

ORIGINAL RESEARCH

HEART FAILURE

Outcomes After Donation After Circulatory Determination of Death Cardiac Transplantation



An International, Multicenter Retrospective Study

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ABSTRACT

BACKGROUND As donation after circulatory determination of death (DCD) heart transplantation (HT) becomes more widely adopted, there is a need to establish the most clinically effective method of organ procurement.

OBJECTIVES This international, multicenter study compares outcomes of DCD HT across Europe and the United States between recipients whose donor hearts were retrieved using thoraco-abdominal normothermic regional perfusion (taNRP) with those whose hearts were recovered using direct procurement and perfusion (DPP).

METHODS This was a retrospective observational study across 22 heart transplant centers in Belgium, Spain, the United Kingdom, and the United States. This study included all patients undergoing DCD HT at participating centers, from the start of each center's DCD program through January 1, 2023. DCD HT with recovery using either taNRP or DPP were compared with one another. Posttransplant outcomes included: 1) survival at 1 year; 2) incidence of severe primary graft dysfunction (PGD); and 3) episodes of treated, biopsy-proven acute-cellular rejection (ACR) in the first year following transplantation.

RESULTS A total of 504 DCD HTs took place in the study period. Survival at 1 year was similar for taNRP and DPP recipients (91% vs 88%; $P = 0.100$). taNRP recipients had a lower rate of severe PGD (7.6% vs 19.2%; $P < 0.001$) and fewer episodes of biopsy-proven, ACR requiring treatment in the first year post-transplantation (13% vs 25%; $P < 0.001$).

CONCLUSIONS In an international study of DCD HT, recipients of hearts retrieved by taNRP technique had lower rates of severe PGD and fewer episodes of biopsy-proven ACR in the first year when compared with those retrieved by using DPP. These results should be further investigated with randomized control trials. (JACC Heart Fail. 2025;13:102473)
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**ABBREVIATIONS
AND ACRONYMS****ACR** = acute-cellular rejection**DBD** = donation after brain death**DCD** = donation after circulatory determination of death**DPP** = direct procurement and perfusion**FTIT** = functional total ischemic time**FWIT** = functional warm ischemic time**HT** = heart transplantation**MCS** = mechanical circulatory support**MMF** = mycophenolate mofetil**mTORi** = mammalian target of rapamycin inhibitor**PGD** = primary graft dysfunction**RCT** = randomized controlled trial**SCS** = static cold storage**taNRP** = thoraco-abdominal normothermic regional perfusion

Heart transplantation (HT) improves survival and quality of life for patients with advanced heart failure refractory to medical treatment.¹ However, HT is limited by donor organ availability. In recent years, HT waiting lists have increased across both Europe and the United States. The number of waitlisted candidates increased by 84% from 2011 to 2023 in the United Kingdom, and by 28% from 2011 to 2022 in the United States.²⁻⁴ As waiting lists grow, there is a need to increase the availability of suitable donor hearts.

Donation after the circulatory determination of death (DCD) has been shown to increase the donor pool. Early estimates have predicted that DCD HT may increase the size of the donor pool by 30%.⁵ Among recipients of DCD hearts, survival up to 5 years has been shown to be comparable to recipients of donation after neurological determination of death (commonly referred to as donation after brain death [DBD]) hearts.⁶⁻⁸

Recovery of DCD hearts follows 1 of 2 strategies, both aimed at minimizing the potential insult of warm ischemia that occurs between withdrawal of life-sustaining treatment in the donor and confirmation of death by circulatory criteria. In thoraco-abdominal normothermic regional perfusion (taNRP), the donor heart is reperfused in situ before organ recovery, after which it is preserved using either ex situ perfusion or static cold storage (SCS).⁹ Conversely, in direct procurement and perfusion (DPP), the organ is retrieved directly following declaration of donor death and preserved using machine perfusion during transport from donor to recipient hospitals.¹⁰ To date, comparisons of DCD HT outcomes using these strategies has been limited to small, single-center studies or limited by data availability on a national level.^{11,12}

We sought to compare transplant outcomes among recipients of DCD hearts by method of organ recovery: taNRP vs DPP.

METHODS

STUDY DESIGN. This study was a retrospective international multicenter observational study. Data were collected from 22 transplant centers across Belgium, Spain, the United Kingdom, and the United States. Consecutive patients who underwent DCD HT at participating centers between February 28, 2015, and January 1, 2023, were enrolled. Follow-up was censored on January 1, 2024. Data were collected from preoperative and intraoperative records and collated in each center before analysis. Donor, intraoperative, and recipient data were collected. Details of participating centers and parameters collected are included in the [Supplemental Methods](#).

PRIMARY AND SECONDARY OUTCOMES. Primary outcomes included: 1) recipient survival; 2) severe primary graft dysfunction (PGD) defined as requirement for mechanical circulatory support (MCS) post-transplantation as per 2014 ISHLT (International Society of Heart and Lung Transplantation) consensus statement; and 3) biopsy-proven acute-cellular rejection (ACR) grade ≥ 2 as defined by the ISHLT criteria.^{13,14} Secondary outcomes included: 1) duration of posttransplant mechanical ventilation; 2) days in the intensive care unit; 3) immunosuppression utilization—defined as use of immunosuppressants overall post-transplantation; 4) estimated glomerular filtration rate at 1-year post-transplantation; and 5) heart function assessed on echocardiography at 1-month and 1-year post-transplantation.

