ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Severe primary graft dysfunction in heart transplant recipients using donor hearts after circulatory death: United States experience

Peter D. Cho, BS,[a] Samuel T. Kim, MD,[b,c] Hedwig Zappacosta, BS,[b] John P. White, BA,[b] Stephanie McKay, BA MPH,[b] Reshma Biniwale, MD, MS,[c] and Abbas Ardehali, MD[c]

From the [a]Drexel University College of Medicine, Philadelphia, PA, USA; [b]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; and the [c]Department of Surgery, Division of Cardiac Surgery, University of California, Los Angeles, CA, USA.

KEYWORDS:
Heart transplantation;
Donation after determination of circulatory death;
Donation after brain death;
Primary graft dysfunction;
Normothermic regional perfusion

OBJECTIVE: This study compares the incidence of severe Primary Graft Dysfunction (PGD) in a contemporaneous cohort of donors after circulatory death (DCD) and brain death (DBD) heart transplant recipients.
METHOD: The United Network for Organ Sharing database was queried for isolated adult heart transplant recipients from 9/2023 to 6/2024. Heart recipients were stratified based on the organ donation type (DCD vs DBD). DCD heart recipients were further categorized based on the procurement method: time between circulatory death to cross-clamp: ≤ 30 minutes (Direct Procurement and Preservation, DPP), > 30 minutes (Normothermic Regional Perfusion, NRP). Outcomes of interest included: severe PGD (Left/Bi-Ventricular; LV/BiV) at 24 hours and Severe Graft Dysfunction at 72 hours (patients with severe PGD at 24 hours that remain on mechanical support at 72 hours).
RESULTS: A total of 2590 adult heart transplant recipients were identified, of which 17.1% underwent DCD heart transplantation. DCD heart recipients were less likely to be on inotrope (36.7% vs 41.6%, p=0.046) and ECMO (4.1% vs 9.9%, p < 0.001) prior to transplant than DBD heart recipients. DCD heart recipients were more likely than DBD heart recipients to develop severe PGD (LV/BiV) at 24 hours (9.5% vs 5.1%, p < 0.001). The Severe Graft Dysfunction at 72 hours (2.3% vs 2.9%, p=0.67) and 30-day mortality were similar between the 2 groups. Recipients of DCD heart procured with DPP or NRP had similar severe PGD (LV/BiV) at 24 hours (9.4% vs 9.7%, p=0.93).
CONCLUSION: Severe PGD at 24 hours is higher among the DCD than DBD heart recipients, but Graft Dysfunction improves by 72 hours.
J Heart Lung Transplant 2025;44:760–769

Abbreviations and acronyms: AOR, Adjusted Odds Ratio; BiV, Bi-Ventricular; CI, Confidence Interval; CONSORT, Consolidated Standards of Reporting Trials; DCD, Donation after Circulatory Death; DBD, Donation after Brain Death; DPP, Direct Procurement and Perfusion; ECMO, Extracorporeal Membrane Oxygenation; IABP, Intra-Aortic Balloon Pump; IQR, Interquartile Range; LVAD, Left Ventricular Assist Device; LV, Left Ventricular; NRP, Normothermic Regional Perfusion; PGD, Primary Graft Dysfunction; RV, Right Ventricular; UNOS, United Network for Organ Sharing; US, United States; VAD, Ventricular Assist Device

Reprint requests: Abbas Ardehali, Professor of Surgery and Medicine, 62-186 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095.
E-mail address: aardehali@mednet.ucla.edu.

https://doi.org/10.1016/j.healun.2024.11.027

Introduction

Despite significant improvements in heart failure management, heart transplantation remains the gold standard for many patients with advanced heart failure. The demand for heart transplantation continues to exceed the availability of donor hearts. The number of patients awaiting heart transplantation increased by 28.1% from 2011 to 2022.[1] To accommodate the increasing need for donor hearts, new strategies have been adopted to expand the donor pool, such as extending the donor criteria to include Hep C positive donors.[2,3] Meanwhile, donation after circulatory death (DCD) has become a significant source of donor organs in lung, liver, and kidney transplantation, with the number of potential donors steadily increasing over the past decade.[1] In recent years, the development of ex-situ heart perfusion technology has facilitated the successful reperfusion and assessment of the donor heart after determination of circulatory death, heralding a new era in heart transplantation.[4,5]

Transplant centers in Australia and the United Kingdom led the initiative to assess the efficacy of utilizing DCD hearts, using ex-situ heart perfusion.[6,7] Normothermic Regional Perfusion (NRP) also emerged as an alternative strategy to ex-situ heart perfusion, in order to reperfuse and assess the donor hearts in situ.[8,9] Several single-center studies have emerged in the past few years to demonstrate that heart transplantation with DCD hearts has comparable 1 and 5-year survival outcomes as heart transplantation with donor hearts after brain death (DBD).[10–12] Recent analyses of the United Network for Organ Sharing (UNOS) database by Kwon and colleagues also showed comparable 1-year survival in recipients of DCD and DBD hearts, despite a higher rate of acute transplant rejection episodes.[13] However, the incidence of severe primary graft dysfunction (PGD) after DCD heart transplantation in a large cohort is unknown. Given this gap in the literature, the objective of the current study is to compare the incidence of severe PGD in a contemporaneous cohort of recipients of DCD and DBD hearts.

Methods

Study Population

All adult patients undergoing single-organ heart transplantation between September 2023 and June 2024 were retrospectively reviewed using the UNOS database (Figure 1). The deceased donor database was also queried to classify donors into categories of DCD and DBD, which was subsequently merged with the recipient data file. Among DCD donors, organ procurement methods were further stratified into direct procurement and perfusion (DPP) vs NRP strategies, categorized by the time period between the declaration of circulatory death to cross-clamp time for flush perfusion. Based on prior literature, we considered perfusion time greater than 30 minutes as NRP and less than or equal to 30 minutes as DPP.[10,13,14] Low-volume centers were defined as centers performing less than 25 percentile of all centers performing DCD heart transplantation in the US. The top 75 percentile was considered as the control group for this study.

