SURGERY FOR CONGENITAL HEART DISEASE

PEDIATRIC HEART TRANSPLANTATION: IMPROVING RESULTS IN HIGH-RISK PATIENTS

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Objectives: Our institutional experience with 73 pediatric patients undergoing cardiac transplantation between January 1, 1990, and December 31, 1999, was reviewed to determine the impact of unconventional donor and recipient management protocols implemented to extend the availability of this therapy.

Methods and results: The introduction of donor blood cardioplegic solution with added insulin was associated with a significant improvement in patient and graft survival (hazard ratio [Cox] = 0.25, $P = .08$), despite significantly longer ischemic times with this protocol compared with the use of crystalloid-based donor procurement techniques ($P < .01$). Eleven patients underwent intentional transplantation of ABO-incompatible donor hearts with the aid of a protocol of plasma exchange on bypass. In this subgroup, there were 2 early deaths caused by nonspecific graft failure (n = 1) and respiratory complications with mild vascular rejection (n = 1), and there was 1 late death caused by lymphoma. ABO-incompatible transplantation was not a risk factor for death by multivariate analysis. The postoperative course in these patients suggests minimal reactivity directed against incompatible grafts on the basis of low anti-donor blood group antibody production, in association with a favorable rejection profile. Ten of 13 patients requiring preoperative support with an extracorporeal membrane oxygenator survived transplantation; there were 3 additional late deaths in this subgroup (hazard ratio = 2.88, $P = .05$).

Conclusions: The results with pediatric cardiac transplantation continue to improve as a result of changes in both surgical and medical protocols permitting successful treatment of patients conventionally considered at high risk or unsuitable for transplantation. (J Thorac Cardiovasc Surg 2001;121:782-91)

Pediatric heart transplantation has gained popularity in the past decade with improved early results and long-term outcomes.[1-3] We have adopted a number of unconventional strategies designed to increase the donor pool and minimize pretransplantation waiting list attrition. This study reviews our experience of heart transplantation in an increasingly high-risk population and the methods undertaken to care for these patients.

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Patients and methods

Patients. Seventy-three patients underwent 79 heart transplantations between February 1990 and December 1999 at the Hospital for Sick Children (HSC), University of Toronto. Patient characteristics are summarized in Table I. The follow-up was 100% complete. The mean follow-up was 33 ± 22 months (range 3-89 months).

Surgical technique. Forty-five percent (33/73) had atrio-atrial anastomoses and 55% (40/73) had separate bicaval anastomoses. Mean total ischemic time was 255 ± 129 minutes (range 51-610 minutes). Total ischemic time exceeded 4 hours in 49% (36/73) of the patients.

Blood-insulin cardioplegic solution. In the period before April 1997, Roe's crystalloid cardioplegic solution was used in the first 36 (49%) patients. Our blood-insulin cardioplegic technique, used in 37 patients since April 1997, requires no special equipment and can accommodate the capabilities of any donor procurement team. The donor cardioplegia dose is calculated to be a minimum of 30 mL/kg up to a maximum of 1 L. After administration of heparin in a dose of 300 U/kg, a volume of donor blood is withdrawn from the ascending aorta before crossclamping and is mixed with cold cardioplegic solution in a 1:1 ratio. Potassium, glucose, and magnesium are added in our pharmacy to a base solution of 1000 mL of Plasma-Lyte 148 solution (Baxter Healthcare Corporation, Deerfield, Ill) to achieve concentrations in the crystalloid component of the transplant cardioplegic solution as follows: sodium 136 mmol, potassium 25 mmol, glucose 12.5 mmol, chlorine 116 mmol, magnesium 21.5 mmol, pH 5.76 to 5.91, and osmolality 334 to 340. Humulin (Eli Lilly and Company, Indianapolis, Ind), biosynthetic recombinant DNA origin regular insulin, is added to achieve a final insulin concentration of 10 U/L.

On arrival at HSC the donor organ is reperfused as follows: recipient blood is taken from the cardiopulmonary bypass circuit and is combined in a 2:1 ratio with high-potassium (45 mmol/L) cardioplegic solution to which the following have been added: $NaHCO_3$ 10 mEq/L, Humulin 30 U/L, and 50% dextrose 8 mL/L (20 mmol). This solution is delivered by pump to the donor organ in an antegrade fashion at approximately 20°C and then cooled to 15°C. The delivered concentration of insulin is 10 U/L of blood cardioplegic solution.

A dose of 30 mL/kg donor weight is given before beginning reimplantation and 15 mL/kg after each anastomosis. Before crossclamp removal, the donor organ is reperfused with a dose of low-potassium 2:1 insulin–blood cardioplegic solution that is warmed from 25°C to 35°C during infusion.

