Direct procurement with machine perfusion and normothermic regional perfusion in donation after circulatory death heart transplantation

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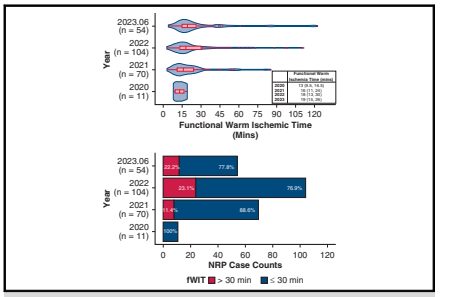
ABSTRACT

Background: Donation after circulatory death (DCD) heart transplants have increased in the United States with direct procurement with machine perfusion (DPP) and thoracoabdominal normothermic regional perfusion (TA-NRP) techniques. There remains a paucity of data examining DPP and TA-NRP outcomes. The purpose of this study was to investigate the impact of the DCD technique on post-transplant outcomes compared to donation after brain death (DBD) donors.

Methods: Adult patients undergoing heart transplantation between December 1, 2019, and June 30, 2023, were identified in the United Network for Organ Sharing registry. DPP and TA-NRP groups were identified using time of death to an aortic cross-clamp time of 30 minutes. Categorical variables were compared using the χ^2 or Fisher exact test, and continuous variables were compared using the Mann-Whitney *U* test. Propensity score matching was performed using a 1:3 match. One-year survival was analyzed using the log-rank test and a Cox proportional hazard regression model.

Results: During the study period, there were 7338 DBD and 419 DCD heart transplants. At 1 year post-transplant, there was no difference in survival between unmatched ($P = .13$) and matched ($P = .36$) DBD and DCD heart recipients. There was an increase in acute rejection and rejection requiring treatment in DCD recipients compared to DBD recipients in the matched cohort. A total of 134 TA-NRP transplants and 242 DPP transplants were performed. One-year survival and post-transplant outcomes were similar in the DPP and TA-NRP groups. TA-NRP functional warm ischemia time (fWIT) was increased significantly during the study period.

Conclusions: In this matched cohort, DCD heart recipients experienced increased acute rejection, both treated and nontreated, compared to DBD heart recipients. Despite differences in the techniques and likely in fWIT, acute rejection, survival, and other secondary outcomes are similar with DPP and TA-NRP. (J Thorac Cardiovasc Surg 2025;170:256-65)



Functional warm ischemia times have increased significantly in TA-NRP DCD cases in the United States.

CENTRAL MESSAGE

Donation after circulatory death heart transplant recipients had a higher rate of acute rejection compared to donation after brain death heart transplant recipients in a matched cohort. Despite differences in technique, acute rejection, survival, and other secondary outcomes were similar in direct procurement with machine perfusion and thoracoabdominal normothermic regional perfusion.

PERSPECTIVE

Donation after circulatory death (DCD) heart transplantation is associated with increased acute rejection compared to donation after brain death heart transplantation but without an appreciable difference in 1-year survival. In this study, DCD procurement technique did not impact acute rejection rate or survival, notwithstanding significantly increased functional warm ischemia times in thoracoabdominal normothermic regional perfusion during the study period.

See Commentary on page 266.

Abbreviations and Acronyms

ASD = absolute standardized mean difference
BMI = body mass index
CI = confidence interval
DBD = donation after brain death
DCD = donation after circulatory death
DPP = direct procurement with machine perfusion
fWIT = functional warm ischemia time
HR = hazard ratio
IABP = intra-aortic balloon pump
IQR = interquartile range
PGF = primary graft dysfunction
PPM = permanent pacemaker
RRT = renal replacement therapy
TAH = total artificial heart
TA-NRP = thoracoabdominal normothermic regional perfusion
UNOS = United Network for Organ Sharing
VAD = ventricular assist device

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Heart transplantation remains the preferred treatment for eligible candidates with end-stage heart failure refractory to optimal medical therapy. In the United States, which accounts for nearly one-half of the annual global volume, heart transplantation rates continue to increase; however, yearly waitlist expansion easily dwarfs this growth. In 2022, more than 4000 new adults were added to the heart transplant waitlist, bringing the total to 7519 candidates.[1] In turn, transplant centers have embraced extended-criteria heart donation and marginal donors in an effort to close the gap.[2,3] More recently, heart transplantation following circulatory death has emerged as a viable option to increase the donor pool with innovative perfusion techniques and procurement protocols, based largely on the ground-breaking work from Australia and the United Kingdom.[4-6]

Modern donation following circulatory death (DCD) heart procurement involves a controlled withdrawal of life-sustaining treatment followed by cardiopulmonary arrest. A standoff period, typically 5 minutes, is observed to ensure the absence of autoresuscitation, thereby meeting the circulatory criteria of death.[7] One of 2 perfusion strategies is then used: either rapid, direct procurement followed by normothermic, ex-situ machine perfusion (DPP) or in situ thoracoabdominal normothermic regional perfusion (TA-NRP). Collectively, these procurement and perfusion strategies account for the rapid expansion of DCD heart transplantation in the United States.

Early US results demonstrate similar survival between and DBD and DCD heart transplantation.[8,9] Furthermore, the use of DCD hearts has decreased the waitlist time for recipients at higher listing status and increased their likelihood of heart transplant while decreasing the incidence of death or deterioration for waitlisted patients.[6,10] However, not all post-transplant outcomes have been similar. Australian and UK data initially suggested higher rates of primary graft dysfunction (PGD) with DCD but similar early and mid-term survival compared to DBD.[4,11] Moreover, rates of acute rejection and subsequent hospitalization have been greater in DCD compared to DBD.[8,12] The role of DCD procurement technique in these adverse outcomes remains largely unknown. This study aimed to investigate the impact of DCD donor heart procurement techniques on post-transplant outcomes compared to the use of DBD donor hearts.

METHODS

Data Source

The United Network for Organ Sharing (UNOS) Standard Transplant and Research file as of September 22, 2023, was used for this retrospective analysis. The file included data for organ donations, transplants, and new listings through June 30, 2023. The thoracic organ transplant recipient file was used to identify all recipients of primary heart transplant performed between December 1, 2019, and June 30, 2023. Recipients age <18 years, retransplant recipients, multiorgan transplant recipients, and patients with unvalidated or incomplete records were excluded. We identified 7758 adult heart transplant recipients during the study period, with 1 patient excluded for missing donor information (Figure 1). Of these recipients, 7338 received a DBD donor heart and 419 received a DCD donor heart. DBD

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Funding for this study was provided by the American Heart Association Heart Failure Strategically Focused Research Network (16SFRN29020000, to Drs Drakos, Stehlik, and Selzman); the National Heart, Lung, and Blood Institute (R01HL135121-01, to Dr Drakos; R01 HL132067-01A1, to Dr Drakos; 2T32HL007576-36, to Dr Kyriakopoulos; T32HL007576-37, to Dr Nickel); the Nora Eccles Treadwell Foundation (Dr Drakos); and the US Department of Veterans Affairs (Merit Review Award I01CX002291, to Dr Drakos).

Read at the 50th Annual Meeting of the Western Thoracic Surgical Association, Vail, Colorado, June 26-29, 2024.

