CARDIOTHORACIC TRANSPLANTATION

INFANT HEART TRANSPLANTATION: IMPROVED INTERMEDIATE RESULTS

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Objectives: Our objectives were to (1) review our experience with heart transplants in infants (age < 6 months), (2) delineate risk factors for 30-day mortality, and (3) compare outcomes between our early and recent experience. **Methods:** Records of all infants listed for transplantation in our center before September 1996 were analyzed. Early and recent comparisons were made between chronologic halves of the accrual period. Univariate analysis was used to analyze potential risk factors for 30-day mortality (categorical variables, Fisher's exact test; continuous variables, nonparametric Wilcoxon rank-sum test). Multivariable analysis included univariate variables with p values ≤ 0.10 . Actuarial survivals were estimated (Kaplan-Meier) and compared by the log-rank test. **Results:** Fifty-one of the 60 infants listed for transplantation were operated on (waiting list mortality 15%). Thirty-day mortality was 18% overall, 30% in the first 3 years and 10% in the last 3 years ($p = 0.07$). Sepsis was the commonest cause of early death (4/9). Univariate analysis suggested four potential risk factors for early death: preoperative mechanical ventilation ($p = 0.01$), prior sternotomy ($p = 0.002$), preoperative inotropic drugs ($p = 0.08$), and warm ischemia time ($p = 0.08$). Multivariable analysis indicated that prior sternotomy ($p = 0.01$) was an independent risk factor for 30-day mortality. Actuarial survivals were 80%, 78%, and 70% at 1, 2, and 3 years, and these figures improved between early and recent groups ($p = 0.05$). Late deaths were most commonly due to acute rejection (3/5). **Conclusions:** Results of heart transplantation in infancy improve with experience. Prior sternotomy increases initial risk. Intermediate-term survival for infants with end-stage heart disease is excellent. (J Thorac Cardiovasc Surg 1998;116:242-52)

Orthotopic heart transplantation is the only available treatment option for children with unreconstructible congenital heart defects and severe car-

diomyopathies. In addition, some centers now prefer transplantation over the Norwood procedure for infants with hypoplastic left heart syndrome and for other congenital heart defects that require high-risk single ventricle repairs. Intermediate results of pediatric heart transplantation now approach the results achieved in adult patients, with 2-year actuarial survivals of 70%.¹ Because the number of pediatric heart transplants performed by individual institutions has been relatively small, the Pediatric Heart Transplant Study (PHTS) conducted a multi-institutional analysis to provide data on survival and risk factors for perioperative mortality in children aged 1 to 18 years.² This group demonstrated that younger age, requirement for pretransplantation mechanical assistance, and nonidentical donor-recipient ABO match were independent risk factors for early mortality. Similarly, International Society for Heart and Lung Transplant (ISHLT) data dem-

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onstrate decreased survival for children undergoing transplantation under 1 year of age relative to older children.¹

Infants currently comprise the largest segment of pediatric patients undergoing heart transplantation in our center. ISHLT data indicate a similar worldwide trend, with the total number of infant heart transplantations performed numbering fewer than 100 per year.¹ Unfortunately, the scarcity of donor organs in this age group has limited the experience of most pediatric heart transplant programs to fewer than 35 infants.³⁻⁵ The only larger reported series is from Loma Linda, California.^{6,7} Consequently, few single-center data are available regarding intermediate outcomes and perioperative risk factors for infant heart transplantation.

Our cumulative experience with heart transplantation in patients 18 years and younger now totals 112 transplants in 110 patients. We⁸ have previously reported intermediate results in our patients older than 6 months at the time of transplantation. The purposes of this study are (1) to review our experience with heart transplantation performed in infants listed at age less than 6 months, (2) to identify risk factors for 30-day mortality in this age group, and (3) to compare early and intermediate outcomes between our early and more recent experience.

Methods

Patients and data collection. The records of all 60 infants aged 180 days or less who entered our heart transplantation protocol between June 1990 and August 1996 were retrospectively reviewed. This accrual period was selected so that all listed patients either underwent transplantation or died awaiting transplantation. All infants surviving to transplantation underwent operation before January 1, 1997. No patients were lost to follow-up. Autopsies were obtained in all cases of hospital and late mortality.

