Should Heart Transplant Recipients With Early Graft Failure Be Considered for Retransplantation?

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Background. **The purpose of this study was to determine if orthotopic heart transplantation performed within 90 days of an initial heart transplant (re-Tx) should be a contraindication to retransplantation based on inferior outcomes when compared with primary orthotopic heart transplantation recipients (control).**

Methods. **De-identified data were obtained from the United Network for Organ Sharing. The study population included all adult heart transplant recipients greater than 18 years old from 1995 to 2008 (n = 26,804). Multivariable regression was performed in order to assess the simultaneous effect of multiple risk factors on posttransplant graft failure (PTGF) at 90 days. Secondary outcomes of interest included infection, stroke, and dialysis during the transplant hospitalization as well as primary nonfunction of the graft at 90 days.**

Results. **Among the study cohort, there were 90 (0.34%) re-Tx patients. Median survival in this group was 1.6 years compared with 10.5 years for controls. Unadjusted PTGF, infection, dialysis, and primary nonfunction were significantly higher ($p < 0.001$) in the re-Tx group. After risk adjustment, however, PTGF ($p = 0.545$), infection ($p = 0.696$), dialysis ($p = 0.664$), stroke ($p = 0.115$), and primary nonfunction ($p = 0.531$), did not differ significantly between the 2 groups.**

Conclusions. **When controlling for pretransplant recipient characteristics, retransplantation within 90 days of a previous transplant is not associated with increased morbidity or mortality. However, unadjusted overall survival was significantly worse in the re-Tx group. This suggests that although retransplantation at 90 days alone is not a risk factor for inferior outcomes, given the significant comorbidities of these patients, the indications for retransplantation within 90 days are rare and must be critically examined.**

(Ann Thorac Surg 2011;92:923–8)

Primary graft failure (PGF) remains the most common cause of morbidity and mortality in the early posttransplant period [1]. Primary graft failure is broadly defined as severe dysfunction of the cardiac allograft characterized by low cardiac output, hypotension, and high filling pressures in the absence of secondary causes of graft failure such as hyperacute rejection, unresponsive pulmonary hypertension, or technical surgical problems [2]. According to the International Society of Heart and Lung Transplantation Registry, from January 1992 to June 2006, the most common cause of death within the first 30 days after heart transplantation was PGF, which accounted for nearly one-third of deaths [3].

To support recipients with graft failure, a number of new therapies have been applied in clinical practice, most notably, temporary mechanical circulatory support (MCS) [4, 5]. Recent studies of temporary MCS have found only moderate success with this indication [6–8]. Less than 50% of patients with early graft failure treated with MCS recovered or survived until retransplantation [9]. In the absence of graft recovery, retransplantation remains the only definitive treatment for PGF. However, the outcomes of retransplantation after early graft failure have not been well studied in a large series due, in part, to the low prevalence of this complication.

The goal of this study was to assess whether a previous orthotopic heart transplant within the past 90 days should be a contraindication to retransplantation. Using national data from the United Network for Organ Sharing (UNOS), this study compares morbidity and mortality in heart transplant recipients retransplanted within 90 days to primary heart transplant recipients (controls). We hypothesized that unadjusted and risk-adjusted survival among recipients retransplanted at less than 90 days would be inferior compared with controls.

Material and Methods

Data Collection

Approval for this study was granted by Columbia University's Institutional Review Board, and use of these

Accepted for publication April 6, 2011.

Presented at the Forty-sixth Annual Meeting of The Society of Thoracic Surgeons, Fort Lauderdale, FL, Jan 25–27, 2010.

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Published by Elsevier Inc

0003-4975/$36.00
doi:10.1016/j.athoracsur.2011.04.053

Abbreviations and Acronyms

CI = confidence interval
eGFR = estimated glomerular filtration rate
MCS = mechanical circulatory support
OHT = orthotopic heart transplant
OR = odds ratio
PGF = primary graft failure (at any time)
PTGF = posttransplant graft failure at 90 days
Re-Tx = retransplanted within 90 days of previous transplant
UNOS = United Network for Organ Sharing
VAD = ventricular assist device

data is consistent with the UNOS Data Use Agreement. The Standard Transplant Analysis and Research Dataset were provided by UNOS (data source no. 061809−6). The dataset contains de-identified information collected from the UNetSM database forms, including the transplant candidate registration form, the transplant recipient registration form, and the transplant recipient follow-up form. These data are the basis for the UNOS Thoracic Registry.