The primary endpoint of this study was the incidence of severe PGD (Left/Bi-Ventricular; LV/BiV) at 24 hours post-transplantation, using the 2014 ISHLT Consensus Statement.[15] PGD data was routinely collected by UNOS starting on September 14, 2023. Severe PGD was defined as left or bi-ventricular dysfunction after transplant that required mechanical circulatory support such as extracorporeal membrane oxygenation (ECMO) and/or ventricular assist device (VAD) at 24 hours.[15,16] Secondary endpoints included PGD (right ventricular; RV) at 24 hours, Severe Graft Dysfunction at 72 hours (defined as patients with severe PGD (LV-BiV) at 24 hours who had remained on mechanical support at 72 hours), 72-hour mortality, acute rejection episodes, renal replacement therapy during the index hospitalization, early (30-day and in-hospital) mortality, graft failure, and length of hospital stay. Graft failure was defined as death or re-transplantation due to graft loss.

Baseline characteristics

Baseline characteristics at the time of transplant were compared between DCD and DBD cohorts. Recipient variables included age, gender, race, blood type, body mass index (BMI), functional status [1–10], smoking history, diabetes mellitus, cerebrovascular disease, pulmonary hypertension, primary diagnosis, admission status, UNOS heart allocation status [1–6], prior cardiac surgery history, anti-arrhythmic agents, inotrope, left ventricular assistant device (LVAD), temporary ventricular assistant device (tVAD), defined as VADs inserted percutaneously, intra-aortic balloon pump (IABP), ventilator, ECMO at transplant, waitlist duration, creatinine, and total bilirubin values. The following donor characteristics were compared between the two groups: age, gender, race, blood type, cause of death, BMI, smoking history, alcohol and drug use history, diabetes mellitus, hypertension, left ventricular ejection fraction, organ ischemic time, and distance from donor to recipient. Heart size was estimated using predicted heart mass and was considered a mismatch if the absolute difference between predicted donor and recipient heart mass was equal to or greater than 20%.[17]

Statistical analyses

Categorical variables are displayed as frequencies of the cohort, while continuous variables are shown as medians with interquartile ranges (IQR) for skewed distributions and means with standard deviations for normal distributions. Categorical measures were compared using the Chi-Squared test. For all continuous variables, those with normal distribution were compared using a 2-tailed, unpaired t-test, while the variables with skewed distribution were compared using the Wilcoxon rank-sum test. A multivariable logistic regression analysis was performed to identify the predictors of severe PGD at 24 hours following transplantation. A forward stepwise approach was used for

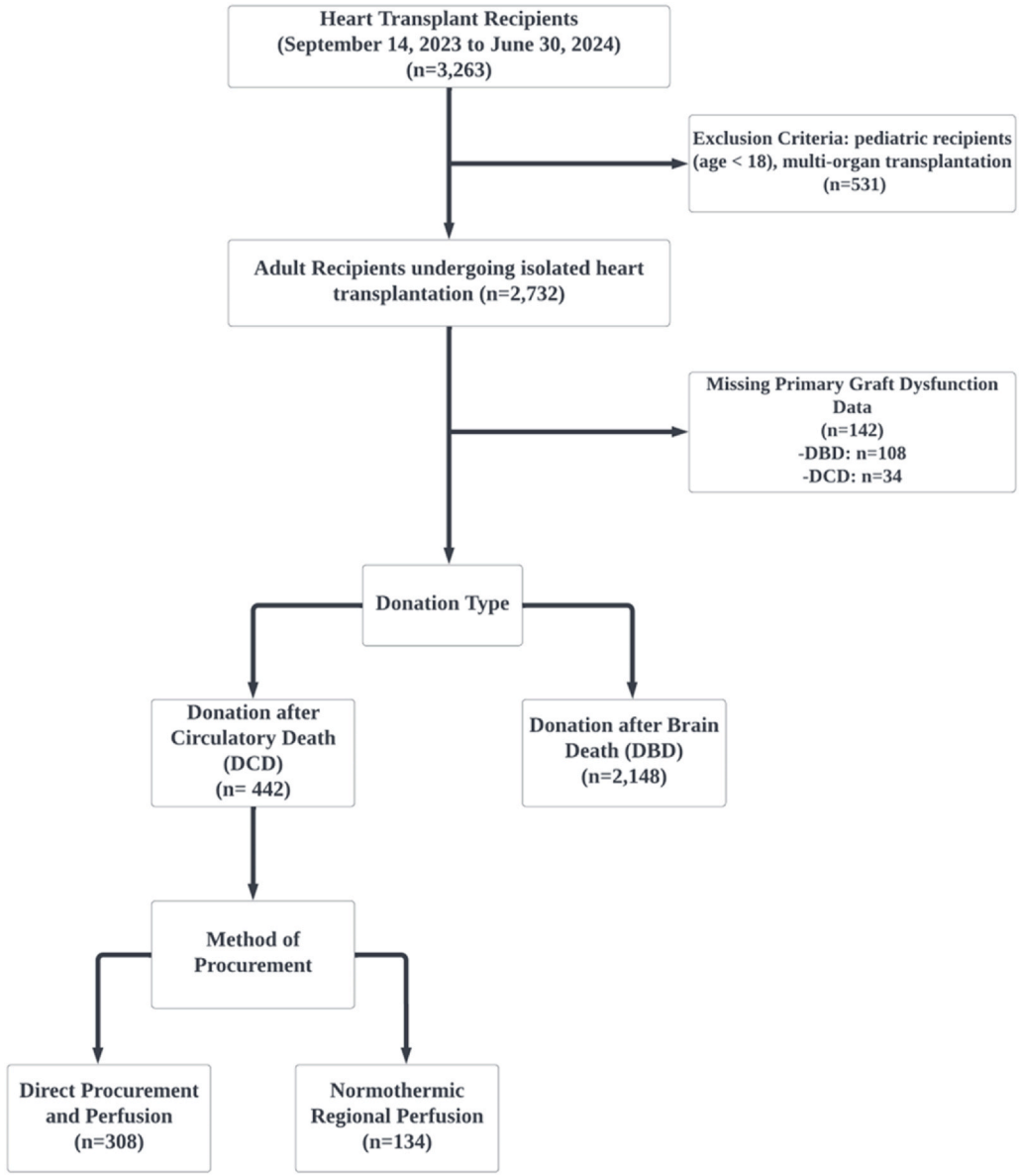

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of heart donors stratified by donation type and methods of procurement.

multivariable modeling. Specifically, baseline characteristics of recipients and donors that reached significance ($p < 0.20$) in univariable analysis were included in the multivariable model. In all statistical analyses, two-tailed p-values less than 0.05 were considered significant. All analyses in the study were performed using STATA 18.0 (StataCorp, College Station, TX). This study was considered exempt from review by the Institutional Review Board at the University of California, Los Angeles, as the study only involved de-identified data.

