Preoperative risk factors predict survival following cardiac retransplantation: Analysis of the United Network for Organ Sharing database

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Background: The aim of our study was to identify preoperative risk factors affecting overall survival after cardiac retransplantation (ReTX) in a contemporary era.

Methods: The United Network for Organ Sharing database was used to identify patients undergoing ReTX between 1995 and 2012. Of the total 28,464 primary transplants performed, 987 (3.5%) were retransplants. The primary outcome investigated was overall survival. The influence of preoperative donor and recipient characteristics on survival were then tested with univariate logistic regression and multivariate Cox regression models.

Results: Of 987 patients who underwent ReTX, median survival was 9 years. Estimated survival at 1, 3, 5, 10, and 15 years following retransplant was 80% (95% confidence interval [CI], 78%-83%), 70% (95% CI, 67%-73%), 64% (95% CI, 61%-67%), 47% (95% CI, 43%-51%), and 30% (95% CI, 25%-37%), respectively. Clinical predictors of survival using multivariable analysis included donor age (relative risk [RR], 1.14; $P = .004$), ischemic time > 4 hours (RR, 1.48; $P = .004$); preoperative support with extracorporeal membrane oxygenator (RR, 3.91; $P < .001$), and the time between previous and current transplant ($P = .004$). Patients with ReTX have 1.27 times higher relative risk of death compared with patients undergoing primary transplant only (RR, 1.27; 95% CI, 1.13-1.42; $P < .001$).

Conclusions: Patients who undergo cardiac ReTX can expect to have a 1-year survival less than a patient undergoing primary transplant with an acceptable median overall survival. Both donor and recipient preoperative factors contribute to overall survival following cardiac ReTx. Donor characteristics include age of the donor and ischemic time. Recipient factors include the need for extracorporeal membrane oxygenator and the number of days between the first and second transplant. Optimal survival following cardiac ReTX can best be predicted by choosing patients who are farther out from their initial transplant, not dependent upon preoperative extracorporeal support, and by choosing donor hearts younger in age and those likely to have shorter ischemic times. (J Thorac Cardiovasc Surg 2014;147:1972-7)

Supplemental material is available online.

Cardiac retransplantation (ReTX) remains an option for those patients with primary graft failure following

transplant. The International Society for Heart and Lung Transplantation (ISHLT) estimates the median survival for primary heart transplants to be 10 years, but little is reported or known about long-term outcomes or survival in recipients of ReTx.¹ Previous reports have documented 1-year survival between 23% and 65% following ReTX.²⁻⁷ This fact has led some to conclude that ReTX should be limited, given the scarcity of suitable cardiac donors.³⁻⁸ Our study provides a review of ReTX in the United States from 1995 through 2012 using data submitted to the United Network for Organ Sharing (UNOS) database, a prospectively collected registry that collects voluntary data from all United States transplant centers. This analysis focused on evaluation of overall survival following ReTX and identification of the preoperative donor and recipient risk factors that determine outcomes. This analysis is limited to a contemporary cohort of patients who have undergone cardiac ReTX in the United States from 1995 to 2012 to provide updated information on risk factors and overall survival.

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Supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Oct 22, 2013; revisions received Jan 20, 2014; accepted for publication Feb 3, 2014; available ahead of print March 15, 2014.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2014.02.013>

Abbreviations and Acronyms

ECMO = extracorporeal membrane oxygenator
 IABP = intra-aortic balloon pump
 ISHLT = International Society for Heart and Lung Transplantation
 ReTX = retransplantation
 UNOS = United Network for Organ Sharing

METHODS

Study Patients and Data Collection

Our review is a retrospective analysis of all 987 patients, at least 18 years of age, from the UNOS database of adult patients who underwent heart ReTX between 1995 and 2010. Information collected regarding recipients (ie, age at initiation, age at retransplant, gender, citizenship, initial body mass index, serum total albumin, ventricular assist device before retransplant, preoperative dependence on inotropes, ventilator status, intra-aortic balloon pump [IABP] status, extracorporeal membrane oxygenation [ECMO] status, diabetes, and dialysis) and information regarding donors (age, gender, and left ventricular ejection fraction of donor hearts). These variables were submitted to univariate analysis. Significant factors were then subjected to multivariate analysis.