DEFINITIONS OF ISCHEMIC TIMES.

1. Functional total ischemic time (FTIT): time from donor systolic blood pressure <50 mm Hg until reperfusion

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2. Functional warm ischemic time (FWIT): time from donor systolic blood pressure <50 mm Hg until cold cardioplegia
3. Functional cold ischemic time (FCIT): time from cold cardioplegia until reperfusion ex situ⁶

In Spain the onset of FWIT and FTIT starts when donor systolic blood pressure is <60 mm Hg.

PATIENT SELECTION. Twenty-four centers with established DCD programs were invited to share their data for this study. Twenty centers contributed their data, of which, 4 centers retrieved DCD hearts using both taNRP and DPP. The [Supplemental Methods](#) describe reasons for use of each technique.

STATISTICAL ANALYSIS. Continuous variables were summarized as medians and IQRs and are reported as median (Q1-Q3). Comparisons between groups were performed using the Mann-Whitney *U* test to account for non-normal distributions. Categorical variables were summarized as proportions, and comparisons between groups were made using Fisher's exact test. Statistical significance for the primary outcome was set at a 5% level. All analyses were conducted in Python 3.12.1, with the pandas2.1.4, SciPy1.11.4, and lifelines0.28.0 libraries, with the survival 3.7-0 library from R 4.4.1, imported with rpy2.¹⁵⁻¹⁷

Survival post-transplantation and rejection-free survival were assessed using a Kaplan-Meier estimator. Time to event was defined as the time from transplantation to death, retransplantation, or the end of follow-up for the overall study period. Survival curves were estimated for the DPP and taNRP groups, with survival difference across the entire time course assessed with the log-rank test and HRs. Differences between groups at specific time points were evaluated using a log(-log)-transformed survival curve with a chi-squared test.¹⁸

To better examine differences in ACR, we compared the incidence of first and total biopsy-proven ACR events in the first year post-transplantation and the number of patients between the DPP and taNRP groups. We adjusted for differences in biopsy schedules by comparing the number of rejections relative to the number of biopsies performed in the first year. To compare the risk of ACR between the groups, we used a Kaplan-Meier survival analysis, defining time to the first episode of ACR as the primary event. Patients who died without experiencing a rejection event were censored at their time of death. Group comparisons were conducted in a manner consistent with the overall survival analysis using the log-rank test and time point comparisons.

In addition, we fitted a mixed-effects Cox proportional hazards model to evaluate the relationship between predictor variables and overall survival, and time to ACR events. To account for potential unobserved heterogeneity across centers, a gamma-distributed frailty term was included, allowing for random effects by center,^{19,20} implemented using the coxph function from the survival library. The proportional hazards assumption for Cox models was evaluated using the Schoenfeld residuals method. Propensity score matching was used to compare overall survival and rejection-free (death-censored) survival while minimizing baseline differences between treatment groups. Full details of the characteristics and methods used to compare groups can be found in [Supplemental Table 1](#).

To assess for risk factors of severe PGD, a logistic regression was fitted (using statsmodels), with ORs with 95% CIs and *P* values reported. Multicollinearity was assessed using variance inflation factor analysis.

There were no missing data for survival, rates of severe PGD, or ACR. Data for demographic comparisons were missing at random, except for donor and recipient age—with 14 cases (or 2.8% of study participants) from 1 center. The number of available data points is included in [Tables 1 to 3](#).

ETHICS. Centers in the study had appropriate Institutional Review Board approval to take part in the study. These data were anonymous and the need for informed consent was therefore waived. Centers taking part in the study operated under appropriate local jurisdictions.

RESULTS

During the study period, 504 DCD HTs (223 taNRPs, 281 DPPs) were performed in the participating sites.

DONOR DATA. [Table 1](#) shows recipient and donor demographics categorized according to recovery technique. There were no significant differences in donor height, weight, age, sex, or sex mismatched transplants between groups. The median time from transplantation to the censor date was 1,069 days in the DPP group vs 744 days in the taNRP group (*P* < 0.001). The median pre-withdrawal left ventricular ejection fraction for all hearts in this study was 60%. There were a similar number of livers (0.65 vs 0.76; *P* = 0.31) and lungs (0.38 vs 0.48; *P* = 0.37) retrieved per donor in the DPP and taNRP groups. There were significantly more kidneys retrieved per DPP donor, compared with taNRP donors (1.84 vs 1.76; *P* = 0.005).

