Risk Factor Analysis in Pediatric Heart Transplantation

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Background: Steady assessment of risk factors will enable identification of patients at higher risk for post-transplant death, and may thus improve organ utilization and outcomes. In this study we aimed to identify the risk factors of mortality in pediatric heart transplantation.

Methods: Between November 1989 and February 2004, there were 116 orthotopic heart transplantations performed in patients <18 years of age at our institution.

Results: The 30-day mortality risk was 12% (dilated cardiomyopathy 7%, congenital heart disease 26%; univariate analysis: $p = 0.023$). The main cause of 30-day mortality was primary graft failure (36%). The late mortality rate was 31 per 1,000 person-years. The main causes of late mortality were acute rejection (44%) and cardiac allograft vasculopathy (26%). The 1-, 5-, 10- and 15-year survival rates were 85%, 77%, 65% and 53%, respectively. Male donor (odds ratio [OR] 6.33, 95% confidence interval [CI] 1.11 to 36.01) and cardiopulmonary bypass >210 minutes (OR 43.05, 95% CI 1.11 to 1,669) were risk factors for 30-day mortality. Risk factors for 1- and 5-year mortality were body weight ratio <0.8 (OR 40.36, 95% CI 3.04 to 536.47) and male donor (OR 3.36, 95% CI 1.05 to 10.75), respectively. Recipient age <1 year (OR 64.65, 95% CI 1.69 to 2,466.77) and donor–recipient body surface area mismatch of <0.9 (OR 10.58, 95% CI 1.03 to 108.25) were risk factors for 10-year mortality.

Conclusions: Pediatric heart transplantation can be performed with an expectation of excellent results. Certain risk factors suggest poorer outcomes. J Heart Lung Transplant 2008;27:408–15. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Pediatric heart transplantation has been accepted as the best therapeutic option for end-stage heart diseases. To date, nearly 6,500 procedures have been performed worldwide.[1] Despite encouraging long-term survival and perceived quality of life,[2,3] graft half-life after pediatric heart transplantation has remained at nearly 13 years.[4] Deaths are mainly due to acute rejection and early and late allograft failure.[5,6] The shortage of donor hearts, increasing demand, and constraint of financial or medical resources necessitate optimal organ utilization. Steady assessment of risk factors of mortality will enable identification of patients at higher risk for post-transplant death, and may thus improve organ utilization and outcomes. We aimed to identify the risk factors of mortality in a pediatric heart transplantation population.

METHODS

Study Population

All patients <18 years of age undergoing heart transplantation at the Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center North Rhine Westphalia, Bad Oeynhausen, Germany, between November 1989 and February 2004 were included in this study. Our ethics committee approved this study, and the need for individual informed consent was waived. The annual transplant distribution data are presented in Figure 1.

Recipient selection criteria included existing end-stage heart failure without other feasible medical or surgical treatment options; absence of systemic diseases, infection, stroke or recent pulmonary infarction; stable family history; compliance; and evidence of strong motivation. Currently, we exclude patients with renal failure who require hemodialysis. Donor hearts were obtained from beating-heart, brain-dead individuals through cooperation with the Eurotransplant organization. Donor assessment was based on complete clinical laboratory evaluation and echocardiography. The generally used criteria to determine a suitable donor included no active infection or malignancy,

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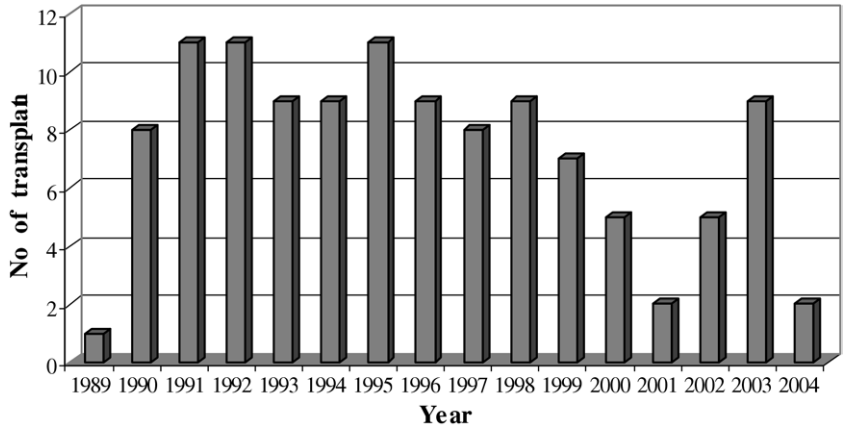

