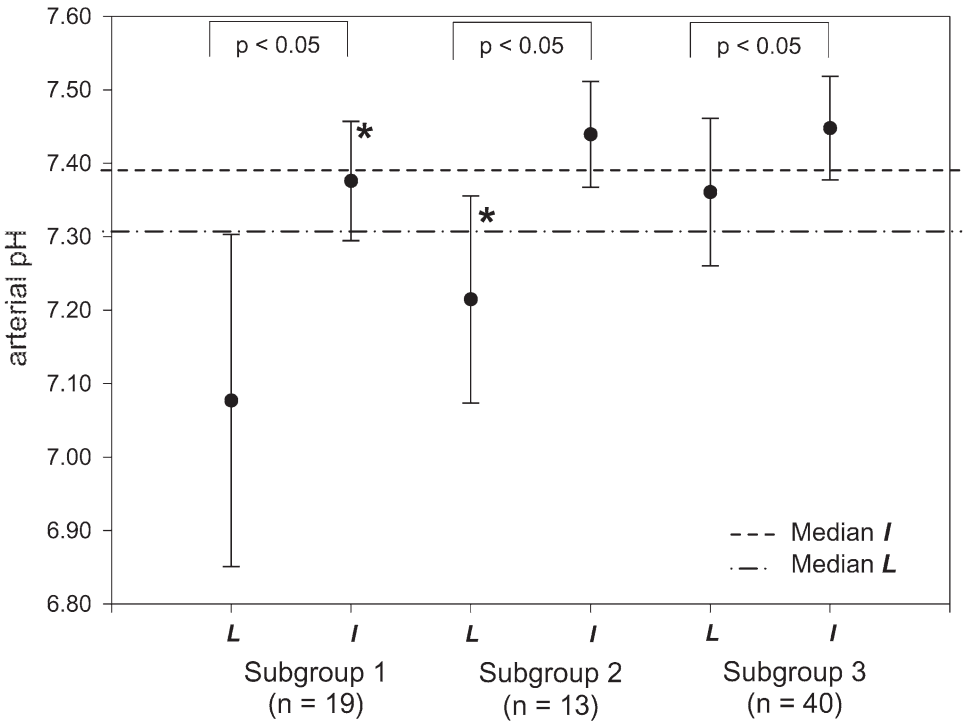

Figure 1. Lowest recorded *(L)* and immediate *(I)* preoperative arterial pH values according to type of preoperative management. *Columns* and *error bars* represent mean and upper and lower SDs, respectively. *Asterisk* indicates significant difference ($P < .05$) versus corresponding values of group 3. Median is for entire cohort.

severe hepatic fibrosis and failure, and 1 patient died after early balloon dilatation of severe coarctation.

Among the 6 in-hospital deaths since 1996, right ventricular dysfunction, which made weaning from cardiopulmonary bypass impossible, was the most prevalent cause (n = 3). Other reasons were the severe obstruction of the anastomosis between native aorta and pulmonary trunk (n = 1), excessive shunt flow (n = 1), and intracranial bleeding (n = 1). Preexisting organ damage was not a cause of death during this period.

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Discussion

Despite improvements in surgical techniques and postoperative care, the first stage of reconstructive palliation of HLHS remains at substantial risk for adverse outcome. Risk factor analysis conducted to evaluate the early stage I mortality have proposed various controversial causes.[5,6,9,15,19]

The reasons for mortality are multifactorial, and the potential risk factors are likely to be different for each hospital caring for patients with HLHS. In previous studies, anatomic and surgical factors, as well as the hazardous toxic effect of metabolic acidosis, were discussed. The degree of metabolic acidosis in parallel circuits reflects the extent of pulmonary overcirculation burdening a critically diminished systemic perfusion. For that reason, it seems important to analyze factors contributing to that hemodynamic imbalance, such as some specific therapeutic features of neonatal medicine often started in absence of a definite diagnosis of HLHS. Although the prerequisite for improved preoperative care is higher awareness and more rapid diagnosis, simple and appropriate guidelines for the primary management of the baby with HLHS by referring pediatricians are at least similarly or even more important.

