Over two decades of pediatric heart transplantation: How has survival changed?

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Objective: In 1984, the first successful infant heart transplant was performed at Texas Children's Hospital. This study analyzes the 21-year experience with pediatric heart transplantation at Texas Children's Hospital to assess whether and how survival has changed over time.

Methods: Between November 1, 1984, and October 3, 2005, 164 consecutive orthotopic heart transplants were performed on 154 patients. *Characteristics:* mean age 7.1 ± 6.0 years, mean body surface area 0.8 ± 0.5 m². *Diagnosis at transplant:* cardiomyopathy 53.0% (n = 87), congenital heart defect 39.0% (n = 64), retransplant 7.9% (n = 13). Multivariate risk factor analysis of 32 variables was completed by Cox proportional hazards regression models.

Results: Mean follow-up was 5.9 ± 4.8 years. Overall Kaplan-Meier survival was 82% at 1 year, 65% at 5 years, and 54% at 10 years. After 1995, Kaplan-Meier survival (91% at 1 year and 71% at 5 years) was significantly improved over pre-1995 survival (71% at 1 year, 57% at 5 years, and 48% at 10 years; $P = .026$). Hospital survival improved in the post-1995 era (96%) compared with the pre-1995 era (77%; $P < .001$). Life-table analysis by yearly increments demonstrates only an improved survival (pre-1995, 71% → post-1995, 91%) in the first posttransplant year ($P = .001$); every subsequent year the mortality rates are the same ($P = .92$). Risk factors for overall mortality are prolonged postoperative intubation (>5 days) and longer cardiopulmonary bypass time.

Conclusions: Primarily attributable to an increase in early survival, overall pediatric heart transplant survival is improved. However, after the first posttransplant year, the rate of mortality has not changed in 21 years. This highlights the need for new therapies to treat children both with or in need of a heart transplant.

On December 6, 1967, Dr Adrian Kantrowitz and his associates¹ in Brooklyn, New York, performed the first pediatric heart transplant on a 17-day-old infant with Ebstein anomaly. This occurred just 3 days after Dr Christian Barnard's² first human-to-human transplant on December 3, 1967, in South Africa.³ In 1984, nearly 20 years later, the first successful infant heart transplant was performed by Dr Denton Cooley and his colleagues⁴ on an 8-month-old girl at Texas Children's Hospital (TCH).

Pediatric heart transplantation has become an accepted management strategy for pediatric patients with end-stage heart failure resulting from cardiomyopathy or

Abbreviations and Acronyms

CHD	= congenital heart disease
ISHLT	= International Society for Heart and Lung Transplantation
MMF	= mycophenolate mofetil
PVRI	= pulmonary vascular resistance index
TCH	= Texas Children's Hospital

inoperable congenital heart disease (CHD). Since 1982, more than 6000 pediatric heart transplants have been performed, with consistent improvement in survival.⁵ Increasing early survival, most likely a manifestation of the advancements in perioperative management, has been the driving force improving outcomes.^{5,6} Although not statistically proven, the rate of late attrition of pediatric patients undergoing heart transplantation has seemingly not changed since the advent of cyclosporine in the early 1980s.^{4,5,7,8} No therapies in the past 20 years have significantly changed the rate of chronic rejection; thus, the uncertainty of long-term survival remains. The objective of this study is to review the 21-year experience with pediatric heart transplantation at a single institution, assessing how survival has changed over time and the variables that affect survival.

Patients and Methods

A retrospective analysis of all pediatric heart transplants performed at TCH between November 11, 1984, and October 3, 2005, was completed with the permission of the Internal Review Board of Baylor College of Medicine. There were 165 consecutive heart transplants performed on 155 patients. One patient received a heterotopic heart transplant and his data are excluded from all analyses.

