Clinical Factors Implicated in Primary Graft Dysfunction After Heart Transplantation: A Single-center Experience

R.A. Quintana-Quezada[a,*], I. Rajapreyar[a], A. Postalian-Yrausquin[a], Y.C. Yeh[a], S. Choi[b], B. Akkanti[c], A. Sieg[d], P. Weeks[d], M. Patel[a], J. Patel[a], S. Nathan[a], B. Kar[a], P. Loyalka[a], and I. Gregoric[a]

[a]Center for Advanced Heart Failure, University of Texas Health Science Center at Houston/Memorial Hermann Hospital, Texas Medical Center, [b]Division of Clinical and Translational Sciences, Department of Internal Medicine, [c]Division of Critical Care, Pulmonary and Sleep, University of Texas Medical School at Houston, and [d]Department of Pharmacy, Memorial Hermann – Texas Medical Center, Houston, Texas

ABSTRACT

Background. Primary graft dysfunction (PGD) is a frequent complication after cardiac transplantation and remains one of the leading causes of mortality in these patients. The objective of this case-control study is to identify donor and surgical procedure's factors associated with PGD, and further guide possible strategies to prevent PGD.

Methods. Retrospective analysis of the medical records of patients who underwent cardiac transplantation at Memorial Hermann Hospital at Texas Medical Center between October 2012 and February 2015.

Results. The study population included 99 patients, of which 18 developed PGD. Univariate analysis of donor characteristics revealed opioid use ($P = .049$) and death owing to anoxia ($P = .021$) were associated with PGD. The recipient/donor blood type match AB/A was significantly associated with PGD ($P = .031$). Time from brain death to aortic cross clamp (TBDACC) of $\geq$3 and $\geq$5 days were also found to be associated with PGD ($P = .0011$ and .0003, respectively). Multivariate analysis confirmed that patients with a time from brain death to aortic cross clamp $\geq$3 and $\geq$5 days had lesser odds of developing PGD (odds ratio, 0.098 [$P = .0026$] and OR, 0.092 [$P = .0017$], respectively].

Conclusions. Our study showed that a longer time from brain death to aortic cross clamp was associated with lower odds of developing PGD. Therefore, postponing heart procurement for a few days after brain death seems to be beneficial in preventing PGD.

SINCE the first cardiac transplantation in 1967, patient outcomes have improved significantly as a consequence of new surgical techniques, more effective immunosuppressive agents, better organ preservation, prophylaxis against opportunistic infections, and early rejection recognition with endomyocardial biopsies [1–5]. Nonetheless, primary graft dysfunction (PGD) remains a leading cause of 30-day mortality in these patients. The true incidence of PGD is hard to estimate owing to reporting variability by different heart transplant centers and the previous lack of a standardized definition. In April 2013, a consensus conference on PGD developed guidelines to define, diagnose, and treat patients with PGD after cardiac transplantation. This consensus included data from 47 transplant centers, comprising a total of 9901 patients who underwent heart transplants. Among those patients, 733 (7.4%) developed PGD. Of those, 30-day and 1-year mortality was 30% and 35%, respectively. The leading reported causes of death were multiorgan system failure (70%), primary graft failure (20%), and sepsis (10%). PGD was defined as left ventricle (LV), biventricular (BV), or right ventricle (RV) failure that occurs within 24 hours after cardiac transplantation, not attributable to a discernible etiology such

*Address correspondence to Raymundo Alain Quintana-Quezada, MD, University of Texas Health Science Center at Houston, 6410 Fannin St, Suite 920, Houston, Texas 77030. E-mail: Raymundo.A.Quintanaquezada@uth.tmc.edu

0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.02.073

as hyperacute rejection, pulmonary hypertension, or a surgical complication, events that would be considered secondary graft dysfunction [6]. The increasing number of patients active on the waiting list for cardiac transplantation, the potential complications that ventricular support devices may be associated with, and the currently limited donor availability may cause the donor selection process to become more lenient. The objective of this case-control study is to identify donor and surgical procedural factors associated with PGD and to further guide possible strategies to prevent PGD.