Received for publication June 26, 2024; revisions received Sept 12, 2024; accepted for publication Oct 7, 2024; available ahead of print Oct 26, 2024.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2024.10.033

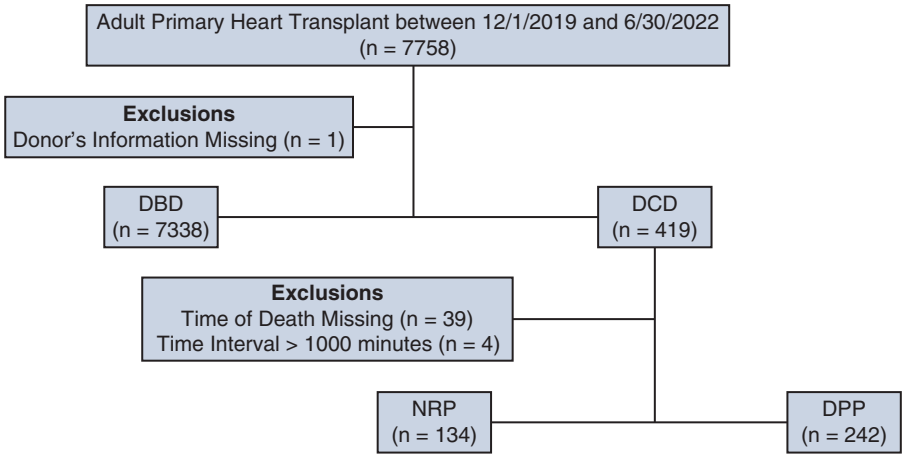

FIGURE 1. Inclusion and exclusion of eligible subjects from the United Network for Organ Sharing (*UNOS*) Standard Transplant and Research (*STAR*) files. *DBD*, Donation after brain death; *DCD*, donation after circulatory death; *NRP*, normothermic regional perfusion; *DPP*, direct procurement and perfusion.

and DCD donors were identified in the deceased donor file and matched with recipients using the encrypted donor identifier variable.

To identify DPP and TA-NRP DCD procurements, the time of death to aortic cross-clamp time was calculated, with an interval >30 minutes used to identify TA-NRP, as reported previously.[9] Similar to prior reports, 2 distinct distributions representing DPP and TA-NRP procurements emerged using this protocol. Of the 419 DCD transplants, 134 hearts were procured with TA-NRP and 242 were procured with DPP. Forty-three DCD transplants were excluded from the analysis, 39 for missing information on time of death and 4 for erroneous timing data (time to aortic cross clamp >1000 minutes) (Figure 1). For TA-NRP procurements, functional warm ischemia time (fWIT) was calculated as the time between the start of the agonal phase (marked by systolic blood pressure (SBP) <80 mm Hg or oxygen saturation <80%) until the declared time of death. Standard UNOS definitions were used to define donor and recipient characteristics and recipient outcomes. Of note, there is no standard definition in UNOS for acute rejection or treated acute rejection. Transplant recipient follow-up information is entered directly by individual transplant centers into the Transplant Information Electronic Data Interchange (TIEDI) within the OPTN data entry system. Transplant centers select an option for acute rejection, if and when it occurs, and specify whether treatment is required along with the treatment regimen provided. This study was approved by the Institutional Review Board at the University of Utah with a waiver of informed consent (IRB 00072747, latest approval on June 14, 2024).

Primary and Secondary Outcomes

When comparing DBD and DCD recipients, our primary outcome was 1-year post-transplant survival. Secondary outcomes included postoperative adverse events, such as acute rejection, treated acute rejection, stroke, renal replacement therapy (RRT), and permanent pacemaker (PPM) implantation. Only transplants performed before June 30, 2022, were included in the analyses of outcomes to allow for a 12-month follow-up. One-year survival and secondary outcomes also are reported for DCD DPP versus TA-NRP. The monthly volumes of DBD, DCD, and the 2 DCD procurement techniques were evaluated using the entire date range of the data file. The subgroup analysis of DCD procurement techniques investigated 30-day and 1-year survival of TA-NRP survivors and recipient and donor characteristics of survivors and nonsurvivors of TA-NRP.

Statistical Analyses

Demographic and clinical characteristics of recipients and donors are presented as median (interquartile range [IQR]) for continuous variables and as count (percentage) for categorical variables. Baseline characteristics were compared between groups using the Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. A propensity score was estimated by fitting a logistic regression model that adjusted for the following covariates: recipient age, sex, race/ethnicity, body mass index (BMI), creatinine, total bilirubin, history of diabetes, prior cardiac surgery, urgent status at listing, days on waitlist, pretransplant mechanical ventilation, ventricular assist device (VAD)/total artificial heart (TAH), intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation, inotrope use, and location pretransplant, and donor age, sex, race/ethnicity, BMI, left ventricular ejection fraction, history of diabetes, cause of death, sex match, ABO identical, CMV serostatus match, organ travel distance, and total center volume. One-to-3 matching between the DCD and DBD groups was implemented using nearest-neighbor matching with a caliper width of 0.2 of the standard deviation of the logit of the propensity score without replacement. Covariate balance before and after matching was assessed using absolute standardized mean difference (ASD). Covariates with an ASD <0.1 were considered well-balanced between the 2 groups. Missing data were not imputed. Only complete cases were reported and analyzed. Kaplan-Meier survival analysis with the log-rank test was conducted to compare 1-year survival between groups. The unadjusted hazard of 30-day mortality for TA-NRP was estimated using a Cox proportional hazards regression model. Post-transplant adverse events were compared between groups using the χ^2 or Fisher exact test. Transplant center volume was divided into quartiles during the study period, including DBD, TA-NRP, and DPP. The 1-year observed mortality (unadjusted) was analyzed. A multivariable Cox regression model was constructed to evaluate the risk of 1-year mortality among the volume quartiles of centers. Statistical analysis was performed using RStudio version 2023.06.2. All tests were 2-tailed, and a P value < .05 was considered significant.

RESULTS

Transplant Totals and Trends

Between December 1, 2019, and June 30, 2023, 14,123 total heart transplants were performed in the US as recorded in the UNOS registry. Among these, 13,174 hearts were procured from DBD donors, and the other 949 hearts were from DCD donors. After excluding transplants performed after June 30, 2022, retransplants, recipients age <18 years, multiorgan recipients, and cases with incomplete data, 7757

primary heart transplant recipients were identified, including 7338 DBD recipients and 419 DCD recipients. DCD monthly volume increased significantly over the study period, from 2.5% (n = 7 of 283) in December 2019 to 13.9% (n = 56 of 403) in June 2023 (Pearson r = 0.894; $P < .001$) (Figure E1). TA-NRP monthly volume increased significantly over the same period, from 16.7% (n = 1 of 6) in January 2020 to 39.2% (n = 20 of 51) in June 2023 (Pearson r = 0.782; $P < .001$) (Figure E2). Whereas only DPP DCD heart transplants were performed in 2019 (n = 7 of 7; 100%), as of June 30, 2023, 178 of 261 (68%) DPP DCD transplants and 83 of 261 (38%) TA-NRP DCD transplants were performed.

DBD and DCD Recipient and Donor Characteristics

Baseline clinical characteristics were mostly similar in the DBD and DCD groups, with several exceptions (Table 1). In the unmatched cohort, DCD recipients were more often male (80.2% [n = 336 of 419] vs 74.2% [n = 5444 of 7338]; $P = .007$), had a higher BMI, were more often transplanted at nonurgent status (78.5% [n = 329 of 419] vs 39.8% [n = 847 of 7338]; $P < .001$), and spent longer on the waitlist. DBD recipients were more often supported with an IABP or extracorporeal membrane oxygenation, on inotropes, and located in the intensive care ICU pretransplant. Conversely, durable VADs were more common in DCD recipients (41.8% [n = 175 of 419] vs 34.8% [n = 2555 of 7338]; $P = .004$). DCD recipients received donor hearts procured at greater distances from the transplant center, and higher-volume centers were more likely than lower-volume centers to perform DCD transplantation. After matching, baseline characteristics were well-balanced with an ASD <0.1, but donor organ travel distance and transplant center volume remained significantly higher in DCD recipients.

