Salvage of severe primary graft dysfunction following heart transplantation using extracorporeal life support

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ABSTRACT

Primary graft dysfunction (PGD) is the leading cause of early mortality after heart transplantation. Typically, mechanical circulatory support is necessary to provide hemodynamic support and to enable graft recovery. However, both the reported incidence of PGD and the reported salvage rates with extracorporeal membrane oxygenation (ECMO) vary widely. This may partly be due to variations in the definition of PGD and its levels of severity. We analyzed a prospectively maintained database of 255 transplant recipients at our institution to determine the effectiveness of ECMO support in those who develop severe PGD as defined by the International Society for Heart and Lung Transplantation consensus guidelines. Nineteen (7.5%) patients (aged 32–69 years) developed severe PGD and were treated with veno-arterial (VA) ECMO, which was initiated in the operating room at the time of transplant in most patients. The majority received VA ECMO through femoral cannulation. Two patients required veno-venous ECMO for respiratory support after VA ECMO separation. The 30-day in-hospital survival rate following transplantation was 63% ($n = 12$). In conclusion, ECMO proved to be a viable option for early hemodynamic support in patients with severe PGD and has become our preferred modality for mechanical circulatory support in these patients.

KEYWORDS Cardiac transplant; extracorporeal membrane oxygenation; mortality; severe primary graft dysfunction

The prevalence of end-stage heart failure continues to rise,¹ and the gold standard treatment remains cardiac transplantation. Despite advances in patient selection, treatment, and management, the leading cause of death in the first 30 days after transplantation remains primary graft dysfunction (PGD).² PGD occurs when the donor heart is not able to meet the circulatory requirements of the recipient posttransplant. Prior to the 2014 consensus definition of PGD,³ comparisons across centers were difficult due to varying classifications and criteria for PGD. In order to facilitate reporting and investigation of modifiable risk factors, the International Society for Heart and Lung Transplantation (ISHLT) formulated guidelines for both the definition and diagnosis of PGD after cardiac transplantation.³ These guidelines require the diagnosis of PGD to be made within 24 hours of completion of the

transplant surgery and define *severe* PGD as the dependence on mechanical circulatory support. At our institution, extracorporeal membrane oxygenation (ECMO) is the preferred mechanical circulatory support modality to manage patients with severe PGD and to maintain hemodynamic support and perfusion of vital organs.⁴ Here, we analyzed outcomes and risk factors of severe PGD following cardiac transplantation and describe our experience salvaging severe PGD with ECMO in a high-volume transplant center.

METHODS

The study was approved by the institutional review board at Baylor Scott & White Research Institute (Dallas, Texas). We retrospectively analyzed the medical records of all patients who underwent cardiac transplantation at our center

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between November 2012 and March 2016. Donor and recipient characteristics were compared between patients who developed severe PGD and those without severe PGD. Determination of severe PGD was according to the ISHLT consensus definition by retrospectively evaluating posttransplant functional status within 24 hours after heart transplantation.³

Hemodynamic instability requiring ECMO support was characterized by low cardiac output (cardiac index <2 L/min/m²) with pulmonary capillary wedge pressure >20 mm Hg or central venous pressure >15 mm Hg in the absence of pulmonary hypertension and with isolated right ventricular dysfunction. These parameters had to be unresponsive to volume replacement, rhythm control, and use of two inotropes. Once the diagnosis of severe PGD was established, ECMO support was initiated expeditiously, typically through femoral cannulation. Continuous heparin infusion was initiated on the second postoperative day if surgical bleeding had subsided (target partial thromboplastin time 50–700 s). ECMO support was maintained and gradually weaned in accordance with clinical and echocardiographic assessments. ECMO removal was considered in patients tolerating low ECMO flow rates (1–2 L/min) without decrement in hemodynamic parameters or graft function by echocardiographic evaluation. No other forms of mechanical circulatory support (such as intra-aortic balloon pumps) were used in these patients. Support was discontinued in patients deemed unable to recover according to multidisciplinary judgment and/or by consent and request from the family.

To identify risk factors for severe PGD, an initial set of candidate risk factors was first analyzed with univariate logistic regression. Subsequently, a stepwise multivariate model for severe PGD was built using the factors from the univariate analysis that yielded a *P* value <0.2 . All factors retained in the final multivariate model were statistically significant (*P* <0.05). All statistical analyses were performed using SAS software (Version 9.4; SAS Institute, Cary, NC).