Results

Baseline characteristics of recipients and donors

During the study period, 17.1% (n=442) of all adult heart transplants were from DCD heart donor. Recipient variables at transplant stratified by donation type are displayed in Table 1. Recipients of DCD hearts were less likely to have pulmonary hypertension (53.4% vs 61.6%, p=0.001) than recipients of DBD hearts. The use of life support at transplant, including inotropes (36.7% vs 41.6%, p=0.046), IABP (16.3% vs 21.0%, p=0.029), and ECMO (4.1% vs 9.9%, $p < 0.001$), was less frequently observed in the recipients of DCD hearts than those of DBD hearts. Similarly, the proportion of patients listed as Status 1 (6.6% vs 17.5%, $p < 0.001$), Status 2 (46.2% vs 56.8%, $p < 0.001$), and in the intensive care unit (51.6% vs 65.5%, $p < 0.001$) were also lower in the DCD than the DBD group. However, the percentage LVAD at transplant was significantly higher in recipients of donor hearts after circulatory death compared to brain death (26.7% vs 19.7%, p=0.017).

The donors in DCD group were younger than donors in DBD group (31 ± 9 years vs 33 ± 10 years, $p < 0.001$) (Table 2). The left ventricular ejection fraction of the donor

Table 1 Baseline Characteristics of Heart Recipients Stratified by Donation Type

	DCD	DBD	p-value
	N=442	N=2148	
Age (years)	56 (45–63)	56 (46–63)	0.55
Gender			< 0.001
Male	355 (80.3%)	1515 (70.5%)	
Female	87 (19.7%)	633 (29.5%)	
Race			0.008
White	289 (65.4%)	1199 (55.8%)	
Black	88 (19.9%)	535 (24.9%)	
Hispanic	42 (9.5%)	273 (12.7%)	
Asian	14 (3.2%)	80 (3.7%)	
Other	9 (2.0%)	61 (2.8%)	
Blood Type			0.29
A	171 (38.7%)	810 (37.7%)	
AB	14 (3.2%)	103 (4.8%)	
B	57 (12.9%)	318 (14.8%)	
O	200 (45.2%)	917 (42.7%)	
BMI (kg/m^2)	27.92 (± 4.95)	27.81 (± 5.12)	0.69
Functional Status [1–10]*	4 (2–7)	3 (2–6)	0.002
Smoking History	191 (43.2%)	818 (38.2%)	0.05
Diabetes Mellitus	129 (29.2%)	656 (30.7%)	0.54
Cerebrovascular Disease	43 (9.8%)	177 (8.3%)	0.34
Pulmonary Hypertension	236 (53.4%)	1323 (61.6%)	0.001
Primary Diagnosis			0.034
Nonischemic Dilated Cardiomyopathy	239 (54.1%)	1128 (52.5%)	
Ischemic Cardiomyopathy	106 (24.0%)	567 (26.4%)	
Congenital Heart Defect	9 (2.0%)	100 (4.7%)	
Restrictive Cardiomyopathy	27 (6.1%)	101 (4.7%)	
Valvular Heart Disease	10 (2.3%)	20 (0.9%)	
Re-transplantation	8 (1.8%)	43 (2.0%)	
Hypertrophic Cardiomyopathy	16 (3.6%)	83 (3.9%)	
Other	27 (6.1%)	106 (4.9%)	
Admission Status			< 0.001
ICU	228 (51.6%)	1400 (65.5%)	
Hospitalization	55 (12.4%)	344 (16.1%)	
Non-Hospitalization	159 (36.0%)	395 (18.5%)	
Listing Status			
Status 1	29 (6.6%)	375 (17.5%)	< 0.001
Status 2	204 (46.2%)	1220 (56.8%)	< 0.001
Status 3–6	208 (47.1%)	533 (24.8%)	< 0.001
Prior Cardiac Surgery	86 (19.6%)	494 (23.4%)	0.087
Number of Prior Sternotomies	0 (0–1)	0 (0–1)	0.72
Anti-Arrhythmic Agents	188 (43.7%)	970 (46.0%)	0.39
Inotropes at Transplant	162 (36.7%)	893 (41.6%)	0.046
LVAD at Transplant	62 (26.7%)	216 (19.7%)	0.017
tVAD at Transplant	50 (11.4%)	284 (13.2%)	0.28
IABP at Transplant	72 (16.3%)	452 (21.0%)	0.029
Ventilator at Transplant	7 (1.6%)	54 (2.5%)	0.13
ECMO at Transplant	18 (4.1%)	213 (9.9%)	< 0.001
Waitlist Duration (days)	27 (8–123)	27 (10–80)	0.31
Creatinine (mg/dL)	1.18 (± 0.44)	1.18 (± 0.48)	0.89
Total Bilirubin (mg/dL)	0.70 (0.40–1.00)	0.70 (0.40–1.00)	0.88

Data are presented as median (IQR) and mean (SD) for continuous measures with skewed and normal distribution, respectively. Categorical measures are presented as n (%).

BMI = body mass index; DBD = donation after brain death; DCD = donation after circulatory death; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; ICU = intensive care unit; IQR = interquartile range; LVAD = left ventricular assist device; SD = standard deviation; tVAD = temporary ventricular assist device.

*Karnofsky functional status indicates a measure of recipients' physical capability to perform daily activities. Lower numbers denote sicker patients.