Pretransplant characteristics were mostly similar in the TA-NRP and DPP groups with several differences (Table 2). TA-NRP recipients spent fewer days on the waitlist (median 35.5 [IQR, 12.0-118] days vs 60.5 [IQR, 17.0-240] days for DPP; $P = .024$). DPP recipients were more likely to have a durable VAD (47.5% [n = 115 of 242] vs 35.1% [n = 47 of 134]; $P = .026$) and to receive donor hearts procured at greater distances compared to TA-NRP recipients (median, 413 [IQR, 225-603] miles vs 221 [IQR, 40.3-442] miles; $P < .001$). TA-NRP was used more frequently by higher-volume centers; the median total heart transplant volume during the study period was 201 [IQR, 131-368] vs 129 [IQR, 121-297] for DPP; $P = .004$).

DBD and DCD Heart Transplant Outcomes

One-year post-transplant survival was similar between the DBD recipients and DCD recipients ($P = .13$) (Figure E3). The Cox proportional hazards regression model for the overall cohort demonstrated no difference in mortality risk (unadjusted hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.51-1.09). Propensity score matching yielded similar 1-year survival in DBD and DCD transplant recipients (matched cohort HR, 0.82; 95% CI, 0.53-1.26; $P = .36$) (Figure E4). No significant difference was observed when comparing 1-year survival between DCD TA-NRP and DPP (95.3% vs 92.0%; $P = .19$) (Figure 2).

Post-transplant secondary outcomes were compared between DBD and DCD recipients (Table 3). In the unmatched cohort, there were no differences in acute rejection, acute rejection requiring treatment, need for RRT or PPM, or stroke. In the matched cohort, DCD recipients had a higher incidence of acute rejection (20.8% [n = 79 of 379] vs 15% [n = 136 of 901]; $P = .015$) and treated acute rejection (11.6% [n = 44 of 379] vs 7.8% [n = 70 of 901]; $P = .036$). Comparing secondary outcomes in DCD TA-NRP and DPP recipients revealed no differences in acute rejection, acute rejection requiring treatment, the need for RRT or PPM, or stroke (Table 4).

TA-NRP Clinical Characteristics, 30-Day Survival, and Transplant Center Volume

TA-NRP DCD donor and recipient clinical data were further examined for differences that could be associated with poor outcomes. The 30-day mortality was comparable in TA-NRP and DPP DCD recipients ($P = .235$) (Table E1). TA-NRP recipient and donor characteristics were compared between 30-day survivors and nonsurvivors (Table E2). Statistically significant differences between recipients who did not survive at 30 days and those who survived were higher preoperative bilirubin (total bilirubin: median, 0.6 [IQR, 0.5-0.8] mg/dL vs 1.5 [IQR, 1.2-3.2] mg/dL; $P = .019$) and more frequent urgent transplant as status 1 or 2 (21.2% [n = 38 of 179] vs 75.0%; $P = .036$). fWIT increased significantly over the study period (Spearman R = 0.165; $P = .010$) (Figure 3). Furthermore, the TA-NRP procurements with an fWIT >30 minutes increased from 0 of 11 (0.0%) in 2020 to 12 of 54 (22.2%) by June 2023. Cox regression model univariable analysis showed no change in 30-day mortality risk with an increase in fWIT (unadjusted HR, 1.01; 95% CI, 0.96-1.06).

To analyze the impact of transplant center volume on DBD, TA-NRP, and DPP volume and outcomes, 148 US transplant centers were divided into quartiles based on total heart transplant volume during the study period (Table E3). A total of 7757 heart transplants were included in analysis, with 39 transplants excluded for missing DCD procurement data. TA-NRP and DPP DCD transplants were performed mostly in the fourth quartile (highest-volume) transplant centers, although these centers performed a higher percentage of DPP transplants compared to TA-NRP transplants (Table E4). The 1-year observed mortality (unadjusted) was highest in transplant centers in volume quartile 2

TABLE 1. Baseline characteristics of recipients and donors in DBD and DCD heart transplantation

Characteristic	All patients			Propensity score–matched patients			
	DBD (N = 7338)	DCD (N = 419)	*P* value	DBD (N = 901)	DCD (N = 379)	*P* value	ASD
Recipients							
Age, y, median [IQR]	57.0 [47.0-64.0]	57.0 [46.0-64.0]	.950	57.0 [46.0-63.0]	57.0 [47.0-64.0]	.525	0.042
Male sex	5444 (74.2)	336 (80.2)	.007	714 (79.2)	300 (79.2)	>.10	0.006
Race/ethnicity							
White	4328 (59.0)	280 (66.8)	.011	564 (62.6)	250 (66.0)	.637	0.057
Black	1891 (25.8)	94 (22.4)		221 (24.5)	86 (22.7)		0.036
Hispanic	768 (10.5)	31 (7.4)		75 (8.3)	30 (7.9)		0.002
Other	351 (4.8)	14 (3.3)		41 (4.6)	13 (3.4)		0.065
Body mass index, kg/m^2, median [IQR]	27.5 [24.1-31.3]	29.2 [25.8-32.8]	<.001	28.8 [25.1-32.8]	28.7 [25.7-32.8]	.631	0.011
Creatinine, mg/dL, median [IQR]	1.20 [0.94-1.50]	1.20 [0.97-1.50]	.616	1.20 [0.99-1.50]	1.20 [0.960-1.50]	.920	0.020
Total bilirubin, mg/dL, median [IQR]	0.70 [0.48-1.10]	0.70 [0.49-0.90]	.228	0.60 [0.50-1.0]	0.70 [0.49-0.90]	.528	0.037
Diabetes, n (%)	2214 (30.2)	134 (32.0)	.469	266 (29.5)	121 (31.9)	.431	0.049
Prior cardiac surgery, n (%)	3098 (43.1)	195 (47.2)	.109	424 (47.1)	180 (47.5)	.936	0.010
Primary diagnosis, n (%)							
Nonischemic cardiomyopathy	4069 (55.5)	226 (53.9)	.290	471 (52.3)	206 (54.4)	.893	0.027
Ischemic cardiomyopathy	1944 (26.5)	126 (30.1)		262 (29.1)	108 (28.5)		0.016
Hypertrophic/restrictive cardiomyopathy	594 (8.1)	36 (8.6)		81 (9.0)	34 (9.0)		0.017
Congenital heart disease	263 (3.6)	10 (2.4)		24 (2.7)	10 (2.6)		0.006
Other	468 (6.4)	21 (5.0)		63 (7.0)	21 (5.5)		0.044
Urgent status at transplant, n (%)	4491 (61.2)	90 (21.5)	<.001	251 (27.9)	89 (23.5)	.121	0.003
Days on waitlist, median [IQR]	31.0 [9.00-145]	46.0 [14.0-202]	<.001	45.0 [11.0-227]	44.0 [14.0-202]	.744	0.007
Mechanical ventilation, n (%)	145 (2.0)	4 (1.0)	.196	9 (1.0)	3 (0.8)	>.10	0.021
Inotropes, n (%)	3021 (41.2)	99 (23.6)	<.001	241 (26.7)	93 (24.5)	.452	0.010
VAD/TAH, n (%)	2555 (34.8)	175 (41.8)	.004	389 (43.2)	159 (42.0)	.733	0.011
IABP, n (%)	2159 (29.4)	44 (10.5)	<.001	123 (13.7)	44 (11.6)	.368	0.001
ECMO, n (%)	431 (5.9)	4 (1.0)	<.001	16 (1.8)	4 (1.1)	.462	0.036
Location before transplant, n (%)			<.001			.405	
ICU	4178 (56.9)	82 (19.6)		214 (23.8)	80 (21.1)		0.030
Hospitalized not in ICU	997 (13.6)	66 (15.8)		162 (18.0)	63 (16.6)		0.028
Not hospitalized	2163 (29.5)	271 (64.7)		525 (58.3)	236 (62.3)		0.004
Organ travel distance, miles, median [IQR]	223 [97.0-391]	350 [136-569]	<.001	232 [123-468]	340 [126-567]	.002	0.039
Total center volume, n, median [IQR]	97.0 [64.0-147]	201 [121-297]	<.001	148 [95.0-297]	201 [119-297]	.003	0.007
Donors							
Age, y, median [IQR]	32.5 [26.0-40.0]	29.0 [23.0-35.0]	<.001	30.0 [23.0-36.0]	29.0 [23.0-35.0]	.668	0.020
Male sex, n (%)	5285 (72.0)	367 (87.6)	<.001				0.004
Race/ethnicity			<.001			.775	
White	4525 (61.7)	321 (76.6)		673 (74.7)	286 (75.5)		0.014
Black	1224 (16.7)	41 (9.8)		96 (10.7)	40 (10.6)		0.036
Hispanic	1366 (18.6)	49 (11.7)		121 (13.4)	46 (12.1)		0.028
Other	223 (3.0)	8 (1.9)		11 (1.2)	7 (1.8)		0.031
LVEF, %, median [IQR]	60.0 [56.0-65.0]	61.0 [58.5-65.0]	.012	61.0 [59.0-65.0]	61.0 [58.0-65.5]	.962	0.004
Cause of death, n (%)							
Anoxia	3402 (46.4)	198 (47.3)	<.001	436 (48.4)	182 (48.0)	.982	0.006
Cerebrovascular/stroke	968 (13.2)	21 (5.0)		54 (6.0)	20 (5.3)		0.010
Head trauma	2780 (37.9)	188 (44.9)		388 (43.1)	166 (43.8)		0.004
CNS tumor	26 (0.4)	2 (0.5)		4 (0.4)	2 (0.5)		0.019
Others	162 (2.2)	10 (2.4)		19 (2.1)	9 (2.4)		0.003
Body mass index, kg/m^2, median [IQR]	27.2 [23.8-31.6]	26.6 [23.8-30.8]	.125	26.7 [23.2-31.1]	26.5 [23.8-30.8]	.960	0.024
Diabetes, n (%)	309 (4.3)	9 (2.2)	.047	18 (2.0)	9 (2.4)	.829	0.045
Sex match, n (%)	5847 (79.7)	346 (82.6)	.169	744 (82.6)	310 (81.8)	.799	0.017
ABO identical	6266 (85.4)	357 (85.2)	.972	773 (85.8)	325 (85.8)	>.10	0.004
CMV match, n (%)	3811 (51.9)	189 (45.1)	.008	436 (48.4)	176 (46.4)	.564	0.027