TABLE 1 Donor Demographics

	DPP	Count	taNRP	Count	P Value
Height, cm	177.80 (171.0-182.9)	281 (100)	175.00 (170.0-182.9)	223 (100)	0.385
Weight, kg	80.00 (70.0-95.8)	281 (100)	79.40 (69.1-90.7)	223 (100)	0.071
Age, y	32.00 (25.0-38.0)	267 (95)	32.00 (23.0-41.0)	223 (100)	0.974
Male	238 (84.3)	281 (100)	185 (83.0)	223 (100)	0.716
Donor: recipient sex					
M:M	200 (71.2)		154 (69.1)		0.625
M:F	37 (13.2)		26 (11.7)		0.685
F:M	17 (6.0)		16 (7.2)		0.718
F:F	27 (9.6)		22 (9.9)		1.000
Donor predicted heart mass, g	198.03 (179.3-219.2)	267 (95)	185.88 (165.4-206.4)	222 (99.6)	<0.001
Median time from transplant to data collection, d	1,069.00 (678.0-1,516.0)	281 (100)	744.00 (542.0-1,074.5)	223 (100)	<0.001
Pre-withdrawal LVEF, %	60.00 (55.0-65.0)	246 (87.5)	60.00 (60.0-65.0)	208 (93.2)	0.001
Kidneys per donor	1.84	261 (92.9)	1.76	191 (85.2)	0.005
Livers per donor	0.65	261 (92.9)	0.76	191 (85.2)	0.31
Lungs per donor	0.38	261 (92.9)	0.48	190 (85.2)	0.37
Cause of death		281 (100)		222 (99.6)	
Anoxia	86 (30.6)		45 (20.2)		
Stroke	74 (26.3)		62 (27.8)		
Trauma	84 (29.9)		83 (37.2)		
Other	37 (13.2)		32 (14.3)		
Unknown	0		1 (0.4)		
Race		276 (98.2)		162 (72.6)	
White	225 (80.1)		141 (63.2)		
Asian	2 (0.7)		1 (0.4)		
Black	30 (10.7)		6 (2.7)		
Hispanic	13 (4.6)		13 (5.8)		
Mixed	3 (1.1)		0		
Other	3 (1.1)		1 (0.4)		
Unknown	5 (1.8)		61 (27.4)		

Values are median (Q1-Q3) or n (%), unless otherwise indicated. Demographic data for all patients in this study. The kidneys, livers, and lungs refer to the average number of kidneys, livers, and lungs that were transplanted from each donor.

DPP = direct procurement and perfusion; F = female; LVEF = left ventricular ejection fraction; M = male; taNRP = thoraco-abdominal normothermic regional perfusion.

OPERATIVE DATA. The DPP group had a significantly shorter FWIT (13 minutes vs 15 minutes; $P = 0.005$) but a significantly longer FTIT (39 minutes vs 15 minutes; $P < 0.001$) compared with taNRP. There was a significantly shorter ex situ perfusion time in taNRP hearts ($n = 23$) preserved with ex situ machine perfusion, compared with the DPP group (184 minutes vs 258 minutes; $P < 0.001$).

RECIPIENT DEMOGRAPHICS. There were significantly fewer taNRP patients on inotropic support pretransplantation (26% vs 36.3%; $P = 0.016$). There were a similar number of patients on pretransplant MCS in both groups (34.2% vs 29.1%; $P = 0.25$, DPP and taNRP groups, respectively). There was no significant difference in the percentage difference in predicted heart mass difference between taNRP and DPP groups (-1.16% vs -0.35% ; $P = 0.62$). Full details on the recipient demographics can be found in the [Supplemental Results](#).

RECIPIENT OUTCOMES. As shown in the [Central Illustration](#), there were no significant differences in post-transplantation median survival probability between taNRP and DPP cohorts at 30 days (97% vs 96%; $P = 0.80$), 1 year (91% vs 88%; $P = 0.10$), or 3 years (85% vs 78%; $P = 0.10$), or across the entire study period (HR: 0.67 [95% CI: 0.43-1.04]; chi-square test = 3.17; $P = 0.08$). To further support this, a mixed-effects Cox model demonstrated that the method of procurement was not significantly associated with overall survival (HR: 0.74 [95% CI: 0.36-1.52]; $P = 0.339$) ([Supplemental Figure 1](#)). However, the subgroup analysis using propensity score matching demonstrated that survival in the taNRP group did indeed differ significantly from the DPP subgroup (chi-square test = 15.69; $P = 0.038$) ([Supplemental Figure 2](#)).

Significantly more patients in the DPP group had severe PGD (19.2% vs 7.6%; $P < 0.001$).