Study Population

Between January 1, 1995 and December 31, 2008, there were 26,804 heart transplant recipients aged 18 years and older. Patients were divided into 2 groups based on retransplant status. The control group (n = 26,696) consisted of primary transplant recipients (ie, patients who received only 1 heart transplant during the study period). The retransplant group (re-Tx) consisted of patients (n = 90) who were retransplanted within 90 days of a previous heart transplant during the study period (there were an additional 18 patients retransplanted beyond 90 days who were not included in the risk-factor analysis). Follow-up data were provided through June 18, 2009, with a mean follow-up time of 4.72 ± 3.80 years (range, 0 to 14.2 years). Patients were followed from the date of transplant until death, cardiac retransplantation, or date of last known follow-up which was the last day of follow-up data provided by UNOS. The analysis included 126,356 graft-years at risk.

Outcomes and Definitions

Our primary outcome measure was posttransplant graft failure at 90 days (PTGF), which was defined as patient death or retransplantation. Secondary outcomes of interest were in-hospital morbidity, including incidence of infection, stroke, and need for dialysis, as well as primary nonfunction of the graft at 90 days (PNF). In this analysis, primary nonfunction is defined as death or retransplantation within 90 days of the index cardiac transplant due to graft failure not related to rejection, infection, or technical surgical issues.

Data Analysis

Continuous variables were reported as mean ± standard deviation and compared using the Student *t* test. To compare categoric variables, the χ^2 test was used. Multivariable logistic regression was performed (backward, remove $p >$ 0.15) to assess the simultaneous effect of multiple variables on the primary and secondary outcome measures. Patients with missing data were excluded from regression analysis; no imputation methods were employed. The odds ratio (OR) and 95% confidence interval (95% CI) were reported for each variable. To analyze unadjusted long-term survival, Kaplan-Meier analysis was used with the log-rank test. The conventional p value of 0.05 or less was used to determine the level of statistical significance. All reported p values are two-sided. All data were analyzed using the statistical software package, Stata 9 (Stata Corp, College Station, TX).

Results

Study Population

There were a total of 26,804 heart transplant recipients considered in the analysis. There were 26,696 patients who received a single transplant during the study period and 108 patients who received a second transplant within 1 year of their index transplant. Of these retransplant patients, 50% (n = 54) were retransplanted in 5 days or less, and 83.3% (n = 90) were retransplanted within 90 days. The 18 patients retransplanted beyond 90 days were not included in the risk-factor analysis. The baseline characteristics of the re-Tx group at the time of retransplantation and the control group at the time of initial transplantation are shown in Table 1. There were several significant differences between groups. While the control group was older, the re-Tx group had laboratory markers of renal and hepatobiliary impairment that were higher than the control group. Also, the re-Tx group had a higher proportion of patients who were intubated, on inotropes, and requiring mechanical circulatory support prior to retransplantation.

Posttransplant Graft Survival

Compared with controls, unadjusted PTGF rates were lower for re-Tx patients across all time points, including 90 days. Consequently, overall actuarial survival was significantly worse in the re-Tx patients compared with the control group ($p < 0.001$) [Fig 1]. The median survival in the re-Tx cohort was 1.6 years compared with 10.5 years for controls. When all patients retransplanted were stratified by length of time from the index heart transplant (0 to 90 days, 90 days to 1 year, and > 1 year), there was a significant stepwise increase in mortality as time from index transplant decreased ($p < 0.001$). Considering all patients retransplanted during the study period, median survival was 2.7 years for patients retransplanted at 90 days to 1 year (n = 18), and 8.4 years among patients retransplanted at greater than 1 year (n = 670).

Secondary Outcomes

In the re-Tx cohort, unadjusted rates of in-hospital infection ($p < 0.001$), need for dialysis ($p < 0.001$), and primary graft nonfunction ($p < 0.001$) were significantly higher than in the control group [Fig 2]. However, the rate of stroke was similar between groups ($p = 0.993$).