Transplantation of ABO-incompatible organs. Since January 1996, patients referred to the HSC in Toronto for heart transplant assessment have been offered participation in an experimental procedure of accepting the first available size-compatible donor, regardless of blood group, in families who elected cardiac transplantation after counseling regarding the available competing surgical approaches. Eleven patients, in all but 3 cases young infants, underwent transplantation against standard ABO blood group antigen recommendations. Patient characteristics for this subgroup are summarized in Table II. Ethical committee approval was obtained for each patient.

The circulating plasma volume was sequestered at the onset of cardiopulmonary bypass and was replaced with banked plasma of appropriate blood type that lacked antibody directed against both donor and recipient blood groups.

Immunosuppression. Immunosuppression according to our protocol consists of induction therapy with a rabbit-derived polyclonal antithymocyte antibody preparation and subsequently standard triple-drug immunosuppression with a calcineurin inhibitor (either cyclosporine [INN: ciclosporin] or tacrolimus), prednisone, and an antimetabolite (either azathioprine or mycophenolate mofetil). Intravenous methylprednisolone was used for treatment of acute rejection.

Table I. *Clinical characteristics*

	No.	*%*
No. of patients	73	100
Age	7.0 ± 6.2 y	1 d–18 y
Age (median)	5.8 years	
Sex		
Boys	45	62
Girls	28	38
Diagnosis		
Idiopathic cardiomyopathy	25	34
Restrictive cardiomyopathy	5	7
Congenital heart disease	32	44
Hypoplastic left heart syndrome	10	14
Cardiac tumor	1	1
Preoperative UNOS classification		
Status 1	26	36
Status 2	2	3
Status 3	19	26
Status 4	23	32
Preoperative ECMO	13	18
No. of heart transplants		
1	73	100
2	5	7
3	1	1

UNOS, United Network for Organ Sharing; *ECMO,* extracorporeal membrane oxygenation.

Rejection surveillance was performed with endomyocardial biopsies on a weekly basis during the first postoperative month, every second week during the next 2 months, and monthly up to 6 months.

Donor/recipient weight mismatch. The donor recipient weight mismatch index for all patients was 1.6 ± 0.8 (minimum: 0.7, maximum: 4.9).

Cardiac catheterization. When pulmonary vascular resistance (PVR) was high or reactivity a concern, a preoperative cardiac catheterization (n = 44) was performed. Postoperatively, PVR was measured at the time of cardiac catheterizations performed during scheduled endomyocardial biopsies. PVR was calculated as the difference between mean pulmonary arterial and pulmonary capillary wedge pressures divided by the cardiac output, expressed in Wood units (millimeters of mercury per liter per minute), and indexed for body surface area as PVRI (millimeters of mercury per liter per square meter).

Extracorporeal membrane oxygenation (ECMO). Thirteen patients were bridged to heart transplantation with venoarterial ECMO—8 patients to their first heart transplantation and 5 patients to their second. In addition, 2 patients had ECMO for post-transplantation support. Preoperative diagnoses in this group included cardiomyopathy in 5 patients, unsuccessful repair of congenital heart disease in 2 patients, and graft failure in 8 patients. Two patients were cannulated in the neck, 1 patient in both the neck and the groin, 1 patient in the groin, and 11 patients through the chest. Average blood loss during ECMO was 6.4 $mL \cdot kg^{-1} \cdot h^{-1}$.

Definitions and statistical analysis. High-risk patients were defined by the presence of one of the following: ECMO (n =

Table II. *Patient characteristics for ABO-incompatible heart transplants*

Diagnosis	*Age at HTx*	*Recipient blood group*	*Donor blood group*	*Duration of follow-up*	*Comments*
DCM	7.5 y	O	A	209 d	Died, PTLD
HLHS	25 d	O	AB	4 y	Alive
DCM	149 d	O	B	3 d	Re-Tx, alive 3.2 y
HLHS	1 d	O	A	30 d	Died, graft hypertrophy
DCM	1.2 y	O	B	24 d	Died, respiratory failure
HLHS	63 d	A	B	2.3 y	Alive
RAI	55 d	O	A	1.9 y	Alive
HLHS	2 d	O	B	1.2 y	Alive
HLHS	50 d	O	B	345 d	Alive
HLHS	1.2 y	O	A	274 d	Alive
HLHS	83 d	O	A	92 d	Alive

DCM, Dilated cardiomyopathy; *HLHS,* hypoplastic left heart syndrome; *RAI,* right atrial isomerism; *HTx,* heart transplantation; *Re-Tx,* retransplantation.

Table III. *Early and late mortality*

	No.	*%*
Early mortality	10	14
Cause of death in summary		
Graft failure	3	
Pulmonary hypertension	1	
Rejection	2	
Pulmonary venous obstruction	1	
Multiple organ failure	2	
Graft hypertrophy	1	
Late mortality	5	7
Cause of death in summary		
PTLD	3	
CAD	2	
Total No. (early and late) of deaths	15/73	21

PTLD, Post-transplantation lymphoproliferative disease; *CAD,* coronary artery disease.