TABLE 2 Intraoperative Data and Recipient Demographics

	DPP	Count	taNRP	Count	P Value
Intraoperative parameters					
Functional warm ischemic time, min	13.00 (11.0-17.0)	226 (80.4)	15.00 (11.0-21.0)	218 (97.8)	0.005
Functional cold ischemic time, min ^a	24.00 (12.0-33.5)	239 (85.1)	N/A		
Functional total ischemic time, min	39.00 (29.8-47.0)	216 (76.9)	15.00 (11.0-21.0)	218 (97.8)	<0.001
Static cold storage, min ^b	N/A		131.50 (69.5-176.5)	200 (100)	
Time on the OCS, min ^c	258.00 (216.0-307.0)	268 (95.4)	184.00 (163.0-221.5)	23 (100)	<0.001
Recipient demographics					
Recipient pulmonary vascular resistance, WU	2.00 (1.4-2.8)	272 (96.8)	1.93 (1.4-2.6)	172 (77.1)	0.330
Height, cm	175.30 (167.6-182.0)	281 (100)	174.00 (163.0-180.0)	223 (100)	0.019
Weight, kg	85.00 (73.5-98.0)	281 (100)	83.00 (72.5-99.0)	223 (100)	0.464
Age, y	53.00 (44.0-61.0)	267 (95)	55.00 (46.0-63.0)	221 (99.1)	0.034
Male	217 (77.2)	281 (100)	196 (88)	223 (100)	0.914
Patients with diabetes	86 (31)	278 (98.9)	101 (45.3)	223 (100)	0.002
Recipient predicted heart mass, g	197.87 (167.1-217.6)	267 (95)	184.75 (159.2-206.6)	221 (99.1)	0.002
Percentage difference between recipient and donor predicted heart mass	-1.16 (-12.9 to 8.4)	267 (95)	-0.5 (-12.3 to 7.7)	221 (99.1)	0.70
Race		278 (98.9)		202 (90.6)	
White	187	(66.5)	167	(74.9)	
Black	66	(23.5)	21	(9.4)	
Asian	16	(5.7)	0	(0)	
Hispanic	6	(2.1)	11	(4.9)	
Mixed	1	(0.4)	2	(0.9)	
Other	8	(2.8)	1	(0.4)	
Unknown	3	(1.1)	21	(9.4)	
Recipient cause of heart failure		281 (100)		220 (98.7)	
Dilated	155	(28.7)	64	(28.7)	
Ischemic	78	(48.4)	108	(48.4)	
Hypertrophic	21	(7.6)	17	(7.6)	
Other ^a	27	(13.9)	31	(13.9)	
Unknown	0	(0)	3	(1.3)	
Preoperative inotropic support (% of patients on at least 1 inotrope)	36.3	280 (99.6)	26.0	222 (99.6)	0.016
Patients requiring MCS pretransplant	96 (34.2)	281 (100)	65 (29.1)	223 (100)	0.25
LVAD	76 (79.1)		59 (90.8)		
BiVAD	9 (9.4)		3 (4.6)		
RVAD	1 (1)		0		
ECMO	4 (4.2)		2 (3.1)		
Impella	3 (3.1)		1 (1.5)		
TAH	1 (1)		0		

Values are median (Q1-Q3) or n (%), unless otherwise indicated. ^ataNRP as a technique does not have a functional cold ischemic time. ^bIn this study, DPP was used exclusively with normothermic ex situ machine perfusion. The use of static cold storage directly after DPP would result in an energy depleted heart being placed on ice with poor outcomes. ^cA subset (21) of taNRP hearts, predominantly from the Royal Papworth Hospital (19), were performed with ex situ machine perfusion. This is not standard practice internationally.

BiVAD = biventricular assist device; ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device; MCS = mechanical circulatory support; N/A = not applicable; OCS = Organ Care System; RVAD = right ventricular assist device; TAH = total artificial heart; other abbreviations as in [table 1](#).

In both groups, the predominant form of post-transplantation MCS was venoarterial extracorporeal membrane oxygenation (92.5% DPP and 88.2% taNRP). A logistic regression model demonstrated that taNRP was associated with a significantly lower incidence of postoperative MCS use (OR: 0.32 [95% CI: 0.18-0.59]; $P < 0.001$) ([Supplemental Figure 3](#)). Further information on recipient outcomes can be found in [Supplemental Table 2](#).

IMMUNOLOGICAL DATA. There was no significant difference in the number of sensitized patients

between groups. The proportion of patients with a calculated panel reactive antibody $>10\%$ was 17.4% and 14.3% ($P = 0.46$), and $>80\%$ was 2.9% and 2.3% ($P = 0.78$) in the DPP and taNRP groups, respectively. There was no significant difference in the development of de novo donor-specific anti-HLA antibodies 15.6% vs 12% between the DPP and taNRP groups ($P = 0.192$).