Preoperative management. The primary diagnostic tool in all cases was transthoracic two-dimensional echocardiography. Cardiac catheterization was used selectively to clarify anatomy not clearly delineated by echocardiography and for preoperative palliative procedures. Pulmonary vascular resistance was not specifically determined because of the young age of this population. Pulmonary artery banding was undertaken to protect the pulmonary bed in patients with high-flow left-to-right shunts (e.g., unbalanced atrioventricular septal defects) when deemed appropriate. The preoperative management of hypoplastic left heart syndrome (HLHS) evolved considerably during the course of this study. Patients with HLHS and ductus-dependent systemic circulations were maintained on intravenous alprostadil (prostaglandin E₁). Initially, strategies to reduce preoperative pulmonary vascular resistance were used in the hope of avoiding donor right

heart failure after transplantation. More recently, we followed strategies to increase pulmonary vascular resistance to maintain hemodynamic stability while awaiting transplantation.⁹ Inhaled nitrogen was administered to limit pulmonary blood flow during the initial management of patients with HLHS. Most patients were weaned from nitrogen within 6 weeks. Atrial septal defects were left restrictive unless excessive hypoxemia mandated balloon atrial septostomy. Diuretics and inotropic support were minimized. Mechanical ventilation was avoided whenever possible. Patients with HLHS variants (i.e., Shone's syndrome) anticipated to have adequate antegrade aortic arch flow to support systemic circulatory requirements long enough to allow transplantation underwent ductal division and coarctation repair.

Perioperative management. Perioperative pulmonary artery pressures and mixed venous oxygen saturations were continuously measured in all patients with oximetric pulmonary artery catheters (Abbott Laboratories, Inc., Chicago, Ill.). Donor hearts were procured in standard fashion including extra great vessel lengths as dictated by recipient anatomy. Roe's solution was used for donor cardioplegia. Whenever possible, total ischemia time was limited to less than 4 hours. The majority of cases were performed by a cardiothoracic surgery resident assisted by an attending cardiothoracic surgeon. Circulatory arrest was used during the entire implantation procedure for all ductus-dependent patients with HLHS and when required by patient anatomy or small size. Circulatory arrest followed by low-flow bypass was not used. Isoproterenol and dopamine were routinely used for inotropic support. Dobutamine and epinephrine were used when additional inotropic support was required. Beginning in October 1993, inhaled nitric oxide and intravenous milrinone infusions were routinely used when elevated pulmonary vascular resistance was anticipated or encountered. Perioperative immunosuppression consisted of cyclosporine (INN: ciclosporin), azathioprine, and methylprednisolone. Induction therapy with antithymocyte serum (American Medical Resources, Nashville, Tenn.) was used with rapid discontinuation of methylprednisolone. Serial echocardiograms were used extensively to detect early rejection according to established criteria.¹⁰

Long-term management. After hospital discharge, infants were serially examined and echocardiograms performed frequently. Corticosteroids were not used for long-term immunosuppression. Cyclosporine and azathioprine were given for the first 18 months. More recently, mycophenolate mofetil was used in lieu of azathioprine. Endomyocardial biopsy was used only rarely in the assessment of acute rejection. Routine catheterizations with endomyocardial biopsies and coronary angiograms (recently including intravascular ultrasound) were performed 18 and 36 months after transplantation to detect chronic rejection and cardiac allograft vasculopathy. In the absence of chronic rejection and cardiac allograft vasculopathy, azathioprine was discontinued after 18 months, and cyclosporine monotherapy was used thereafter. Functional development was subjectively assessed by nurse coordinators and transplant cardiologists at each follow-up visit. For purposes of outcome analysis, functional development was determined by review of most current

Table I. Diagnoses of 51 infants undergoing transplantation

Diagnosis	No.
HLHS (ductus-dependent)	25
Shone's syndrome	8
Pulmonary atresia, intact ventricular septum, sinusoids	4
Unbalanced AVSD	3
Hypertrophic cardiomyopathy	2
Tricuspid atresia, TGA, hypoplastic RV, coarctation	2
Tricuspid atresia, TGA, IAA, hypoplastic RV	1
Tricuspid atresia, sinusoids, EFE, complete heart block	1
Truncus arteriosus, TS, TI, hypoplastic LV	1
Truncus arteriosus, TS, truncus arising from RV	1
SV, single atrium, AVSD, left SVC, bilateral IVC, polysplenia	1
SV, pulmonary atresia, TAPVR, asplenia	1
Spongy myocardium	1

AVSD, Atrioventricular septal defect; EFE, endocardial fibroelastosis; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; IVC, inferior vena cava; LV, left ventricle; RV, right ventricle; SV, single ventricle; SVC, superior vena cava; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TI, truncal valve insufficiency; TS, truncal valve stenosis.

follow-up documentation and categorized as good or developmentally delayed.

Definitions. Waiting list time for patients listed in utero was calculated from the date of birth. Pretransplantation procedures were defined as any operative or catheter-based intervention attempted to correct or palliate a congenital cardiac defect. Total ischemia time was defined as the time between donor aortic clamping and reperfusion of the donor heart. Warm ischemia time was considered to equal the circulatory arrest time or recipient total aortic clamp time when standard bypass techniques were used. The heterogeneous group of congenital heart diseases in this series cannot allow meaningful risk analysis by individual lesion; therefore diagnoses were categorized as HLHS or non-HLHS. July 15, 1993, was the chronologic midpoint of this series and was chosen as the dividing point between our early and recent experience. Respiratory failure was defined as postoperative mechanical ventilation exceeding 10 days. Delayed posttransplantation interventions were defined as any operative or catheter-based intervention (excluding routine biopsies and angiography) required as a direct consequence of transplantation and occurring more than 30 days after transplantation.