Table IV. *Hospital mortality in low- and high-risk groups*

	Deaths		
	No. of patients	*No.*	*%*
Low-risk patients	41	5	12
High-risk patients	32	5	16
ECMO	32	5	16
ABO-I	11	2	18
High PVRI	12	2	17
Re-Tx	6	1	17
Total No. of hospital deaths		10/73	14

ECMO, Extracorporeal membrane oxygenation; *ABO-I,* ABO-incompatible transplantation; *PVRI,* pulmonary vascular resistance index; *Re-Tx,* retransplantation.

13), PVRI greater than 4 Wood units (n = 12), ABO-incompatible heart transplantation (n = 11), and retransplantation (n = 5). Forty-four (32/73) percent of the patients were considered at high risk according to this definition. Coronary artery disease (CAD) was defined as a significant stenosis (>70%) on coronary angiogram, by autopsy, or by the requirement for retransplantation as a result of late graft failure. Data were analyzed by means of SAS 6.12 for Windows (SAS Institute, Inc, Cary, NC). Descriptive statistics include the mean ± standard deviation (standard error in figures) for continuous variables and frequency tables for categoric variables. Late survival and time-dependent morbidity were portrayed by Kaplan-Meier analysis; multivariable models were derived by means of Cox regression using the PROC PHREG program (SAS Institute, Inc).

Results

Early outcome. The hospital mortality rate was 14% (10/73). Causes of early and late deaths are listed in Table III. In patients requiring pretransplantation ECMO the hospital mortality rate was 23% (3/13). Among the patients considered at high risk, the hospital mortality rate was 16% (5/32) (Table IV).

Survival. Survival at 1 and 5 years was 85% ± 4% and 73% ± 8%, respectively (Fig 1). Five patients died during the follow-up period. Three patients died of post-transplantation lymphoproliferative disease (PTLD) and 2 patients of coronary artery disease (CAD) (Table III). Freedom from death or retransplantation at 1 and 5 years was 80% ± 5% and 68% ± 9%, respectively (Fig 2). Freedom from any of the following events—death, retransplantation, CAD, or PTLD—was 79% ± 5% and 45% ± 11% at 1 and 5 years, respectively (Fig 3).

Multivariate analysis showed that ECMO (hazard ratio 2.88, $P = .05$) was an independent risk factor for death. Multivariate analysis also suggests that crystalloid cardioplegia (hazard ratio for blood-insulin cardioplegia 0.25, $P = .08$) was significant as a risk factor for death.

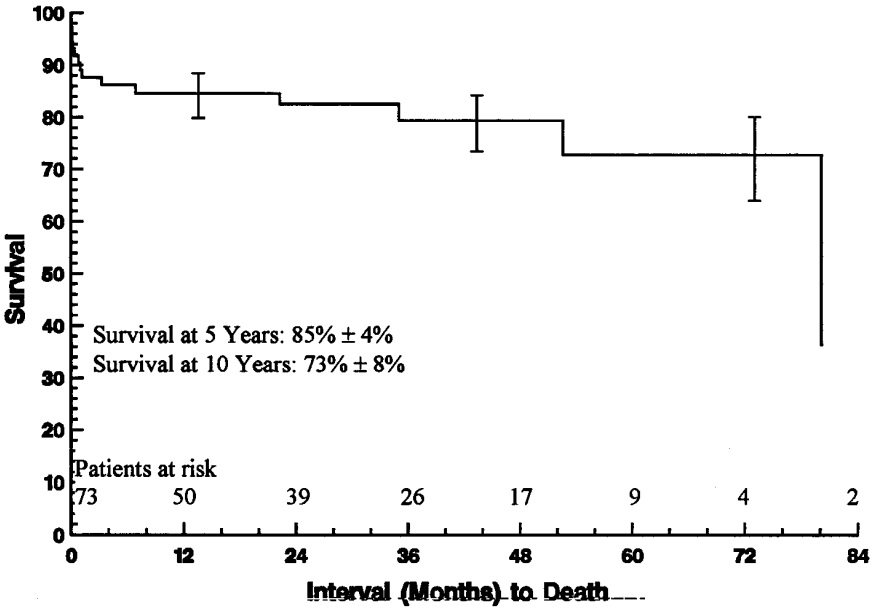

Fig 1. Actuarial survival for all patients undergoing heart transplantation.