Figure 1. Annual distribution data for pediatric heart transplantation.

human immunodeficiency virus (HIV) and hepatitis negativity, normal cardiac anatomy, and function at echocardiography after appropriate resuscitation. Both donor and recipient were matched for ABO blood-type compatibility and body weight (ratio within ±20%). An older donor was accepted if coronary artery disease could be excluded.

Surgical Procedures

Donor hearts were retrieved as part of the multiple-organ procurement effort. The heart was decompressed during harvesting to avoid coronary air embolization. Just prior to stopping ventilation, both caval veins were ligated and divided to empty the right heart. The left atrial appendage was opened to empty the left heart. After ascending aortic cross-clamping, 30 to 40 ml/kg cardioplegia solution (Bretschneider–Custodiol; Kohler Chemie, Alsbach-Hahnlein, Germany) was administered to arrest and cool the heart. After dividing the ascending aorta and pulmonary artery, the heart was explanted by transecting both caval veins and the four pulmonary veins preserving the sinus node, its artery and sino-atrial pathways. For cases in which a reconstructive procedure was planned, graft harvesting included the entire aortic arch and descending aorta, pulmonary artery bifurcation and main pulmonary arteries, superior vena cava and pulmonary veins. Graft preservation was achieved through a combination of topical hypothermia and cold crystalloid cardioplegia solution. During transportation, temperature was kept between 4°C and 5°C. Procurement and recipient surgical teams were in frequent communication to accurately coordinate the arrival of the donor heart and explantation of the recipient heart. Implantation of the donor heart was performed orthotopically, using the biatrial technique.[7]

Immunosuppressive Protocol

The initial immunosuppressive regimen included 3 to 4 mg/kg azathioprine (adjusted to renal and hepatic function), 0.25 mg/kg cyclosporine and 125 mg methylprednisolone (all intravenous). Shortly before releasing the aortic cross-clamp, 125 mg methylprednisolone was administered. In the absence of renal failure or severe circulatory deterioration, 0.1 to 0.2 mg/kg/day cyclosporine (intravenous) was infused to achieve and maintain a serum level of 300 to 400 μg/liter. Administration of 1 to 4 mg/kg/day azathioprine and 3 × 125 mg/day methylprednisolone was also performed. Oral application of all drugs was preferred after Day 3 postoperatively. The long-term immunosuppressive regimen consisted of 4 to 6 mg/kg/day cyclosporine and 0 to 2 mg/kg/day azathioprine (dose adjusted to maintain a white blood cell count of >4,000 g/liter). Long-term use of steroid was avoided if possible. In cases of acute rejection, 15 mg/kg/day prednisolone was administered or target trough level of cyclosporine was increased. If acute rejection occurred under normal trough levels, cyclosporine was switched to tacrolimus. Refractory rejection was treated with anti-thymocyte globulin or monoclonal antibody OKT3.

Primary graft failure was defined as a severe impairment of systolic graft function affecting the right, left or both ventricles, accompanied by hypotension, low cardiac output and high filling pressures.[8] Acute rejection episodes were diagnosed by clinical findings, electrocardiography, echocardiography and cytoimmunologic monitoring (if necessary, endomyocardial biopsy), and defined as any event leading to the acute augmentation of immunosuppressive therapy, which basically corresponds to ISHLT Grade ≥3A.[9] Cardiac allograft vasculopathy was defined either angiographically or at autopsy as a narrowing of ≥50% in one primary vessel or ≥50% in two branch vessels. Routine coronary angiog-

raphy was performed at 1, 5 and 10 years, unless coronary artery disease outside that schedule was suspected.

Data Collection and Follow-up

Pre- and intra-operative data have been recorded ad hoc in a computerized database. Donor, recipient and intra-operative characteristics were retrieved for analyses. Autopsies were obtained in the majority of death cases. Follow-up information was obtained through outpatient clinic reports or by telephone interview with patients, their relatives and (or) the referring physician, and was 100% complete.