Table 2 Baseline Characteristics of Donors Stratified by Donation Type

	DCD	DBD	p-value
	N=442	N=2148	
Age (years)	31 (± 9)	33 (± 10)	< 0.001
Gender			< 0.001
Male	350 (79.2%)	1490 (69.0%)	
Female	92 (20.8%)	688 (32.0%)	
Race			< 0.001
White	333 (75.3%)	1300 (60.5%)	
Black	38 (8.6%)	349 (16.2%)	
Hispanic	55 (12.4%)	425 (19.8%)	
Asian	7 (1.6%)	42 (2.0%)	
Other	9 (2.0%)	32 (1.5%)	
Blood Type			0.38
A	153 (34.6%)	738 (34.4%)	
AB	4 (0.9%)	36 (1.7%)	
B	40 (9.0%)	235 (10.9%)	
O	245 (55.4%)	1139 (53.0%)	
Cause of Death			< 0.001
Anoxia	227 (51.4%)	1071 (49.9%)	
Stroke	38 (8.6%)	289 (13.5%)	
Head Trauma	153 (34.6%)	733 (34.1%)	
CNS Tumor	0 (0.0%)	12 (0.6%)	
Others	24 (5.4%)	43 (2.0%)	
BMI (kg/m^2)	27.21 (23.76–31.90)	27.25 (23.85–31.56)	0.93
Smoking History	70 (16.2%)	288 (13.9%)	0.19
Heavy Alcohol Use	129 (30.7%)	430 (21.0%)	< 0.001
Illicit IV Drug Use*	70 (15.2%)	370 (17.5%)	0.33
Diabetes Mellitus	23 (5.2%)	125 (5.9%)	0.78
Hypertension	71 (16.2%)	385 (18.2%)	0.32
Left Ventricular Ejection Fraction (%)	64 (60–66)	60 (57–65)	0.003
Ischemic Time (hours)	5.15 (± 2.08)	3.76 (± 1.33)	< 0.001
Distance from Donor to Recipient (miles)	262.5 (115–480)	282 (127–437)	0.55
DCD Parameters (minutes)			
Withdrawal Phase**	2 (1–5)		
Agonal Phase[a]	18 (13–27)		
DPP Time	8 (5–10)		
NRP Time	84.5 (66–122)		
Donor/Recipient Match			
Gender Mismatch[b]	71 (16.1%)	417 (19.4%)	0.10
Heart Size Mismatch[c]	71 (21.3%)	368 (17.1%)	0.11

Data are presented as median (IQR) and mean (SD) for continuous measures with skewed and normal distribution, respectively. Categorical measures are presented as n (%).

BMI = body mass index; CNS = central nervous system; DBD = donation after brain death; DCD = donation after circulatory death; DPP = direct procurement and perfusion; IQR = interquartile range; NRP = normothermic regional perfusion; SD = standard deviation

*History of illicit drug use includes steroids, cocaine, heroin, amphetamine, opioid, and marijuana.

**Withdrawal phase is defined as time interval from withdrawal of life support to start of agonal phase.

[a]*Agonal phase is defined as time interval from systolic pressure less than 80 mm Hg and/or oxygen saturation below 80% to declaration of death.*

[b]*Gender mismatch is defined as transplant from a female donor to a male recipient and* vice versa.

[c]*Heart size is estimated using predicted heart mass and considered a mismatch if the absolute difference between predicted donor and recipient heart mass was equal to or greater than 20%.*

hearts was also higher in the DCD group when compared to those in the DBD group (64 (IQR: 60–66) % vs 60 (IQR: 57–65) %, p=0.003). Allograft ischemic time was higher in the recipients of DCD hearts than those of DBD hearts (5.15 ± 2.08 h vs 3.76 ± 1.33 h, p < 0.001).

Incidence of severe PGD

Recipients of DCD hearts were more likely to experience severe PGD (LV/BiV) at 24 h (9.5% vs 5.1%, p < 0.001) when compared to those of DBD hearts (Table 3). The

Table 3 Perioperative Outcomes of Heart Transplant Recipients Stratified by Donation Type

	DCD	DBD	
	N=442	N=2148	p-value
Primary Graft Dysfunction (LV/BiV) at 24 h[a]			
Severe	42 (9.5%)	111 (5.1%)	< 0.001
Moderate/Mild	17 (3.8%)	62 (2.8%)	0.29
Severe Graft Dysfunction at 72 h*	10 (2.3%)	62 (2.9%)	0.67
Primary Graft Dysfunction (RV) at 24 h	20 (4.5%)	66 (3.1%)	0.13
72-Hour Mortality	2 (0.5%)	11 (0.5%)	0.87
Acute Transplant Rejection	43 (9.8%)	317 (15.1%)	0.004
Renal Replacement Therapy	81 (18.5%)	383 (18.2%)	0.80
Stroke	19 (4.3%)	82 (3.9%)	0.68
30-Day Graft Failure	16 (3.6%)	47 (2.2%)	0.081
30-Day Mortality	15 (3.4%)	44 (2.1%)	0.091
In-Hospital Mortality	16 (3.6%)	71 (3.3%)	0.77
Length of Hospital Stay (days)	17 (12–24)	17 (13–25)	0.43

Data are presented as median (IQR) for continuous measures and n (%) for categorical measures. BiV = Bi-Ventricular; DBD = donation after brain death; DCD = donation after circulatory death; LV = Left Ventricular; PGD = Primary Graft Dysfunction; RV = Right Ventricular

*Severe Graft dysfunction at 72 h was defined as patients with severe PGD (LV-BiV) at 24 h who had remained on mechanical support at 72 h

[a]*The degree of primary graft dysfunction severity is defined using the ISHLT criteria.*[15,16] *Severe primary graft dysfunction is defined as left or bi-ventricular dysfunction immediately after transplant that required extracorporeal membrane oxygenation or ventricular assist device.*

multivariable logistic regression model (Table 4) also demonstrated that DCD hearts (adjusted odds ratio (AOR): 1.77; 95% confidence interval (CI): 1.17–2.74, p=0.008), an increasing number of prior sternotomies (AOR: 1.49, 95% CI:1.23–1.80, p < 0.001), anti-arrhythmic agents (AOR: 1.37; 95% CI: 1.15–1.63, p < 0.001), inotrope use at transplant (AOR: 0.54; 95% CI: 0.37–0.80, p=0.002), ECMO support as a bridge to transplant (AOR: 1.94; 95% CI: 1.14–3.29, p=0.015), and undersized donor hearts (AOR: 1.98; 95% CI: 1.05–3.71, p=0.033) were independent predictors of severe PGD (LV/BiV) at 24 h. However, the incidence of Severe Graft Dysfunction at 72 h was comparable between recipients of DCD and DBD hearts (2.3% vs 2.9%, p=0.67). There were no significant differences in the need for renal placement therapy (18.5% vs 18.2%, p=0.80), 30-day mortality (3.4% vs 2.1%, p=0.091), and length of hospital stay (17 (IQR: 12–24) days vs 17 (IQR: 13–25) days, p=0.43) between DCD and DBD groups.