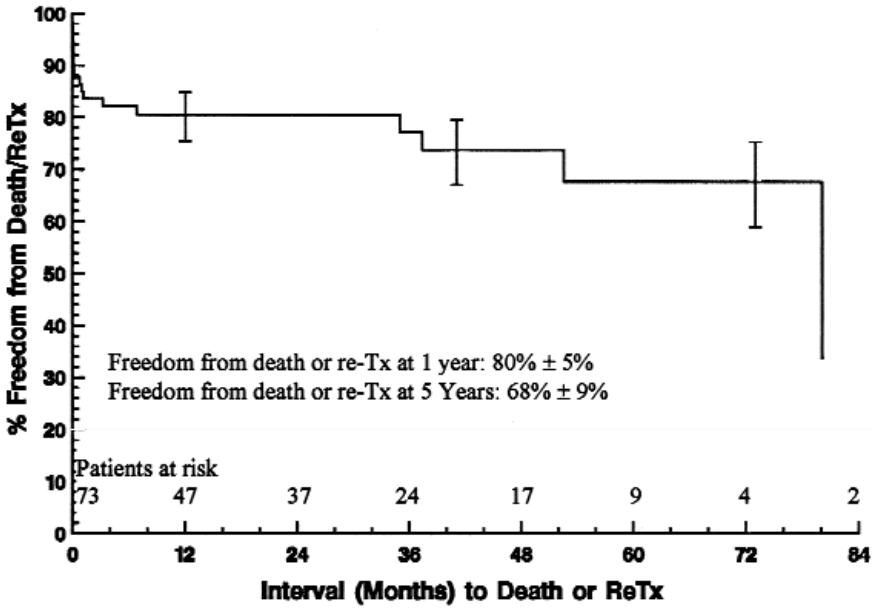

Fig 2. Actuarial freedom from death or retransplantation *(re-Tx).*

Preoperative PVR, ABO incompatibility, and total ischemic time were not predictors of death. Actuarial survival was significantly decreased for patients with pretransplantation ECMO compared with those without ($P < .01$) (Fig 4). Actuarial survival was significantly lower for patients receiving crystalloid cardioplegia versus blood cardioplegia ($P < .01$) (Fig 5).

PVR. PVR was 4.8 ± 6.6 (mean ± SD Wood units) preoperatively, 4.8 ± 6.7 at 1 month, and 2.4 ± 2.5 at 1 year after transplantation, respectively (before transplantation vs 1 year; $P = .03$; factorial analysis of variance). At the corresponding time intervals, PVRI was 3.4 ± 2.8 (mean ± SD Wood units × m^2), 2.6 ± 2.4 and 1.9 ± 1.5, respectively (before trans-

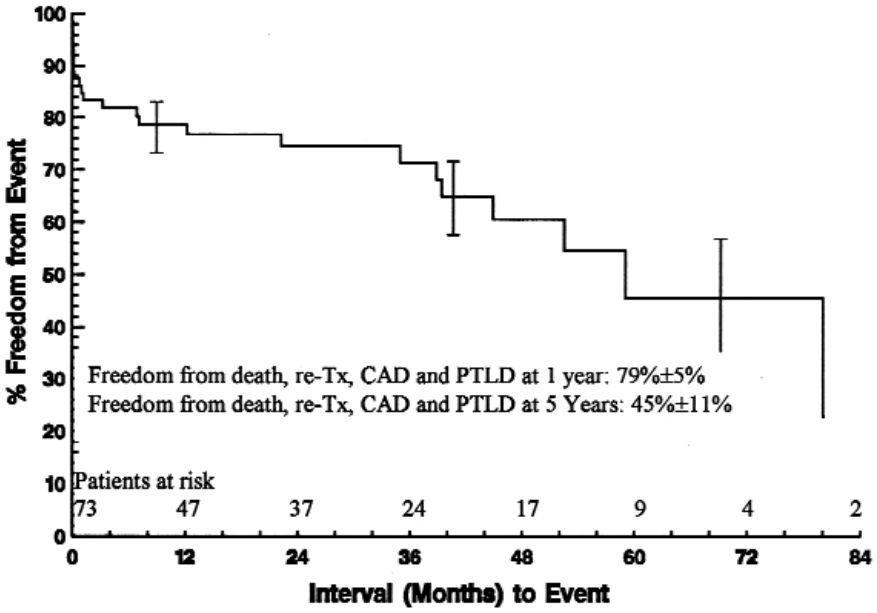

Fig 3. Actuarial freedom from death, retransplantation *(re-Tx),* coronary artery disease *(CAD),* or post-transplantation lymphoproliferative disease *(PTLD).*