Mean age at transplant was 7.1 ± 6.0 years (median 5.2 years [20 days–21 years]), with a mean body surface area of 0.8 ± 0.5 m². Age distribution at time of transplantation was as follows: 17.7% (n = 29) infants (age < 1 year old), 48.8% (n = 80) children (1 year old < age < 11 years old), and 33.5% (n = 55) adolescents (11 years old ≤ age ≤ 20.3 years old). Four patients were older than 18 years, all of whom had CHD. Diagnoses at transplant were cardiomyopathy in 53.0% (n = 87 [dilated 70% (61), restrictive 16% (14), hypertrophic 8% (7), other 6% (5)]), congenital heart defect in 39.0% (n = 64 [ie, hypoplastic left heart syndrome 16, D-transposition of the great arteries 11, failing Fontan circulation 7]), and cardiac graft failure 7.9% (n = 13). Ethnic diversity in this series consisted of 46.3% white (n = 76), 29.9% Hispanic (n = 49), 18.9% African American (n = 31), and 4.9% other (n = 8). Patients had a mean of 0.9 ± 1.1 (0–5) prior cardiac operations. Pulmonary vascular resistance index (PVRI) was calculated on 67% (104) of the transplant candidates with an average PVRI of 3.1 ± 2.1 Wood units · m² (0.2–10.5 Wood units · m²). Preoperative patient characteristics are listed in Table 1.

Concomitant procedures were performed in 38% of transplants (n = 63) and consisted of donor patent foramen ovale closure in 9.1% (n = 15), mechanical circulatory support removal in 9.1% (n =

TABLE 1. Patient variables analyzed for risk factors

Variable	No. of Pts. (%)
Preoperative characteristics	
Female	59 (38%)
Inpatient	87 (57%)
Intubated	33 (21%)
Inotropic support	74 (48%)
Renal insufficiency*	7 (5%)
Mechanical circulatory support	12 (8%)
PVRI > 5 Woods units × m ²	all 22 (14%), fixed 13 (8%)
Prior sternotomy	76 (49%)
Postoperative morbidities	
Prolonged postop intubation	27 (18%)
Renal insufficiency*	14 (9%)
Mechanical circulatory support	7 (5%)
Arrhythmia	47 (31%)
Receiving blood products	82 (53%)
Inhaled nitric oxide therapy	26 (17%)
Infection	47 (31%)
Mediastinal infection†	5 (3%)
Bleeding†	15 (10%)

Pts., Patients; PVRI, Pulmonary vascular resistance index. *Requiring dialysis. †Requiring reoperation.

15), pacemaker removal in 8.5% (n = 14), shunt takedown in 8.5% (n = 14), aortic arch reconstruction in 8.5% (n = 14), complex pulmonary artery reconstruction in 5.5% (n = 9), mechanical circulatory support placement in 1.8% (n = 3), kidney transplant in 1.2% (n = 2), and other in 6.7% (n = 11). Mean cardiopulmonary bypass time was 144 ± 68 minutes (35–490 minutes).

The donor graft is presently perfused with Celsior solution, and for patients less than 1 year old, a noncommercial buffered hyperkalemic extracellular solution (Melbourne solution) is used. Bialtrial anastomoses were performed exclusively until 1995 (n = 78). After 1995, transplants were routinely performed by a standard bicaval anastomotic technique with caval and pulmonary artery anastomoses completed with the heart beating. Inhaled nitric oxide was first used for transplant patients at TCH in June of 1994.

Presensitized patients (panel reactive antibodies by flow cytometry to class I and class II HLA antigens greater than 10%) were (1) listed with unacceptable antigens based on specific HLA antibody titrations, (2) preoperatively treated with intravenous immunoglobulin and rituximab, and/or (3) transplanted with an exchange transfusion on cardiopulmonary bypass and, if there was a retrospective positive cross-match, treated with plasmapheresis, intravenous immunoglobulin, and rituximab. The immunosuppressive protocol has not included induction therapy. Patients routinely receive mycophenolate mofetil (MMF) (20 mg/kg) (previously azathioprine 1mg/kg) preoperatively and methylprednisone (10 mg/kg) intraoperatively. Postoperatively, the patients receive and are discharged on triple immunosuppressive therapy: a calcineurin inhibitor, an antimetabolite, and steroids. Tacrolimus was first used in October of 1998 but was not regularly prescribed until 2002; since then, it has been used in 47% (17/36) of patients. Patients are followed up frequently in clinic and with endocardial biopsies for the first year, after which a clinic visit or biopsy is every 6 months.

TABLE 2. Immunosuppression regimen for all primary transplants after 1998

	D/C (n = 70)	D/C %	1 y (n = 56)	1 y %	5 y (n = 13)	5 y %	F/U (n = 56)	F/U %
Cyclosporine A	53	76%	34	61%	9	69%	32	57%
Tacrolimus	17	24%	22	39%	4	31%	24	43%
Prednisone	70	100%	56	100%	13	100%	55	98%
MMF	54	77%	28	50%	4	31%	24	43%
Azathioprine	0	0%	0	0%	0	0%	0	0%
Rapamycin	3	4%	5	9%	1	8%	3	5%

D/C, Discharge; F/U, most recent clinic visit; MMF, mycophenolate mofetil.