DPP vs NRP

Among 442 DCD donors, approximately 30.3% (n=134) of the donor hearts were procured using the NRP method, while the remaining 69.7% (n=308) were procured using DPP. Figure 2 shows the bimodal distribution of time from

Table 4 Multivariable Logistic Regression Model with Severe PGD (LV/BiV) at 24 h Post-transplantation

	Adjusted Odds Ratio	95% CI	p-value
Donation Type			
DBD Heart	Reference	Reference	Reference
DCD Heart	1.77	[1.17–2.74]	0.008
Recipient Characteristics			
Age (per year)	1.00	[0.99–1.01]	0.19
BMI (per 1 kg/m^2)	1.01	[0.98–1.04]	0.43
Diabetes Mellitus	0.91	[0.62–1.32]	0.61
Number of Prior Sternotomies (per 1)	1.49	[1.23–1.80]	< 0.001
Anti-Arrhythmic Agent	1.37	[1.15–1.63]	< 0.001
Inotropes at Transplant	0.54	[0.37–0.80]	0.002
IABP at Transplant	0.61	[0.36–1.04]	0.07
ECMO at Transplant	1.94	[1.14–3.29]	0.015
Undersized Donor Heart*	1.98	[1.05–3.71]	0.033
Organ Ischemic Time (per 1 h)	1.08	[0.97–1.19]	0.15

BiV = Bi-Ventricular; BMI = body mass index; CI = confidence interval; DBD = donation after brain death; DCD = donation after circulatory death; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; LV = Left Ventricular; PGD = primary graft dysfunction.

*Heart size is estimated using predicted heart mass and considered undersized if the difference between predicted recipient and donor heart mass was equal to or greater than 20%.

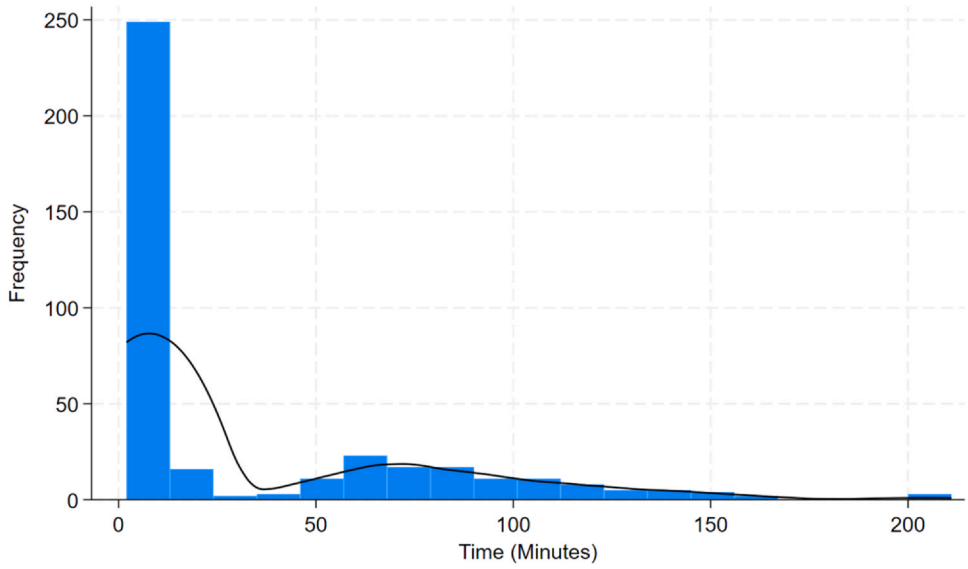

Figure 2 Histogram of time interval between donor declaration of circulatory death to cross-clamp time (left-sided cohort is designated as direct procurement and perfusion and right-sided cohort past 30 min is designated as normothermic regional perfusion).

declaration of circulatory death to cross-clamp to illustrate a demarcation in this time spectrum. Thirty minutes after declaration of death has been previously used for separating the 2 methods of procurement.[13,18] In sensitivity analyses, we performed additional studies using 15 min or 45 min from the declaration of death as the separation point. We found no significant changes in the number of cases or the clinical endpoints. For DPP and NRP groups, median times from declaration of death to cross-clamp (cardioplegic solution administration) were 8 (IQR: 5–10) minutes and 84.5 (IQR: 66–122) minutes, respectively. Recipients of DCD hearts procured using DPP or NRP methods experienced similar rates of severe PGD (LV/BiV) at 24 h (9.4% vs 9.7%, p=0.93). Severe Graft Dysfunction at 72 h was not different between the 2 groups (2.3% vs 2.2%, p=0.98) (Table 5). Recipients of DCD hearts procured using DPP and NRP methods also had similar 30-day mortality (3.3% vs 3.7%, p=0.80) post-transplantation.

Center volume

The distribution of DCD heart transplants volume among the US centers is shown in Figure S1. The median number

Table 5 Perioperative Outcomes of DCD Heart Transplant Recipients Stratified by Method of Procurement

	DPP	NRP	
	N=308	N=134	p-value
Primary Graft Dysfunction (LV/BiV) at 24 h[a]			
Severe	29 (9.4%)	13 (9.7%)	0.93
Moderate/Mild	12 (3.9%)	5 (3.7%)	0.93
Severe Graft Dysfunction at 72 h*	7 (2.3%)	3 (2.2%)	0.98
Primary Graft Dysfunction (RV) at 24 h	15 (4.9%)	5 (3.7%)	0.60
72-Hour Mortality	1 (0.3%)	1 (0.7%)	0.55
Acute Transplant Rejection	34 (11.1%)	9 (6.8%)	0.16
Renal Replacement Therapy	47 (15.4%)	24 (17.9%)	0.49
Stroke	17 (5.6%)	2 (1.5%)	0.055
30-Day Graft Failure	11 (3.6%)	5 (3.7%)	0.94
30-Day Mortality	10 (3.3%)	5 (3.7%)	0.80
In-Hospital Mortality	11 (3.6%)	5 (3.7%)	0.94
Length of Hospital Stay (days)	17 (13–23)	15.5 (12–24.5)	0.26

Data are presented as median (IQR) for continuous measures and n (%) for categorical measures. BiV = Bi-Ventricular; DCD = donation after circulatory death; DPP = Direct Procurement and Perfusion; LV = Left Ventricular; PGD = Primary Graft Dysfunction; RV = Right Ventricular; NRP = Normothermic Regional Perfusion.