RESULTS

General characteristics of the recipients and their donors are presented in *Table 1*. Of 255 patients who underwent heart transplantation during the study period, 19 (7.5%) were diagnosed with severe PGD and initiated on ECMO support. Comparison between patients who developed severe PGD with the recipients who did not showed that patients with severe PGD were more likely to have a history of ischemic cardiomyopathy, were less likely to be on life support at the time of transplant, had a smaller donor-recipient weight ratio by body weight and heart mass, and had longer cold ischemic times.

Details of ECMO support and outcomes while on support are outlined in *Table 2*. Two of the 19 patients with severe PGD were already on ECMO support prior to transplant. Most patients received peripheral ECMO, and the median support duration was 5 days. Common complications encountered in these patients during ECMO support

Table 1. Preoperative characteristics of patients with and without severe primary graft dysfunction^a

	Severe primary graft dysfunction ^a		
Variable	Yes (<i>n</i> = 19)	No (<i>n</i> = 226)	<i>P</i> value
Recipient variables			
Age (years)	58 [43, 63]	59 [52, 65]	0.42
Male	16 (84%)	178 (75%)	0.58
Black	3 (16%)	42 (18%)	0.95
White	13 (68%)	153 (65%)	
Other	3 (16%)	41 (17%)	
Ischemic cardiomyopathy	14 (74%)	107 (46%)	0.03
Diabetes mellitus	1 (5%)	37 (16%)	0.32
Creatinine (mg/dL)	1.5 [1.3, 2.0]	1.4 [1.2, 1.6]	0.08
Body mass index (kg/m ²)	33 [26, 35]	28 [25, 31]	0.054
Hospitalized	7 (37%)	53 (23%)	0.17
ICU prior to transplant	0	26 (12%)	0.23
Life support at transplant	4 (21%)	111 (48%)	0.03
LVAD	7 (37%)	75 (32%)	0.62
UNOS status 1A	6 (32%)	84 (36%)	0.81
PVR (Wood units)	2.27 [1.27, 2.77]	1.97 [1.16, 3.25]	0.94
Wait list time (days)	10 [5, 71]	24 [9, 110]	0.14
Donor variables			
Age (years)	37 [22, 44]	34 [24, 44]	0.93
Male	6 (32%)	109 (46%)	0.24
Black	0	41 (17%)	0.006
White	14 (74%)	175 (74%)	
Other	5 (26%)	20 (9%)	
Cause of death			0.54
Anoxia	6 (32%)	93 (39%)	
Head trauma	5 (26%)	73 (31%)	
Other	8 (42%)	70 (30%)	
Previous CPR	1 (5%)	56 (24%)	0.08
Body mass index (kg/m ²)	29 [27, 34]	29 [24, 34]	0.36
Donor-recipient weight ratio	0.77 [0.72, 0.88]	0.95 [0.81, 1.14]	0.005
Body weight difference	23% [13, 28]	5% [−14, 19]	0.006
Heart mass difference	23% [11, 33]	8% [−6, 19]	0.001
LV wall thickness (cm)	1.00 [0.90, 1.10]	1.04 [0.90, 1.20]	0.60
Ejection fraction	64% [56, 70]	61% [55, 67]	0.89
Cold ischemic time (min)	254 [195, 287]	218 [172, 266]	0.04

^aData are presented as median [Q1, Q3] for continuous variables and *n* (%) for categorical variables.

CPR indicates cardiopulmonary resuscitation; ICU, intensive care unit; LV, left ventricle; LVAD, left ventricular assist device; PVR, pulmonary vascular resistance; UNOS, United Network for Organ Sharing.

Table 2. ECMO parameters and early outcomes (n = 19)

Parameter	Result
Patients on ECMO prior to transplant	2 (11%)
Duration of pretransplant ECMO support (days)	1 and 6
Type of ECMO	
Central	3 (16%)
Peripheral	16 (84%)
Duration of total ECMO support (days)	Median 5 (range 1–12)
Primary outcome	
Death on device support	2 (11%)
30-day in-hospital death, off device	5 (26%)
Recovery (weaned off device support)	12 (63%)
Retransplant	0 (0%)
Major morbidity during ECMO support	
Stroke	1 (5%)
Sepsis/bacteremia	4 (21%)
Renal failure	8 (42%)

ECMO indicates extracorporeal membrane oxygenation.

were renal failure and sepsis. Twelve patients (63%) were successfully weaned from ECMO and survived beyond discharge from the hospital (although one of these patients died only 2 days after discharge). For comparison, [Table 3](#) presents postoperative outcomes in patients with severe PGD side by side to a cohort, transplanted over the same study period, who not did develop severe PGD. The severe PGD group showed longer lengths of stay, greater amounts of transfused blood products, greater mortality, and higher incidence of renal failure and infections.