Patients were considered lost to follow-up if contact by TCH had not been made within 18 months of the study's completion.

Rejection was considered to be a biopsy score of the International Society for Heart and Lung Transplantation (ISHLT) grade 3A or higher or the clinical suspicion of rejection regardless of biopsy score. Acute cellular rejection on the basis of histologic examination only without evidence of hemodynamic changes was treated with pulsed steroids. However, if there was hemodynamic compromise, then first-line therapy was either antithymocyte globulin or OKT3 (monoclonal antibody to CD3 positive T cells). The TCH immunosuppressive regimen was recorded and the incidence of rejection was analyzed for the cohort of patients receiving a primary cardiac transplant after 1998 (n = 70), when MMF became the primary antimetabolite and tacrolimus use began (Table 2).

Statistical Methods

Descriptive statistics for nominal and numerical data included ratios, medians with ranges, and means with standard deviations. The χ^2 test was used to compare hospital and 1-year survivals between the early and late eras. All risk factor and Kaplan–Meier analyses were based on the patient's first transplant at TCH (n = 154). Survival analyses were performed with the Kaplan–Meier method and then compared with the log-rank test. All survivals are Kaplan–Meier unless the ratio of survivors to patients in the cohort of interest is specified. Early era (November 1984 to July 1995; n = 66) and late era (July 1995 to October 2005; n = 88) survival was also analyzed in yearly increments with the Cutler–Ederer method (life-table analysis) to determine the probability of survival within each 1-year time period of follow-up, independent of survival before or after that 1-year interval. Comparison of early and late era life tables was performed with the Wilcoxon–Gehan statistic.

Thirty-two covariates were organized according to clinical categories as follows: (1) patient variables, (2) donor variables, and (3) intraoperative and postoperative variables (Appendix 1). Donor graft data were supplied by the United Network for Organ Sharing research division and were only available after 1987, capturing 81% to 90% of the TCH cohort depending on the variable. Multivariate risk factor analyses were completed for discrete and continuous variables by the Cox proportional hazards model. Significant risk factors found from these analyses, excluding continuous variables, were further analyzed by odds ratios with 95% confidence intervals to determine whether they were independent risk factors. Overall mortality, 1-year mortality, 5-year mortality, and 5-year mortality conditional on 1-year survival were tested for risk factors. For the 104 patients who had PVRI data, a separate Cox proportional hazards model including all patient variables

was used to determine whether PVRI as a continuous variable was a risk factor for overall and conditional 5-year mortality. All analyses were conducted with SPSS 13.0 (SPSS, Inc, Chicago, Ill).

Results

Postoperative morbidity is listed in Table 1. The median length of intubation was 1 day (0–164 days). The median intensive care unit and hospital lengths of stay were 7 days (0–164 days) and 17 days (0–169 days), respectively. Hospital and 1-year survivals for the post-1995 era (96% [84/88] and 91% [80/88]) were significantly higher than for the pre-1995 era (77% [51/66] and 71% [47/66]) ($P < .001$, $P = .003$).

The median wait time (n = 146, 89% capture) for a recipient on the United Network for Organ Sharing list was 61 days (0–498 days). The median donor age (n = 147, 90% capture) was 4 years (0–28 years) and the median weight ratio (n = 134, 82% capture) was 1.2 (0.7–3). In regard to donor-recipient gender pairing (n = 137, 89% capture), the number of male donor to female recipients was 35 (54% of all female recipients) and of female donors to male recipients was 37 (37% of all male recipients). Comparing each of the gender-mismatched recipient cohorts with their respective gender-matched recipient cohorts revealed gender-mismatched male recipients to have a lower survival, with 49% survival at 10 years versus 78% for gender-matched male recipients ($P = .053$). Median donor ischemic time reported by TCH records was 232 minutes (68–452 minutes).

From January of 1999 to October of 2005, 61% (43/70) of patients had rejection during the first year of transplant, with 40% of this group (17/43) having only one episode of rejection. The Kaplan–Meier survival curves of those patients with and those without rejection in the first year were not significantly different ($P = .35$).