DBD, Donation after brain death; *DCD*, donation after circulatory death; *ASD*, absolute standardized mean difference; *IQR*, interquartile range; *VAD*, ventricular assist device; *TAH*, total artificial heart; *IABP*, intra-aortic balloon pump; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *LVEF*, left ventricular ejection fraction; *CNS*, central nervous system; *ABO*, blood group antigen system; *CMV*, cytomegalovirus.

TABLE 2. Baseline characteristics of recipients and donors in TA-NRP and DPP heart transplantation

Characteristic	TA-NRP (N = 134)	DPP (N = 242)	*P* value
Recipients			
Age, y, median [IQR]	58.0 [49.0-64.8]	55.0 [44.0-64.0]	.110
Male sex, n (%)	110 (82.1)	188 (77.7)	.381
Race/ethnicity, n (%)			
White	91 (67.9)	156 (64.5)	.604
Black	26 (19.4)	61 (25.2)	
Hispanic	12 (9.0)	18 (7.4)	
Other	5 (3.7)	7 (2.9)	
Body mass index, kg/m^2, median [IQR]	29.4 [26.2-32.9]	28.6 [25.7-32.5]	.189
Creatinine, mg/dL, median [IQR]	1.20 [0.980-1.49]	1.20 [0.963-1.50]	.632
Total bilirubin, mg/dL, median [IQR]	0.600 [0.460-0.800]	0.700 [0.500-1.10]	.038
Diabetes, n (%)	41 (30.6)	79 (32.6)	.770
Prior cardiac surgery, n (%)	62 (46.6)	113 (47.5)	.959
Primary diagnosis, n (%)			
Nonischemic cardiomyopathy	68 (50.7)	139 (57.4)	.309
Ischemic cardiomyopathy	48 (35.8)	62 (25.6)	
Hypertrophic/restrictive cardiomyopathy	9 (6.7)	20 (8.3)	
Congenital heart disease	2 (1.5)	7 (2.9)	
Other	7 (5.2)	14 (5.8)	
Urgent status at transplant, n (%)	25 (18.7)	58 (24.0)	.289
Days on waitlist, d, median [IQR]	35.5 [12.0-118]	60.5 [17.0-240]	.024
Mechanical ventilation, n (%)	2 (1.5)	2 (0.8)	.619
Inotropes, n (%)	26 (19.4)	67 (27.7)	.097
VAD/TAH, n (%)	47 (35.1)	115 (47.5)	.026
IABP, n (%)	13 (9.7)	27 (11.2)	.792
ECMO, n (%)	1 (0.7)	3 (1.2)	>.100
Location before transplant, n (%)			
ICU	21 (15.7)	52 (21.5)	.143
Hospitalized not in ICU	18 (13.4)	43 (17.8)	
Not hospitalized	95 (70.9)	147 (60.7)	
Organ travel distance, miles, median [IQR]	221 [40.3-442]	413 [225-603]	<.001
Total center volume, n, median [IQR]	201 [131-368]	129 [121-297]	.004
Donors			
Age, y, median [IQR]	28.5 [23.0-35.0]	29.0 [23.3-35.0]	.950
Male sex, n (%)	120 (89.6)	209 (86.4)	.464
Race/ethnicity, n (%)			
White	66 (49.3)	115 (47.5)	.375
Black	4 (3.0)	31 (12.8)	
Hispanic	24 (17.9)	17 (7.0)	
Other	3 (2.2)	4 (1.7)	
LVEF, %, median [IQR]	63.5 [60.0-68.8]	61.5 [57.0-65.0]	.134
Cause of death, n (%)			
Anoxia	66 (49.3)	115 (47.5)	.375
Cerebrovascular/stroke	5 (3.7)	11 (4.5)	
Head trauma	59 (44.0)	110 (45.5)	
CNS tumor	2 (1.5)	0 (0)	
Other	2 (1.5)	6 (2.5)	
Body mass index, kg/m^2, median [IQR]	26.5 [24.0-30.5]	26.6 [23.7-30.8]	.601
Diabetes	2 (1.5)	6 (2.5)	.801
Sex match	112 (83.6)	197 (81.4)	.698
ABO identical	115 (85.8)	208 (86.0)	>.100
CMV match	61 (45.5)	106 (43.8)	.831

TA-NRP, Thoracoabdominal normothermic regional perfusion; *DPP*, direct procurement with machine perfusion; *IQR*, interquartile range; *VAD*, ventricular assist device; *TAH*, total artificial heart; *IABP*, intra-aortic balloon pump; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *LVEF*, left ventricular ejection fraction; *CNS*, central nervous system; *ABO*, blood group antigen system; *CMV*, cytomegalovirus.

(Table E5). One-year mortality was significantly lower in the fourth quartile volume centers compared with second quartile volume centers (HR, 0.67; 95% CI, 0.55-0.83; $P < .001$). One-year mortality was significantly lower in the third quartile volume centers compared with second quartile volume centers (HR, 0.75; 95% CI, 0.60-0.94; $P = .136$). However, differences in 1-year mortality between first quartile and second quartile volume centers were not significant (HR, 0.73; 95% CI, 0.51-1.04; $P = .084$). These data show that 94.5% of DCD heart transplants occur at the highest-volume (third and fourth quartile) centers. These centers had the lowest risk of 1-year mortality in a multivariable Cox regression model.