Study Variables

Dependent variables were mortality at 30 days, 1 year, 5 years and 10 years, respectively, after transplantation. Independent variables were recipient characteristics (age, gender, body height and weight, body surface area and blood group, transplant indication, previous cardiac surgery, transplant status, waiting time, need for ventricular assist device), donor characteristics (age, gender, body height and weight, body surface area, blood group, cause of death, natrium concentration, cardiopulmonary resuscitation), donor–recipient mismatch (age, gender, body weight ratio, body surface area, blood type) and operative characteristics (ischemic time, cardiopulmonary bypass, transplant period).

Statistical Analysis

All analyses were done using SPSS software, version 13.0 (SPSS, Inc., Chicago, IL). Results are expressed as mean ± standard deviation or median (interquartile range, IQR) for continuous variables, and as count (percentage) for categorical variables. Univariate logistic regression analysis was performed to show the association between dependent variable (mortality) and independent variable (recipient, donor, operative characteristics). To control confounding effects, variables with $p \leq 0.05$ were entered into a multivariate logistic regression analysis to determine the independent risk factors for mortality. $p \leq 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

One hundred sixteen consecutive pediatric heart transplantations have been performed. Baseline characteristics are presented in Table 1. Median recipient age was 6 years (IQR 1.6 to 13.9 years). Of the 116 patients, 59% ($n = 68$) were male and 41% ($n = 48$) were female. Recipient mean body height was 116.3 ± 42.9 cm, and median body weight was 16.2 kg (IQR 9 to 43.6 kg). Recipient median body surface area was 0.7 m^2 (IQR 0.5 to 1.4 m^2). Indications for transplantation were

Table 1. Baseline Characteristics ($N = 116$)

Characteristics	
Recipient age (years)	
<1	19 (16)
1–10	53 (46)
>10	44 (38)
Male recipient	68 (59)
Recipient body height (cm)[a]	116.3 ± 42.9
Recipient body weight (kg)[b]	16.2 (9–43.6)
Recipient body surface area (m^2)[b]	0.7 (0.5–1.4)
Indication for heart transplantation	
Dilated cardiomyopathy	84 (72)
Congenital heart disease	32 (28)
Recipient blood group	
A	56 (48)
B	8 (7)
0	44 (38)
AB	8 (7)
Previous cardiac surgery	25 (22)
High-urgency status	13 (11)
Waiting time (days)[b]	36.5 (14.3–89)
Ventricular assist device	11 (10)
Donor age (years)	
<1	24 (21)
1–10	56 (48)
>10	36 (31)
Male donor	64 (55)
Donor body height (cm)[b]	111 (82–157.5)
Donor body weight (kg)[b]	17.5 (10–45)
Donor body surface area (m^2)[b]	0.7 (0.5–1.4)
Donor blood group	
A	46 (40)
B	7 (6)
0	58 (50)
AB	5 (4)
Donor cause of death	
Head trauma	64 (55)
Spontaneous bleeding	11 (10)
Others	41 (35)
Donor natrium concentration (mEq/liter)[a]	147.7 (11.6)
Cardiopulmonary resuscitation in donor	33 (28)
Age mismatch	22 (19)
Gender mismatch	55 (47)
Body weight ratio mismatch	
<0.8	12 (10)
0.8–1.2	61 (53)
>1.2	43 (37)
Body surface area ratio mismatch	
<0.9	25 (22)
0.9–1.1	42 (36)
>1.1	49 (42)
Blood type non-identical	16 (14)
Ischemic time >240 minutes	28 (24)
Cardiopulmonary bypass (minutes)	
<90	37 (32)
90–149	57 (49)
150–209	18 (16)
>210	4 (3)

Table 1. (continued)

Characteristics	
Transplant period	
1989–1993	41 (35)
1994–1998	45 (39)
1999–2004	30 (26)

Values are count (percentage) unless otherwise indicated.
[a]Mean (± standard deviation).
[b]Median (interquartile range).