Statistical Analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage. The Kaplan-Meier curve analysis along with 95% confidence intervals (CIs) was used to assess overall survival following ReTX. A single variable Cox proportional hazards regression model was used to evaluate associations of recipient and donor characteristics with overall survival following ReTX; relative risks (RRs) and 95% CIs were estimated. A multivariable Cox proportional hazards regression model was used to assess if any significant association of recipient and donor characteristics still hold while controlling for other confounding variables. No adjustment for multiple testing was made in these exploratory analyses. Statistical analysis was performed using SAS (version 9.2; SAS Institute, Inc, Cary, NC) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A summary of recipient and donor information is displayed in [Table 1](#) for the 987 study recipients. Median age of recipient at retransplant was 50 years (range, 18-74 years). Recipients requiring mechanical circulatory support before ReTX included 38 patients (3.9%). Most of the recipients were men (71%) and US citizens (99%). The median initial body mass index of recipients was 25.9 (range, 12.3-50.7). The majority of patients (63%) had serum total albumin ≤ 3 . Twenty-six recipients (3%) were receiving ECMO, 58 (6%) had an IABP, 74 (7.5%) required ventilator support, and a total of 474 (48%) required inotropic support before transplant. Two hundred twenty-four (23%) recipients had type 1 or type 2 diabetes diagnosed before transplant and 112 (11.5%) were receiving hemodialysis or peritoneal dialysis before transplant.

The median donor age was 30 years (range, 9-63 years), and 66% donors were men. Almost all donor hearts (97%) had left a ventricular ejection fraction of 50% or more. The median ischemic time was 3.3 hours (range, 1.0-9.2 hours). The distribution of number of retransplant procedures in the United States from 1995 to 2012 is given in [Table 2](#). The range of number of retransplants was 40 to 71; the lowest number of retransplants occurred during 1997 and the highest during 2011. The distribution of retransplants by region is listed in [Appendix Table E1](#).

The median follow-up length was 3.1 years (range, 0-17.1 years), and a total of 426 patients (43%) died during follow-up. Estimated survival at 1, 3, 5, 10, and 15 years following retransplant was 80% (95% CI, 78%-83%), 70% (95% CI, 67%-73%), 64% (95% CI, 61%-67%), 47% (95% CI, 43%-51%), and 30% (95% CI, 25%-37%), respectively ([Table 3](#) and [Figure 1](#)). Associations of survival with recipients and donor characteristics in univariate and multivariate analysis are displayed in [Table 4](#). With the multivariable Cox regression analysis, recipient characteristics associated with increased risk of death included support with ECMO (RR, 3.91; $P < .001$), and time between previous transplant and current transplant ($P = .004$) ([Figure 2](#)). Donor characteristics associated with increased risk of death included age (RR, 1.14; $P = .004$) and ischemic time (RR, 1.48; $P = .004$). Although univariate analysis demonstrated that the age of recipient at transplant, total serum albumin, need for mechanical ventilation, and presence of IABP had shown significant association with survival, these variables did not meet statistical significance in the multivariate analysis. In comparison with the ReTx patients >1 year from primary transplant versus those receiving primary transplants during the same period, ReTX patients have 1.27 times higher RR of death compared with patients with primary transplant only (RR, 1.27; 95% CI, 1.13-1.42; $P < .001$) ([Figure 3](#)).

DISCUSSION

ReTX has remained controversial since the first reports more than 30 years ago.⁸ This was primarily due to the shortage of suitable donors for cardiac transplantation. Currently, 400 patients die every year waiting for a suitable donor heart. The lack of suitable donor hearts, in addition to the poor outcomes historically associated with ReTX, has led several authors to conclude that the practice of cardiac ReTX poses an ethical dilemma and should therefore be limited.⁹⁻¹⁴ Survival following ReTX during the 1970s and the early 1990s was particularly poor in patients receiving retransplant within 1 month of the first transplant.^{5,6,15}

Because reports of ReTX emerged from the ISHLT during the early 1990s showing that the 1-year survival following ReTX was only 42%, some members of the European community believed that ReTX should not be