DISCUSSION

The use of DCD heart transplantation is increasing rapidly in the United States, which has reduced waitlist times and waitlist mortality.[6,8,10] Early experience in the United Kingdom and Australia have consistently demonstrated survival equivalence between DCD and DBD transplantation.[4,5,11,13] Previous UNOS registry analyses similarly have demonstrated equivalent survival but higher rates of acute rejection among DCD recipients.[8,9] However, further evaluation of DCD procurement techniques has been inhibited by the newness of TA-NRP for heart procurement in the United States. We sought to use the UNOS registry to provide a more robust appraisal—to include 1-year survival analysis—of the US DCD landscape and expand understanding of the impact of procurement technique.

Our investigation aligns with prior experience with DCD. We note that DBD and DCD heart transplantation yielded similar 1-year survival. However, we identified significantly more acute rejection in the propensity-matched DCD population compared to DBD. Another study found a near-50% increase in the incidence of treated rejection prior to discharge in matched DCD recipients in the United States between 2019 and 2021.[9] Our updated analysis extending from 2019 to 2023 corroborates these findings on a larger scale.

The etiology of this rejection risk remains unclear. It has been postulated that this may reflect differences in provider approach with a stronger proclivity for anti-rejection treatment in DCD recipients.[9] Others have reported an elevated risk for acute rejection not only prior to discharge (23.3% vs 18.4%; $P = .044$), but also for rejection-related hospitalization (23.4% vs 11.4%; $P = .003$), within a mean 14.9 months after DCD transplant compared to DBD recipients.[12] Procurement technique, warm ischemia, donor and recipient comorbidities, clinical acuity, inflammatory milieu, and even mechanism of brain versus circulatory death all offer potential mechanistic explanations for the impacted inflammatory and immune responses in DCD recipients. Examining the UNOS data shows significant differences between matched DBD and DCD groups only in total transplant center volume (median, 148 [IQR, 95.0-297] transplants/year vs 201 [IQR, 119-297] transplants/year; $P = .003$) and organ travel distance (median, 232 [IQR, 123-468] miles vs 340 [IQR, 126-567] miles; $P = .002$). Unfortunately, these results do not provide much insight. Indeed, although it is conceptually reasonable that greater organ travel distance may confer a greater risk of acute rejection, it is more difficult to attribute this to higher center volume.

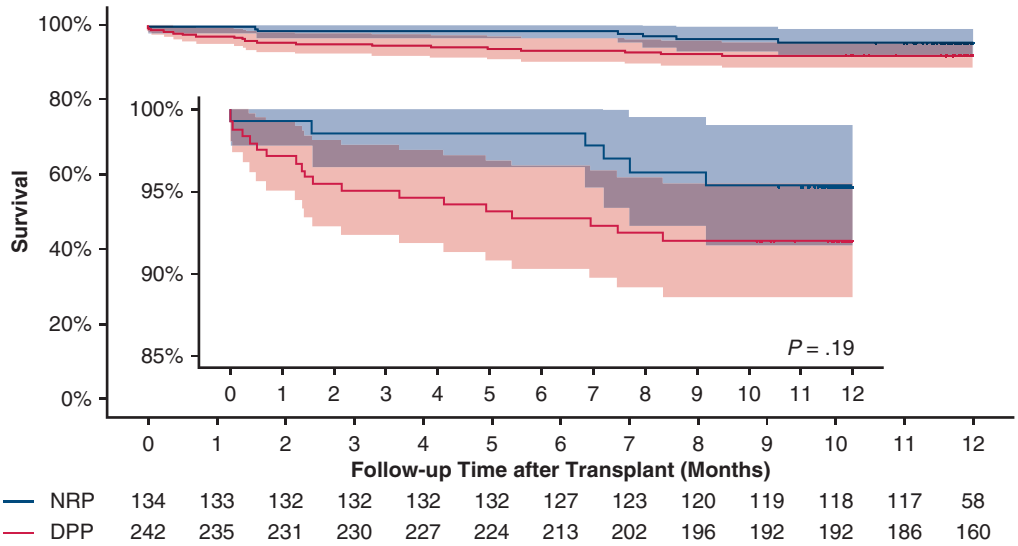

FIGURE 2. One-year survival after heart transplantation using donation after circulatory death (*DCD*) donors stratified by procurement technique. Expanded vertical axis (85%-100%) is shown in the inset for a more detailed view. *Shaded areas* represent 95% confidence intervals. *NRP*, Normothermic regional perfusion; *DPP*, direct procurement and perfusion.

TABLE 3. Post-transplant outcomes in DBD and DCD heart transplantation

Outcome	All patients			Propensity score–matched patients		
	DBD (N = 7338), n (%)	DCD (N = 419), n (%)	*P* value	DBD (N = 901), n (%)	DCD (N = 379), n (%)	*P* value
Treated acute rejection	653 (8.9)	47 (11.2)	.128	70 (7.8)	44 (11.6)	.036
Acute rejection	1231 (16.8)	83 (19.8)	.123	136 (15.1)	79 (20.8)	.015
Post-transplant dialysis	1204 (16.4)	71 (17.0)	.817	130 (14.5)	62 (16.4)	.428
Post-transplant pacemaker	119 (1.6)	3 (0.7)	.221	14 (1.6)	2 (0.5)	.176
Stroke	261 (3.6)	14 (3.3)	.914	33 (3.7)	14 (3.7)	>.100

DBD, Donation after brain death; *DCD*, donation after circulatory death.

The glaring difference between DBD and DCD transplantation is the warm ischemia endured by DCD hearts. Although classically associated with PGD, it may be hypothesized that the warm ischemia of DCD is driving the increased acute rejection. Recognizing the differences in DBD and DCD procurement, as well as the differences within the DCD techniques themselves, we attempted to tease out the impact of DCD procurement approach. Although DPP recipients spent more time on the waitlist (median, 60.5 [IQR, 17.0-240] days vs 35.5 [IQR, 12.0-118] days; $P = .024$), were more likely to be supported by a VAD or TAH prior to transplant (35.1% [n = 47 of 134] vs 47.5% [n = 115 of 242]; $P = .026$), and had a longer organ travel distance (median, 221 [IQR, 40.3-442] miles vs 413 [IQR, 225-603] miles; $P < .001$), overall survival was not significantly different compared to TA-NRP procurement (95.4% [n = 370 of 388] vs 97.8% [n = 179 of 183]; $P = .235$) (Table E1). Furthermore, the rate of rejection necessitating treatment was not significant (13.2% [n = 32 of 242] for DPP vs 9.7% [n = 13 of 134] for TA-NRP; $P = .4$) despite a numerically higher trend. Although a larger sample may increase the clarity of this potential signal, based on these data, the increased risk of acute rejection in DCD transplantation is not driven by procurement technique.

With increasing TA-NRP procurements and recognizing that an optimal warm ischemia cutoff time of 36 minutes was identified based on risk of 30-day mortality in DPP,[14] we sought to investigate whether such a cutoff might exist for TA-NRP. Evaluation of the TA-NRP experience from 2020 to the first half of 2023 highlights progressive lengthening of the fWIT (Figure 3). Whereas no cases in 2020 used an fWIT >30 minutes, by 2023 that percentage had risen to 22.2% of cases. Despite this change, adverse outcome rates did not increase. Unlike in DPP, wherein the odds of 30-day mortality were 20 times greater for an fWIT ≥36 minutes,[14] we did not identify such a threshold for TA-NRP fWIT. Instead, there was no significant association with increasing fWIT and post-transplant adverse outcomes such as RRT ($P = .965$), PPM ($P = .135$), post-transplant stroke ($P = .723$), treated acute rejection ($P = .912$), and 30-day mortality ($P = .95$).

These data suggest that as experience with DCD heart transplantation and, specifically, TA-NRP procurement has increased, so too has the willingness to procure and transplant hearts with longer ischemic times that initially may have been discarded. With that in mind, the need for a standardized definition of fWIT bears mentioning. Currently, UNOS still defines the agonal phase as systolic blood pressure <80 mm Hg or oxygen saturation <80%. fWIT criteria vary among transplant centers and organ procurement organizations, such that examination of this critical time is inhibited by irregularity. Although it remains possible that centers have liberalized agonal phase parameters during DCD procurement during the study period, we are not able to decipher these changes within the UNOS. Undoubtedly, there is an fWIT beyond which rates of PGD become prohibitive; however, without standardization, that cutoff will remain opaque.

