Primary graft dysfunction does not lead to increased cardiac allograft vasculopathy in surviving patients

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Objective: Early injury is associated with the development of cardiac allograft vasculopathy in heart transplantation. We examined whether adult heart transplant recipients surviving primary graft dysfunction were more susceptible to the development of cardiac allograft vasculopathy than their nonprimary graft dysfunction counterparts.

Methods: A total of 857 patients who underwent heart transplantation between January 1994 and December 2008 at our institution were reviewed. Primary graft dysfunction was defined as the need for extracorporeal membrane oxygenation, open chest, or intra-aortic balloon pump placement within 72 hours of transplantation. Cardiac allograft vasculopathy was defined as $\geq$50% coronary artery stenosis in any vessel. Allograft survival was defined by patient death or need for retransplantation.

Results: Completed follow-up was available for 32 patients in the primary graft dysfunction group and 701 patients in the nonprimary graft dysfunction group. Mean recipient ages (56 years vs 55 years, respectively; $P = .50$) and ischemic times (220 minutes vs 208 minutes, respectively; $P = .35$) were similar. Donor age was significantly higher in the primary graft dysfunction group (38 years vs 32 years, $P = .02$). Five-year survivals for the primary graft dysfunction and nonprimary graft dysfunction groups were 46.9% versus 78.9% ($P < .001$). Conditional 5-year survivals in patients surviving the first year were 78.9% and 88.3% for the primary graft dysfunction and nonprimary graft dysfunction groups, respectively ($P = .18$). Within a 30-day postoperative period, there were more deaths in the primary graft dysfunction group (28.1% vs 2.3%, $P < .0001$) and more retransplants (6.25% vs 0%, $P = .002$). Of the patients surviving past 30 days, only 2 (8.7%) of the primary graft dysfunction patients developed cardiac allograft vasculopathy versus 144 (21.0%) in the nonprimary graft dysfunction group ($P < .001$).

Conclusions: Primary graft dysfunction was associated with lower 30-day, 1-year, and 5-year allograft survival rates. Surviving patients, however, did not show increased tendency toward cardiac allograft vasculopathy development. (J Thorac Cardiovasc Surg 2013;145:869-73)

Primary graft dysfunction (PGD) of heart allografts is a condition in which the newly transplanted organ is unable to meet the circulatory requirements of the recipient during the peri- and postoperative periods as a result of left ventricular, right ventricular, or biventricular dysfunction.[1] Unlike lung transplantation, in which PGD was defined formally and given a standard grading system in 2005 by an International Society of Heart and Lung Transplantation working group, PGD in heart transplantation has received relatively little attention.[2] Thus, despite being one of the most common causes of 30-day mortality after heart transplant, with an estimated incidence of up to 40%, there currently exists no widely accepted diagnostic criteria or definition for the disorder.[3,4] The causes of PGD are not completely understood; however, intrinsic donor organ abnormalities and recipient characteristics such as pulmonary hypertension, inadequate donor heart preservation, and/or nonspecific host-mediated inflammatory injury are implicated.[5]

Although PGD affects early survival adversely, chronic rejection known as cardiac allograft vasculopathy (CAV) is the predominant limitation to survival in heart transplantation beyond 1 year.[6] Both immune- and nonimmune-related factors remain associated with the development of CAV and it is reasonable to hypothesize that the allograft injury that leads to PGD in transplanted hearts will ultimately place the organ at heightened risk for development of CAV as well. This hypothesis is supported by abundant evidence in the lung transplantation literature regarding the relationship between PGD and the development of bronchiolitis obliterans syndrome, the corollary of chronic rejection in pulmonary allografts.[7-9] The causal relationship between cardiac PGD and the development of CAV, however, has yet to be clearly established.

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Abbreviations and Acronyms
CAV = cardiac allograft vasculopathy
ECMO = extracorporeal membrane oxygenation
IABP = intra-aortic balloon pump
PGD = primary graft dysfunction
UCLA = University of California at Los Angeles

The objective of this study is to discern whether patients surviving PGD in heart transplantation are subsequently at elevated risk for the development of CAV. In addition, we compare long-term allograft function and survival in patients surviving PGD versus the non-PGD cohort.