Data analysis and statistical methods. Patient height and weight at the time of transplantation and at most recent follow-up were compared with National Center for Health Statistics growth curves.¹¹ Potential predictors of 30-day mortality included diagnosis, recipient weight, donor/recipient weight ratio, age at transplantation, time awaiting transplantation, preoperative dependence on mechanical ventilation, preoperative dependence on inotropic agents, total ischemia time, warm ischemia time,

Table II. Major pretransplantation interventions

Procedures	No.
Balloon atrial septostomy	19 (15)
Coarctation repair and PA band	6
Modified Blalock-Taussig shunt	5
PA band	4
Balloon aortic valvuloplasty	4 (3)
Coarctation repair	3
Diaphragm plication	2
Central aortopulmonary shunt	1
Aortopulmonary shunt band and pacemaker	1
Mitral valve replacement	1
Common AV valve repair and PA band	1
Interrupted arch repair and PA band	1
Open atrial septostomy	1
Balloon truncal valvuloplasty	1
Balloon pulmonary valvuloplasty	1
Total	51 (32)

Numbers in parentheses indicate number of affected patients. AV, Atrioventricular; PA, pulmonary artery.

prior sternotomy, recipient blood type, and nonidentical ABO match. These predictors were evaluated by univariate analysis by means of Fisher's exact test for categorical variables and nonparametric Wilcoxon rank-sum test for continuous variables. Multivariable analysis was performed with logistic regression including all variables with p values ≤ 0.10 by univariate analysis. Age at listing, age at transplantation, recipient weight, donor/recipient weight ratio, diagnosis, waiting time to transplantation, total ischemia time, warm ischemia time, hospital stay, intensive care stay, time of mechanical ventilation, time of inotropic support, and 30-day mortality were compared between early and recent groups by means of Fisher's exact test for categorical variables and the nonparametric Wilcoxon rank-sum test for continuous variables. Survival curves were estimated with the use of the Kaplan-Meier method and survival curves were compared between the early and recent series by means of the log-rank test. The Cox proportional hazards model was used to model survival for the early and recent series with transplantation as a time-dependent covariate. Patients listed but not undergoing transplantation were included in the latter analysis. Patients electively removed from the waiting list were excluded. All statistical analyses were performed with the SAS System version 6.12 (SAS, Inc., Cary, N.C.).¹²

Results

Pretransplantation course. Fifty-one of 60 infants entered into our transplant protocol during this study underwent orthotopic heart transplantation. The diagnoses of all patients undergoing transplantation are listed in Table I. All nine patients not undergoing transplantation died. Six with HLHS and one patient with a restrictive cardiomyopathy died while on the waiting list, and two infants (1

Table III. Operative variables and outcomes for the entire series

Variable	Mean $\pm$ SD	Median	Range
Age at listing (days)	38.7 $\pm$ 45.6	15	0-160
Age at transplantation (days)	107.4 $\pm$ 66.4	95	10-315
Wait to transplantation (days)	68.6 $\pm$ 47.1	65	7-297
Weight at transplantation (kg)	4.8 $\pm$ 1.1	4.6	2.5-7.8
Donor/recipient weight ratio	1.79 $\pm$ 0.63	1.75	0.79-3.33
Total ischemia (min)	233.9 $\pm$ 75.1	240	69-526
Warm ischemia (min)	61.4 $\pm$ 13.0	61	37-99
Hospital stay (days)	26.3 $\pm$ 67.6	10	1-439
Intensive care stay (days)	23.5 $\pm$ 65.6	7	0-419
Ventilator support (days)	16.0 $\pm$ 58.7	4	0-419
Inotropic support (days)	6.3 $\pm$ 4.8	5	0-28

Table IV. Causes of 30-day mortality

Patient	Diagnosis	Cause of death	Postop. day
2	HLHS	<i>Enterobacter</i> sepsis	20
6	Unbalanced AVSD	<i>Candida</i> sepsis	7
9	Hypertrophic cardiomyopathy	Sudden death	1
11	HLHS	Pulmonary hypertensive crisis	3
15	SV, PA, TAPVR, asplenia	Technical	Intraoperative
20	Shone's syndrome	<i>Pseudomonas</i> sepsis	20
32	Truncus arteriosus, TS	Technical	Intraoperative
36	HLHS	Pulmonary hypertensive crisis	8
49	SV, polysplenia	<i>Pseudomonas</i> sepsis	3

AVSD, Atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; PA, pulmonary artery; SV, single ventricle; TAPVR, total anomalous pulmonary venous return; TS, truncal valve stenosis.