Limitations

This study has multiple limitations. As a retrospective review of the UNOS registry, it is subject to confounding and selection bias based on data availability. At present, the standard UNOS definitions within the registry are lacking important details related to DCD procurement. The NRP

TABLE 4. Post-transplant outcomes in TA-NRP and DPP heart transplantation

Outcome	TA-NRP (N = 134), n (%)	DPP (N = 242), n (%)	*P* value
Treated acute rejection	13 (9.7)	32 (13.2)	.400
Acute rejection	21 (15.7)	55 (22.7)	.134
Post-transplant dialysis	24 (17.9)	38 (15.8)	.696
Post-transplant pacemaker	2 (1.5)	1 (0.4)	.290
Stroke	5 (3.7)	9 (3.7)	>.100

TA-NRP, Thoracoabdominal normothermic regional perfusion; *DPP*, direct procurement with machine perfusion.

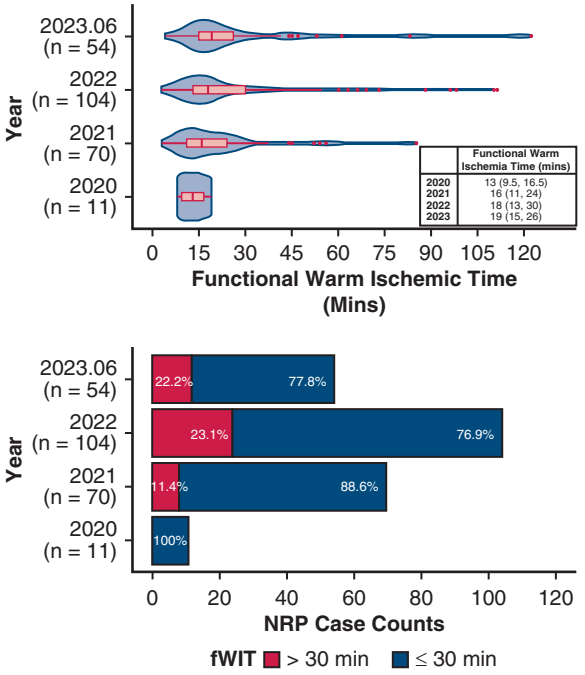

FIGURE 3. Functional warm ischemia time (*fWIT*)—determined from the start of the agonal phase (systolic blood pressure <80 mm Hg or oxygen saturation <80%) to the listed time of death for each donor—for normothermic regional perfusion (*NRP*) procurements stratified by year from 2020 to 2023. The violin plot (*top*) highlights the progressive and statistically significant increase in fWIT. The bar chart (*bottom*) demonstrates the increase in the proportion of NRP procurements with fWIT >30 minutes from 2020 to 2023.

and DPP procurement techniques are not directly captured within UNOS and are deduced by time calculations. While this method has been used previously, and the data clearly fall into a bimodal distribution without crossover, it is still possible that this could have contributed to errant classification. Clearly identifying DCD heart donors using DPP and TA-NRP procurement techniques appears to be a reasonable first step that can be added to the dataset in enhanced future studies.

In addition, the UNOS dataset does not contain the variables needed to determine the total fWIT in DCD procurement cases. Therefore, we calculated the fWIT from the start of the agonal phase, which is documented in UNOS, to the time of death based on the available data. The fWIT extends beyond the time of death until aortic cross-clamping in DPP cases and until reperfusion in TA-NRP cases. The additional fWIT may vary case-by-case and between the 2 techniques, which is a limitation of our study. However, some insight into the additional fWIT after declaration of death can be gained from single-center case series. In an early single-center TA-NRP experience, the average fWIT was 19 $\pm$ 5 minutes, with chest entry times between 1 and 4 minutes.[15] For their center's TA-NRP cases, Smith and colleagues[16] reported a mean time of 11.13 $\pm$ 1.13 minutes from skin incision to initiation of cardiopulmonary bypass. As transplant centers have gained experience with TA-NRP, it is likely that variability in reperfusion times after chest entry has decreased. Similarly, time-specific data from declaration of death to aortic cross-clamping and cardioplegia in DPP procurement is unavailable in the UNOS and randomized trials with DPP to date. In a randomized noninferiority trial comparing post-transplant outcomes between DCD DPP donors and DBD donors, the fWIT in DPP donors did not exceed 30 minutes.[17] These data would be particularly informative and allow for a more comprehensive evaluation of the impact of increasing fWIT.

CONCLUSIONS

DCD heart transplantation continues to increase in the United States. Mirroring this increase is the concomitant rise of TA-NRP procurement. In a matched cohort, DCD heart recipients experienced increased acute rejection, both treated and nontreated, compared to DBD. Despite differences in the techniques, acute rejection, survival, and other secondary outcomes were similar between DPP and TA-NRP procurement. DCD transplantation appears well poised to expand the donor pool and offer therapy for the growing end-stage heart failure population.

Audio

Audio Recording: You can listen to the audio recording of the presentation and discussion associated with this paper: https://doi.org/10.1016/j.jtcvs.2024.10.033.

Conflict of Interest Statement

Dr Drakos reported consulting for Abbott Laboratories and Pfizer and receipt of research support from Novartis and Merck. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: heart transplantation, donation after circulatory death, thoracoabdominal normothermic regional perfusion, functional warm ischemia time