dilated cardiomyopathy in 72% (84 of 116) of patients and congenital heart disease in 28% (32 of 116). Twenty-two percent (25 of 116) of recipients had prior cardiac surgery, 5 of whom had more than one. Eighty-nine percent (103 of 116) of recipients were electively transplanted. Median waiting time was 36.5 days (IQR 14.3 to 89 days). Ten percent (11 of 116) of recipients required ventricular assist device support as a bridge to transplantation. The median age of donors was 5 years (IQR 1.1 to 12 years). Donor gender was equally distributed. Donor median body weight was 17.5 kg (IQR 10 to 45 kg). Donor median body surface area was 0.7 m^2 (IQR 0.5 to 1.4 m^2). Donor cause of death was mainly head trauma (55%). Donor mean natrium concentration was 147.7 ± 11.6 mEq/liter; 26% (30 of 116) of donors had natrium concentrations of >155 mEq/liter. Cardiopulmonary resuscitation was required in 28% (33 of 116) of donors.

Donor–recipient mismatch was associated with age (19%), gender (47%), body weight ratio (47%) and body surface area ratio (64%). Most of the transplantations were performed with an identical blood type (86%). Mean ischemic time was 212.1 ± 47.6 minutes; 24% (28 of 116) of patients had an ischemic time of >240 minutes. Median cardiopulmonary bypass was 100.5 minutes (IQR 85 to 128.8 minutes).

Outcomes

There were 14 deaths within 30 days after transplantation, resulting in a 30-day mortality risk of 12% (dilated cardiomyopathy 7%, congenital heart disease 26%; univariate analysis: $p = 0.023$). The main cause of 30-day mortality was primary graft failure (36%) (Table 2). Excluding all 30-day mortality, the total follow-up time was 745 person-years (mean 77.1 ± 54.6 months). Another 23 patients died during the follow-up period, resulting in a late mortality rate of 31 per 1,000 person-years. The main causes of late mortality were acute rejection (44%) and cardiac allograft vasculopathy (26%). The 1-, 5-, 10- and 15-year survival rates were 85%, 77%, 65% and 53%, respectively (Figure 2).

Risk Factors for Mortality

Table 3 summarizes the significant risk factors for mortality according to univariate analyses. Recipient age <1 year, recipient body height and body surface area, congenital heart disease, male donor, donor body height and body surface area, and cardiopulmonary bypass >210 minutes were associated with 30-day mortality. Recipient age <1 year, recipient body height and body surface area, congenital heart disease, donor body height, donor–recipient body weight ratio <0.8 and cardiopulmonary bypass >210 minutes were associated with 1-year mortality. Recipient age <1 year and congenital heart disease, male donor, ischemic time >240 minutes and cardiopulmonary bypass between 150 and 209 minutes were associated with 5-year mortality. Recipient age between 1 and 10 years, high-urgency status, donor age between 1 and 10 years, and donor–recipient body surface area ratio mismatch <0.9 were associated with 10-year mortality. Multivariate analyses identified male donor (odds ratio [OR] 6.33; 95% confidence interval [CI] 1.11 to 36.01) and cardiopulmonary bypass >210 minutes (OR 43.05, 95% CI

Table 2. Causes of Death

	Early ($N = 14$)		Late ($N = 23$)		Total ($N = 37$)	
Cause of death	*n*	%	*n*	%	*n*	%
Primary graft failure	5	36			5	14
Acute rejection			10	44	10	27
Infection	2	14	2	9	4	11
Right ventricular failure	1	7			1	3
Multi-organ failure	1	7			1	3
Pulmonary complication	2	14			2	5
Technical issues	2	14			2	5
Neurologic complication	1	7			1	3
Abdominal complication			1	4	1	3
Non-specific graft failure			1	4	1	3
Cardiac allograft vasculopathy			6	26	6	16
Tumor			1	4	1	3
Unknown			2	9	2	5

Because of rounding, not all percentages add to 100.