MATERIAL AND METHODS

We retrospectively analyzed the medical records of all patients who underwent cardiac transplantation at Memorial Hermann Hospital in the Texas Medical Center between October 2012 and February 2015. PGD was defined as LV, BV, or RV failure that occurred within 24 hours after cardiac transplantation and was not attributable to a surgical complication; this was done according to the definition established by the consensus conference on PGD after cardiac transplantation [6]. Patients with secondary graft dysfunction were excluded; hyperacute rejection was ruled out by performing endomyocardial biopsies, and we did not include patients who developed RV failure owing to elevated pulmonary vascular resistance. Patients with PGD affecting the LV (PGD-LV) were further classified into 3 grades of PGD based on the echocardiographic data, hemodynamic data, and the type of support (pharmacologic or mechanical) required. Mild PGD-LV included patients with an LV ejection fraction of $\leq$40% or right atrial pressure of >15 mm Hg, pulmonary capillary wedge pressure of >20 mm Hg, and a cardiac index of <2.0 L/min/m^2 (for >1 hour) who required low-dose inotropic support (inotrope score < 10). Moderate PGD-LV included patients with an LV ejection fraction of $\leq$40% or right atrial pressure of >15 mm Hg, pulmonary capillary wedge pressure of >20 mm Hg, and cardiac index of <2.0 L/min/m^2 (for >1 hour) requiring high-dose inotropic support (inotrope score > 10); and placement of an intraaortic balloon pump. Severe PGD-LV included patients dependent on LV or BV mechanical circulatory support including extracorporeal membrane oxygenation, an LV assist device, BV assist device, or percutaneous LV assist device not including intraaortic balloon pump. PGD-RV is often harder to quantify; thus, no severity grading system was established. The diagnosis of PGD-RV was established in patients with a right atrial pressure of >15 mm Hg, pulmonary capillary wedge pressure of <15 mm Hg, cardiac index of <2.0 L/min/m^2, and transpulmonary gradient of <15 mm Hg and/or pulmonary artery systolic pressure of <50 mm Hg or in any patient requiring RV assist device placement [6].

Donor and recipient characteristics were studied in patients who developed PGD and then compared with patients without PGD (control group). Drug dosages were converted to micrograms per kilogram per minute and the inotrope score was calculated according to the following formula: dopamine (dose × 1) + dobutamine (dose × 1) + epinephrine (dose × 100) + norepinephrine (dose × 100) + isoproterenol (dose × 100) + milrinone (dose × 15) [7,8]. The doses of vasopressors, phenylephrine and vasopressin were converted to micrograms per kilogram per minute and units per kilogram per minute, respectively, and analyzed separately. Data collection, analysis, and reporting were approved by the institutional review board.

Statistical Techniques

Continuous variables were reported as mean values ± standard deviation or median values (interquartile range) as appropriate, and compared using the Student t test or the Mann–Whitney U test. To compare categorical variables, the χ^2 test was used or Fisher exact test if expected frequencies were <5. All variables determined to be clinically important or suggested by univariate analysis to be significant ($P < .05$) were included in the multivariate regression. Multivariable logistic regression analysis was performed to assess the simultaneous effect of multiple variables on PGD. The 95% confidence interval (CI) and odds ratio (OR) were reported for each variable. All statistical analyses were performed using SAS software (version 9.3, SAS Institute, Cary NC).

RESULTS

We reviewed a total of 102 charts. Three patients were not included in our study owing to incomplete donor records. We found 18 patients who developed PGD, and 81 served as controls. Among the patients with PGD, 4 developed PGD-RV, 9 had severe PGD-LV, 2 had moderate PGD-LV, and 3 had mild PGD-LV. The donor and surgical procedure characteristics are shown in Tables 1 and 2, respectively. Among the donor characteristics, a history of opioid use ($P = .049$) and death owing to anoxia ($P = .021$) were associated significantly with PGD. The recipient/donor blood type match AB/A was significantly associated with PGD ($P = .031$). Time from brain death to aortic cross clamp (TBDACC) of $\geq$3 and $\geq$5 days were also associated with the development of PGD ($P = .0011$ and .0003, respectively). Multivariate analysis (Table 3) confirmed that patients with a TBDACC $\geq$3 days (OR, 0.098; 95% CI, 0.021–0.443; $P = .0026$) and $\geq$5 days (OR, 0.092; 95% CI, 0.010–0.411; $P = .0017$) had progressively lower odds of developing PGD.

DISCUSSION

In our study, the rate of PGD was 18.18%, which is higher than the reported incidence in the consensus conference on PGD [6]. Upon reviewing the donor characteristics, we were unable to find a difference in the number of blood transfusions, inotrope score, phenylephrine dose, vasopressin dose, preharvest donor down time, and ischemic time between the PGD and control group. These variables are well-known to be associated with PGD [9–11]. However, we believe our sample size was not large enough to detect a significant difference. Regarding causes of death, despite previous reports describing trauma as an independent risk factor for the occurrence of primary graft failure [10], our study showed an association between anoxia and PGD ($P > .021$), which disappeared in the multivariate analysis (OR, 4.051; 95% CI, 0.846–19.4; $P = .080$).

Multiple animal and human studies have shown that brain death induces release of catecholamines, cytokines and biologic mediators which, through a series of molecular events, cause deterioration of myocardial contractility and predispose the heart to ischemic injury [12–17]. Cantin et al. [18]