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Post-transplant survival after normothermic regional perfusion versus direct procurement and perfusion in donation after circulatory determination of death in heart transplantation

Gege Ran, BA,[a] Anji E. Wall, MD, PhD,[b] Nikhil Narang, MD,[c,d] Kiran K. Khush, MD, MAS,[e] Jordan R.H. Hoffman, MD, MPH,[f] Kevin C. Zhang, MS,[g] and William F. Parker, MD, PhD[g,h,i,1]

From the [a]Pritzker School of Medicine, University of Chicago, Chicago, Illinois; [b]Department of Transplant Surgery, Annette C. and Harrold C. Simmons Transplant Institute, Baylor University Medical Center, Dallas, Texas; [c]Department of Cardiology, Advocate Christ Medical Center, Chicago, Illinois; [d]Department of Medicine, University of Illinois-Chicago, Chicago, Illinois; [e]Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, California; [f]Division of Cardiothoracic Surgery, University of Colorado, Aurora, Colorado; [g]Department of Medicine, University of Chicago, Chicago, Illinois; [h]Department of Public Health Sciences, University of Chicago, Chicago, Illinois; and the [i]MacLean Center for Clinical Medical Ethics, University of Chicago, Chicago, Illinois.

KEYWORDS:
normothermic regional perfusion;
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BACKGROUND: Since 2019, the annual transplantation rate of hearts donated following circulatory death (DCD) has increased significantly in the United States. The 2 major heart procurement techniques following circulatory death are direct procurement and perfusion (DPP) and normothermic regional perfusion (NRP). Post-transplant survival for heart recipients has not been compared between these 2 techniques.

METHODS: This observational study uses data on adult heart transplants from donors after circulatory death from January 1, 2019 to December 31, 2021 in the Scientific Registry of Transplant Recipients. We identified comparable transplant cases across procurement types using propensity-score matching and measured the association between procurement technique and 1-year post-transplant survival using Kaplan-Meier and Cox proportional hazards model stratefied by matching pairs.

RESULTS: Among 318 DCD heart transplants, 216 (68%) were procured via DPP, and 102 (32%) via NRP. Among 22 transplant centers that accepted circulatory-death donors, 3 used NRP exclusively, and 5 used both procurement techniques. After propensity-score matching on recipient and donor factors, there was no significant difference in 1-year post-transplant survival (93.1% for NRP vs 91.1% for DPP, $p = 0.79$) between procurement techniques.

CONCLUSIONS: NRP and DPP procurements are associated with similar 1-year post-transplant survival. If NRP is ethically permissible and improves outcomes for abdominal organs, it should be the preferred procurement technique for DCD hearts.

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Reprint requests: William F. Parker, MD, PhD, Department of Medicine, University of Chicago, 5841 S Maryland Avenue, MC 6076, Chicago, IL 60637.
E-mail address: wparker@uchicago.edu.
[1] twitter handle: @WF_Parker

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Heart transplantation is a life-saving procedure for end-stage heart disease; however, suitable donor hearts are scarce. Traditionally, heart transplantation was only performed following brain death (DBD) to enable in-situ assessment of cardiac function. From 2019 to 2021, the annual utilization of hearts donated following circulatory death (DCD) has increased from 0.2% to 5.4% in the United States.[1-5] DCD hearts are procured using 1 of 2 methods. In direct procurement and perfusion (DPP) following declaration of death, the donor's heart is immediately cannulated and at least 1,200 ml of autologous blood is removed. The heart is then flushed with a cold preservation solution, excised, and placed on an extracorporeal perfusion and preservation system.[6] During this time, the other organs experience warm ischemia before they can be procured via super rapid recovery. An alternative to DPP is normothermic regional perfusion (NRP). In this method, the procuring team performs central cannulation followed by oxygenated perfusion of both the thoracic and abdominal organs using a modified extracorporeal membrane oxygenation circuit while diverting blood flow away from cerebral circulation.[6-8]