The overall length of follow-up was 5.9 ± 4.8 years (0.4–19.5 years). There are 95 (62%) living patients (79% are followed up at TCH and 21% by adult specialists), and 91% are in New York Heart Association class I. One patient (0.6%) was lost to follow-up. Overall Kaplan–Meier survival (1 year, 82.3%; 5 years, 65.3%; and 10 years, 54.4%) is demonstrated in Figure 1, A. There were 59 deaths over-

Figure 1. A, Kaplan–Meier survival analysis overall and by era of transplant. B, Cutler–Ederer life-table survival analysis by era.

all, with 34% ($n = 20$) from transplant coronary artery disease (diagnosed pre-mortem and post-mortem), 25% ($n = 15$) from postoperative multisystem organ failure, 14% ($n = 8$) from rejection, and all other causes having a frequency of 3% or less. Survival is statistically greater in the late era (30 days, 100%; 1 year, 91%; and 5 years, 71%) compared with the early era (30 days, 89%; 1 year, 71%; and 5 years, 57%) ($P = .026$) (Figure 1, A). Life-table analysis of the early and late eras demonstrates that the probability of survival in the first year was significantly different (early 71% vs late 91%; $P = .001$) between the eras, but after the first year, the probability of survival for each 1-year interval of follow-up is statistically the same ($P = .92$) between the eras (Figure 1, B). Pre-1995 and post-1995 survivals censored for mortality in the first year are not statistically different (Figure 2). Survival analysis for patients with the preoperative diagnoses of cardiomyopathy versus CHD demonstrated no difference ($P = .68$). Early (1-year) survival for patients with CHD was significantly higher in the late era (92%, 36/39) than in the early era (68%, 17/25) ($P = .011$). Comparison of the survival curves for the different age groups demonstrated that infants' survival was worse than that of children ($P = .03$) and adolescents ($P = .013$).

Figure 2. Kaplan–Meier analysis of overall survival censored for 1-year mortality: early versus late era.

Analysis of the age cohorts by era demonstrates that the infants in the late era (30 days, 100%; 1 year, 88%; and 5 years, 60%) have a significantly higher survival than in the earlier era (30 days, 58%; 1 year, 33%; and 5 years, 33%) ($P = .012$). In the late era, infant survival was not different from that of the 1- to 10-year-old ($P = .538$) and the 11- to 20-year-old ($P = .717$) cohorts. Comparison of conditional 5-year survival between the age groups demonstrates that the 11- to 20-year-old cohort did have a significantly lower survival (67%) than those younger than 11 years old (infants 80% and children 86%) ($P = .025$). Independent risk factors for overall, 1-year, 5-year, and conditional 5-year mortality are listed in Table 3. PVRI, analyzed as a continuous variable, was not a risk factor at any level for overall or 5-year conditional mortality.

TABLE 3. Risk factors for mortality

Variable	N	OR	95% CI
Risk factors for overall mortality			
Intubated > 5 days postop	27	2.358	1.015-5.476
CPB time* ($P = .031$)	143		
Risk factors for 1-year mortality			
Inpatient	87	2.559	1.011-6.476
Age < 1 y	28	3.562	1.410-8.998
Early era	66	4.043	1.080-9.955
Intubated > 5 days postop	27	7.495	2.936-19.132
Postop arrhythmia	47	3.711	1.573-8.755
Aortic arch reconstruction	14	4.250	1.338-13.499
Risk factors for 5-year mortality			
Intubated > 5 days postop	27	3.871	1.638-9.151
Risk factors for 5-year mortality conditional on 1-year survival			
White (protective)	58	3.750	1.169 to 12.030
Donor age* ($P = .013$)	116		

OR, Odds ratio; CI, confidence interval; CPB, cardiopulmonary bypass.
*Analyzed as continuous variables in Cox regression hazard model only.