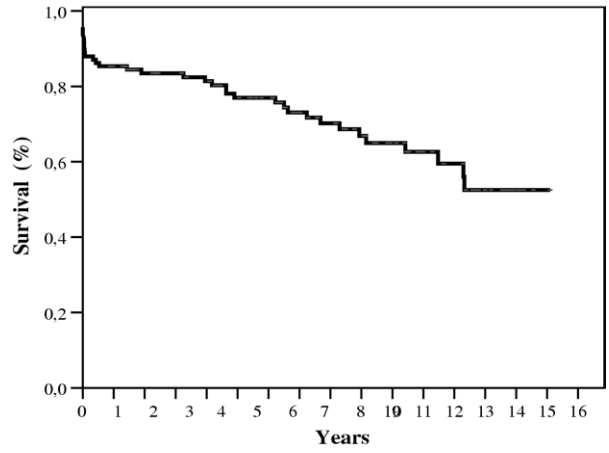

Figure 2. Survival curve for pediatric heart transplantation.

Table 3. Risk Factors For Mortality (Univariate Analyses)

	Mortality			
Variable	30-day	1-year	5-year	10-year
Recipient age (years)				
< 1	7.97 (1.78–35.64)	5.69 (1.42–22.80)	3.86 (1.08–13.75)	1.5 (0.31–7.36)
1–10	1.12 (0.24–5.27)	1.27 (0.34–4.83)	0.83 (0.27–2.54)	0.25 (0.08–0.832)
>10	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Recipient body height (cm)	0.98 (0.96–0.99)	0.98 (0.97–0.99)		
Recipient BSA (m^2)	0.21 (0.05–0.89)	0.29 (0.09–0.99)		
High-urgency status			7.8 (0.90–67.62)	
Transplant indication				
DCM	1 [reference]	1 [reference]	1 [reference]	
CHD	4.52 (1.42–14.37)	3.78 (1.31–10.97)	2.77 (1.06–7.22)	
Donor age (years)				
>10				1 [reference]
1–10				0.26 (0.07–0.91)
<1				0.44 (0.1–1.87)
Male donor	5.77 (1.23–7.34)		3.45 (1.23–9.69)	
Donor body height (cm)	0.98 (0.96–0.99)	0.98 (0.97–0.99)		
Donor BSA (m^2)	0.21 (0.05–0.89)			
BWR mismatch				
< 0.8		4.33 (1.01–18.62)		
0.8–1.2		1 [reference]		
>1.2		1.23 (0.38–3.95)		
BSA mismatch				
< 0.9				4.03 (0.87–18.76)
0.9–1.1				1 [reference]
> 1.1				0.83 (0.27–2.57)
IT >240 minutes			2.6 (0.99–6.85)	
CPB (minutes)				
<90	1 [reference]	1 [reference]	1 [reference]	
90–149	2.06 (0.39–10.78)	1.62 (0.39–6.71)	1.82 (0.56–5.93)	
150–209	3.5 (0.53–23.10)	3.49 (0.69–17.76)	7 (1.65–29.67)	
≥210	52.45 (3.62–760.42)	34 (2.65–436.51)	8,050.39 (0–8.4E + 21)	

Values are expressed as odds ratios with 95% confidence interval in parentheses. BSA, body surface area; BWR, body weight ratio; CHD, congenital heart disease; CPB, cardiopulmonary bypass; DCM, dilated cardiomyopathy; IT, ischemic time.

1.11 to 1,669) as independent risk factors for 30-day mortality. Independent risk factors for 1- and 5-year mortality were body weight ratio <0.8 (OR <40.36, 95% CI 3.04 to 536.47) and male donor (OR 3.36, 95% CI 1.05 to 10.75), respectively. Recipient age <1 year (OR 64.65, 95% CI 1.69 to 2,466.77) and donor–recipient body surface area mismatch <0.9 (OR 10.58, 95% CI 1.03 to 108.25) were independent risk factors for 10-year mortality (Table 4).

DISCUSSION

Only a few investigators have identified risk factors for mortality in pediatric heart transplantation. Canter et al[10] reported that previous sternotomy and donor cause of death other than closed-head trauma were the risk factors of 30-day mortality. Morales et al[11] revealed prolonged post-operative intubation (>5 days) and longer cardiopulmonary bypass time as risk factors for overall mortality. Another multicenter study[12] demonstrated that younger age, pre-transplant mechanical assistance and non-identical ABO blood-type match were independent risk factors of early mortality. Boucek et al[1] showed that being on extracorporeal membrane oxygenation at the time of transplantation, congenital diagnosis leading to transplantation, re-transplantation, the need for a ventilator or hospitalization, year of transplantation, donor age, creatinine, weight ratio, transplant volume and bilirubin increased the risk of 1-year mortality, whereas congenital diagnosis with or without extracorporeal membrane oxygenation, re-transplant, being on a ventilator or hospitalized, year of transplant, female recipient, receiving a heart from a female donor, recipient age, bilirubin and transplant volume increased the risk of 5-year mortality.