HLHS, 1 failed repair of D-transposition of the great arteries and multiple ventricular septal defects) were removed from the waiting list and later died. Overall waiting list mortality was 15%. Excluding the two patients who were removed from the list, waiting list mortality was 12%. There were no deaths while awaiting transplantation during the last 22 months of patient accrual. Mean age at listing was 39 ± 46 days (range, birth to 160 days), and mean wait time for transplantation was 69 ± 47 days. While awaiting transplantation, 32 patients required 51 major interventions (Table II). Nineteen balloon atrial septostomies were performed in 15 patients. Six pretransplantation procedures in five patients necessitated median sternotomies.

Operative course. Thirty-nine boys and 12 girls underwent transplantation at a mean age of 107 ± 66 days. ABO blood groupings of the recipients were 27 type O, 18 type A, and 6 type B. Eight recipients received nonidentical blood group donor hearts. Deep hypothermia with circulatory arrest was used in 33 patients with a mean circulatory

arrest time of 66.2 ± 12.5 minutes. Standard cardiopulmonary bypass was used in the other 18 infants. Perioperative variables and initial courses of the patients are summarized in Table III.

Perioperative course. Thirty-day mortality in this study was 18% (9/51; 95% confidence limits: 7% to 28%). Diagnosis leading to transplantation, cause of death, and time to death of the nine patients who died in the perioperative period are presented in Table IV. Four of nine early deaths were due to sepsis. Renal failure necessitating peritoneal dialysis occurred in all four patients who died of sepsis and in one patient who died 8 days after resuscitation from a pulmonary hypertensive crisis necessitating extracorporeal membrane oxygenation (ECMO).

Univariate analysis identified four variables potentially predictive of 30-day mortality: preoperative dependence on mechanical ventilation ($p = 0.01$), prior sternotomy ($p = 0.002$), preoperative dependence on inotropic agents ($p = 0.08$), and warm ischemia time ($p = 0.08$). No other variables were associated with 30-day mortality. By multivariable analysis, only prior sternotomy ($p = 0.01$) was

Table V. Risk factors for 30-day mortality

Risk factor	Univariate	Multivariable		
	<i>p</i> Value	Odds ratio	95% confidence interval	<i>p</i> Value
Age at listing (days)	0.69			
Age at transplant (days)	0.78			
Wait to transplant (days)	0.85			
Weight at transplant (kg)	0.44			
Donor/recipient weight ratio	0.37			
Nonidentical ABO match	0.18			
Total ischemia (min)	0.68			
Warm ischemia (min)	0.08	1.07	0.99-1.16	0.10
Preoperative mechanical ventilation	0.01	4.26	0.34-53.8	0.26
Preoperative inotropic support	0.08	0.84	0.99-1.16	0.21
Prior sternotomy	0.002	60.1	2.25-999	0.01

independently predictive of 30-day mortality. Table V summarizes the results of the risk factor analysis.

The median hospital and intensive care stays after transplantation for the entire series were 10 and 7 days (Table III). Median durations of mechanical ventilator support and inotropic support were 4 and 5 days, respectively. Inhaled nitric oxide became available to us in October 1993 and was used in 22 of 31 patients undergoing transplantation after that time, for an average duration of 4.2 days (range 1 to 18 days). ECMO was used in five patients (3 HLHS, 1 Shone's syndrome, 1 single ventricle with polysplenia), of whom three were successfully weaned and remain alive. Hemiparesis developed in one ECMO survivor as a result of intracerebral hemorrhage. All three survivors (2 HLHS, 1 Shone's syndrome) had right heart failure as a result of excessive pulmonary vascular resistance and were supported for an average of 3.0 days. Both deaths on ECMO were due to sepsis. One patient with HLHS was placed on ECMO 9 hours after the operation after a pulmonary hypertensive crisis and died of fulminant sepsis after 8 days of support. Another infant placed on ECMO 3 days after the operation was supported only 4 hours and at autopsy was found to have had hemodynamic collapse from overwhelming *Pseudomonas* sepsis.

Table VI details perioperative comparisons between the early and recent series. The percentages of patients with and without HLHS were nearly identical between series (early group, 45% HLHS; recent group, 52% HLHS). The only variable different between groups was a smaller donor/recipient weight ratio in the early group (1.4 ± 0.5 vs 2.0 ± 0.6 , $p = 0.003$). Given the larger number of 30-day deaths in the early group and smaller number of patients in this group, differences in hospital and

intensive care stays are masked by the relatively shorter outcomes of these patients; however, this effect is countered by 2 outliers in the early group with hospital stays of 439 and 235 days. Excluding all 30-day deaths from both the early and recent series and the 2 outliers in the early group as mentioned above, hospital stay for the recent series was shorter than in the early experience (mean 20.8 vs 12.8 days, $p = 0.03$). Similarly, intensive care stay also declined (mean 17.8 vs 9.6 days, $p = 0.04$). Although not statistically significant, the 30-day mortality difference of 30% versus 10% ($p = 0.07$) suggests improved early outcome in the recent series.