Logistic regression modeling identified recipient age <65 years, recipient body mass index ≥ 35 kg/m², ischemic cardiomyopathy, pretransplant ECMO, pretransplant hospitalization, preoperative creatinine ≥ 2.0 mg/dL, and heart mass undersizing $\geq 30\%$ as candidate variables for multivariate modeling ($P < 0.2$). Multivariate modeling identified elevated preoperative creatinine (≥ 2.0 mg/dL) and undersized donor heart mass ($\geq 30\%$) as independent predictors of severe PGD ($P < 0.05$) ([Table 4](#)).

DISCUSSION

The landscape of heart transplantation is changing, with candidate recipients becoming older and more patients being bridged with a mechanical assist device. Although posttransplant outcomes have continued to improve over the decades, PGD remains a leading cause of 30-day mortality.^{5,6} Until recently, PGD risk factors and outcomes were difficult to compare between centers due to varying criteria for PGD, with reports of PGD prevalence varying from 2% to

Table 3. Postoperative outcomes for patients with or without severe primary graft dysfunction^a

Variable	Severe primary graft dysfunction		P value
	Yes (n = 19)	No (n = 236)	
ICU length of stay (days)	14.5 [8, 30]	3 [2, 5]	<0.001
Posttransplant length of stay (days)	17 [16, 32]	9 [7, 14]	<0.001
In-hospital 30-day mortality	7 (37%)	0 (0%)	<0.001
Transfusions (units)			
PRBCs	5 [1, 12] (6.6)	1 [0, 2] (2.1)	0.001
Platelets	1 [0, 5] (3.2)	0 [0, 0] (0.4)	<0.001
FFP	0 [0, 1] (1.4)	0 [0, 1] (1.0)	0.31
Cryoprecipitate	0 [0, 10] (4.6)	0 [0, 0] (0.8)	<0.001
PGD severity			n/a
None	—	190 (81%)	
Mild	—	31 (13%)	
Moderate	—	15 (6%)	
Severe	19 (100%)	—	
Inotrope score	26.5 [18, 36]	17.4 [12.1, 24.6]	<0.001
Reoperation for bleeding	8 (42%)	24 (10%)	<0.001
Renal failure requiring dialysis	4 (21%)	7 (3%)	0.005
Stroke	0	7 (3%)	1.0
Severe rejection (ACR 3) within 3 months	0	5 (2%)	1.0
Bacterial infection	9 (47%)	23 (10%)	<0.001
Fungal infection	6 (32%)	8 (3%)	<0.001
Pneumonia	7 (37%)	10 (4%)	<0.001
Sepsis	3 (16%)	6 (3%)	0.02
Mediastinitis	2 (11%)	1 (0.4%)	0.02
Wound infection	2 (11%)	7 (3%)	0.14
Bloodstream infection	4 (21%)	10 (4%)	0.01
Urinary tract infection	3 (16%)	8 (3%)	0.04

^aListed are median [Q1, Q3] for continuous variables (with the mean indicated in parentheses where indicated) and n (%) for categorical variables.

ACR indicates acute cellular rejection; FFP, fresh frozen plasma; ICU, intensive care unit; PGD, primary graft dysfunction; PRBC, packed red blood cells.