Our study has presented the largest number of pediatric heart transplantations from a single European center, and clearly provides additional comparative information to the current data of the ISHLT (pediatric

Table 4. Risk Factors of Mortality (Multivariate Analyses)

	Mortality			
Variable	30-day	1-year	5-year	10-year
Recipient age (years)				
<1				64.65 (1.69–2,466.77)
1–10				4.24 (0.25–71.63)
>10				1 [reference]
Male donor	6.33 (1.11–36.01)		3.36 (1.05–10.75)	
BWR mismatch				
<0.8		40.36 (3.04–536.47)		
0.8–1.2		1 [reference]		
>1.2		0.67 (0.13–3.53)		
BSA mismatch				
<0.9				10.58 (1.03–108.25)
0.9–1.1				1 [reference]
>1.1				0.77 (0.2–3.05)
CPB (minutes)				
<90	1 [reference]			
90–149	2.26 (0.37–13.98)			
150–209	3.1 (0.34–28.47)			
≥ 210	43.05 (1.11–1,668.52)			

Values are expressed as odds ratios with 95% confidence intervals in parentheses. BSA, body surface area; BWR, body weight ratio; CPB, cardiopulmonary bypass.

registry). Apart from the limited sample size, our single-center study has advantages, such as uniformity in selection criteria, surgical procedure, post-operative management and reporting. We found that male donor and cardiopulmonary bypass >210 minutes were independent risk factors for 30-day mortality. Independent risk factors for 1- and 5-year mortality, respectively, were body weight ratio <0.8 and male donor. Recipient age <1 year and donor–recipient body surface area mismatch <0.9 were independent risk factors for 10-year mortality.

In contrast to a recent study showing female donor as a significant risk factor for mortality,[1] De Santo et al[13] found that donor gender did not significantly modify the short- and mid-term survival after pediatric heart transplantation. However, Kawauchi et al[14] demonstrated that male donor increased the risk of allograft rejection, leading to worse outcome. Statistically, male donor heart did not appear to be superior to a female donor heart. Female donor hearts are perhaps simply unable to support the circulation of male recipients due to their small size or poor ventricular function. Thus, the greater right ventricular mass in the male heart may provide better outcomes, particularly among recipients with pulmonary hypertension. Our results reveal that male donor was associated with an adverse outcome. However, we believe that a correct donor–recipient size match is much more important.

Looking for an appropriate, size-matched heart is difficult in pediatric heart transplantation due to the lack of donors. Nearly half of our transplant procedures were mismatched in body weight ratio. This could partly explain the high specific cause of early mortality due to primary graft failure.[15] Previously, we showed that undersize mismatching in pediatric heart transplantation increased the early mortality risk, especially for congenital heart disease.[16] Our current results reflect the common practice of pediatric heart transplant centers outside North America, where dilated cardiomyopathy is more predominant than congenital heart disease.[1]

Similar to other large single-center studies,[17,18] we found no significant difference in long-term survival between dilated cardiomyopathy and congenital heart disease. This is probably attributable to the significant advancements in surgical experience and the peri-operative care of patients with congenital heart disease undergoing cardiac surgery in general. In addition, patients with congenital heart disease presenting for heart transplantation are now better palliated, making them comparable to other transplant candidates. Despite failing to reach statistical significance in the multivariate analysis, however, we found that heart transplantation for congenital heart disease apparently has a higher early mortality risk than dilated cardiomyopathy. This is probably attributable to previous cardiac surgery and elevated pulmonary vascular resistance, which are well-known in patients with congenital heart disease. Therefore, we prefer a larger donor heart for recipients with pulmonary hypertension or elevated pulmonary vascular resistance. Different kinds of vasodilators and nitric

oxide have been also used to reduce recipients' pulmonary vascular resistance.