*Severe Graft Dysfunction at 72 h was defined as patients with severe PGD (LV-BiV) at 24 h who had remained on mechanical support at 72 h

[a]The degree of primary graft dysfunction severity is defined using the ISHLT criteria.[15,16] Severe primary graft dysfunction is defined as left or bi-ventricular dysfunction immediately after transplant that required extracorporeal membrane oxygenation or ventricular assist device.

Table 6 Perioperative Outcomes of DCD Heart Transplant Recipients Stratified by Center Volume

	Low[a]	Control[a]	p-value
	N=42	N=400	
Primary Graft Dysfunction (LV/BiV) at 24 h[b]			
Severe	5 (11.9%)	37 (9.2%)	0.58
Moderate/Mild	2 (4.7%)	15 (3.8%)	0.75
Severe Graft Dysfunction at 72 h*	2 (4.8%)	8 (2.0%)	0.27
Primary Graft Dysfunction (RV) at 24 h	2 (4.8%)	18 (4.5%)	0.94
72-Hour Mortality	0 (0.0%)	2 (0.5%)	0.65
Acute Transplant Rejection	6 (14.6%)	37 (9.3%)	0.28
Renal Replacement Therapy	8 (19.5%)	73 (18.4%)	0.86
Stroke	1 (2.4%)	18 (4.5%)	0.53
30-Day Graft Failure	2 (4.8%)	14 (3.5%)	0.68
30-Day Mortality	2 (4.8%)	13 (3.3%)	0.61
In-Hospital Mortality	2 (4.8%)	14 (3.5%)	0.68
Length of Hospital Stay (days)	16 (13–24)	17 (12–24)	0.73

Data are presented as median (IQR) for continuous measures and n (%) for categorical measures. BiV = Bi-Ventricular; DBD = donation after brain death; DCD = donation after circulatory death; LV = Left Ventricular; PGD = Primary Graft Dysfunction; RV = Right Ventricular

*Severe Graft Dysfunction at 72 h was defined as patients with severe PGD (LV-BiV) at 24 h who had remained on mechanical support at 72 h

[a]Low center volume group was defined as centers performing number of DCD heart transplants at or below the 25th percentile (≤3), while the Control group was defined as those performing greater than 25th percentile.

[b]The degree of primary graft dysfunction severity is defined using the ISHLT criteria.[15,16] Severe primary graft dysfunction is defined as left or bi-ventricular dysfunction immediately after transplant that required extracorporeal membrane oxygenation or ventricular assist device.

of DCD heart transplant procedures performed was 5 (IQR: 3–10). Low volume centers experienced similar perioperative outcomes including severe PGD (LV/BiV) at 24 hours (11.9% vs 9.2%, p=0.58), Severe Graft Dysfunction at 72 hours (4.8% vs 2.0%, p=0.27), and 30-day mortality (4.8% vs 3.3%, p=0.68) when compared to the other centers (Table 6).

Discussion

This study demonstrates that the incidence of severe PGD at 24 hours post-transplantation is higher among recipients of DCD hearts when compared to those of DBD hearts. However, at 72 hours, Severe Graft Dysfunction rates become similar between the 2 groups. Recipients of DCD and DBD hearts experience comparable 30-day mortality and length of hospital stay following transplantation. Additionally, among recipients of DCD hearts, DPP method of procurement is associated with a similar incidence of severe PGD at 24 hours when compared to NRP method of procurement. These findings suggest that severe PGD in DCD heart transplantation is transient and support the broader utilization of DCD donor hearts.

To meet the escalating demand for heart transplantation, transplant centers have begun embracing organs previously deemed "marginal". This includes the acceptance of donor hearts with low ejection fraction or active Hepatitis C infection, which have demonstrated acceptable outcomes.[19–21] Advancements in ex-situ heart perfusion and NRP have spurred institutions to consider DCD hearts.[5,9,22] Recent analyses of the UNOS database have indicated that adopting DCD heart transplantation practices has improved waitlist outcomes and increased the rate of heart transplants, with comparable early survival rates to DBD heart transplantation.[13,23–25] In 2023, Schroder et al. reported on a prospective, multicenter, randomized, controlled trial of heart transplantation using donor hearts after circulatory death followed by ex-situ heart perfusion vs donor hearts after brain death.[26] The incidence of severe PGD in the recipients of DCD hearts was higher when compared to DBD hearts (15% vs 5%). However, the 6 months survival of recipients of DCD and DBD hearts were similar (94% vs 90%).

This study utilizes recently released data from UNOS on the incidence of PGD after heart transplantation and provides a real-world contemporary analysis of DCD heart transplantation in the US. We found that the incidence of severe PGD following heart transplantation is higher in recipients of DCD hearts when compared to recipients of DBD hearts. This association aligns with prior studies that have also shown higher incidences of severe PGD among DCD heart transplant recipients.[10,26,27] The higher incidence of severe PGD in recipients of DCD hearts may be influenced by warm ischemia during the procurement process, particularly during the agonal phase, where reduced perfusion and oxygenation stress the heart allograft. Warm ischemia disrupts cellular metabolism, leading to mitochondrial dysfunction and the accumulation of by-products such as lactate that exacerbate tissue damage.[15,28] The mandatory 5-minute stand-off period after circulatory death further prolongs ischemia, leading to increased oxidative stress and inflammation during reperfusion. Additionally, cardiac edema associated with ex-situ perfusion may also contribute to high incidence of early graft dysfunction seen in DCD hearts.[22] Collectively, these factors may lead to endothelial damage in the heart allograft, impaired myocardial contractility, and ultimately, the development of PGD following transplantation.[28–30]

