Pediatr Transplantation 1999: 3: 309–314
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Pediatric Transplantation
ISSN 1397-3142

The use of advanced-age donor hearts adversely affects survival in pediatric heart transplantation

Chin C, Miller J, Robbins R, Reitz B, Bernstein D. The use of advanced-age donor hearts adversely affects survival in pediatric heart transplantation
Pediatr Transplantation 1999: 3: 309–314. © Munksgaard, 1999

Abstract: There is a limited supply of adequate donor hearts for cardiac transplantation. The safety of using advanced-age donor hearts has been debated in adult transplantation but has not been studied previously in pediatric recipients. In this retrospective study, survival of 79 pediatric heart transplant recipients was reviewed. Pediatric recipient groups were stratified based on donor age (group 1 donor age > 40 yr, n = 5; group 2 donor age ≤ 40 yr, n = 74). Survival of 267 adolescent (ages 11–17) heart transplant recipients in the United Network for Organ Sharing (UNOS) database was also reviewed. Patients were likewise divided into two groups based on donor age (> 40 yr, n = 12; ≤ 40 yr, n = 255). Survival at one yr was 20% in group 1 vs. 78% in group 2 ($p < 0.005$). Cause of death in all group 1 patients was graft failure secondary to acute rejection. Analysis of risk of death was only significantly attributable to the age of the donor. The increased risk attributable to advanced donor age was also supported by the UNOS data. The UNOS one and two-year Kaplan–Meier survival curves were significantly lower in adolescent patients who received donor hearts > 40 yr of age. One-year survival was 58% (older donors) vs. 85% (younger donors, $p < 0.005$) and two-year survival was 44% (older donors) vs. 79% (younger donors, $p < 0.005$). Advanced-age donor hearts should be contraindicated in pediatric transplantation with the exception of critically ill patients who may not be able to wait for a younger heart.

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Key words: pediatric – heart transplantation – donor age

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Accepted for publication 13 May 1999

Over the past several years a shortage of adult donor hearts has markedly increased recipient waiting time in adult heart transplantation. Since 1990, the annual number of heart transplant operations has plateaued (1), at least in part owing to the limited numbers of available donors. In pediatrics, this donor shortage has impacted upon mainly the adolescent age group as they may be competing with adults for the same donor pool. The use of advanced-age donor hearts has been debated in the adult literature but has yet to be agreed upon. In children, however, this issue has not been widely addressed and pediatric centers have different policies regarding the use of advanced-age donor hearts. Some investigators have suggested that one criterion for cardiac donation should be a donor age of fewer than 40 yr (2). However, because of the scarcity of donor organs and the fact that adolescent patients are often large enough to accommodate an adult-sized heart, some adolescents have received older hearts. The purpose of this report is to determine the risks of using older donor hearts in pediatric-age recipients.

Abbreviations: UNOS, United Network for Organ Sharing; PRA, panel-reactive antibodies; HLA, human leukocyte antigen; CVA, cerebrovascular accident; CsA, cyclosporin A; LVH, left ventricular hypertrophy; LVFS%, left ventricular shortening fraction; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; ISHLT, International Society of Heart and Lung Transplantation; ECG, electrocardiogram.

Patients and methods

Patient groups

Between July 1981 and May 1994, 79 pediatric patients (defined as < 18 yr of age) underwent cardiac transplantation at Stanford University. This population of patients was divided into two groups based on donor age. Group 1 patients received donor hearts greater than 40 yr of age (n = 5, Tables 1 and 2). All of these patients suffered from idiopathic dilated cardiomyopathies. Group 1 also did not represent a particularly high-risk pretransplant group at the time of transplant as none was at high risk of dying acutely. No patients in group 1 required assist devices pretransplant and none were retransplants. In the patients who died, their clinical courses prior to death were unremarkable for early warning signs of impending mortality. All procedures followed were in accordance with institutional guidelines.

The following is a brief clinical summary for each of the group 1 patients.