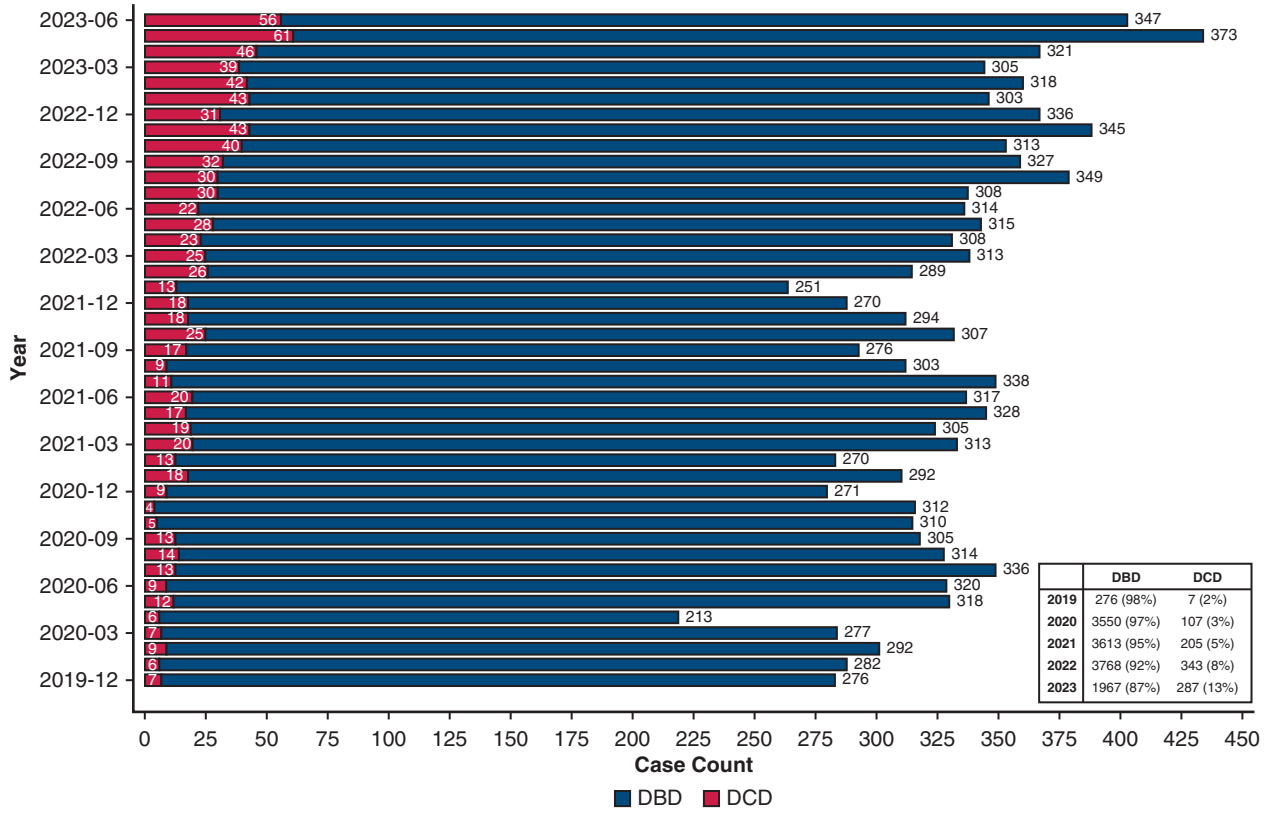

FIGURE E1. United States total quarterly heart transplant volume by donor type, December 2019 to June 2023. Overall heart transplant volume has increased since 2019, and donation after circulatory death (*DCD*) transplantation has increased steadily both in absolute terms and in the proportion of total heart transplant volume. *DBD*, Donation after brain death.

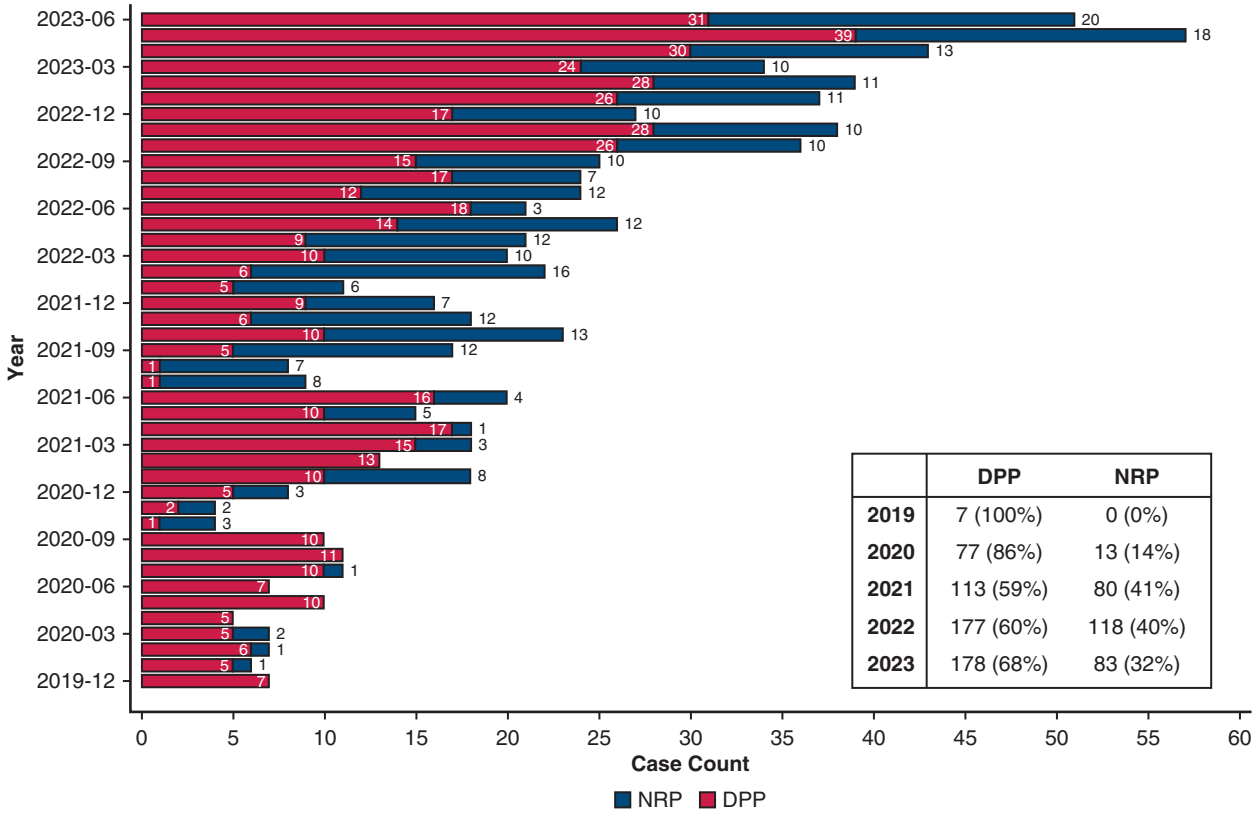

FIGURE E2. United States quarterly donation after circulatory death (*DCD*) heart transplant volume by procurement technique, December 2019 to June 2023. NRP procurement utilization has increased since the advent of DCD heart transplantation in the United States in 2019, with 32% of DCD procurements using normothermic regional perfusion (*NRP*) as of June 2023. *DPP*, Direct procurement and perfusion.

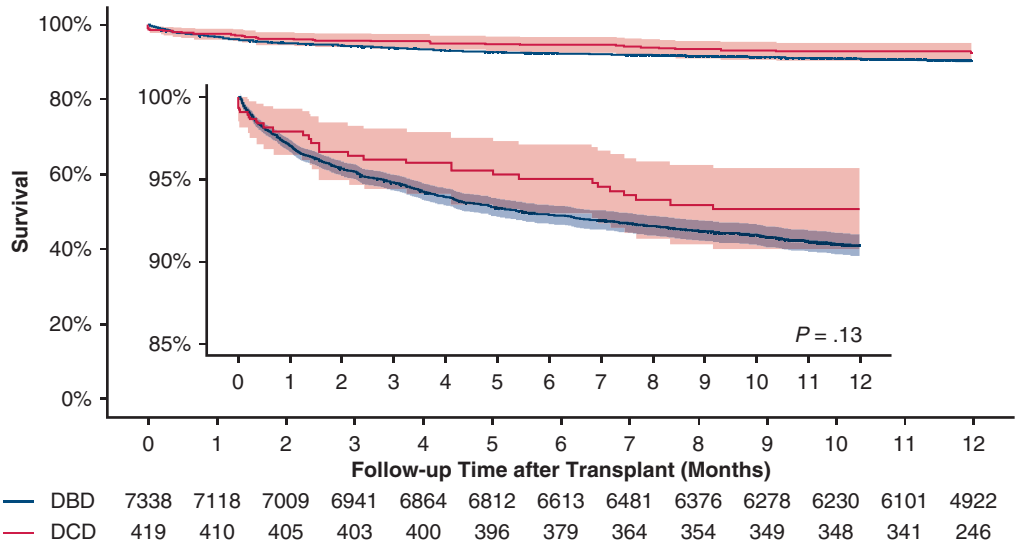

FIGURE E3. One-year survival after heart transplantation using donation after brain death (*DBD*) versus donation after circulatory death (*DCD*) donors in the overall cohort (not propensity score–matched). Expanded vertical axis (85%-100%) is shown in the inset for a more detailed view. *Shaded areas* represent 95% confidence intervals. Outcomes were comparable between DBD and DCD recipients during the 12 months after transplant.