Perioperative complications. Fifty-two complications occurred in 23 of the 42 operative survivors and are listed in Table VII. Eight cardiac arrests were successfully resuscitated in six patients. Three patients' chests were reopened on an emergency basis, and one of these patients was placed on ECMO. The remaining arrests responded to external compressions and pharmacologic resuscitation. Delayed sternal closure was required in seven patients: three after decannulation from ECMO, two after emergency open chest resuscitations, and two patients' chests were intentionally stented open in the postoperative period to allow for resolution of myocardial edema. There were no wound complications in these patients. Two patients underwent exploration for postoperative mediastinal hemorrhage, one of whom was supported by ECMO.

Long-term results. Mean follow-up length for the series was 27.9 ± 21.4 months. Excluding all early deaths, mean follow-up was 33.8 ± 18.8 months (range 7.4 to 81.5 months). Forty-one of the 42 30-day survivors were discharged from the hospital alive. Five late deaths occurred at an average post-transplantation survival of 19.3 ± 8.8 months. One

Table VI. Early versus recent series comparisons

Variable	Early group (n = 20)					Recent group (n = 31)					p Value
	Minimum	10th percentile	Median	90th percentile	Maximum	Minimum	10th percentile	Median	90th percentile	Maximum	
Age at listing (days)	3	4.5	11.5	118.5	138	0	9	18	88	160	0.27
Age at transplantation (days)	16	40	93	174	207	10	42	96	246	315	0.49
Wait to transplantation (days)	7	31.5	51.5	91.5	95	7	30	70	138	297	0.30
Weight at transplantation (kg)	2.5	3.4	4.3	6.2	7.8	3.4	3.8	4.6	6.1	7.2	0.43
Donor/recipient weight ratio	0.8	0.9	1.3	2.1	2.3	1.0	1.2	2.1	2.7	3.3	0.003
Total ischemia (min)	90	135	220	270	285	69	132	253	329	526	0.07
Warm ischemia (min)	37	43.5	62	84.5	99	43	46	60	71	84	0.39
Hospital stay (days)	1	2.5	11.5	145.5	439	1	7	9	20	47	0.07
Intensive care stay (days)	0	2.5	11.5	145.5	419	0	4	7	13	43	0.06
Hospital stay (days)*	9	10	11.5	40	56	5	7	10	20	47	0.03
Intensive care stay (days)*	3	5	11.5	40	56	3	4	7	17	43	0.04
Inotropic support (days)	0	1.5	5	15	18	0	3	5	9	28	0.84
Ventilator support (days)	0	2	4	50	419	0	2	4	10	38	0.70

Asterisks (*) indicate comparisons after censoring 2 outliers from the early group and all 30-day mortalities from each group (see text). Diagnoses were similar between groups (early 9/20 HLHS, recent 16/31 HLHS).

late death occurred in a patient who remained hospitalized 235 days. This patient had multiple complications, required nine major posttransplantation interventions, and ultimately died of overwhelming sepsis. Acute rejection was the most common cause of late death, accounting for three deaths. The other late death was caused by posttransplantation lymphoproliferative disease with central nervous system involvement. The latter patient accounted for the only case of posttransplantation lymphoproliferative disease in the entire series. Only one patient in the series had a second transplantation. Actuarial survival of the entire series is depicted in Fig. 1. One-, 2-, and 3-year survivals were 80%, 78%, and 70%, respectively. Mean lengths of follow-up for the early and late groups were 35.2 ± 29.6 months and 23.1 ± 12.2 months, respectively. Fig. 2 depicts actuarial survival of the early and recent groups. Actuarial survival was improved in the recent group ($p = 0.05$), with a

Table VII. Perioperative complications in 30-day survivors

Complication	No.
Cardiac arrest	8 (6)
Acute rejection	8 (6)
Delayed sternal closure required	7
Respiratory failure	7
Septicemia	4
Renal failure requiring peritoneal dialysis	3
Graft failure requiring ECMO	3
Cytomegalovirus infection	2
Bleeding requiring reoperation	2
Small bowel obstruction	2 (1)
SVC obstruction/chylothorax	1
Chylothorax	1
Hemothorax	1
Pneumothorax	1
Intracerebral hemorrhage	1
Calcium chloride extravasation	1
Total	52 (23)

Numbers in parentheses indicate number of affected patients. ECMO, Extracorporeal membrane oxygenation; SVC, superior vena cava.