In our cohort, as in those of other centers,[6,20] the increased in-hospital mortality among patients without prenatal diagnosis emphasizes the importance of knowing about the cardiac diagnosis for establishing appropriate early postnatal medical management. Especially in neonates without a prenatal diagnosis of HLHS, artificial respiration is used to improve hemodynamic condition. In our cohort of patients, however, artificial respiration proved a significant risk factor for both the development of organ dysfunction and in-hospital mortality according to multifactorial analysis. The most likely explanation is the negative impact of ventilation on pulmonary hyperperfusion as a result of the recruitment of previously nonventilated and consequently poorly perfused lung areas. The systemic consequences are prolonged periods of metabolic acidosis with preoperatively still lower pH values in patients receiving ventilatory assistance, independent of such other therapeutic components as inotropic medication and afterload reduction, resulting in severe organ dysfunction, specifically often irreversible hepatic injury (Table 1). Tweddell and colleagues[14] iden-

tified preoperative mechanical ventilation as the only risk factor for death until 6 months after stage I palliation. Although avoidance of preoperative mechanical ventilation was recommended in a review of Pearl and associates,[21] only our study has specifically evaluated the effect of ventilatory support on preoperative organ dysfunction and overall outcome in infants with HLHS. However, we did not use inspired gas mixtures that added nitrogen or carbon dioxide. Tabbutt and colleagues[22] evaluated the impacts of hypoxia and hypercarbia in a randomized short-term (10 minutes) crossover trial and recommended hypercarbia because of the increased oxygen delivery for infants with HLHS with severe hemodynamic deterioration. However, they pointed out that the majority of preoperative infants do not require controlled ventilation before operation and recommended further studies to determine the role for inspired gases. To date, no experience with longer use of either ventilation strategy until surgery has been published.

Because many of the patients receiving ventilatory support were sedated so that they would tolerate low-tidal volume ventilation, inotropic support with epinephrine and dopamine was given to increase low blood pressures. Even though only univariate, not multivariate, risk factor analysis showed an impact of inotropic support on in-hospital mortality, it seems likely that it increased systemic afterload and facilitated pulmonary hyperperfusion, which had already been stimulated by artificial respiration. Other groups who have used preoperative mechanical ventilation in most of their cases have reported the need for inotropic support by approximately half of their patients.[4] However, they did not see a significant influence of preoperative inotropic support on survival after the Norwood operation.

Afterload reduction with nitroprusside was the keystone in the treatment of 40 patients without ventilatory support during our second observational period. Despite high estimates of $\dot{Q}p/Qs$ after referral, the hemodynamic burden was well tolerated, with no persistent metabolic acidosis or organ injury. In most of our patients, pulmonary overcirculation was still present at the time of surgery; however, improved systemic circulation was reflected by an alkaline shift in arterial pH. The therapeutic concept is that lowering systemic vascular resistance allows a gradual increase in systemic blood flow while avoiding any active increase in pulmonary blood flow (eg, artificial respiration). For intensive care after the Norwood operation, the same concept of afterload reduction by phenoxybenzamine to improve systemic oxygen delivery was introduced by Tweddell and coworkers[23] in 1999. Hoffman and colleagues[24] from the same institution recently reported a lower arteriovenous oxygen content difference across the whole oxygen saturation scale after the Norwood operation in patients treated with phenoxybenzamine than in control patients. The principle of pharmacologic control of systemic vascular resistance is obviously working in the preoperative setting. It is possible that only its use allowed avoidance of preoperative artificial respiration. Instead of nitroprusside or α-blockers, phosphodiesterase inhibitors such as milrinone, with inotropic as well as potent afterload-reducing action, may be useful drugs, especially for patients with poor ventricular function or functional tricuspid insufficiency.

In our study, preoperative development of organ dysfunction was identified as an independent significant risk factor for in-hospital mortality. Jonas and associates[6] and Tworetzky and coworkers[7] have already mentioned this problem but did not systematically study either the potential reasons or the prevention of organ dysfunction. According to our data, organ dysfunction was likely caused or at least facilitated by the hemodynamic consequences of artificial respiration, inotropic support, and lack of afterload reduction.