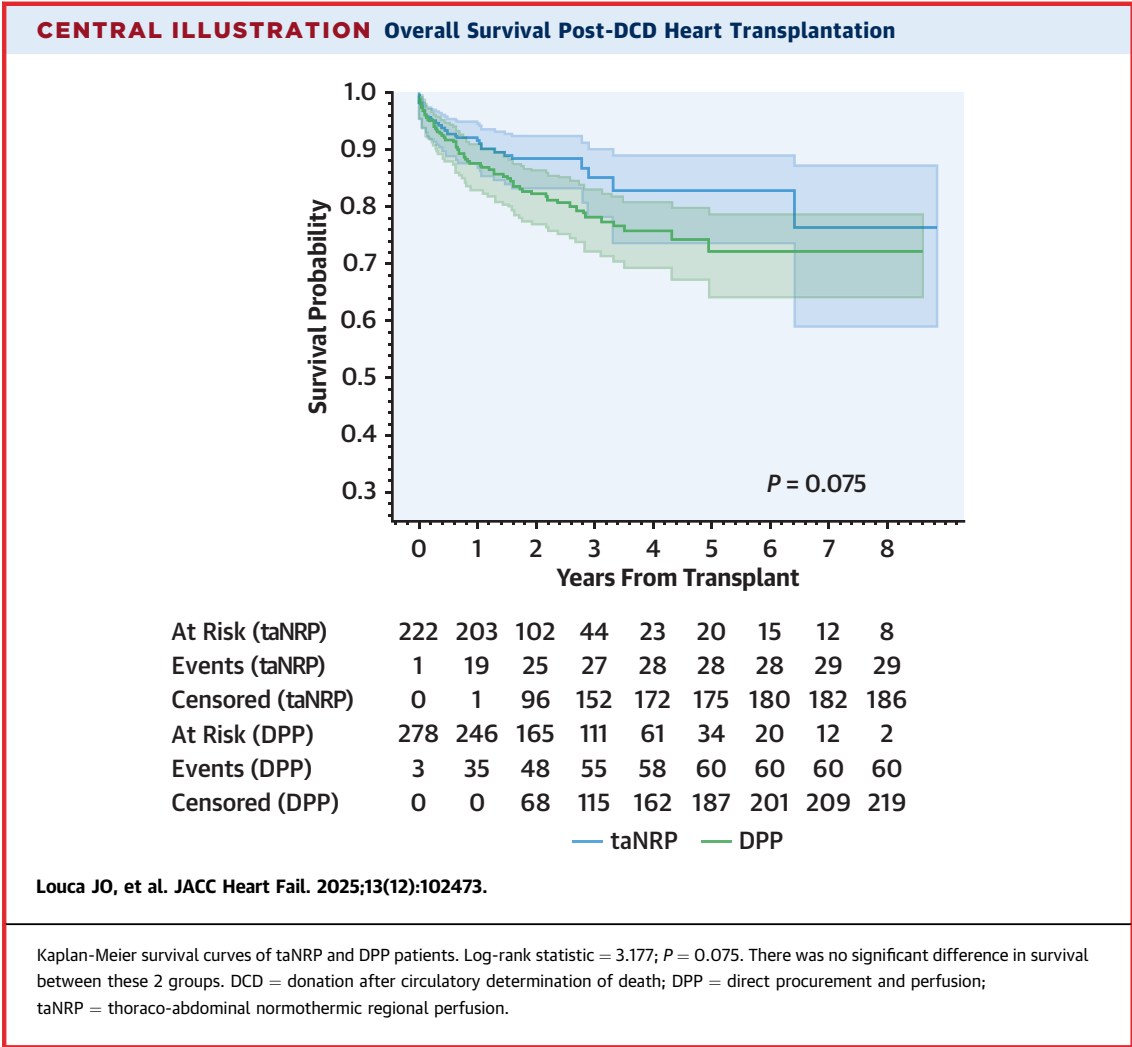
The DPP group had a significantly higher rate of treated ACR in the first year post-transplantation as shown in [Table 3](#). Death-censored, rejection-free

TABLE 3 Recipient Outcomes and Immunological Data

	DPP	Count	taNRP	Count	P Value
Survival at 30 d, %	96 (93-98)	281 (100)	97 (93-98)	223 (100)	0.8
Survival at 1 y, %	88 (83-91)	281 (100)	91 (87-94)	223 (100)	0.16
Survival at 3 y, %	78 (72-83)	136 (100)	85 (78-90)	50 (100)	0.1
Postoperative MCS	54 (19.2)	281 (100)	17 (7.6)	223 (100)	<0.001
ECMO	50 (92.6)		15 (88.2)		
RVAD	4 (7.4)		2 (11.8)		
Ventilator hours	41.00 (18.0-86.0)	273 (97.2)	18.4 (12.0-35.6)	198 (88.8)	<0.001
ICU stay, d	7.00 (5.0-12.0)	272 (96.8)	7.00 (4.7-12.0)	196 (87.9)	0.808
LVEF at 1 mo	57.50 (55.0-63.5)	261 (96.3)	63.80 (59.0-67.0)	212 (98.1)	<0.001
LVEF at 12 mo	57.45 (55.0-62.5)	238 (96.7)	61.00 (56.0-65.0)	193 (94.6)	<0.001
TAPSE at 1 mo, mm	11.00 (8.0-13.0)	237 (87.5)	13 (10-15.9)	169 (78.2)	<0.001
TAPSE at 1 y, mm	12.50 (10.0-15.0)	224 (91.1)	14 (11-16.75)	165 (80.9)	0.008
Proportion of patients with eGFR >60 mL/min/1.73 m ² at time of transplantation ^a	56.2	274 (97.5)	65.5	221 (99.1)	0.063
Proportion of patients with eGFR >60 mL/min/1.73 m ² at 1 year post-transplantation ^a	28.8	238	33.6	191	0.269
Immunological data					
Total number of ACRs requiring treatment in first year	105	281 (100)	34	223 (100)	
2R ACR in first year	99		34		
3R ACR rejection in first year	6		0		
Patients who had an episode of acute rejection requiring treatment in the first year	71 (25.3)		29 (13)		<0.001
Rejection rates requiring treatment per patient (defined as total number of rejection episodes/N × 100)	37.4		15.2		<0.001
Patients with ≥2 episodes of rejection, %	7.5		1.8		<0.001
Total number of biopsies/cf-DNA in year 1—according to routine surveillance schedule	2,642	281 (100)	1,423	223 (100)	
Average number of surveillance tests in year 1 per patient ^a	9.4		6.38		<0.001
Rejections per surveillance test, rate in first year of transplant according to routine schedule ^a	4		2.4		0.002
Rate of patients with at least 1 episode of rejection per surveillance test	2.6		2		0.243
Patients having their first episode of acute rejection in first 6 mo of operation	61 (21.7)		26 (11.7)		0.003
Patients having their first episode of acute rejection between 6 mo and 12 mo postoperative	10 (3.6)		3 (1.3)		0.16
Patients with panel reactive antibody/calculated reaction frequency >10%	49 (17.6)	279 (99.2)	32 (14.9)	215 (96.4)	0.463
Patients with panel reactive antibody/calculated reaction frequency >80%	8 (2.9)	279 (99.2)	5 (2.3)	215 (96.4)	0.78
Patients with de novo donor-specific anti-HLA antibodies post-transplantation at any point	43 (15.6)	275 (97.9)	25 (12)	208 (93.4)	0.192
Recipients who are CMV positive, %	41.3	274 (97.5)	28.3	223 (100)	0.001
Immunosuppressant use		281 (100)		223 (100)	
Patients who received induction therapy	242 (86)		126 (57)		<0.001
ATG	98 (40.5)		33 (26.2)		
Basiliximab	104 (43)		84 (66.7)		
ATG + Basiliximab	40 (16.5)		9 (7.1)		
Ever on a calcineurin inhibitor	271 (97.9)	277 (98.6)	217 (97.3)	223 (100)	0.148
Ever on mycophenolate mofetil	224 (79.7)	281 (100)	216 (96.9)	223 (100)	<0.001
Ever on an mTOR inhibitor	58 (21.4)	272 (96.8)	70 (31.4)	223 (100)	0.024
Ever on steroids	281 (100)	281 (100)	222 (99.6 ^a)	223 (100)	0.44