Discussion

More than two decades of experience at a single institution with pediatric heart transplantation has allowed the unique opportunity to analyze how survival has changed over time. The results of the current series substantiate the observations of the 2005 ISHLT registry in that survival in the late era of pediatric heart transplantation is significantly greater than in the earlier era.⁵ This difference is clearly driven by an improvement in early survival as highlighted in the current series by the significant increase in the post-1995 hospital (96% vs 77%) and 1-year (91% vs 71%) survivals when compared with the pre-1995 era. This improvement in early survival is likely due to the progress in critical care and operative management of transplant patients and, in particular, patients with CHD and infants. In the present series, the early (1-year) survival of infants between the eras (post-1995 88% vs pre-1995 33%) clearly improved, to the extent that in the modern era, infant survival was the same as for children and adolescents. Previous series have found that patients with cardiomyopathy fared better than those with CHD.⁵ However, the current series, like other large single-center series, have found their survivals to be similar.^{9,10} This is probably secondary to the significant advancements in the perioperative care of patients with CHD undergoing cardiac surgery in general. These improvements are evidenced in this series by the significant increase in early survival for patients with CHD between the early (68%) and the late (92%) eras. Also, CHD patients presenting for transplant in the modern era are better palliated, perhaps making them superior transplant candidates.

As reported by other authors and supported by the TCH results, when comparing the early and modern experiences with pediatric heart transplantation, the rate of mortality (ie, the slope of the Kaplan–Meier survival curve) after the first year is the same.⁵ In an attempt to quantify this observation, we used the Culter-Ederer method to analyze the pre-1995 and post-1995 survivals in yearly increments to determine the probability of survival over each 1-year period of follow-up. This analysis revealed that during the first year after transplant, the pre-1995 cohort had a 71% chance of survival, significantly lower than the 90% chance for the post-1995 era. However, the probability of survival in every subsequent 1-year interval was not statistically different between the eras and averaged 95% for the early era and 96% for the post-1995 era. This was further verified by creating survival curves for the pre-1995 and post-1995 eras that censored early mortality so that a direct comparison of midterm and late survival was possible without early mortality contamination. These curves are not significantly different and, in fact, are virtually identical (Figure 2). Therefore, after the first post-transplant year of follow-up, the mortality rate for pediatric heart transplantation has not changed in more than

20 years, despite shifting trends in immunosuppression (ie, increased use of MMF and tacrolimus).

In addition to survival analyses between eras, the longevity of the TCH series allowed survival analysis of multiple factors that could affect survival. Male recipients who received female donor hearts had a decreased survival compared with male recipients who were donor gender matched. Patient status permitting, gender-matched donor selection for male recipients could result in improved survival.^{11,12}

Prolonged intubation was the most consistent and dominant risk factor, in that it increased the risk of death overall as well as at 1 and 5 years, more than any other risk factor. The transplant team's aggressive policy toward extubation has resulted in a median length of cumulative intubation of 1 day. Therefore, the inability to extubate a patient within 5 days after transplantation clearly indicated a poor clinical course, as evidenced by the 56% mortality (15/27) seen in this cohort. Prolonged intubation is more likely a reliable predictor for death than a cause.

Risk factors for 5-year mortality conditional on 1-year survival allow the effect of early mortality to be eliminated so that risk factors reflect the true risks for late mortality. Being white increased the probability of survival at 5 years once early mortality was censored. Differences in pediatric post-heart transplant survival among ethnic groups have been documented before. Series have found Hispanic and African American patients (91% of TCH's non-white cohort) to be at increased risk for recurrent rejection and thus death.^{10,13} Increasing donor age was an independent risk factor for conditional 5-year survival. This has been demonstrated in another pediatric series that had a proportion of older (>40 years) donors, but in the current series, only 4 of the donors were more than 20 years old with the oldest being 28 years old.¹⁴ Another possible explanation is that the adolescent cohort, who has a significantly lower 5-year conditional survival, contains the patients most likely to receive older donor hearts. Therefore, perhaps increasing donor age is serving as a surrogate to identify the adolescent group, which has been recognized by multiple centers to have an increased rate of late attrition, primarily related to compliance issues.^{5,15}

Since the 1980s, pediatric heart transplantation has become a safe and effective management strategy for pediatric patients with end-stage heart failure. Improving survival in pediatric cardiac transplantation is predominately related to increased early survival. For patients surviving the first posttransplant year, the subsequent mortality rate has not changed in more than 21 years. This highlights the ongoing need for novel therapies to treat children with or in need of a heart transplant.

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Discussion

Dr Vaughn A. Starnes (Los Angeles, Calif). Dr Morales and associates are to be congratulated on an excellent paper retrospectively reviewing 21 years of experience at the TCH. During that time, they performed 165 transplants on 155 recipients. As noted in the paper, children with cardiomyopathy made up more than 50% of the patients, another approximately 40% were children with CHD, and 7.9% were children with graft failure.