Although preoperative enterocolitis, transient renal and hepatic dysfunction, and seizures did not considerably influence in-hospital mortality after the Norwood procedure in some reports,[9,25] hepatic injury was the most prevalent cause of overall mortality of our early series. Hepatic involvement was the most frequent cause of organ dysfunction, which proved a significant risk factor for in-hospital mortality even by multivariate analysis. In accordance with Jonas and associates[6] and Moodie and colleagues[12] but in contrast to Kern and coworkers,[9] we observed several cases of severe hepatic damage with irreversible collapse of coagulation factor synthesis strictly associated with severe preoperative metabolic acidosis. In addition, if hepatic dysfunction was not completely alleviated at the time of surgery, life-threatening bleeding complications or postoperative hepatic failure occurred. The histologic examination of 4 liver specimens revealed widespread centrilobular liver necrosis, substantiating the severity of underlying organ damage. Thus only patients with complete recovery of liver function, characterized by normalization of previously elevated transaminase values, intact synthesis of coagulation factors, and bilirubin conjugation, are suitable candidates for the Norwood procedure.

Limitations of the Study

Our results are based on the retrospective analysis of two periods with different preoperative management strategies in our institution between 1993 and 2000, and therefore the different therapeutic interventions were not randomized or blinded. The focus was directed toward factors of preoperative management likely to contribute

to end-organ dysfunction and its influence on overall outcome. However, it cannot be completely ruled out that different surgical factors more specific than shortening of cardiac arrest time, which was significant by univariate but not multivariate statistical analysis of in-hospital mortality, or other than the unchanged postoperative strategies of pharmacologic and ventilatory support may also be responsible for the changed outcome. The continuously increasing and difficult to measure human experience, Marc deLeval's "human factor,"[26] may have had an effect; however we argue that this factor is rather unlikely to be responsible, because we could demonstrate no linear yearly trend of decrease in in-hospital mortality within both periods but found uniform percentages of hospital mortality each year. Analysis with the Cochran-Armitage trend test, which is specifically designed to analyze trends with time, indicates that it is very unlikely that the changes result from continuously improving surgical or postoperative management experience. In addition, if the surgical experience had an effect of major importance in lowering in-hospital mortality, the shortened cardiac arrest time probably would have shown statistical significance by multivariate analysis; however, this was not the case. The trend toward the use of smaller modified Blalock-Taussig shunts (3.5 mm instead of 4 mm), which probably has influenced the ease of the postoperative course, also had no significant effect on in-hospital mortality.

Conclusions

This study of preoperative management of neonates with HLHS showed a significant improvement in outcome as a consequence of systemic afterload reduction with vasodilating agents. This already accepted postoperative therapeutic principle of vasodilator therapy has a positive effect on the balance of systemic and pulmonary blood flows and may have helped to avoid preoperative artificial respiration, a significant risk factor for preoperative dysfunction of end organs and in-hospital mortality. Both changes not only make intensive care for most neonates with HLHS much easier but are likely to have a positive effect on overall outcome.

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TABLE E1. Frequency table of type of preoperative treatment

	Subgroup 1 (n = 19)	Subgroup 2 (n = 13)	Subgroup 3 (n = 40)
Ventilation alone	6	3	0
Inotropes*	9	0	0
Vasodilation*	0	8	40
Vasodilation and inotropes*	4	2	0

Subgroup 1, Ventilatory support plus inotropes and vasodilators before or soon after admission until operation; *Subgroup 2,* ventilatory support for reasons of transport security and lasting less than 24 hours, plus inotropes, vasodilators, or both; *Subgroup 3,* no ventilatory support at any time before surgery and regular systemic afterload reduction. *Treatment in addition to ventilatory support in subgroups 1 and 2.

TABLE E2. Frequencies of risk factors among neonates with HLHS

Risk factor	1992-1995 (n = 23)	1996-2000 (n = 49)
Absence of prenatal diagnosis	17	31
Age on admission (<median)	7	26
Lowest recorded pH (<10th percentile)	5	4
Ventilatory support	21	11
No systemic vasodilation	17	1
Inotropic support	13	2
Prerepair pH (<median)	16	23
Presence of aortic atresia	13	29
Diameter of ascending aorta (<median)	7	23
Ventricular dysfunction	4	3
Tricuspid insufficiency	9	12
Age at operation (<median)	9	21
Organ dysfunction	10	9
Deep hypothermic cardiac arrest time (<median)	9	26
Shunt size (indexed, mm^2)	13.26	12.84