Values are median (Q1-Q3) or n (%), unless otherwise indicated. ^aThe predominant surveillance screening test was biopsy; 23 of the 504 cases were routinely screened with cf-DNA throughout the first year.

ACR = acute-cellular rejection; ATG = antithymocyte globulin; cf-DNA = circulating free DNA; CMV = cytomegalovirus; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; mTOR = mammalian target of rapamycin; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in [Tables 1 and 2](#).



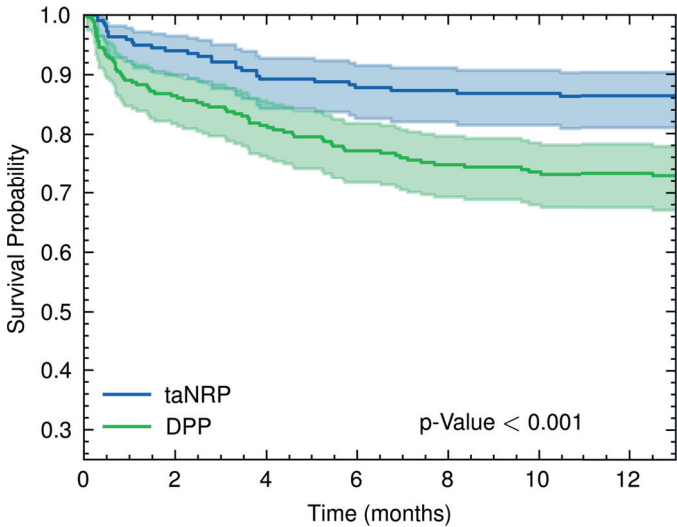
survival was significantly higher in the taNRP group compared with DPP (HR: 0.45 [95% CI: 0.30-0.69]; chi-square test = 14.45; $P < 0.001$) (Figure 1). In addition to this, the subgroup analysis of the propensity score-matched group demonstrated a significant difference in rejection-free survival between taNRP and DPP subgroups (chi-square test = 15.69; $P < 0.001$) (Supplemental Figure 4). A Cox model further demonstrated that death-censored, rejection-free survival was significantly higher in the taNRP group (HR: 0.53 [95% CI: 0.31-0.90]; $P = 0.02$) (Supplemental Figure 5).

There were significant differences in immunosuppression between the 2 groups. Mycophenolate mofetil (MMF) utilization was higher in the taNRP group during the whole study (96.9% vs 79.7%; $P < 0.001$). Mammalian target of rapamycin inhibitor (mTORi) utilization was higher in the taNRP cohort overall (31.4% vs 21.4%; $P = 0.024$). Subgroup analysis

of rejection rates of patients who were only on MMF demonstrated higher rejection rates in the DPP group ($P < 0.001$) (Supplemental Figure 6). However, there was no significant difference in rejection rates in the subgroup of patients on mTORi ($P = 0.086$) (Supplemental Figure 7).

A subgroup comparison of centers performing both techniques supported the preceding findings. See Supplemental Figures 8 and 9 for further information on survival and death-censored rejection free survival in this subgroup. See Supplemental Tables 3 to 5 for further information on donor, operative, and recipient demographics in this subgroup. We accounted for differences in outcomes over time by comparing the first half of cases in each center compared to the second half. There was no significant difference in survival or death-censored rejection free survival in either the taNRP or DPP groups (Supplemental Figures 10 to 13).

FIGURE 1 Death-Censored Rejection-Free Survival in the First Year Post-Transplantation



Month	0	1	2	3	4	5	6	7	8	9	10	11	12
At Risk (taNRP)	222	207	200	195	188	187	182	181	179	178	178	177	175
Events (taNRP)	0	9	13	17	23	23	26	27	27	28	28	29	29
Censored (taNRP)	1	7	10	11	12	13	15	15	17	17	17	17	19
At Risk (DPP)	278	241	230	223	212	205	199	195	189	186	181	179	179
Cumulative Events (DPP)	0	30	37	42	50	55	61	64	67	68	70	71	71
Censored (DPP)	3	10	14	16	19	21	21	22	25	27	30	31	31

Death-censored rejection-free survival after heart transplantation in the first year post-transplantation. The log-rank statistic = 14.45; $P < 0.001$. DCD = donation after circulatory determination of death; DPP = direct procurement and perfusion; taNRP = thoraco-abdominal normothermic regional perfusion.