Although the incidence of severe PGD at 24 hours was higher in DCD vs DBD heart transplantation, the incidence of Severe Graft Dysfunction became similar at 72 hours. This observation suggests that DCD-associated severe PGD may have a different phenotype when compared to DBD-associated severe PGD, as it is more transient with improvement in 72 hours post-transplantation. The potential mechanisms of the transient nature of severe PGD in recipients of DCD hearts may be related to the younger donors with more physiological reserve, as well as the reversibility of the warm ischemic injury incurred during

the circulatory arrest and procurement phase. However, despite the observed improvement in recipients of DCD hearts within 72 hours after transplantation, prompt intervention and intensive care monitoring to restore graft function upon the onset of severe PGD remain essential. Ayer and colleagues have emphasized the importance of optimizing post-transplant care protocols, including preparedness for the use of mechanical circulatory support, to mitigate the impact of severe PGD in recipients of DCD hearts.[27] It is also notable that the short-term outcomes of the DCD and DBD heart transplant recipients were similar, despite a higher incidence of severe PGD in the DCD group. This observation may be due to improvements in peri-operative care of heart transplant recipients with PGD, including earlier institution of mechanical support.

This study represents the most up-to-date comparison of the two currently available methods of DCD heart procurement (DPP and NRP). Our analysis demonstrates that DPP is being used more commonly in the US, and the incidence of severe PGD in transplant recipients of DCD hearts is similar between DPP and NRP methods of donor heart procurement. This finding expands on the Papworth series that reported no difference in the use of mechanical circulatory support for PGD following DCD heart transplantation using NRP and DPP procurement techniques.[10] Despite the similarities in clinical outcomes, the ethical considerations associated with NRP and the logistics demands of implementing this technique must be carefully weighed against the cost of DPP and the limitations of current technology to optimally reperfuse the heart.

The findings of this study hold several implications for the heart transplant community. Our results indicate that the higher incidence of severe PGD in recipients of DCD hearts appears to be a transient phenomenon, providing reassurance for the continued use of DCD hearts in heart transplantation. Additionally, the flexibility in choosing between DPP and NRP methods of procurement without compromising patient outcomes provides valuable options for heart transplant centers, allowing them to optimize their practices based on available resources and expertise. The observation that nearly 17% of heart transplants in the US in this study are from DCD donors heralds a new pool of donors that can potentially expand the donor heart pool. With the number of DCD donors in the US increasing by 18.5% in the past decade,[1] our heart transplant community can leverage this growing resource with some assurance regarding the reversibility of severe PGD in DCD heart transplantation. Finally, the ischemic time for DBD hearts in this study is close to four hours, reflecting a marked increment seen since the 2018 heart allocation policy changes. Historically, prolonged ischemic times have been associated with increased mortality risk,[31] but modern advancements, such as ex-situ perfusion and temperature-controlled storage technologies may be helping to mitigate this risk. Future studies could provide further insights into how these technologies influence organ utility rate and post-transplant outcomes in the modern era.

This study is subject to several limitations that warrant consideration. First, as a retrospective review of a large national registry, it is inherently limited by variability in data entry and missing data. Additionally, the database lacks granularity for further analyses of the DCD cohort, hindering the identification of potential confounders. For instance, variables detailing warm ischemic times and biomarkers measuring myocardial tissue injury, such as lactate and troponin levels, were not captured. Moreover, organ ischemic time data for DCD donor hearts reperfused via DPP or NRP may not accurately reflect true ischemic exposure, as these hearts were not under traditional ischemic conditions during reperfusion/transportation. Furthermore, information on DCD organ procurement methods (DPP vs NRP) had to be derived under the assumption that an interval between declaration of donor death and cross-clamp time exceeding 30 minutes translated to NRP. A thorough assessment of these assumptions is necessary to prevent misclassification of donors after circulatory death. Despite these limitations, this study is the largest contemporary analysis of severe PGD incidence of DCD and DBD heart transplantation.

In conclusion, this study shows that recipients of DCD hearts have higher rates of severe PGD at 24 hours, but similar rates of Severe Graft Dysfunction at 72 hours following transplantation compared to those receiving DBD hearts, suggesting a transient nature of PGD after DCD heart transplantation. Recipients of DCD and DBD hearts experience similar 30-day mortality and length of hospital stay post-transplant. There is no difference in the incidence of severe PGD at 24 hours among recipients of DCD hearts procured via DPP and NRP. These findings from a national contemporary database indicate that severe PGD in DCD heart transplantation may be reversible and provide assurance that DCD hearts can be broadly utilized.

Funding

This study was supported by the Sam Malik Foundation.

Acknowledgments

This study was supported by the Sam Malik Foundation.

Relevant disclosures

None.

Disclosures

Nothing to disclose.

Appendix A. Supporting information

Supplemental data associated with this article can be found in the online version at doi:10.1016/j.healun.2024.11.027.