TABLE E3. Preoperative laboratory results of patients with and without organ injury, with hepatic dysfunction as subset of organ injury

	No.	Aspartate aminotransferase (U/L)	Lactate dehydrogenase (U/L)	Conjugated bilirubin (μmol/L)	Factor II (%)	Factor V (%)	Creatinine (μmol/L)
Organ injury	19	271 ± 198*	2261 ± 885*	8.6 ± 8.6*	37.5 ± 20.2*	42.6 ± 27.5	175 ± 30*
Hepatic injury and no surgery†	6	475 ± 142*	2732 ± 703*	18.8 ± 8.6*	23.2 ± 4.7*	24.9 ± 5.2*	199 ± 34*
Hepatic injury with surgery	7	292 ± 93*	1956 ± 451*	5.1 ± 1.8*	27 ± 5.2*	34.4 ± 7.1*	167 ± 26
No organ injury	53	34.9 ± 25.6	689 ± 341	0	58.3 ± 13.6	66.1 ± 12.4	148 ± 21

Organ injury (n = 19) included hepatic and renal injury (n = 13), necrotizing enterocolitis (n = 5), and preoperative seizures (n = 1). Worst values recorded for aspartate aminotransferase and lactate dehydrogenase; immediate preoperative recorded values recorded for conjugated bilirubin, factor II, and factor V. *Significant difference from patients without organ injury. †In group without surgery, values recorded at time of decision against surgery.

E Ventricular Dysfunction

At the time of admission severe right ventricular dysfunction was observed in 5 of 19 neonates with organ dysfunction (26%) but only 2 of 53 without organ dysfunction (4%). Immediately before surgery, severe ventricular dysfunction was still present in 6 of these 7 patients. Because it was not the aim of this study to investigate specific reasons for preoperative right ventricular dysfunction, no further analysis of contributing factors was performed.

E In our series, ventricular dysfunction represented the next most frequent preoperative organ disease after liver injury. The frequent coincidence of preoperative right ventricular dysfunction and hepatic failure may point to a common harmful etiology, most likely circulatory shock and its metabolic consequences. Tworetzky and coworkers[7] reported a higher occurrence of ventricular dysfunction and tricuspid regurgitation among patients with postnatally diagnosed HLHS than among those with a prenatal diagnosis. Lloyd and colleagues[11] suggested that postnatally acquired ventricular dysfunction could have been avoided by early appropriate management. In our experience, consequent afterload reduction with nitroprusside increases systemic cardiac output and prevents ventricular dysfunction. In contrast, respiratory and ino-

tropic support are more likely to prevent recovery of ventricular function, because they contribute to sustained pulmonary overcirculation with consecutive right ventricular enlargement and potentially harmful reduction of systemic cardiac output, which may also influence coronary perfusion. In contrast to previous investigators, significant preoperative tricuspid regurgitation, aortic atresia, diameter of the ascending aorta, and shunt size were not found to be significant predictors of outcome.[5]

E To find parameters that describe the preoperative hemodynamic deterioration and may have prognostic value, we examined the lowest preoperatively recorded and prerepair pH values, neither of which was correlated significantly with the development of preoperative organ dysfunction but both of which were correlated with in-hospital mortality, as already described by Jonas and associates.[6] Although these values are clinically useful, a specific cutpoint cannot be given. Laboratory parameters documenting complete preoperative recovery from organ dysfunction, especially of the liver, are much more important in this regard.

E Because the retrospective type of the study, we were not able to describe right ventricular dysfunction by quantitative measures, such as fractional area change or myocardial performance index. As in previous studies,[14] we had to use qualitative judgements.

We are aware of the poor reliability of some values such as the lowest recorded pH, often taken from a capillary gas sample in the referring hospital, or the $\dot{Q}p/Qs$ calculations. The systemic venous saturations were often not very consistent, the pulmonary venous saturation was not measured but only assumed according to ventilatory status, and the mixed venous saturation may vary depending on the precise site of the tip of the central venous line. However, even if the lowest recorded pH was likely overestimated, there was no predictive value concerning the development of organ dysfunction.