NRP may have several advantages to DPP in DCD heart transplantation. First, NRP is associated with increased rates of donor heart organ utilization compared to DPP, presumably because the process of reanimation of the heart during NRP allows for a better assessment of organ function before procurement.[9,10] Second, NRP substantially reduces warm ischemic time for the other organs and may better reverse injury from warm ischemia than ex vivo perfusion.[11,12] NRP has been shown to decrease rates of delayed graft kidney function, suggesting that NRP may improve long-term outcomes for abdominal organ recipients compared with DPP and super rapid recovery.[1,7,12-16]

However, NRP is ethically controversial. Some argue that the resumption of cardiac activity and perfusion of the thoracic and abdominal organs reverses the permanence of circulatory arrest used to declare the donor dead.[17] Others argue that NRP is permissible since it does not lead to a spontaneous resumption of circulation and enables more patients and families to fulfill their wishes of organ donation in the setting of circulatory arrest. If NRP is permissible and provides better outcomes for abdominal organ recipients and equivalent outcomes for thoracic organ recipients, it would be ethically obligatory to use this procedure over DPP. In this observational study, we quantified the adoption of NRP and DPP heart procurement techniques across the United States and determined the association of procurement technique with post-transplant survival.

Methods

Data source and study period

We used data from the Scientific Registry of Transplant Recipients (SRTR)—a registry that includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. Since this was a secondary analysis of a prospectively obtained de-identified cohort, this study was deemed exempt by the University of Chicago Institutional Review Board.

We identified all adult patients who received a heart-only transplant of a DCD organ between January 1, 2019 and December 31, 2021, using the March 2023 version of the SRTR dataset. We selected our cohort so that each recipient had at least 1 year of follow-up to reduce the risk of ascertainment bias from informative censoring.[18,19] We excluded recipients who were less than 18 years of age at the time of transplantation, had an inactive listing status, had an outdated candidate listing status at the time of transplant, or had incomplete information on important outcomes or explanatory variables (described below).

Determining procurement methodology

Since UNOS does not collect organ procurement practice for each transplant procedure, we used a method developed by Wall et al[7] to distinguish between NRP and DPP. Due to the rapid nature of DPP, the time from the declaration of circulatory death to the time of aortic cross-clamping is significantly shorter in DPP cases compared to NRP cases. This creates a clear discontinuity in the distribution of death-to-cross-clamp time among DCD transplants (Figure 1). We considered DCD transplants with a death-to-cross-clamp time of 30 minutes or less as having undergone DPP, and those with greater than 30 minutes of death-to-cross-clamp time as having undergone NRP.

Primary outcome: Death after heart transplantation

The primary outcome of this study was post-transplant survival. Post-transplant deaths were limited to those verified by the OPTN, which has been recently shown to be sufficient for 1-year post-transplant outcomes. Recipients who remained alive were censored at the last follow-up date.

Donor and recipient covariates

To compare baseline differences between recipients of hearts procured via NRP versus DPP, we included components of the index for mortality prediction after cardiac transplantation (IMPACT) score, which predicts post-transplant survival in the recipient: recipient age, sex, race, serum bilirubin, dialysis between listing and transplant, heart failure etiology, history of infection in the pre-transplant period, treatment with an intra-aortic balloon pump, temporary circulatory support, or left-ventricular assistive device before transplant.[20] Additionally, we included each recipient's blood type, body mass index (BMI), cardiac output, pulmonary capillary wedge pressure, and