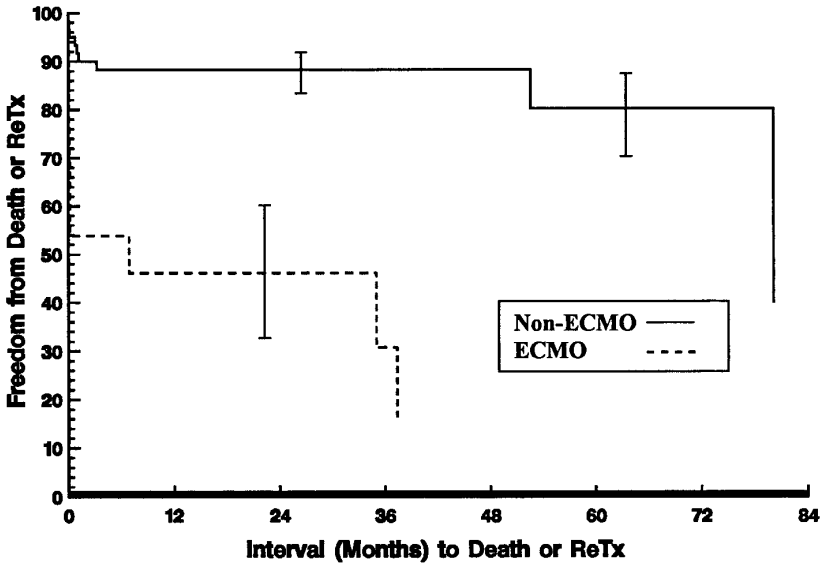

Fig 4. Actuarial survival for patients with pretransplantation extracorporeal membrane oxygenation *(ECMO)* versus those without. *ReTx,* Retransplantation.

plantation vs 1 year; $P = .007$ [factorial analysis of variance]). Preoperatively, PVRI was higher than 4 Wood units × m^2 in 12 patients (16%), higher than 6 Wood units × m^2 in 8 patients (11%), and higher than 8 Wood units × m^2 in 2 patients (3%). Preoperative PVR or PVRI was not a risk factor for death by multivariate analysis.

Superior vena cava (SVC) stenosis. Three patients had significant SVC obstruction postoperatively and required stent implantation in the SVC.

Immunosuppression. Immunosuppressive therapy at discharge and at follow-up is shown in Fig 6.

Waiting list issues. Mean time on the waiting list for all patients who eventually received a heart transplant

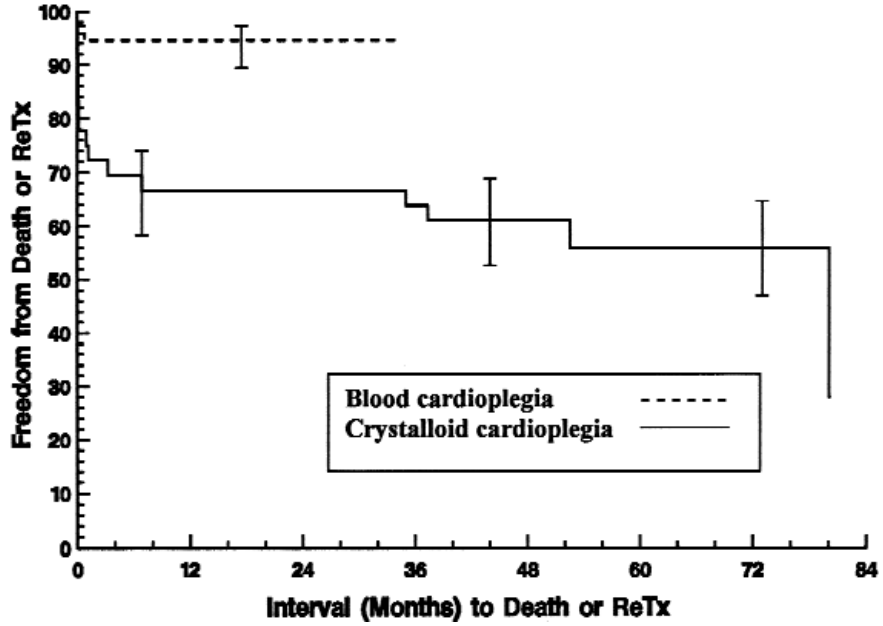

Fig 5. Actuarial survival for patients receiving blood cardioplegia versus crystalloid cardioplegia. *ReTx,* Retransplantation.

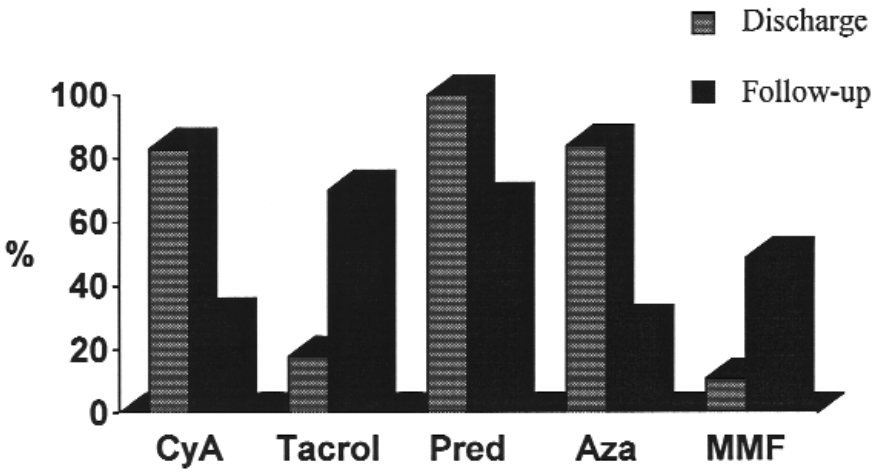

Fig 6. Immunosuppression at discharge from hospital and at late follow-up. *CyA,* Cyclosporine; *Tacrol,* tacrolimus; *Pred,* prednisone; *Aza,* azathioprine; *MMF,* mycophenolate mofetil.