Patient 1. Patient 1 developed a fever and cough the day prior to admission, post-transplant day 31. On the day of admission to the hospital, he complained of nausea without emesis. A chest X-ray was unchanged compared with previous examinations, however, by echocardiogram, the LVFS% dropped from 30% to 6%. He was given 1 gram of intravenous methylprednisolone and transferred to the ICU. Owing to blood pressure instability, he required dopamine (20 mcg/kg/min), dobutamine (15 mcg/kg/min), and epinephrine (50 ng/kg/min). A full 3-day course of intravenous methylprednisolone was planned and a repeat course of OKT3 was started. He was intubated on day 1 of admission secondary to metabolic acidosis. He shortly developed acute renal failure necessitating placement of a Tenckhoff catheter for peritoneal dialysis. On day 2, his inotropic drips were increased but he developed worsening multiorgan failure secondary to a low cardiac output. After three cardiac arrests requiring CPR he developed central nervous system compromise and support was withdrawn. He was pronounced dead on day 33 post-transplant. Prior to his admission he had three previous biopsies, all negative for rejection, the most recent on day 20 post-transplant. Autopsy results showed mild-to-moderate acute rejection with global ischemic damage to the myocardium. There was minimal coronary artery disease with a single 10–20% occlusive lesion in the mid-right coronary artery.

Patient 2. Patient 2 presented with a single episode of emesis the day prior to admission, post-transplant day 21. His LVFS% was 28–35%; the chest X-ray was unchanged from previous studies. As arrangements were being made to perform a cardiac biopsy, he had another episode of emesis, fainted and became asystolic. Resuscitation measures were performed immediately, including intubation and mechanical ventilation. Despite open chest massage, he died on day 22 post-transplant. He had two previous surveillance biopsies, both negative for rejection, the last biopsy performed on day 16 post-transplant. The autopsy was consistent with severe acute rejection with multifocal myocardial necrosis. The coronary arteries had changes consistent with a mild component of chronic ongoing rejection. There was no evidence for coronary artery disease.

Patient 3. Patient 3 died 5.5 yr post-transplantation. Her first year post-transplant was uncomplicated, with six negative biopsies, three mild (grade 1A), two focal moderate (grade 2), and one moderate (grade 3A) rejection episodes. Coronary angiography done at each year post-transplantation showed no evidence for coronary artery disease. A pericardial stripping was performed for constrictive cardiomyopathy. She clinically improved briefly but later developed signs of a restrictive cardiomyopathy and died while awaiting re-transplantation.

Patient 4. Patient 4 had a cardiac biopsy on day 12 post-transplant that was negative for

Table 1. Group 1 pretransplant characteristics

Patient no.	Age (yr)	Sex	Blood type	Status at listing	Year of Tx	Days alive	Pre-transplant inotropic support
1	15.9	M	A	1	1980	33	dopa – 5
2	11.5	M	O	1	1992	22	dobut – 13, amrinone – 10
3	17.0	F	O	1	1993	2024.0	dopa – 3
4	13.1	M	B	2	1993	25	None
5	12.7	F	AB	1	1994	28	dopa – 5

All inotropes are expressed in micrograms/kg/min. M, male; F, female; Tx, transplant; dopa, dopamine; dobut, dobutamine.

Table 2. Donor characteristics for the group 1 patients

Patient no.	Age (yr)	Sex	Blood type	Ischemic time (min)	Cause of death	LVH by EKG	Echo	Hx of HTN	Peak inotropic support
1	43	M	O	104	CVA	no	normal	no	dopa – 5
2	51	F	O	88	CVA	no	normal	10 yr	dopa – 8
3	41	F	O	208	CVA	no	normal	no	dopa – 20, dobut – 10
4	43	F	O	182	CVA	borderline	borderline LVH	no	dopa – 17
5	41	M	AB	184	CVA	no	mild LVH	no	dopa – 7

All inotropes are expressed in micrograms/kg/min. M, male; F, female; CVA, cerebrovascular accident; LVH, left ventricular hypertrophy; HTN, hypertension; dopa, dopamine; dobut, dobutamine.