As noted by the author, this series compares favorably with the International Registry of Heart and Lung Transplant survival statistics and the causes for transplant.

As we see in this report, as also true of the registry, our improvement in survival over time has been primarily related to our early graft survival, particularly in the first year after the transplant event. As noted by these authors, an increase of 20% over this decade between 1995 and after 1995, it increased from

APPENDIX 1. Thirty-two variables analyzed to determine risk factors for mortality and definitions

Patient variables (n = 16)	
Ethnicity	
African American	
White	
Hispanic	
Era	
Early era	November 1, 1984-June 30, 1995
Age	
Age < 1 year old	
11 ≤ age ≤ 20 years old	
Sex	
Female	
Diagnosis	
Congenital heart disease	
Hypoplastic left heart syndrome	
Failing Fontan circulation	
Body surface area (m ²)*	((Height (cm) × Weight (kg))/3600) ^{1/2}
Inpatient	Hospital admission > 24 hours before transplant
Renal insufficiency†	Requiring dialysis
Inotropic support‡	
Intubation‡	
Mechanical circulatory support‡	
Donor variables (n = 4)	
Cold ischemic time*	
Donor age*	
Donor/recipient weight ratio*	
Positive cross-match	
Intraop and postop variables (n = 12)	
Cardiopulmonary bypass time*	
Concomitant complex pulmonary artery reconstruction	
Concomitant aortic arch reconstruction	
Prior systemic-pulmonary artery shunt	
Re-sternotomy	
Renal insufficiency†	Requiring dialysis
Prolonged intubation‡	> 5 cumulative days of intubation
Mechanical circulatory support‡	
Arrhythmia	Recurrent and/or requiring treatment
Receiving blood products	Any blood product during intensive care unit stay
Infection	Positive culture and antibiotic treatment
Inhaled nitric oxide therapy‡	

*Analyzed as continuous variable. †Up until time of transplant. ‡During posttransplant hospital stay.

71% to 91% during that period of time; that survival statistic paralleled the course over the next 5 to 10 years.

The authors bring up some interesting findings that are also true in the registry, that ethnicity does affect survival, with the pediatric white population faring better than the African American or Hispanic transplant recipients.

The other interesting factor was that the mismatch between genders was very compelling. The mismatch of a male recipient receiving a female donor heart had a significant importance over time and, in fact, at 10 years the survival difference was 49% versus 70%. I thought that was a very compelling argument about trying to match gender.

I have three questions.

The ISHLT reported a significant negative impact with an odds ratio of 2.1 on the influence of CHD as a pretransplant diagnosis on the outcome of the recipient. You found no statistical difference between the cardiomyopathy group and the CHD group. Could you explain that?

Dr Morales. I think if we look into the two different eras, in the pre-1995 era it was a risk factor. In the post-1995 era, in which we now have a dedicated congenital heart surgery center, including surgeons, anesthesiologists, and intensivists, CHD is no longer a risk factor because of the large improvement in early survival. I believe that this is why, overall, it did not come out as a risk factor in our analysis.

Dr Starnes. My second question concerns the negative impact of prolonged intubation. With your odds ratios on 1- and 5-year survivals (7.4 and 3.8, respectively) as a negative impact of this factor, I would view this more as a surrogate for a very sick pretransplant patient with other comorbidities. Are you suggesting that intubation is an independent risk factor outside of the comorbidities that might go along with that?

Dr Morales. I agree with you that it probably has something to do with their pretransplant status; however, the statistical analysis would say that prolonged intubation is itself an independent risk factor for mortality.

Dr Starnes. Again, regrettably, the long-term outcome has remained the same over the past 20 years, and the survival beyond 3 years is still affected by coronary artery disease, with death due to coronary disease representing 30% to 35% in most series and 34% in your series. Given this, has your group taken on any novel immunosuppressive approaches? I noted in your manuscript that some 5% of your patients were receiving rapamycin.

Dr Morales. When a patient has transplant artery coronary disease, one thing that we have changed in the past 5 to 8 years is prescribing rapamycin. Almost all of our applications of rapamycin are for transplant coronary disease. We have also started prescribing pravastatin (Pravachol) as possible prophylaxis against transplant coronary disease once the patients reach adolescence.

Dr Roland Hetzer (*Berlin, Germany*). I want to congratulate the Houston group for this enormous experience. Our own activities among more than 1500 heart transplants include 140 infants and children under the age of 18 years during the past 20 years. Our 10-year survival in this transplanted group was 70%. We have attributed this to very close, meticulous monitoring of rejection by electrophysiologic telemetric methods.