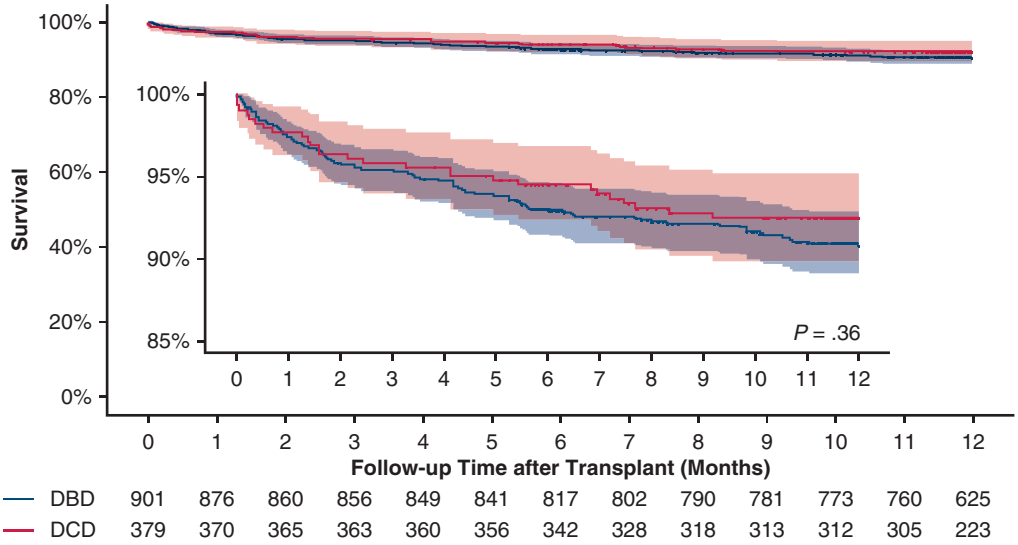

FIGURE E4. One-year survival after heart transplantation using donation after brain death (*DBD*) versus donation after circulatory death (*DCD*) donors in the propensity score–matched cohort. Expanded vertical axis (85%-100%) is shown in the inset for a more detailed view. *Shaded areas* represent 95% confidence intervals. Outcomes were comparable between matched DBD and DCD recipients during the 12 months after transplant.

TABLE E1. 30-day mortality in TA-NRP and DPP heart transplantation (December 1, 2019, to May 31, 2023)

30-day mortality	TA-NRP (N = 183)	DPP (N = 388)	*P* value
Alive, n (%)	179 (97.8)	370 (95.4)	.235
Dead, n (%)	4 (2.2)	18 (4.6)	

TA-NRP, Thoracoabdominal normothermic regional perfusion; *DPP*, direct procurement with machine perfusion.

TABLE E2. Survivor and nonsurvivor characteristics in TA-NRP (30-day mortality)

Characteristic	Survivors (N = 179)	Nonsurvivors (N = 4)	*P* value
Recipients			
Age, y, median [IQR]	59.0 [49.0-65.0]	59.5 [54.0-66.3]	.462
Male sex, n (%)	148 (82.7)	3 (75.0)	.540
Race/ethnicity, n (%)			
White	123 (68.7)	4 (100)	.749
Black	34 (19.0)	0 (0)	
Hispanic	17 (9.5)	0 (0)	
Other	5 (2.8)	0 (0)	
Functional ischemic time, min, median [IQR]	17.0 [12.0-23.5]	20.0 [8.50-35.8]	.950
Total ischemic time, min, median [IQR]	205 [149-239]	245 [229-252]	.159
Diabetes	60 (33.5)	2 (50.0)	.268
Total bilirubin pretransplant, mg/dL, median [IQR]	0.610 [0.460-0.840]	1.50 [1.20-3.20]	.019
Creatinine pretransplant, mg/dL, median [IQR]	1.20 [0.990-1.50]	1.42 [1.29-1.73]	.301
Dialysis	6 (3.4)	1 (25.0)	.112
Prior cardiac surgery	75 (41.9)	1 (25.0)	<.100
Urgent status at transplant	38 (21.2)	3 (75.0)	.036
Organ travel distance, miles, median [IQR]	221 [30.0-441]	380 [177-547]	.448
Pretransplant VAD/TAH	55 (30.7)	2 (50.0)	.231
Pretransplant inotropes	34 (19.0)	1 (25.0)	.576
Pretransplant ECMO	2 (1.1)	0 (0)	<.100
Pretransplant mechanical ventilation	2 (1.1)	0 (0)	<.100
Pretransplant location			
ICU	30 (16.8)	1 (33.3)	.268
Hospitalized not in ICU	30 (16.8)	1 (33.3)	
Not hospitalized	119 (66.5)	1 (33.3)	
CMV serostatus pretransplant			
Positive	93 (52.0)	3 (100.0)	.249
Negative	84 (46.9)	0 (0)	
Donors			
Age, y, median [IQR]	30.0 [24.0-35.0]	31.5 [27.5-35.3]	.623
Race/ethnicity			
White	134 (74.9)	4 (100)	>.100
Black	7 (3.9)	0 (0)	
Hispanic	33 (18.4)	0 (0)	
Other	5 (2.8)	0 (0)	
Male sex	158 (88.3)	4 (100)	>.100
Body mass index, kg/m^2, median [IQR]	26.8 [24.0-30.6]	25.6 [23.1-26.9]	.296
LVEF, %	64.0 [60.0-68.0]	58.5 [56.5-63.8]	
Diabetes	2 (1.1)	0 (0)	>.100
Hypertension	20 (11.2)	0 (0)	>.100
Prior cardiac arrest	76 (42.5)	1 (25.0)	.622
Clinical infection	145 (81.0)	4 (100)	>.100
CMV seropositive	115 (64.2)	3 (75.0)	>.100
ABO identical	156 (87.2)	4 (100)	>.100
CMV match	88 (49.2)	2 (50.0)	>.100
Sex match	153 (85.5)	3 (75.0)	.475

TA-NRP, Thoracoabdominal normothermic regional perfusion; *IQR*, interquartile range; *VAD*, ventricular assist device; *TAH*, total artificial heart; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *CMV*, cytomegalovirus; *LVEF*, left ventricular ejection fraction; *ABO*, blood group antigen system.

TABLE E3. Transplant center quartiles for primary heart transplantation

Technique	Quartile (transplant volume)				Overall (N = 7718)
	Q1 (N = 483)	Q2 (N = 1222)	Q3 (N = 1987)	Q4 (N = 4026)	
TA-NRP, n (%)	0 (0)	14 (1.1)	9 (0.5)	115 (2.9)	138 (1.8)
DPP, n (%)	3 (0.6)	4 (0.3)	13 (0.7)	222 (5.5)	242 (3.1)
DBD, n (%)	480 (99.4)	1204 (98.5)	1965 (98.9)	3689 (91.6)	7338 (95.1)

TA-NRP, Thoracoabdominal normothermic regional perfusion; *DPP*, direct procurement with machine perfusion; *DBD*, donation after brain death.

TABLE E4. DCD TA-NRP and DPP volume by transplant center volume quartile

Transplant center volume quartile	TA-NRP (N = 134)	DPP (N = 242)	Overall (N = 376)
First quartile, n (%)	0 (0)	3 (1.2)	3 (0.8)
Second quartile, n (%)	14 (10.4)	4 (1.7)	18 (4.8)
Third quartile, n (%)	9 (6.7)	13 (5.4)	22 (5.9)
Fourth quartile, n (%)	111 (82.8)	222 (91.7)	333 (88.6)

DCD, Donation after circulatory death; *TA-NRP*, thoracoabdominal normothermic regional perfusion; *DPP*, direct procurement with machine perfusion.

TABLE E5. One-year observed mortality (unadjusted) by transplant center volume quartile

Status	Transplant center volume quartile				Overall (N = 7757)
	Q1 (N = 483)	Q2 (N = 1223)	Q3 (N = 1992)	Q4 (N = 4059)	
Alive, n (%)	442 (91.5)	1081 (88.4)	1808 (90.8)	3742 (92.2)	7073 (91.2)
Dead, n (%)	41 (8.5)	142 (11.6)	184 (9.2)	317 (7.8)	684 (8.8)