DISCUSSION

This study is the largest international multicenter observational study to examine outcomes in DCD HT comparing DPP and taNRP donor heart procurement methods. In this study, post HT survival was similar in taNRP and DPP recipients. Recipients in the taNRP cohort also had a significantly lower rate of severe PGD and a lower rate of ACR.

SURVIVAL POST-DCD HT. Recipients in our study had 1-year median survival probability of 91% in taNRP and 88% in DPP, and median 3-year survival probability of 85% in taNRP and 78% in DPP groups. This is comparable to the 1-year post-transplant survival (93.1% for normothermic regional perfusion vs 91.1% for DPP; $P = 0.79$) reported in the U.S. observational study.¹¹

Previous studies have reported no significant difference in survival between recipients of DCD and DBD HT in the short to midterm.^{6,7} One- and 3-year survival in our study are similar to DBD HT recipients as reported in the ISHLT registry (1-year 85.8%, 3-year 79.76%).¹ In the propensity score-matched groups, the taNRP group was associated with improved survival. However, given the retrospective nature of this study, there is a need for a randomized controlled trial (RCT) before any definitive conclusions on survival can be made.

SEVERE PGD. In this study, the rate of severe PGD was 14.1%. In the U.S.-based RCT comparing DPP DCD with DBD HT, Schroder et al⁷ reported a severe ISHLT PGD rate of 15% in the DCD group. The rate of MCS use post-transplantation was significantly higher in the DPP group compared with the taNRP group. In our study, there were no significant differences in the mean predicted heart mass difference between groups with similar proportions of sex-matched transplants. However, the DPP group had longer preservation times and a greater proportion of recipients on pretransplant inotropic support. These may have contributed to the higher rate of severe PGD in the DPP group. Indeed, a logistic regression estimating factors predicting PGD demonstrated that both use of DPP and use of preoperative inotropic support were associated with an increased risk of PGD in this study (Supplemental Figure 3).

We have previously proposed that the mechanism of PGD development after DCD cardiac transplantation is cardiac stunning due to the ischemic time.⁸ Indeed, in this study the DPP group had a significantly longer FTIT. Alternatively, it may be that the use of normothermic perfusion (ex situ machine perfusion) results in higher rates of reversible PGD. Hearts perfused ex situ demonstrate deterioration in both systolic and diastolic function.²¹⁻²³ The reasons for this are unclear and likely multifactorial. Hearts perfused ex situ accumulate edema, which resolves soon after implantation. Moreover, these hearts demonstrate an inflammatory state ex situ, due to a variety of factors, including the interaction between blood and plastic tubing.^{22,23} This may result in a reversible “cardiomyopathy” in some hearts procured with DPP.

There was no difference in survival at 1 and 3 years in the DPP group despite the higher severe PGD rate. The lower rates of severe PGD in the taNRP group are similar to those in DBD HT and may represent a potential advantage of taNRP over DPP.⁶ The long-term effect of severe PGD in DCD HT requires further investigation.

RATES OF ACR. In the DPP group, 25.3% of patients had an episode of ACR requiring escalation of immunosuppression in the first year. Recipients in the taNRP group had a significantly lower rate of ACR, as seen in [Figure 1](#). An ACR rate of ~30% has been previously reported in studies using DPP hearts.^{12,24} The rate of ACR in the taNRP group was only 13% in the first year, similar to the rate that has previously been reported in taNRP and DBD recipients.^{1,6,25} Rejection was higher during the first 6 months but not between 6 and 12 months post-transplantation in the DPP group. This higher rejection rate in the DPP group cannot be attributed to differences in recipient sensitization or de novo donor-specific anti-HLA antibody formation. The higher rate of rejection in the DPP group compared with the taNRP group persisted in a sensitivity analysis of only patients who were treated with MMF ($P < 0.001$). There was no significant difference in rejection rate between DPP and taNRP patients in a sensitivity analysis of only patients who were with an mTORi, but the number of patients in this comparison was low. taNRP was also associated with an increased rejection-free survival in the propensity score-matched group, further supporting the notion that taNRP is associated with lower rates of rejection.

The DPP cohort had a significantly higher rate of routine biopsy due to differing surveillance biopsy schedules between the centers. However, the taNRP group still had a significantly lower rate of ACR per surveillance test, suggesting that the difference between the 2 groups was not only due to the difference in biopsy schedule, but also due to a method-specific difference.

It is our supposition that taNRP exerts a protective effect on the endothelium. It may be that the longer FTIT in DPP, or alternatively the inflammatory milieu the heart is exposed to during machine perfusion results in greater endothelial damage with subsequent exposure of donor antigens to the recipient immune system.

RATES OF ORGAN UTILIZATION. Data from abdominal normothermic regional perfusion suggest that in situ perfusion offers benefits both for organ function and organ utilization, with a greater number of organs used *per* donor as well as a lower incidence of delayed graft function in kidneys and a lower rate of ischemic cholangiopathy in livers.²⁶⁻²⁹ Moreover, taNRP can be performed with SCS, meaning that there is a reduced need for expensive and complicated ex situ perfusion machines.³⁰

Importantly, this study suggests that taNRP does not affect the rate of lung utilization in DCD donors.