TABLE 1. Recipient and donor characteristics

Variable*	Overall sample (N = 987)
Age at retransplant (y)	50 (18-74)
Age at initiation (y)	49 (15-73)
Sex (male)	697 (70.6)
US citizenship	973 (99)
Initial BMI	25.9 (12.3-50.7)
Acute rejection episodes	
1	41 (7.7)
2	30 (5.6)
3	464 (86.7)
Graft failure cause	
Hyper acute rejection	26 (35.1)
Acute rejection	12 (16.2)
Chronic rejection	21 (28.4)
Unknown	15 (20.3)
Days listed as status 1	0 (0-224)
Days listed as status 1a	0 (0-692)
Days listed as status 1b	0 (0-1904)
Days listed as status 2	14 (0-2491)
Ischemic time (h)	3.3 (1.0-9.2)
Length of hospital stay (d)	2 (0-9)
Serum total albumin	
≤3	391 (63.0)
>3	230 (37.0)
VAD before transplant	38 (3.9)
Cardiac output obtained while on inotropes	176 (22.3)
Inotropes	474 (48.0)
Ventilator	74 (7.5)
IABP	58 (5.9)
ECMO	26 (2.6)
Diabetes	
Type 1	23 (2.4)
Type 2	81 (8.3)
Unknown	120 (12.3)
Dialysis at listing	
Hemodialysis	69 (7.1)
Peritoneal dialysis	4 (0.4)
Unknown	39 (4.0)
Donor age (y)	30 (9-63)
Donor sex (male)	654 (66.3)
Left ventricular ejection fraction of donor heart (%)	
30	4 (0.5)
40	16 (2.2)
≥50	719 (97.3)

The sample median (range) is given for continuous variables and number (percent) is given for categorical variables. *BMI*, Body-mass index; *VAD*, ventricular assist device; *IABP*, intra-aortic balloon pump; *ECMO*, extracorporeal membrane oxygenation. *Information was not available for the following variables: citizenship (n = 4), initial BMI (n = 30) acute rejection episodes (n = 452), ischemic time (n = 79), length of stay (n = 254), graft failure cause (n = 913), left ventricular ejection fraction of donor heart (n = 248), serum total albumin (n = 366), cardiac output obtained while on inotropes (n = 196), diabetes (n = 11), and dialysis at listing (n = 11).

performed at all.¹³ A single center from France (Schnetzler and colleagues⁵) reported on 24 patients undergoing retransplant compared with 47 patients undergoing primary

TABLE 2. Number of retransplants, by year

Year of retransplant	Retransplant sample (N = 987)	Proportion of total heart transplants in United States
1995	47 (4.8)	47/2363 (2.0)
1996	44 (4.5)	44/2343 (1.9)
1997	40 (4.1)	40/2293 (1.7)
1998	67 (6.8)	67/2348 (2.9)
1999	55 (5.6)	55/2188 (2.5)
2000	42 (4.3)	42/2199 (1.9)
2001	49 (5.0)	49/2202 (2.2)
2002	51 (5.2)	51/2155 (2.4)
2003	42 (4.3)	42/2057 (2.0)
2004	51 (5.2)	51/2015 (2.5)
2005	64 (6.5)	64/2125 (3.0)
2006	53 (5.4)	53/2193 (2.4)
2007	60 (6.1)	60/2209 (2.7)
2008	64 (6.5)	64/2163 (3.0)
2009	60 (6.1)	60/2211 (2.7)
2010	67 (6.8)	67/2332 (2.9)
2011	71 (7.2)	71/2322 (3.1)
2012	60 (6.1)	60/2378 (2.5)

Values are given as n (%).

transplant as controls. Survival at 1 and 5 years for ReTX were 45.5% and 31.2%, respectively, compared with 59.4% and 38.8% for controls.⁵ In another report¹⁶ comparing the survival of patients undergoing retransplant at a single US institution compared with data from the ISHLT, survival was found to be as high as 64% at 1 year, provided that certain criteria were met. They identified the “ideal candidate” for ReTX as a patient who had an interval between transplants >6 months, a date of second operation after 1985, and without preoperative mechanical support.¹⁶ Despite these attempts to refine the criteria for ReTX, many centers still refused to adopt this practice.

TABLE 3. Survival following retransplant procedure

Length of time after retransplant (y)	Proportion of survival (95% CI)
1	80 (78-83)
2	75 (72-78)
3	70 (67-73)
4	68 (65-71)
5	64 (61-67)
6	60 (57-64)
7	56 (53-60)
8	54 (50-58)
9	50 (46-54)
10	47 (43-51)
11	44 (40-48)
12	41 (37-46)
13	38 (33-43)
14	36 (31-41)
15	30 (25-37)

Values are given as %. *CI*, Confidence interval.

FIGURE 1. Survival following retransplantation. Dashed lines represent 95% confidence intervals.