was 78 ± 98 days (median 45 days; range 0-540 days). Nineteen percent (22/116) of patients listed for a heart transplant died after a mean of 30 ± 42 days (range 1-184 days) on the waiting list. Nine patients were listed for heart transplantation but improved clinically and were subsequently removed from the list. Surgical alternatives were pursued in 7 patients originally listed for heart transplantation. Five patients were still listed for transplantation as of December 31, 1999.

Since January 1996, 22 infants less than 6 months of age were listed for transplantation. Two patients died at 6 and 9 weeks after being listed. Fifteen patients underwent cardiac transplantation; 9 received ABO-incompatible grafts and 6 patients underwent ABO-compatible transplantation. Two patients were removed from the list due to cerebral bleeding (n = 1) and the presence of a lethal genetic syndrome (n = 1). Three patients underwent other surgical options. Thus, on an

intent-to-treat basis, 89% (16/18) survived the waiting list period. Before 1996, 12 patients less than 6 months of age were listed for heart transplantation. Seven died, 2 underwent transplantation, and 3 patients underwent the modified Norwood procedure. Thus, before 1996, only 17% (2/12) listed for heart transplantation actually underwent this procedure.

CAD. CAD developed in 7 (7/63, 11%) patients after transplantation. Two patients died of CAD, 1 of whom underwent a second transplant operation. Three patients had stenosis of the left anterior descending artery on follow-up coronary angiography: one of these patients underwent successful stent insertion in the left anterior descending coronary artery; one patient has been listed for retransplantation because of progressive heart failure and CAD.

PTLD. PTLD developed in 9 (9/63, 14%) patients after transplantation. Three of these patients have died as a result of PTLD. Two additional patients with PTLD died as a result of coexisting CAD. The remaining 4 patients in whom PTLD developed are in remission at most recent follow-up.

Discussion

Over the past decade, pediatric heart transplantation has become successful therapy for end-stage congenital heart disease and idiopathic cardiomyopathy.[1-3] The survival at 1 and 5 years in our experience is similar to what has been previously reported by the Pediatric Heart Transplant Study Group,[4] by the Registry of the International Society of Heart and Lung Transplantation,[1] and by others.[2] Kanter and associates[2] published excellent results with a 4% early (30 days) mortality rate but with 5-year survivals similar to those reported in our series. Our experience indicates that favorable survival results can be achieved even in recipients with clinical features traditionally considered to put them at high risk for transplantation.

Wider application of pediatric heart transplantation is prevented by the shortage of donor organs of appropriate size, especially in the neonatal recipients. Waiting list mortality for infants can be as high as 40%, especially in those centers accepting a large proportion of patients with ductus-dependent cardiac lesions.[5,6] The traditionally accepted premise of donor-recipient blood group compatibility prevents the more efficient allocation of organs on the basis of medical urgency. We have also observed that organs from blood group AB or B pediatric donors may not be used due to scarcity of appropriately sized ABO-compatible recipients, despite recipient registration with national and international networks.

Our waiting list outcomes are comparable with those of previously reported studies.[7] Waiting list attrition in the neonatal group has declined in our recent experience. We attribute this decline to improvement in the medical management of the ductus-dependent circulation. However, we suggest that the use of ABO-incompatible grafts further contributed to a decline in waiting list attrition and improved organ allocation in this subset of patients.

ABO-incompatible cardiac transplantation was performed in infants to increase the availability of organs in this high-risk group. In a survey from 66 centers worldwide, Cooper[8] found that 8 (0.16%) of 4895 patients underwent inadvertent ABO-incompatible heart transplantation. The risk of hyperacute rejection was very high (5/8) in this group, with only 2 long-term survivors.

Our experience indicates that ABO-incompatible transplantation can be performed without significantly increased mortality or morbidity. We attribute the lack of hyperacute rejection in our experience to the preemptive removal of anti-A and anti-B antibodies during plasma exchange on bypass before graft reperfusion and/or the low pretransplantation antibody titers typical of recipients in the first year of life. This result is predicted by both experimental evidence[9] and limited experience in renal transplantation,[10] in which the risk of hyperacute rejection is related to pre-existing antibody titers in the recipient. Patients receiving ABO-incompatible grafts showed a tendency to produce lower levels of antibodies directed against the incompatible blood group antigen than against the nonexpressed antigen. Furthermore, little or no evidence of vascular rejection was seen, and persistent cellular rejection did not occur during follow-up in recipients of ABO-incompatible grafts. No patient in this subgroup of patients has had CAD develop during the limited follow-up extending to 4 years. Thus, the clinical and immunologic course would imply that a degree of operational tolerance had occurred in this subset of patients, although longer follow-up is clearly required to make this determination.