rejection. He developed a fever and was observed in the hospital but ultimately discharged after blood and urine cultures showed no evidence for an infectious process. He was followed as an outpatient for 3 days with a low-grade fever and malaise prior to readmission to the hospital. Echocardiograms done during this time period showed a LVFS% of 28–35%. On the day of readmission, his LVFS% dropped to 22% and was accompanied by symptoms of increasing malaise and poor perfusion. In the ICU he was treated with isoproterenol (3 ng/kg/min), dobutamine (2 mcg/kg/min) and pulsed with intravenous methylprednisolone (1 gram/day for 3 days). A biopsy done on day 29 post-transplant was consistent with ISHLT grade 3B rejection. On day 5 of admission the LVFS% was 20% which prompted a second 3-day course of methylprednisolone, increasing his inotropic requirement to dopamine (5 mcg/kg/min) and dobutamine (5 mcg/kg/min). Early the next morning he decompensated further, requiring mechanical ventilation. He eventually became asystolic and required CPR. This was unsuccessful and the patient died on day 25. The autopsy was consistent with severe acute rejection without evidence for coronary artery disease.

Patient 5. Patient 5 complained of right shoulder and neck pain 2 days prior to admission on post-transplant day 22. On the day of admission she developed a fever with shortness of breath. A chest X-ray showed neither infiltrates nor a change in heart size. An ECG was normal and an echocardiogram showed hyperdynamic left ventricular function (LVFS% = 52). Other laboratory studies included a white blood cell count of 15,300 units/mm^3 with 12% bands. The patient was admitted to the hospital and was started on i.v. antibiotics. The next day she became diaphoretic and uncomfortable. She was transferred to the ICU and intubated. CPR was subsequently performed owing to a deteriorating cardiac rhythm. This was unsuccessful and the patient died on day 26 post-transplant. A surveillance biopsy done on day 17 post-transplant was negative for rejection. The autopsy showed severe acute rejection with mild graft coronary artery disease in all vessels but without coronary artery thrombosis.

Group 2 patients. Group 2 patients received donor hearts of fewer than 40 yr of age (n = 74). As a donor-age matched control, adult patients (group 3, n = 40) who underwent cardiac transplantation at Stanford during the same time period and who received older hearts (donor age > 40 yr old) were also evaluated to compare survival rate with survival rate in the pediatric groups. All donors were matched for ABO blood group compatibility. Other strategies for preoperative donor-recipient matching included approximation of body weight and heart size as determined by chest X-ray, and screening for circulating antibodies to human lymphocyte antigens with PRA. Post-transplantation HLA typing was performed

Donor preservation, recipient immunosuppression and rejection surveillance

Preservation techniques were the same for all donors. A crystalloid cardioplegia solution was used (500cc D_5W, 12.5% mannitol, 15 mEq/500cc KCl, 12.5 mEq/500 cc $NaHCO_3$). The time period of this study encompasses only the CsA era. All patients in group 1 received triple immunosuppressive therapy. CsA dose was adjusted to maintain an early post-transplant trough serum level between 150 and 250 ng/mL (determined by fluorescence polarization immunoassay, TDx, Abbott Laboratories, Chicago, IL, USA) and between 100 and 200 ng/mL thereafter. Azathioprine was adjusted to achieve a total white blood cell count between 4000 and 5000/mm^3. Prednisone therapy was initiated in the early post-operative period at a dose of 0.6 mg/kg/d, weaned gradually to 0.2 mg/kg/d over the first 6 months, and then weaned further,

if tolerated, with the aim of becoming steroid-free by one to two years post-transplantation. A 14-day course of OKT3 was used as induction therapy in 100% (n = 5) of patients in group 1 and 62% (n = 46) of patients in group 2. Other modes of therapy in group 2 patients included CsA, prednisone and antithymocyte globulin (n = 6); CsA and prednisone alone (n = 7); CsA, azathioprine, and prednisone without induction therapy (n = 13); and CsA and azathioprine alone (n = 2).

Monitoring for acute rejection consisted of routine endomyocardial biopsy with histologic examination of four or more pieces of right ventricular endomyocardium (3). Early post-operative acute rejection with evidence of myocardial necrosis (ISHLT grade 3 or greater) was treated with i.v. methylprednisolone (15 mg/kg/d) for 3 days. Acute rejection appearing after the first year post-transplant, if asymptomatic, was usually treated with high doses of oral prednisone (2 mg/kg/d) for 3 days, with subsequent tapering to maintenance prednisone doses over a 2-week period.