More recent data have shown improved survival following ReTX. Srivastava and colleagues,⁶ using ISHLT registry data from 1987 through 1998, reported a 65% 1-year survival for 514 patients undergoing ReTX. Another important conclusion from that study was that overall survival following ReTX approached that of primary transplant if the interval between transplants was >2 years. These conclusions, however, were only valid for centers performing at least 9 heart transplants per year and for patients who were not dependant on a ventilator or a left ventricular assist device.

The data presented in our study are unique in that the population studied represents a large sample of patients undergoing ReTX subject to contemporary selection processes,

surgical techniques, and methodology that therefore provides a unique perspective on patients undergoing ReTX. In our large cohort, survival at 1, 3, and 5 years was 80%, 70%, and 64%, respectively, which is significantly higher than that previously published. The reasons for improved survival have not yet been clearly elucidated; however, more refined retransplant candidate screening selection processes; improvement in surgical and perioperative techniques; and better posttransplant medical protocols, including advances in immunosuppressive therapy, all serve as potential explanations.

Previously published studies have shown that preoperative mechanical ventilation, high serum creatinine, and older recipient age are associated with poorer graft

TABLE 4. Associations of recipient and donor characteristics with overall survival following retransplant*

Variable	Single variable analysis		Multivariable analysis	
	RR (95% CI)	P value	RR (95% CI)	P value
Age at retransplant (10-y increase)	1.08 (1.01-1.15)	.034	1.08 (0.99-1.17)	.072
Gender (male)	0.85 (0.69-1.04)	.12	NI	N/A
Donor age (10-y increase)	1.11 (1.03-1.20)	.004	1.14 (1.05-1.25)	.004
Time between previous transplant and retransplant (y)†				
≤1	1.00 (reference)	N/A	1.00 (reference)	N/A
>1 ≤ 5	0.54 (0.38-0.75)	<.001	0.66 (0.44-1.01)	.053
>5	0.43 (0.32-0.58)	<.001	0.53 (0.36-0.78)	.001
Ischemic time (>4 h)	1.52 (1.20-1.92)	<.001	1.48 (1.12-1.87)	.004
Serum total albumin (>3)	0.71 (0.54-0.94)	.017	NI	N/A
Inotropes	1.14 (0.95-1.38)	.17	NI	N/A
Ventilator	2.44 (1.81-3.29)	<.001	1.29 (0.82-2.03)	.27
IABP	1.86 (1.32-2.63)	<.001	1.03 (0.66-1.60)	.90
ECMO	5.68 (3.60-8.97)	<.001	3.91 (2.08-7.38)	<.001
Diabetes	1.21 (0.97-1.51)	.092	NI	N/A
Dialysis at listing	1.43 (1.09-1.90)	.011	1.12 (0.77-1.63)	.56

RR, Relative risk; CI, confidence interval; NI, not included in the multivariable analysis; N/A, not applicable; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation. *RRs, 95% CIs, and P values result from Cox proportional hazards regression models. Relative risks correspond to presence of the given characteristic (categorical variables) or the increase given in parenthesis (continuous variables). All variables with P value ≤ .05 in a single variable analysis were included in multivariable analysis (n = 797), except serum total albumin because of the large amount of missing information (missing = 366) with this variable. †Test of overall difference for single-variable analysis: P < .001. Test of overall difference for multivariable analysis: P = .003.

FIGURE 2. Survival following retransplantation according to the time between previous transplant and retransplant.

survival.¹⁷ The data from our study emphasize both donor and recipient risk factors. Univariate analysis showed that donor age; recipient age; days between first transplant and ReTX; serum albumin; ventilator status; and pretransplant dependence on IABP, ECMO, or dialysis were significant predictors of outcome.

Regarding recipient risk factors for decreased survival following ReTX, further stratification with multivariate analysis demonstrated reduced survival for recipients requiring pretransplant ECMO and those having had a shorter time between transplants. Patients who received an immediate transplant for primary graft failure had a much worse prognosis than those who had an indolent course of chronic heart failure with a longer time course after their initial transplant. Although current guidelines from the American Society of Transplant Surgeons suggest the interval between transplants be at least 6 months,³ data from our study suggest that optimal survival following ReTX occurs when the interval between the initial transplant and retransplant is at least 1 year, with at least 5 years

being the optimal interval. According to the data reported in our study, dependence on ECMO before transplant confers a dismal prognosis and therefore should serve as a relative contraindication to ReTX. Mechanical support with ECMO was the strongest RR factor for decreased survival. Contrary to previously published reports, recipient factors not found to be statistically significant included pretransplant ventilator status and dependence on inotropic support. The majority of patients undergoing ReTX were, in fact, treated with inotropes without a significant effect on overall patient survival following transplant.