References

1. Colvin MM, Smith JM, Ahn YS, et al. OPTN/SRTR 2022 Annual Data Report: heart. Am J Transplant 2024;24(2):S305-93. https://doi.org/10.1016/j.ajt.2024.01.016.
2. T. Jenkins R, M. Shah M, L. Larson E, L. Zhou A, M. Ruck J, Kilic A. Expanding the criteria for heart transplantation donors: a review of DCD, increased ischemic times, HCV, HIV, and extended criteria donors. Heart Surg Forum 2023;26(5):E639-55. https://doi.org/10.59958/hsf.6677.
3. Kim ST, Xia Y, Ho JK, Lowery E, McCarthy DP, Ardehali A. Lung transplantation from hepatitis C+ donor lungs: reassuring midterm outcomes. J Heart Lung Transplant 2024;43(2):337-45. https://doi.org/10.1016/j.healun.2023.10.014.
4. Ardehali A, Esmailian F, Deng M, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. Lancet 2015;385(9987):2577-84. https://doi.org/10.1016/S0140-6736(15)60261-6.
5. Dhital KK, Iyer A, Connellan M, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet 2015;385(9987):2585-91. https://doi.org/10.1016/S0140-6736(15)60038-1.
6. Messer S, Page A, Axell R, et al. Outcome after heart transplantation from donation after circulatory-determined death donors. J Heart Lung Transplant 2017;36(12):1311-8. https://doi.org/10.1016/j.healun.2017.10.021.
7. Chew HC, Iyer A, Connellan M, et al. Outcomes of donation after circulatory death heart transplantation in Australia. J Am Coll Cardiol 2019;73(12):1447-59. https://doi.org/10.1016/j.jacc.2018.12.067.
8. Messer S, Page A, Colah S, et al. Human heart transplantation from donation after circulatory-determined death donors using normothermic regional perfusion and cold storage. J Heart Lung Transplant 2018;37(7):865-9. https://doi.org/10.1016/j.healun.2018.03.017.
9. Alamouti-fard E, Garg P, Wadiwala IJ, et al. Normothermic regional perfusion is an emerging cost-effective alternative in donation after circulatory death (DCD) in heart transplantation. Published online June 29 Cureus2022. https://doi.org/10.7759/cureus.26437. Published online June 29.
10. Messer S, Cernic S, Page A, et al. A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors. J Heart Lung Transplant 2020;39(12):1463-75. https://doi.org/10.1016/j.healun.2020.10.001.
11. Joshi Y, Scheuer S, Chew H, et al. Heart transplantation from DCD donors in australia: lessons learned from the first 74 cases. Transplantation 2023;107(2):361-71. https://doi.org/10.1097/TP.0000000000004294.
12. Siddiqi HK, Trahanas J, Xu M, et al. Outcomes of heart transplant donation after circulatory death. J Am Coll Cardiol 2023;82(15):1512-20. https://doi.org/10.1016/j.jacc.2023.08.006.
13. Kwon JH, Ghannam AD, Shorbaji K, et al. Early outcomes of heart transplantation using donation after circulatory death donors in the United States. Circ Heart Fail 2022;15(12). https://doi.org/10.1161/CIRCHEARTFAILURE.122.009844.
14. Hoffman JRH, McMaster WG, Rali AS, et al. Early US experience with cardiac donation after circulatory death (DCD) using normothermic regional perfusion. J Heart Lung Transplant 2021;40(11):1408-18. https://doi.org/10.1016/j.healun.2021.06.022.
15. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant 2014;33(4):327-40. https://doi.org/10.1016/j.healun.2014.02.027.
16. Notice of OPTN Data Collection Changes Report Primary Graft Dysfunction in Heart Transplant Recipients August 3,2021-September 30, 2021. Dev Meas Heart Prim Graft Dysfunct 2021.
17. Khush KK, Cherikh WS, Chambers DC, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. J Heart Lung Transpl 2019;38(10):1056-66. https://doi.org/10.1016/j.healun.2019.08.004.
18. Ran G, Wall AE, Narang N, et al. Post-transplant survival after normothermic regional perfusion versus direct procurement and perfusion in donation after circulatory determination of death in heart transplantation. J Heart Lung Transplant 2024;43(6):954-62. https://doi.org/10.1016/j.healun.2024.02.1456.
19. Li SS, Osho A, Moonsamy P, et al. Trends in the use of hepatitis C viremic donor hearts. J Thorac Cardiovasc Surg 2022;163(5):1873-1885.e7. https://doi.org/10.1016/j.jtcvs.2020.09.044.
20. Chen CW, Sprys MH, Gaffey AC, et al. Low ejection fraction in donor hearts is not directly associated with increased recipient mortality. J Heart Lung Transplant 2017;36(6):611-5. https://doi.org/10.1016/j.healun.2017.02.001.
21. Madan S, Saeed O, Vlismas P, et al. Outcomes after transplantation of donor hearts with improving left ventricular systolic dysfunction. J Am Coll Cardiol 2017;70(10):1248-58. https://doi.org/10.1016/j.jacc.2017.07.728.
22. White CW, Messer SJ, Large SR, et al. Transplantation of hearts donated after circulatory death. Front Cardiovasc Med 2018;5. https://doi.org/10.3389/fcvm.2018.00008.
23. Chen Q, Emerson D, Megna D, et al. Heart transplantation using donation after circulatory death in the United States. J Thorac Cardiovasc Surg 2023;165(5):1849-1860.e6. https://doi.org/10.1016/j.jtcvs.2022.05.005.
24. Kwon JH, Blanding WM, Shorbaji K, et al. Waitlist and transplant outcomes in organ donation after circulatory death. Ann Surg 2023;278(4):609-20. https://doi.org/10.1097/SLA.0000000000005947.
25. Gernhofer YK, Bui QM, Powell JJ, et al. Heart transplantation from donation after circulatory death: Impact on waitlist time and transplant rate. Am J Transplant 2023;23(8):1241-55. https://doi.org/10.1016/j.ajt.2023.04.026.
26. Schroder JN, Patel CB, DeVore AD, et al. Transplantation outcomes with donor hearts after circulatory death. N Engl J Med 2023;388(23):2121-31. https://doi.org/10.1056/NEJMoa2212438.
27. Ayer A, Truby LK, Schroder JN, et al. Improved outcomes in severe primary graft dysfunction after heart transplantation following donation after circulatory death compared with donation after brain death. J Card Fail 2023;29(1):67-75. https://doi.org/10.1016/j.cardfail.2022.10.429.
28. Benck L, Kransdorf EP, Emerson DA, et al. Recipient and surgical factors trigger severe primary graft dysfunction after heart transplant. J Heart Lung Transplant 2021;40(9):970-80. https://doi.org/10.1016/j.healun.2021.06.002.
29. Nicoara A, Ruffin D, Cooter M, et al. Primary graft dysfunction after heart transplantation: Incidence, trends, and associated risk factors. Am J Transplant 2018;18(6):1461-70. https://doi.org/10.1111/ajt.14588.
30. Truby LK, Takeda K, Topkara VK, et al. Risk of severe primary graft dysfunction in patients bridged to heart transplantation with continuous-flow left ventricular assist devices. J Heart Lung Transplant 2018;37(12):1433-42. https://doi.org/10.1016/j.healun.2018.07.013.
31. Kwon JH, Huckaby LV, Sloan B, et al. Prolonged ischemia times for heart transplantation: impact of the 2018 allocation change. Ann Thorac Surg 2022;114(4):1386-94. https://doi.org/10.1016/j.athoracsur.2022.02.029.