METHODS

The study was approved by the University of California at Los Angeles (UCLA) institutional review board. A total of 857 patients transplanted at UCLA Medical Center between January 1994 and December 2008 were reviewed retrospectively. Primary graft dysfunction was defined in patients who required (1) extracorporeal membrane oxygenation (ECMO), (2) open chest, and/or (3) usage of an intra-aortic balloon pump (IABP) within 72 hours of transplantation. Venoarterial ECMO was instituted via right atrial and aortic cannulation either with or without concomitant open chest. Patients who presented to the operating room with an IABP in place a priori as a result of poor native heart function were excluded because the balloon pumps were removed on postoperative day 1 by protocol to avoid the risk of bleeding during the immediate perioperative period and not because of the specific needs of the new allograft. Patients with positive donor-specific antibodies were excluded to remove hyperacute rejection as a potential cause of early graft failure from this study.

Patients underwent annual coronary angiography as part of routine surveillance after an initial baseline study around day 60 posttransplantation. Cardiac allograft vasculopathy was defined as the presence of $\geq$50% stenosis of 1 or more vessels. All donors older than the age of 40 years received coronary angiograms as part of the initial evaluation, and the presence of coronary artery disease excluded them from further consideration for nonalternate list candidates. Allograft survival was examined at 30 days, 1 year, and 5 years posttransplantation and was defined as either recipient death or the need for retransplantation. Donor and recipient ages and ischemic times were documented. Patients were followed for an average of 3.2 years after transplantation, with a range from 0 days to 13.2 years.

Continuous variables were reported as mean $\pm$ standard deviation and were compared with the Student *t* test. Categoric data were analyzed using 2×2 contingency tables, with *P* values determined by the Fisher exact test. Mortality curves were established using Kaplan-Meier (actuarial) curves, with *P* values generated by the log-rank test. Multivariable analyses were performed with the use of a proportional hazards regression model for competing risks. Two-tailed *P* values $< .05$ were considered statistically significant.

RESULTS

Of the 857 patients reviewed, 815 patients constituted the non-PGD group and 42 were identified with PGD according to the following criteria: 13 patients (30.9%) had institution of ECMO, 23 patients (54.8%) had IABP, and 6 patients (14.3%) were left with an open chest without concomitant ECMO or IABP. Open chest was utilized in conjunction with 1 or both of the other therapeutic maneuvers as follows: ECMO+IABP in 4 patients, ECMO alone in 1 patient, and IABP alone in 4 patients. These cases were classified either as ECMO in the first 2 categories and IABP in the third group. A total of 610 of the non-PGD group and 30 of the PGD group were males (74.8% vs 71.4%, $P = .59$).

The average recipient ages for the PGD and non-PGD control groups were 56 ± 13 years versus 55 ± 13 years ($P = .50$). The donor ages were 38 ± 15 years versus 32 ± 14 years ($P = .02$) for the PGD and control groups, respectively. Ischemic time was 220 ± 85 minutes versus 208 ± 66 minutes ($P = .35$) for PGD and non-PGD categories. Table 1 shows the 3 variables in multivariable analysis. When adjusting for recipient age and ischemic time, there is a 2% increase in the odds of PGD for every 1-year increase in the donor age.

We have complete follow-up on 733 patients, of whom 701 are non-PGD patients and 32 are PGD patients. Of the 23 PGD patients with allograft survival beyond 30 days, 2 developed CAV (8.7%) at an average time of 1.4 years posttransplant. Of the 684 non-PGD patients surviving past 30 days, 144 (21.0%) developed CAV at an average of 4.4 years after transplantation. The difference in incidence of CAV between the 2 groups is statistically significant ($P = .02$).

Figure 1 shows 5-year Kaplan-Meier survival curves for both PGD and non-PGD groups, respectively. Five-year survival was 78.9% versus 46.9% in the non-PGD patients versus PGD patients, respectively ($P < .001$). Corresponding survival rates at 30 days and 1 year were 97.7% versus 89.4% and 87.5% versus 56.3%, respectively. Within the immediate 30-day posttransplant period, 9 of 32 PGD patients expired compared with 16 of 701 in the control group (28.1% vs 2.3%, $P < .0001$). Two of the primary graft dysfunction patients required retransplantation compared with none in the control group (6.25% vs 0%, $P = .002$).

Conditional survival curves past the first year shown in Figure 2 were similar for both the PGD and non-PGD groups, suggesting that patients who survived the initial insult of PGD did not experience a worse long-term outcome compared with their non-PGD counterparts (78.9% vs 88.3%, $P = .182$).

DISCUSSION

Based on the hypothesis that early injury is associated with the development of CAV in cardiac transplantation, we examined whether adult heart transplant recipients surviving PGD were more susceptible to the development of CAV than their non-PGD counterparts. Although PGD in lung transplantation has been strongly associated with both diminished long-term survival as well as increased incidence of bronchiolitis obliterans syndrome,[7,10-13] the corresponding issue in cardiac allografts has not received similar scrutiny in the literature. There are no similar