Fig. 1. Kaplan-Meier survival curve of 51 infants having transplantation over a 6-year period. *Tick marks* indicate censored observations. *Error bars* denote one standard error.

Fig. 2. Kaplan-Meier survival curves of 20 patients (early series) listed for heart transplantation before July 15, 1993, and 31 patients (recent series) listed thereafter ($p = 0.05$). *Tick marks* indicate censored observations. *Error bars* denote one standard error.

2-year survival of 86%. With the use of the Cox proportional hazards model with transplantation analyzed as a time-dependent covariate, survival was also better in the recent group ($p = 0.04$, risk ratio 0.39), and transplantation did not affect the difference between groups ($p = 0.99$).

Eighteen operative survivors have had no acute rejections at an average time at risk of 31.9 ± 18.5 months. Of nine patients surviving less than 30 days, only one had acute rejection. The number of acute rejections in the remaining long-term survivors ranged from one to six episodes per patient. Cardiac allograft vasculopathy developed in two patients. One patient required a second transplant operation 67.7 months after the initial transplantation because

of severe cardiac allograft vasculopathy. Cardiac allograft vasculopathy was identified at postmortem examination in a second patient who died of acute rejection 30.4 months after transplantation. The requirement for major interventions after transplantation was substantial. Excluding all interventions undertaken within the first 30 posttransplantation days, 18 major interventions were required in 10 patients (Table VIII).

At the time of transplantation the mean height and weight for the entire series corresponded to the 7th and 5th percentiles based on standard growth curves. At most recent follow-up, mean standardized heights and weights of operative survivors were in the 20th and 16th percentiles, respectively.

Among 37 remaining survivors, current functional performance was good in 34 and developmentally delayed in 3.

Discussion

Heart transplantation has become an established therapy in children with heart disease not amenable to other options. In addition, transplantation has been used for HLHS in several centers.^{3,7} Consequently, the number of pediatric transplants performed increased rapidly after the introduction of this therapy. As previously observed in adults, the number of pediatric heart transplants has now plateaued. Approximately 100 procedures in the infant age group per year were reported to the ISHLT in 1994 and 1995.¹ Considering that 1500 to 2000 infants per year are born in North America with HLHS, not to mention other causes of end-stage heart disease, the number of potential candidates who could benefit from transplantation far exceeds the supply of donors. Unfortunately, little information exists to guide appropriate allocation of scarce infant donor organs.

Previous reported single-center experiences with infant heart transplantation have not demonstrated perioperative risk factors for mortality, most likely because of relatively small sample sizes.³⁻⁵ The Loma Linda series, despite 153 patients, also did not delineate any preoperative risk factors predictive of mortality.⁶ One report by Turrentine and colleagues¹³ suggested that a donor/recipient weight ratio greater than 2.5 adversely affected survival. However, a much larger study specifically examining donor/recipient weight ratio found that size mismatching did not influence perioperative mortality.¹⁴ Within the range of our data, we did not observe an influence of donor/recipient weight ratio on 30-day mortality. By multivariable analysis the Loma Linda series suggested an association between graft total ischemia time greater than 240 minutes and operative mortality ($p = 0.07$). We did not observe this association; however, the median ischemia time of our series was 240 minutes compared with 270 minutes in the Loma Linda series. In addition, the power of their series was much greater, with a threefold larger sample size.

Our results indicate that prior sternotomy increases the risk of 30-day mortality after heart transplantation in infancy. However, the wide 95% confidence intervals for this variable (Table V) and the small size of our study introduces inherent uncertainty, and this result must be interpreted with

Table VIII. Major delayed posttransplantation interventions

Procedure	No.
Recoarctation balloon angioplasty	5
Balloon angioplasty for ascending aorta stricture	2
SVC balloon angioplasty	2 (1)
Tracheostomy	2
Thoracic duct ligation	1
Thoracic duct ligation/direct atrial venous access	1
Thoracotomy for venous access removal	1
Repair diaphragmatic hernia	1
Decortication	1
Lower extremity amputation	1
Retransplantation	1
Total	18 (10)

Numbers in parentheses indicate number of affected patients; SVC, superior vena cava.

this provision in mind. Interestingly, prior sternotomy was predictive of operative mortality in a recent multiinstitutional analysis of 141 infants (age < 1 year) who underwent heart transplants.¹⁵ This report from the PHTS identified three other independent predictors of operative mortality in this age group: nonidentical blood type donor, recipient non-blood group A, and donor cause of death other than head trauma. Unfortunately, our data were too incomplete to allow analysis of donor cause of death as a risk factor, and we did not observe an association between nonidentical donor-recipient blood type or any blood group with 30-day mortality. The small sample size of our data, however, clearly limits the power of our series to delineate these factors.