We found that pretransplantation use of ECMO was a risk factor affecting post-transplantation survival. Nevertheless, the 5-year survival results may be considered acceptable in the ECMO group considering the pretransplantation status of these patients. We found that ECMO was a useful rescue intervention in rapidly deteriorating cardiomyopathy and as a bridge to retransplantation in early or late graft dysfunction. The results from other studies support these recommendations.[11]

Multivariable analysis was consistent with protective effects of blood-insulin cardioplegia. Our data also indicate that prolonged ischemic time (up to 10 hours) can be safely used with blood-insulin cardioplegia.

Since blood-insulin cardioplegia has been used more recently, it could be argued that the improved results are also in part attributable to greater experience after an initial learning curve. The beneficial effects of blood-insulin cardioplegia, however, are supported by experimental[12] and clinical[13] studies.

The precise mechanisms that mediate the protective effects of insulin have not been delineated but may be attributable to the stimulation of specific signaling cascades by this hormone. Insulin binding stimulates tyrosine autophosphorylation of the insulin receptor and activates its intrinsic tyrosine kinase activity, leading to the phosphorylation of insulin receptor substrates and the subsequent activation of phosphatidylinositol-3-OH kinase.[14] The anti-apoptotic effects of insulin and insulin-like growth factor-1 have been linked to the activation of signaling molecules such as insulin receptor substrate-1,[15,16] phosphatidylinositol-3-OH kinase,[17,18] and protein kinase B/Akt.[19] Protein kinase B provides a survival signal that protects cells from apoptosis induced by diverse stresses, including withdrawal of the survival factor insulin-like growth factor-1 from neuronal cells[19] and by detachment of cells from the extracellular matrix.[20] In the current study, however, the effect of insulin cannot be isolated from the effect of blood cardioplegia because both factors operated concomitantly. It should also be noted that in the present study, improved results with blood-insulin cardioplegia were documented in comparison with a specific composition of crystalloid cardioplegic solution that may be inferior to alternative crystalloid solutions used successfully by other groups.[2]

The incidence of SVC stenosis necessitating stent implantation after cavo-caval anastomosis techniques has been relatively high in our experience, despite the use of interrupted suture technique designed to prevent anastomotic narrowing. Six additional patients not included in the current study recently underwent transplantation by means of a cavo-caval technique, and 3 of them have required stent implantation. The hemodynamic significance of SVC stenosis necessitating stent implantation and that of less severe stenoses evident angiographically are unknown and deserve serious consideration in the choice of venous reconnection techniques, particularly in the infant age group.

Our results indicate that pediatric cardiac transplant recipients are subject to a continuing substantial risk of potentially lethal complications including PTLD and CAD. The incidence of PTLD is comparable with that observed in previous studies[2,7,21] and is higher than typically observed in adult recipients.[22] Conversely, the incidence of CAD in our study appears to be similar to that noted in other pediatric reviews[2,23] and lower than typically seen in adult recipients.[24] These complications, as well as the continuing risk of graft rejection, reflect the inadequacies of current immunosuppressive therapy.

Preoperative PVR higher than 5 Wood units and a transpulmonary gradient exceeding 15 mm Hg have been considered as contraindications to heart transplantation in adults.[25] Addonizio and associates[26] showed that PVRI was more discriminating than PVR in predicting postoperative right ventricular failure and that patients with PVRI in the range of 6 to 10 Wood units $\times$ m^2 were considered at high risk for right ventricular failure. However, our study did not reveal that higher PVR or PVRI was a risk factor for early or late death, a finding consistent with the Pittsburgh data.[25] Our experience indicates that there is no upper limit to baseline pretransplantation PVR that precludes successful cardiac transplantation, provided that evidence of reactivity of the pulmonary vascular bed is revealed at the pretransplantation cardiac catheterization. These considerations also apply to patients with restrictive cardiomyopathy who frequently have increased PVR early in the course of their disease.

Conclusions

This experience indicates that strategies designed to increase organ availability in pediatric cardiac transplantation, including the use of ABO-incompatible grafts and substantial extension of acceptable donor ischemic times, can be pursued without significantly increased morbidity or mortality. Further, the use of a blood-insulin cardioplegia protocol appears to confer improved graft protection despite relatively long donor ischemic times.