Owing to the relatively small number of patients in group 1, the UNOS database was also reviewed for differences in survival between pediatric patients who received younger (≤ 40 yr old, n = 255) vs. older (> 40 yr old, n = 12) hearts.

Statistical analysis

Results are expressed as mean ± SD for normally distributed data. Survival curves were generated using the Kaplan–Meier method. Significant differences in survival were assessed using the Mantel–Cox test. Means between groups were analyzed using the Mann–Whitney-*U*-test. A p-value less than 0.05 was considered significant.

Results

Stanford data

Survival at one year was 20% in pediatric patients receiving older hearts (n = 5, group 1) vs. 78% in pediatric patients receiving younger hearts (n = 74, group 2, $p < 0.005$, Fig. 1). Death in the first year in group 1 (n = 4) was due to graft failure secondary to acute rejection. A donor-age-matched group consisting of adults who received older donor hearts (> 40 yr, group 3, n = 40) was also compared against both groups 1 and 2. Survival in group 3 at one year was 83%, which was statistically better than group 1 survival ($p < 0.005$) but not significantly different compared with group 2 survival. Because the high risk group 1 was composed solely of children between 11 and 17 yr of age, we also examined an age-matched subset of group 2 to determine if adolescence was an independent high-risk factor (group 2A, n = 30, patient ages 11–17 who received donor hearts < 40). Group 2A had a one-year survival equivalent to the other pediatric and adult patients at one year (80%, p = NS) and significantly greater than group 1 survival at one year ($p < 0.005$).

There were no statistical differences found with respect to PRA or HLA mismatching between any of the groups. Patients in group 1 were predominantly status 1 (n = 4). The pretransplant recipient status (status 1, n = 24; status 2, n = 38), gender of the recipient (female, n = 40; male, n = 34) and donor (female, n = 29; male, n = 45) were not found to be significant risk factors for death in the group 2 patients. Group 1 patients all received hearts from donors who suffered a CVA. CVA was not a risk factor in group 2 (CVA, n = 7; other causes of donor death, n = 67). Given that four of the five donors in group 1 were blood type O, this variable was also analyzed and found to be non-significant with respect to survival in the group 2 recipients. When comparing survival between the pediatric groups (1 and 2), no statistical differences were found between groups receiving and not receiving induction therapy (OKT3 or antithymocyte globulin). As group 1 patients all received OKT3, group 2 patients were reanalyzed comparing survival of only those patients who received OKT3 (n = 46) vs. those who did not receive any form of induction therapy (n = 24, p = NS). Ischemic times were 153.2 ± 53.5 for group 1, 192.6 ± 90.2 for group 2, and 169.4 ± 52.7 for group 2A (p = NS). Inotropic support pre-donor harvest was predominately with dopamine and

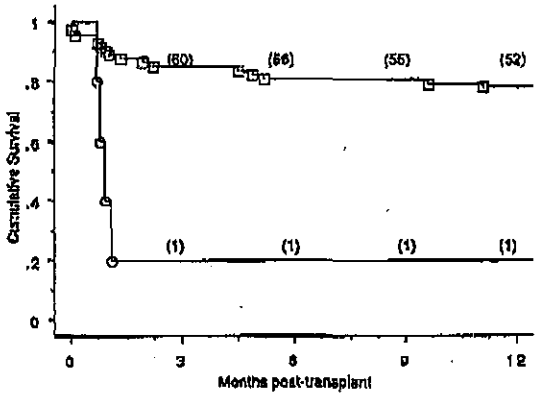

Fig. 1. Cardiac transplant one-year survival at Stanford. Group 1 (○): Pediatric patients who received donor hearts > 40 yr. Group 2 (□): Pediatric patients who received donor hearts < 40 yr.

was not significantly different between groups 1 and 2A (group 1 = 11.4 ± 6.7 mcg/kg/min, group 2A = 11.1 ± 8.1 mcg/kg/min). Only the donor for patient 3 in group 1 required dobutamine (10 mcg/kg/min) in addition to dopamine.