Donor factors significant for reduced survival after ReTX by multivariate analysis included the donor heart age and total ischemic time after harvest.

In the current era, the annual number of ReTX procedures reported in the United States consistently represents 2% to 3% of all transplants. These data were obtained from the UNOS database, which is not an audited registry. Because these data are obtained and reported voluntarily, all outcomes data regarding patients undergoing ReTX may not

FIGURE 3. Survival following retransplantation (ReTx) >1 year from primary transplant (Tx) versus primary Tx.

have been captured, which serves as an important limitation of our study.

Despite this limitation, our study does allow us to draw several important conclusions regarding improved survival following ReTX that contradicts historical data and published guidelines. Most notably, patients who have survived at least 1 year from the primary transplant have better overall survival compared with those who are <1 year out from their initial surgery. Patients surviving at least 5 years from their initial transplant had optimal survival following ReTX. The reason for the improved survival observed following ReTX in our study is likely multifactorial. The reasons for this positive change may be related to improvements in modern therapy, improved immunosuppressive regimens, and/or better selection of retransplant candidates. Nevertheless, patients undergoing ReTX even 1 year from primary transplant continue to have a lower overall survival compared with primary transplants in the same era. The difference may be less than anticipated by transplant centers.

CONCLUSIONS

ReTX remains a viable option for a limited transplant population. Optimal candidates for consideration of ReTX include younger recipients who are at least 1 year out from their primary transplant. ECMO before ReTX is the strongest negative predictor of overall survival and should therefore be considered a relative contraindication to ReTX. Inotropic support before ReTX has no effect on overall survival and should not preclude a patient from ReTX. Cardiac ReTX continues to grow as a viable option for transplant recipients with primary graft failure.

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APPENDIX TABLE E1. Distribution of patients by US regions and US states and territories

Region, state,* or territory	Overall sample (N = 987)
US region	
1	29 (2.9)
2	131 (13.3)
3	136 (13.8)
4	93 (9.4)
5	233 (23.6)
6	25 (2.5)
7	70 (7.1)
8	70 (7.1)
9	76 (7.7)
10	69 (7.0)
11	55 (5.6)
US state or territory	
Alaska	1 (0.1)
Alabama	13 (1.3)
Arkansas	15 (1.5)
Arizona	13 (1.3)
California	187 (19.1)
Colorado	29 (3)
Connecticut	10 (1)
Washington, DC	1 (0.1)
Delaware	5 (0.5)
Florida	61 (6.2)
Georgia	25 (2.6)
Hawaii	1 (0.1)
Iowa	7 (0.7)
Idaho	6 (0.6)
Illinois	28 (2.9)
Indiana	28 (2.9)
Kansas	13 (1.3)
Kentucky	7 (0.7)
Louisiana	16 (1.6)
Massachusetts	11 (1.1)
Maryland	22 (2.3)
Maine	2 (0.2)
Michigan	18 (1.8)
Minnesota	16 (1.6)
Missouri	13 (1.3)
Mississippi	9 (0.9)
Montana	4 (0.4)
North Carolina	27 (2.8)
North Dakota	1 (0.1)
Nebraska	6 (0.6)
New Hampshire	3 (0.3)
New Jersey	56 (5.7)
New Mexico	3 (0.3)
Nevada	2 (0.2)
New York	58 (5.9)
Ohio	24 (2.5)
Oklahoma	6 (0.6)
Oregon	9 (0.9)
Pennsylvania	48 (4.9)
Puerto Rico	6 (0.6)
Rhode Island	3 (0.3)

(Continued)

APPENDIX TABLE E1. Continued

Region, state,* or territory	Overall sample (N = 987)
South Carolina	10 (1)
South Dakota	1 (0.1)
Tennessee	15 (1.5)
Texas	81 (8.3)
Utah	12 (1.2)
Virginia	6 (0.6)
Vermont	2 (0.2)
Washington	13 (1.3)
Wisconsin	21 (2.2)
West Virginia	2 (0.2)
Wyoming	1 (0.1)

Values are given as n (%). *Missing information: States (n = 10).