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Discussion

Dr Thomas L. Spray *(Philadelphia, Pa).* The authors have shown that results with cardiac transplantation in pediatric patients have continued to improve, and they raise the stimulating possibility of increasing use of ABO-incompatible donors for infant recipients. The principle of ABO-incompatible transplantation has been validated in the renal transplant experience, and Dr Coles and his group have been pioneers in applying this procedure to pediatric patients. The benefits of ABO-incompatible transplantation presumably will be the ability to use potentially wasted organs and possibly decrease waiting times for patients in common blood groups, such as group O. The authors, unfortunately, however, did not assess whether organs are being wasted for lack of suitable recipients in the Canadian organ procurement system. Such a situation in the United States is uncommon because of the relatively large number of infants listed at any given time, reflecting the preference for transplantation for hypoplastic left heart syndrome in a few US centers. I believe, though, on the basis of Dr Coles' study, that the organ distribution system in the United States would be well served by analyzing the potential effects of ABO-incompatible transplantation on waiting times for pediatric patients. ABO-incompatible transplantation possibly could provide a great opportunity to decrease waiting times in the sickest patients if it does not divert organs from patients in less common blood groups.

Although the authors have presented a large series of pediatric transplants with good results, the study is actually not designed to show that there are improving results in high-risk patients. The authors defined high-risk patients arbitrarily as those receiving ECMO support, those with ABO-incompati-

ble transplants, those with an elevated PVRI, and those undergoing retransplantation; however, they showed in their results that only ECMO is in fact a risk factor for mortality. The arbitrarily defined high-risk group was not the basis for the study, and results over time in this subset of patients were not examined specifically.

I have several questions for the authors, primarily to gain more information on their experience.

The addition of blood-insulin cardioplegia seems to be associated with improved survival, although only 3 of the 10 early deaths in the experience were related to graft failure. Could you comment on the function of the hearts after the use of this different cardioplegia technique, and could you elaborate on why you believe this has fundamentally changed the morbidity and mortality of the procedure?

Is the improvement in results just a time-related phenomenon or is it in fact related to the cardioplegia technique? Was the date of transplantation ever placed in the model for univariate analysis?

When you do ABO-incompatible transplantations, do you modify the use of the blood-insulin cardioplegia so that the donor heart is reperfused not with recipient blood cardioplegic solution during the implantation but with a modified solution? If not, do you think that the possible administration of recipient blood antigen to the donor has any deleterious consequences when you give cardioplegia? Do you try to wash the blood cardioplegic solution from the donor out of the heart before it is actually exposed to recipient blood?

I noticed that ABO-incompatible transplantation in your experience was used primarily in infants. The experience in adult transplantation crossing blood groups has not been very favorable, with both early and late graft dysfunction in cases in which accidental ABO-incompatible transplantation has been performed. Do you believe this technique can be used for older children and adults? If not, at what age would you consider a patient no longer suitable for ABO-incompatible transplantation?

One final question is related to the high incidence of SVC stenosis noted in the bicaval technique group of transplants. On the basis of the relative frequency of obstruction of the SVC, do you now continue to advocate bicaval anastomosis or have you considered reverting to the atrial anastomosis, especially in young children, to prevent this complication?

Dr Coles. Thank you for your comment, Dr Spray, and your pertinent questions.

With regard to your comment, in several of the patients who underwent ABO-incompatible transplantation, we were offered hearts that otherwise would have been wasted, both from Canada and from the United States. Thus, I think there are unique recipients with respect to blood group who would benefit from incompatible transplantation and therefore improve the global use of neonatal organs.

To answer your question about age threshold, we use ABO-incompatible donor organs primarily in infants. Two older patients, however, 1 of whom was receiving ECMO support, had high pretransplantation anti-blood group–directed antibodies. These antibodies were removed by means of plasma exchange on bypass and the patients have done well postoperatively. One interesting finding is that they actually had lower titers against the relevant donor blood group than against irrelevant blood groups, suggesting a kind of operational tolerance, at least with respect to the donor blood group. Therefore, I think this technique could be cautiously applied to older patients and possibly even adults.

We think that SVC stenosis is an underestimated complication. I believe a careful review of postoperative angiograms obtained at the time of biopsy will often show some narrowing, regardless of the techniques that are used, such as interrupted suture techniques and patching to prevent this complication. As you mentioned, several of our patients required stent implantation. On the basis of that experience, we now prefer to use conventional atrial anastomosis in patients less than 10 kg.

Your point is well taken. It is not possible to separate the era effect from the blood effect from the insulin effect. However, the differences were so dramatic that we would be disinclined to revisit the crystalloid era.

Dr Carl L. Backer *(Chicago, Ill).* I want to echo Dr Spray's concerns about blood-insulin cardioplegia being the reason for your improved results. Our series is parallel to yours, approximately 80 transplants in 10 years. For the first 40 patients we had a 12% mortality; for the last 40 transplants we have had no mortality. The last time period has seen many changes, with the use of modified ultrafiltration, bicaval technique, aprotinin, and changes in immunosuppression protocols. It is very difficult to sort out the changed cardioplegia technique as a single item that has improved your results.

Dr Coles. I agree with your comments.