The longer cardiopulmonary bypass time may lead to severe depletion of clotting factors, and thus there is an increased early mortality risk through post-operative complications, such as massive bleeding.[11] Downsizing to a donor–recipient body weight ratio of 0.65 has been well tolerated by transplant recipients.[19–21] Jeevanandam et al[22] concluded that undersized pediatric hearts can be used successfully to salvage patients and expand the potential donor pool. Costanzo-Nordin et al[19] found that acceptance of undersized donor hearts was not detrimental to allograft function or recipient survival. They concluded that use of undersized donor hearts may maximize the use of critically scarce donor organs. Another study,[23] however, revealed that donor–recipient body weight ratio of <1 was associated with poor outcomes. Our results support the suggestion that the use of an undersized donor heart should be strongly discouraged.[23] Placing a smaller female donor heart into a larger male recipient proved to be a significant risk factor for mortality.[24] Some centers[25,26] demonstrated comparable survival after heart transplantation in infant and older recipients. However, our results have demonstrated that infant recipient (<1 year of age) is a risk factor for 10-year mortality. A previous study[27] identified transplantation in infancy as a factor affecting the development of cardiac allograft vasculopathy.

Similar to the ISHLT registry,[1] we noted that acute rejection and cardiac allograft vasculopathy remained the "Achilles heel" at long-term follow-up. Our immunosuppressive protocol was based on standard triple-drug immunosuppression with cyclosporine, azathioprine and prednisone. Long-term use of steroid was preferably avoided. In contrast to adult heart transplantation, where late reduction of immunosuppression could be a relatively safe procedure, the same approach cannot be applied to pediatric patients, in whom recurrence of acute fatal rejections is a well-known complication.[28] We suggest a reduction of cyclosporine doses and concomitant start-up of other immunosuppressive agents. Recently, tacrolimus has been added to our immunosuppressive protocol. At the end of follow-up, our transplant recipients were treated with cyclosporine (86%), tacrolimus (9%), azathioprine (43%) and steroid (16%). We do not use mycophenolate mofetil (MMF) in our immunosuppressive protocol for pediatric patients because our experiences in adult heart transplantation revealed that MMF was associated with severe gastrointestinal side effects and increased cytomegalovirus (CMV) infection rate.[29]

We found our overall incidence of cardiac allograft vasculopathy to be lower than that reported previously.[1] We believe that the avoidance of steroids in our long-term immunosuppression protocol and prophylactic and aggressive treatment of hypertension and hypercholesterolemia may be responsible for our lower incidence of cardiac allograft vasculopathy.

Our study was limited by the small number of patients, weakening the power of the statistical tests. Such a limitation can be better elucidated with a larger study population and longer follow-up time.

In conclusion, pediatric heart transplantation can be performed with excellent results. The presence of certain risk factors results in poorer outcomes.