UNOS data

In the UNOS registry, 267 adolescent patients (ages 11–17 yr) underwent orthotopic heart transplantation between October 1, 1987 and December 31, 1992. Two hundred and fifty-five patients received younger donor hearts (donor age < 40) and 12 adolescents received older donor hearts (donor age > 40). Survival was 58% at one year and 44% at two years for those adolescents who received older donor hearts (Fig. 2). One- and two-year survival was 85% and 79%, respectively, for those adolescents receiving younger hearts. Kaplan–Meier actuarial survival curves were generated for both groups. Using the Mantel–Cox test, we found a significant decrease in survival in the adolescent group who received older donor hearts vs. those adolescents who received younger donor hearts ($p = 0.004$ at 1 yr, $p = 0.002$ at 2 yr).

Discussion

Controversy exists over the acceptability of advanced age donor hearts for adult orthotopic heart transplantation. Proponents for the use of advanced-age donor hearts include Luciani et al. (4) who reported excellent survival in recipients over 55 yr of age who received hearts from older donors (> 40 yr of age). Alexander et al. (5) found minimal differences in patient survival at one year between donors age 16–45 yr and those aged 45–55 yr. Others have reported similar findings that older donors do not statistically increase the risk of transplantation in adults (6–8).

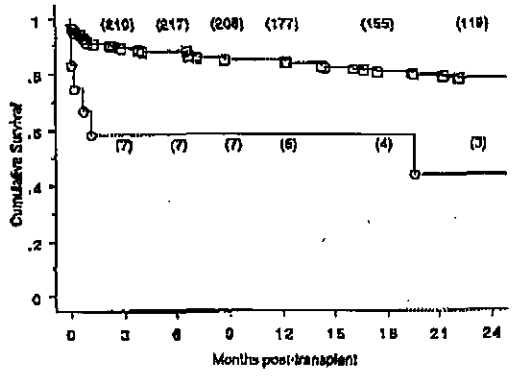

Fig. 2. UNOS cardiac transplant two yr survival. (○): Pediatric patients who received donor hearts > 40 yr. (□): Pediatric patients who received donor hearts < 40 yr.

Opponents to the use of older donor hearts in adults have reported contrary results. In a multi-institutional study, Bourge showed that donor age was a positive risk factor for death ($p = 0.0007$) (9), particularly when the donor exceeded 45 yr of age (10). Others have also found that older donor age increases the risk to the recipient (11) and concluded that these hearts should not be used (12).

There are no documented studies regarding the use of advanced-age donor hearts in the pediatric population, although a few previous studies have included adolescent recipients as part of a larger study population (5, 11). In this study, we have shown that advanced donor age, in the absence of other high-risk factors, is associated with a much poorer outcome at one year post-transplant compared with those patients who received younger hearts. A potential limitation of this study is that the number of patients who received older hearts in our series was small. To minimize the possibility of a type 1 error, we reviewed the UNOS database and confirmed the presence of a significant difference in adolescent post-transplant survival with respect to donor age.

During the time period that this study encompasses, older donor hearts were used in pediatric patients because of donor scarcity, not because of the severity of illness of the recipient. Of all the variables studied, only donor age > 40 yr was found to be a significant risk factor. Angiography was not performed on group 1 donor hearts. Although the echocardiographic and EKG data were normal in all of these donors, it is possible that undiagnosed coronary artery disease could have affected recipient survival. All autopsy specimens in group 1, however, showed evidence of severe acute rejection, with one exception, and in the two with graft coronary artery disease, the findings were minimal. The one patient who, at autopsy, showed only mild-to-moderate rejection, was treated with a full course of i.v. methylprednisolone and started on OKT3 therapy. It is probable that his biopsy result was attenuated by the antirejection therapy and he probably suffered from severe rejection.

Although we cannot identify a specific immunologic mechanism for this phenomenon, all of our patients who died with older donor hearts succumbed to severe acute rejection early in their post-transplant course. This phenomenon was not seen in adults who received older donor hearts. Because all patients who received older hearts were adolescents, we examined whether

this increased risk was associated with recipient age. Adolescence itself was not associated with an increased risk using an age-matched group who received younger donor hearts. We speculate that the older donor graft may be less able to maintain adequate cardiac performance during acute rejection when placed into the milieu of a younger circulatory system. Although the mechanism remains unclear, our findings suggest that advanced-age donor hearts should be contraindicated in pediatric transplantation except in emergency situations where the recipient may not survive long enough to obtain a younger graft.

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