28%.^{7–11} Since standardizing the PGD definition, several studies have re-evaluated the prevalence in various clinical settings.^{6,12–15} Applying the consensus definition, the percentage of patients in this study (7.5%) who developed severe PGD was similar to other recent reports of severe PGD ranging from 6.7% to 8%.^{12,14,15}

Prior studies have established the advantages of ECMO support for salvage of severe PGD.^{16–18} Takeda et al evaluated the salvage of PGD, comparing ECMO and temporary left ventricular assist device (LVAD) support, and concluded

Table 4. Univariate and multivariate predictors of severe primary graft dysfunction

Variable	OR [95% CI]	P value ^a
Univariate analysis		
Male gender	1.74 [0.49–6.12]	0.39
Age ≥65 years ^a	0.29 [0.07–1.29]	0.10
Body mass index ≥35 kg/m ^{2a}	2.55 [0.86–7.60]	0.09
UNOS 1A status	0.81 [0.30–2.22]	0.69
LVAD prior to transplant	1.25 [0.47–3.31]	0.65
ECMO prior to transplant ^a	21.9 [3.4–141]	0.0011
Creatinine ≥2.0 mg/dL ^a	4.82 [1.54–15.08]	0.007
Hospitalized prior to transplant ^a	1.97 [0.74–5.26]	0.18
ICU prior to transplant	<0.001 [<0.001 to >999]	0.97
Prior sternotomy (yes vs no) ^a	1.47 [0.66–3.87]	0.43
Donor age ≥50 years	0.70 [0.15–3.16]	0.64
Donor male gender	0.54 [0.20–1.45]	0.22
Donor ejection fraction <50%	1.15 [0.14–9.51]	0.89
Donor left ventricular wall thickness >1.3 cm	0.71 [0.15–3.23]	0.65
Donor undersized ≥30% by body weight	1.42 [0.30–6.65]	0.66
Donor undersized ≥30% by PHM ^a	5.87 [2.07–16.6]	<0.001
Dorsal muscle surface area (medium vs low)	1.27 [0.33–4.93]	0.73
Dorsal muscle surface area (high vs low)	1.57 [0.42–5.82]	0.50
Multivariate analysis		
Donor undersized ≥30% by PHM	6.86 [2.28–20.63]	<0.001
Creatinine ≥2.0 mg/dL	6.52 [1.90–22.38]	0.003

^aVariables with a P value <0.2 in the univariate analysis were entered into the stepwise multivariate regression model.

CI indicates confidence interval; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LVAD, left ventricular assist device; OR, odds ratio; PHM, predicted heart mass; UNOS, United Network for Organ Sharing.

that ECMO resulted in better clinical outcomes.¹⁵ Forty-four of the 597 patients in their study (7.4%) developed severe PGD within 24 hours after heart transplant. Of the patients managed with ECMO, 89% were weaned from ECMO support, and the reported 30-day mortality was 11%. The higher mortality rate in our study may be a reflection of a higher-risk recipient population: The patients salvaged with ECMO by Takeda et al had a preoperative creatinine level of 1.28 ± 0.44 mg/dL. By comparison, the patients salvaged in our study had a preoperative creatinine of 1.50 mg/dL (1.0–3.8).

Sabatino et al analyzed the effects of ECMO duration on prognosis and found that 50% of patients who were on

ECMO <6 days were discharged, compared to 33% of those on prolonged support.¹² This suggests that the requirement for a longer duration of ECMO support may be a poor prognostic factor. In an earlier study comparing ECMO to right ventricular mechanical support, Taghavi et al also proposed that the shorter duration of mechanical support in their ECMO group could have been beneficial in avoiding complications and may explain the trend for fewer deaths in that group.¹⁹ Sabatino et al reported an overall incidence of severe PGD of 7.4%, with 57% of those with severe PGD able to be weaned from ECMO but only 35% discharged alive with first graft.¹² Our success rate with salvaging severe PGD with ECMO compares favorably, with 53% weaned from ECMO and surviving to discharge. Our findings support the use of ECMO following heart transplantation and emphasize the contribution of procedural risk factors in the outcome of severe PGD in combination with donor and recipient features.

This single-institution retrospective study has several limitations. A relatively small number of cases developed severe PGD. Furthermore, outcomes were based solely on our institutional practice and PGD management, and ECMO procedures were performed per clinical guidelines rather than as a part of a research protocol. Finally, long-term follow-up on the surviving patients is not yet available.

In conclusion, we report a 7.5% rate of severe PGD at our institution, comparable to other estimates utilizing the standardized ISHLT criteria. Although severe PGD still bears a significant mortality, most patients were successfully salvaged with ECMO support and survived to discharge. ECMO remains our preferred salvage therapy for patients who develop severe PGD. Further studies will be needed to establish risk factors for severe PGD utilizing the ISHLT diagnostic criteria in order to identify modifiable risk factors associated with increased survival.

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