The PHTS report found no association between total graft ischemia and early mortality; however, warm ischemia time was not assessed.¹⁵ In addition, no other single-center reports have examined this variable. Although the p value is only at the 90% confidence level, we observed a possible association between warm ischemia and 30-day mortality that we believe is clinically relevant. The reported warm ischemia times in our data (range 37 to 99 minutes) were considered to equal the crossclamp and circulatory arrest times recorded by the perfusionists during each case. Consequently, these times overestimate the true warm ischemia times because our practice is to keep the donor heart on ice until the native heart is excised. From our logistic model the odds ratio for early death at any duration of warm ischemia x (within the range 37 to 99 minutes) is given by the formula $\text{EXP}(\beta[x - 37])$, where $\beta = 0.675$ (i.e., the parameter estimate for this variable). Thus the duration of warm ischemia had an expo-

mental effect on the risk of 30-day mortality. The uncertainty in our data owing to small sample size and the *p* value of only 0.10 implies that this function should not be directly applied by other investigators, although it is logical to expect a marked increase in the risk of early mortality at extended warm ischemia times. Clinically, efforts to minimize warm ischemia should improve outcomes.

Overall 1-month survival in the current series was 82% (95% confidence limits: 72% to 93%), which is comparable with most other series.^{3-7, 13, 15} Causes of early death were similar to those reported previously in this age group. As noted by Chinnock and colleagues,⁶ heart transplantation in infants carries a significant learning curve. The clinical characteristics of our early and more recent series were nearly indistinguishable (Table VI). Although not statistically significant, 1-month survival appears to have improved to 90% (95% confidence limits: 74% to 96%) over the last 3 years of this study compared with 70% (95% confidence limits: 49% to 86%) in the first 3 years. Hospital and intensive care unit stays decreased significantly. Renal failure was less common in the latter half of our series, as only one patient in the recent half required peritoneal dialysis compared with five in the early half. In addition to increased experience, we believe that other advances have improved our results. The perioperative management of pulmonary vascular resistance has improved with the use of milrinone and the recent addition of nitric oxide, and the aggressive use of ECMO has also allowed salvage of three patients who would otherwise have died of excessive pulmonary vascular resistance. Second, in addition to improving pretransplantation survival in patients with HLHS, our strategy to maintain systemic perfusion has improved the hemodynamic stability of these patients, allowing us to avoid the use of mechanical ventilation and inotropic support before transplantation.⁹ Recently, we have discharged several infants with HLHS to home while awaiting transplantation. Other authors have noted that the perioperative management of infants with HLHS is particularly challenging.^{3, 4, 13} The HLHS early mortality in our experience (12%) is similar to that of other series.

Long-term survival in this series is comparable with that of other reports and supports the efficacy of transplantation in this age group, with 2-year survivals of 78% overall and 86% more recently. ISHLT data indicate an overall 2-year survival of 62% for children younger than 1 year of age at

transplantation.¹ Similarly, the PHTS reported a 2-year survival of 69%.¹⁴ The improvement in long-term outcome we found with increased experience was most heavily influenced by the lower early mortality (Fig. 2). Posttransplantation malignant disease and cardiac graft vasculopathy were rare in our experience. With longer follow-up the incidence of these complications may increase.^{6, 16} We believe that these results support our immunosuppression regimen. In particular, avoidance of corticosteroids for long-term immunosuppression appears advantageous in infants and young children. In our experience, growth is satisfactory with progression to higher growth curves during follow-up. In contrast, one center that used long-term triple drug immunosuppression reported that infants undergoing transplantation tended to remain at the same percentile on the growth curve.³ Development of these infants, although only subjectively assessed, appears quite good and compares favorably with that of other children who have undergone major corrective procedures for congenital heart disease during infancy.

In conclusion, our results further support the role of heart transplantation in infants with end-stage heart disease. The large number of pretransplantation and delayed posttransplantation interventions and the substantial incidence of perioperative complications indicate that infant transplantation is an extremely labor-intensive endeavor. Furthermore, substantial resources must be invested in the long-term follow-up of these patients, and the learning curve associated with developing a program for infant heart transplantation is significant. Unfortunately, the scarcity of infant donor hearts is likely to contribute to continued mortality while awaiting transplantation. Advances that improve pretransplantation survival are gratifying but may serve to further increase demand on a limited donor supply. Alternative solutions including xenograft transplantation and mechanical heart systems deserve further research.

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Discussion

Dr. Steven R. Gundry (*Loma Linda, Calif.*). I take particular delight in noting that two of the authors on this paper have been affiliated with our staff at Loma Linda. Mark Boucek, MD, was a faculty member at Loma Linda and David Fullerton, MD, was a fellow on our staff. David Fullerton, who is now a member of the WTSA, won the Samson Prize for a paper on infant heart transplantation while he was at Loma Linda. It is a pleasure to discuss this paper.