REFERENCES

1. Boucek MM, Aurora P, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: tenth official pediatric heart transplantation report—2007. J Heart Lung Transplant 2007;26:796–807.
2. Minami K, von Knyphausen E, Niino T, et al. Long-term results of pediatric heart transplantation. Ann Thorac Cardiovasc Surg 2005;11:386–90.
3. Ross M, Kouretas P, Gamberg P, et al. Ten- and 20-year survivors of pediatric orthotopic heart transplantation. J Heart Lung Transplant 2006;25:261–70.
4. Boucek MM, Waltz DA, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: ninth official pediatric heart transplantation report—2006. J Heart Lung Transplant 2006;25:893–903.
5. Mulla NF, Johnston JK, Vander DL, et al. Late rejection is a predictor of transplant coronary artery disease in children. J Am Coll Cardiol 2001;37:243–50.
6. Razzouk AJ, Chinnock RE, Dearani JA, Gundry SR, Bailey LL. Cardiac retransplantation for graft vasculopathy in children: should we continue to do it? Arch Surg 1998;133:881–5.
7. Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum 1960;11:18–9.
8. Segovia J, Pulpon LA, Sanmartin M, et al. Primary graft failure in heart transplantation: a multivariate analysis. Transplant Proc 1998;30:1932.
9. Billingham ME, Cary NR, Hammond ME, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection. J Heart Transplant 1990;9:587–93.
10. Canter C, Naftel D, Caldwell R, et al. Survival and risk factors for death after cardiac transplantation in infants. A multi-institutional study. Circulation 1997;96:227–31.
11. Morales DL, Dreyer WJ, Denfield SW, et al. Over two decades of pediatric heart transplantation: how has survival changed? J Thorac Cardiovasc Surg 2007;133:632–9.
12. Shaddy RE, Naftel DC, Kirklin JK, et al. Outcome of cardiac transplantation in children. Survival in a contemporary multiinstitutional experience. Circulation 1996;94(suppl):II-69–73.
13. De Santo LS, Marra C, De Feo M, Amarelli C, Romano G, Cotrufo M. The impact of gender on heart transplantation outcomes: a single center experience. Ital Heart J 2002;3:419–23.
14. Kawauchi M, Gundry SR, de Begona JA, et al. Male donor into female recipient increases the risk of pediatric heart allograft rejection. Ann Thorac Surg 1993;55:716–8.
15. Huang J, Trinkaus K, Huddleston CB, et al. Risk factors for primary graft failure after pediatric cardiac transplantation: importance of recipient and donor characteristics. J Heart Lung Transplant 2004;23:716–22.

16. Minami K, Tenderich G, Breymann T, et al. long-term results after orthotopic heart transplantation in pediatric patients with dilated cardiomyopathy and congenital heart disease: influence of height- and weight-mismatching on early mortality. Cardiovasc Eng 1998; 3:144–8.
17. Chen JM, Davies RR, Mital SR, et al. Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. Ann Thorac Surg 2004;78:1352–61.
18. Groetzner J, Reichart B, Roemer U, et al. Cardiac transplantation in pediatric patients: fifteen-year experience of a single center. Ann Thorac Surg 2005;79:53–60.
19. Costanzo-Nordin MR, Liao YL, Grusk BB, et al. Oversizing of donor hearts: beneficial or detrimental? J Heart Lung Transplant 1991;10:717–30.
20. Hosenpud JD, Pantely GA, Morton MJ, et al. Relation between recipient:donor body size match and hemodynamics three months after heart transplantation. J Heart Transplant 1989;8:241–3.
21. Morley D, Boigon M, Fesniak H, et al. Posttransplantation hemodynamics and exercise function are not affected by body-size matching of donor and recipient. J Heart Lung Transplant 1993; 12:770–8.
22. Jeevanandam V, Mather P, Furukawa S, et al. Adult orthotopic heart transplantation using undersized pediatric donor hearts. Technique and postoperative management. Circulation 1994;90:II-747.
23. Tamisier D, Vouhe P, Le Bidois J, et al. Donor–recipient size matching in pediatric heart transplantation: a word of caution about small grafts. J Heart Lung Transplant 1996;15:190–5.
24. Bourge RC, Kirklin JK, Naftel DC, McGiffin DC. Predicting outcome after cardiac transplantations: lessons from the Cardiac Transplant Research Database. Curr Opin Cardiol 1997;12:136–45.
25. Canter CE, Moorehead S, Huddleston CB, Spray TL. Restrictive atrial septal communication as a determinant of outcome of cardiac transplantation for hypoplastic left heart syndrome. Circulation 1993;88:II-456–60.
26. Chiavarelli M, Gundry SR, Razzouk AJ, Bailey LL. Cardiac transplantation for infants with hypoplastic left-heart syndrome. JAMA 1993;270:2944–7.
27. Kuhn MA, Jutzy KR, Deming DD, et al. The medium-term findings in coronary arteries by intravascular ultrasound in infants and children after heart transplantation. J Am Coll Cardiol 2000;36: 250–4.
28. Chin C, Naftel DC, Singh TP, et al. Risk factors for recurrent rejection in pediatric heart transplantation: a multicenter experience. J Heart Lung Transplant 2004;23:178–85.
29. Fuchs U, Tenderich G, Zittermann A, et al. Clinical outcome of heart transplant recipients receiving tacrolimus with or without mycophenolate mofetil. Clin Transplant 2006;20:450–6.