It also had no effect on the rates of liver transplantation. However, lower rates of kidneys were recovered. The lower utilization of kidneys may be explained by the fact that this is a specific subset of taNRP donors, that is, all individuals who also had their hearts retrieved and transplanted. It is worth noting that these data contrast with what has previously been published regarding taNRP and kidney utilization.^{26,29,31}

There are limited data on the outcomes of lung transplants following NRP. Two single-center studies showed no impairment in lung function post-transplantation from taNRP donors, although the cohort sizes were small.^{32,33} Twenty-eight taNRP lung cases from the Spanish experience demonstrated significantly lower rates of PGD than lungs procured during abdominal normothermic regional perfusion.³⁴

HOSPITAL STAY AND HEART FUNCTION POST-TRANSPLANTATION. taNRP recipients spent less than half the amount of time on mechanical ventilation postoperatively in comparison with DPP patients. This most likely represents the higher dependence on MCS in the DPP group and associated greater time on ventilator support. However, median intensive care unit duration was 7 days in both groups, suggesting a similar recovery overall in most patients. Although there were small numerical differences in recipient heart function on echocardiogram between these groups, these were unlikely to have been of clinical significance.

DIFFERENCES IN PRESERVATION TIME. One potential confounding factor that we were not able to address is the difference in preservation times. Hearts procured with DPP were on average associated with longer times on the OCS (Organ Care System) than hearts procured with taNRP with SCS. This may suggest a paradigm, where hearts procured close to the implanting center can use taNRP and hearts that will be procured from distant centers may use taNRP with the OCS.

ETHICAL CONSIDERATIONS. Although taNRP shows potential in DCD HT, its widespread adoption is limited by a combination of logistic issues and ethical concerns regarding violation of the dead donor rule by restarting cerebral perfusion. There is a moratorium on the technique in Belgium and the United Kingdom and is prohibited in Australia, Canada, and many parts of the United States. Groups from both Europe and the United States are investigating the issue of cerebral perfusion during taNRP.³⁵⁻³⁷

STUDY STRENGTHS. This paper is the largest paper on DCD HT with 504 characterized cases and provides

the granularity of data necessary to understand the reasons for differences between these 2 groups. Moreover, the median follow-up of 2.4 years enables examination of short- and medium-term outcomes. This study is also the first to compare taNRP with DPP on a large international scale, providing novel insights into the differences between these 2 techniques. Last, this study is less susceptible to the effects of selection bias, due to the overall similarity between DPP and taNRP for both recipient and demographic outcomes. Further to this, the use of propensity score-matching analyses and mixed-effects Cox models has helped further mitigate the consequences of inherent selection bias.

STUDY LIMITATIONS. Because of the observational nature of this study, it is impossible to determine if there are causal relationships between variables and outcomes. There are missing data for certain variables and these data are not necessarily missing at random. Several variables such as panel reactive antibody and recipient pulmonary vascular resistance were not measured in the same way at all participating centers. Furthermore, some of these data have been previously published;^{6,12,38,39} however, this study has expanded the follow-up time as well as the number of patients, centers, and variables collected.

In common with most similar studies, use of MCS after HT was used as an indicator of severe PGD. We acknowledge that mild and moderate PGD were not measured, and we suspect that a proportion of severe PGD may represent secondary graft dysfunction. FWIT was defined as systolic <50 mm Hg in all centers in this study, except those in Spain who used a definition of systolic <60 mm Hg. This study did not collect data on implant times, which represents an additional period of warm ischemia.

Centers differed in the number and timing of surveillance biopsies performed, and reporting pathologists were center-specific. Two centers also used donor-derived cell-free DNA for surveillance. These factors could affect the likelihood of identifying significant ACR. However, our analysis of rejection per surveillance test showed no change to our findings. Harmonizing schedule for surveillance biopsies in participating centers and having a pathological core laboratory would be required to avoid these biases in any future prospective study.

This study does not include donor cytomegalovirus data, which may confound the differences in ACR rates between the 2 groups. This study also did not

capture the number of hearts that were retrieved but not transplanted from both taNRP and DPP donors. There are limited published data on the turn-down rates of DCD donor hearts; however, a preliminary analysis from the United States has demonstrated a significantly lower turn-down rate for taNRP hearts compared with DPP.⁴⁰

Severe PGD has associated morbidity, which may impact patient quality of life. However, we did not collect any quality-of-life metrics in our study. There is a need for a unified method of quantifying and collecting quality-of-life data post-transplantation.

CONCLUSIONS

In DCD HT, recipients with hearts retrieved using taNRP had a lower rate of severe PGD and ACR in comparison with those retrieved using DPP. An RCT is needed to definitively compare these 2 methods of DCD heart procurement.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In an international retrospective study, taNRP was associated with lower rates of severe primary graft dysfunction and biopsy proven acute rejection. There is a need for a prospective study to further investigate these findings.

TRANSLATIONAL OUTLOOK: This retrospective, international, multicenter study suggests that taNRP is associated with lower rates of biopsy-proven ACR and severe PGD. This study adds to the published data where, until this point, there have been only small single-center comparisons on DPP vs taNRP or large database studies without sufficient granularity to understand the nuances between DPP vs taNRP. An RCT is needed to further understand the differences between these 2 techniques.

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APPENDIX For expanded Methods and Results sections as well as supplemental figures and tables, please see the online version of this paper.