The authors have demonstrated, as have several others in the past, that there is a significant learning curve in infant heart transplantation and it is only when a center commits a large resource in terms of time and people to

acquiring this learning curve that the results so dramatically increase. Perhaps most important is the fact that the authors have adopted a hands-off approach to the management of infants in the preoperative period. Perhaps you would like to comment on that. What have you found that has allowed these infants to survive for 3 or 4 months while awaiting transplantation?

Dr. Mitchell. Our hats have to go off to our cardiologists for really flying in the face of conventional management of these children, particularly those with HLHS. Obviously, all of these children have to be managed with prostaglandins to keep their ducts open to provide systemic perfusion. We have tried to minimize pulmonary flow and preserve systemic perfusion. To accomplish this, we have administered inhaled nitrogen to the children during the early days of life, and usually within 6 weeks they can be weaned from nitrogen. The objective is to try to preserve distal organ function and systemic flow by reducing flow into the lungs, thereby reducing the need for mechanical ventilation and reducing the need for preoperative inotropic support. This strategy has actually worked far better than we anticipated. In fact, in the past 6 months three children with HLHS have actually been sent home with long-term infusions of prostaglandins while awaiting transplantation. We try not to use a lot of diuretics. In fact, we have found that the children can maintain their own fluid balance if they are allowed to eat what they want and if we try not to manipulate their system other than to keep their ducts open and to limit pulmonary blood flow.

Dr. Gundry. We had the same experience. Our neonatologists pioneered this, that is, the less they did, the less mechanical ventilation, the less intravenous solutions in these children, the better the children fared. Second, you noted that your warm ischemia time correlated with a decreased survival. Recently, we have changed our technique, particularly in the children with HLHS, to continue to perfuse the body through the cannula, through the snared ductus, while excising the heart and using sucker bypass to reimplant the right atrial and left atrial anastomoses. Only at that time do we institute circulatory arrest to reconstruct the arch. This has allowed us to cut our circulatory arrest time to approximately 15 minutes in the last 50 children whom we have treated. Do you think that the warm ischemia time with lessened survival implies that more complex reconstructions were needed in these groups, or does it imply that perhaps you had trouble in these patients? You said that two of your deaths were the result of technical errors in complex reconstructions.

Dr. Mitchell. I think the answer to that is yes and no; for example, if you look only at the group of children with HLHS, the total ischemia times averaged 66 minutes, which was above the mean average for the entire group. However, their mortality was the lowest of the three groups. On the other hand, in the children with more complicated defects, there is certainly a longer requirement for ischemia to insert those grafts in. You referred to the two technical problems: One was a child with anomalous pulmonary venous return in whom we could not adequately identify all of the pulmonary venous return, and we never weaned that child off the pump. The second

was a child who had very small pulmonary arteries, which we did not realize in the preoperative workup, again setting us up for acute right heart failure. More complicated cases are going to be associated with longer ischemia times. Certainly there are some confounding influences between time and the particular diagnosis.

Dr. Gundry. Last is your fairly new use of nitric oxide and milrinone in the postoperative management of these children. This is intriguing to me because we have not seen any evidence of pulmonary hypertension, particularly in the children with HLHS, even undergoing transplantation at age 5 or 6 months. Do you think that pulmonary hypertension in your patient population is related to the high altitude at which these children are kept and your operations are performed?

Dr. Mitchell. We think that may be a factor. The problem becomes more severe the longer the children have to wait. However, since we do not have enough numbers to show that statistically, I did not even try. Just anecdotally, several children have waited 5 months and one 6 months. Two of three at that duration have survived, but it has been much more difficult, and some of those children have required ECMO to get through the operation.

Commentary

This series of infants undergoing heart transplantation for congenital heart disease, reported by Mitchell

and associates, supports the fact that infant heart transplantation has now achieved a degree of success comparable with transplantation in older children and adults. Despite variations in immunosuppressive technique and surveillance monitoring, several institutions have presented moderate-sized series of infant heart transplantations with quite excellent results, such as those reported here by Mitchell and associates, with survivals of 70% or greater 2 years after transplantation. Thus it is clear that infant heart transplantation is an effective palliative intervention for children who have no other surgical or medical options. What remains problematic, however, is the fact that human donor availability will never meet the potential demand if this therapy is used in patients with complex congenital heart disease. Thus the success of transplantation for infants with congenital heart disease has brought about an entirely new set of potential problems. These problems await the solution of suitable xenograft organ availability. With the availability of a relatively unlimited donor supply, the outstanding success of infant heart transplantation as described by the Loma Linda group, Mitchell's group, and others may achieve its full potential.

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