I would like you to comment on several issues: the mode of rejection monitoring in children and infants, the impact of chronic

renal failure at long term, the obvious lack of compliance in adolescents, and the diagnostics of transplant vasculopathy, which we have found to be an important factor for survival beyond 10 years after transplantation.

Dr Morales. In terms of how we monitor these children for chronic rejection or acute rejection, we do myocardial biopsies every 2 weeks during the first 3 months, then every 3 months for the first year, then every 6 months for the next 4 years, and yearly thereafter. Our cardiology colleagues also do a great job at clinically following these children quite frequently and often will diagnose a change in their clinical status. At 3 months, we do coronary angiography as a baseline and then follow that up with yearly angiograms to diagnose coronary disease.

Renal failure played a significant cause in only 1 of the 59 deaths in this series, so it actually has not played a major role in our series in regard to mortality. However, it certainly is a widely known morbidity in these patients, whose renal function we follow closely. Two of our patients have required renal transplant.

Adolescent noncompliance has always been a problem, and as you have seen in our slide on conditional 5-year survival, it definitely has a negative impact on late survival. As do most programs, we pride ourselves in developing close and strong relationships with our patients, so through our counseling we try to improve compliance.

Dr Cooley. In that initial operation that we did on an 8-month-old infant, our concern was, then, about the possibility of the influence of immunosuppressive drugs on growth and development. It was very gratifying to see how that little girl grew and became intelligent; she was a good student in school and so forth. It was a real tragedy when she did pass away from coronary occlusive changes.

I missed it in the donors involved. The situation with the donor in our first transplant was rather complex. The donor was another infant from Dallas, Texas. The mother and father, in a fit of anger, had thrown the child out of a second-story window and the child sustained severe brain injury. To get the permission for the donation, we had to go to the jail in Dallas where the mother and father were incarcerated. We brought the baby down to Houston and had the little recipient available. The recipient was an adopted child. So the situation became rather complicated.

I missed it in your policy now at TCH about ABO mismatch in candidates for transplantation. I hear reports of other institutions that are using ABO mismatch. What is the policy at the Children's Hospital in Houston?

Dr Morales. Thank you, Dr Cooley, for your comments. It is quite an honor to have you here at this presentation to give all of us perspective on this field. I am aware that Toronto has had good success with the ABO mismatch. However, we have not performed any ABO mismatch transplants at TCH. It is something that our cardiologists are interested in and they have been investigating this option, but as of this time we have not applied this donor management strategy.

Dr Lucio Parenzan (*Bergamo, Italy*). To find a small heart, as you know, is difficult. Many times you have to fly many hours. What do you think about the new system they have in Germany where they are perfusing the heart during the transplantation? Do you have any data? Do you have any knowledge? Do you think it is a good idea?

Dr Morales. I am not aware of the new system in Germany.

I can say that we did analyze ischemic time, with maximum ischemic time being 7.5 hours, as a continuous variable to see whether it was a risk factor for mortality. Our analysis demonstrated that at no time was ischemic time a risk factor for death. However, having said that, there obviously is an ischemic time in which graft function and mortality would be affected negatively, but it is unclear to me that it is at 4 hours, as we have always been taught.

Dr Adnan Cobanoglu (*Cleveland, Ohio*). I would like to find out more about the retransplants. There were 13 patients. How was the outcome in the retransplantation group?

Dr Morales. We calculated Kaplan–Meier survival curves of the 13 retransplants and of all the primary grafts, and we compared the two groups. We did not find a statistical difference between the

cohorts. However, I do not know how much can be gathered from that analysis, since there were only 13 retransplants. Having said that, our belief now is that their survival is about the same, but we will have to see whether that is true as our numbers and length of follow-up increase.

Dr William A. Baumgartner (*Baltimore, Md*). You said ischemic time is not related to rejection or survival. Increasing evidence suggests that there is a relationship between ischemic time, or injury at the time of procurement, and the future development of coronary artery disease. Have you looked at this correlation?

Dr Morales. We did not look at the issue of ischemic time and chronic rejection in particular. We did show that, at least in our series, ischemic time was not related to death or graft failure in general. This issue of ischemic time and chronic rejection is an interesting one that we should investigate in our series.

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