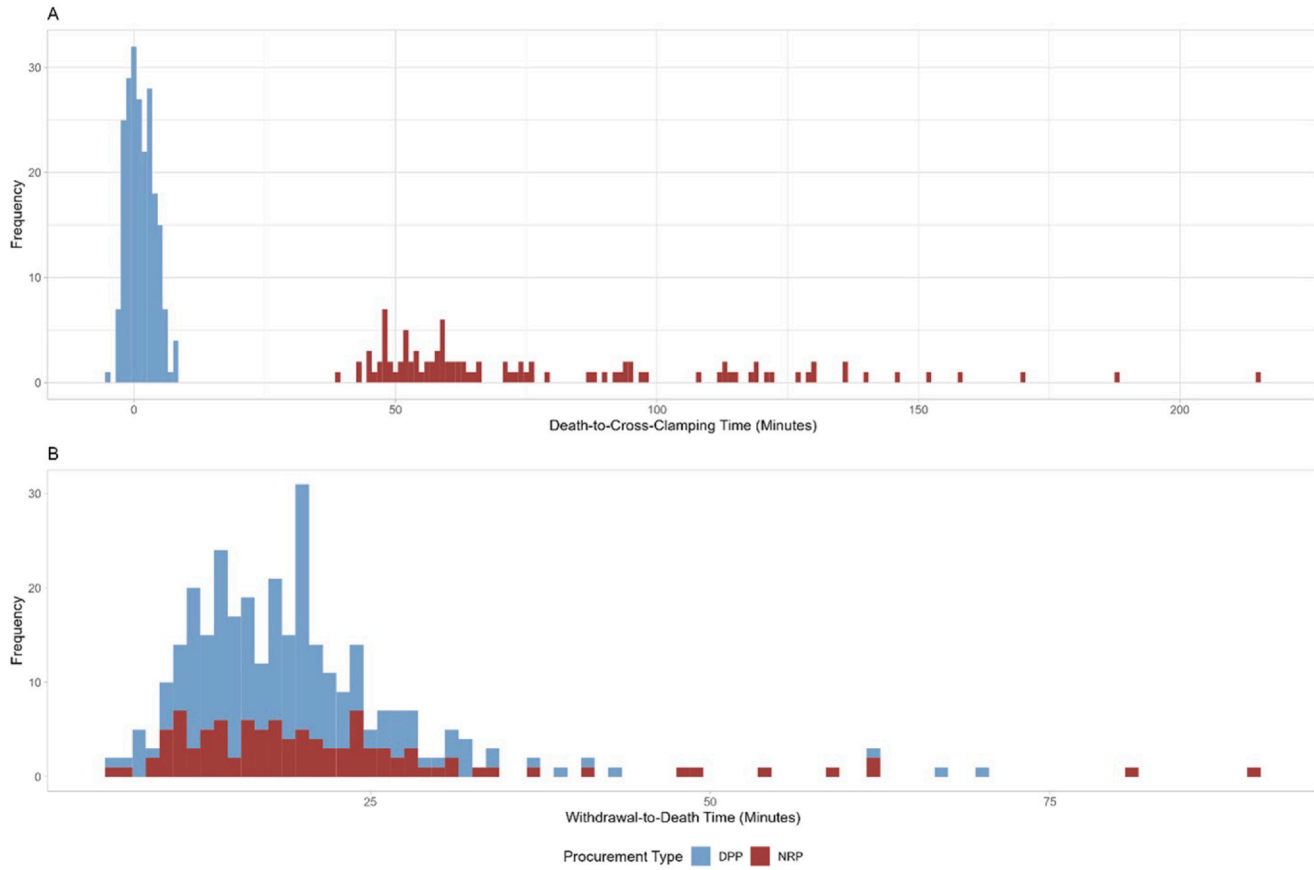

Figure 1 Death-to-clamp time and withdrawal-to-death time by organ procurement type. Distribution of death-to-cross-clamp (A) and withdrawal-to-death time (B) among donated following circulatory death donors, stratified by technique of organ procurement (DPP or NRP). Color indicates the most likely organ procurement technique employed based on discontinuity in the distribution. DPP, direct procurement and perfusion; NRP; normothermic regional perfusion.

functional status as potential factors that may confound the association between procurement technique and post-transplant survival.

We also included donor characteristics that have been shown to influence post-heart transplantation survival, including donor age, sex, and history of smoking.[21] We also considered donor characteristics potentially associated with utilization: donor blood type, BMI, left-ventricular ejection fraction, nucleic acid amplification testing results for hepatitis C virus, and duration of time between withdrawal of life support and proclamation of death (withdrawal-to-death time).

NRP and DPP heart transplant center characteristics

For each transplant center that utilized a DCD donor heart during the study period, we calculated the number of procurements done via DPP and NRP. Additionally, we calculated the distance between donor and recipient hospitals using the haversine formula.[22]

Statistical analysis

We compared differences in the baseline characteristics of donors and recipients with each procurement technique using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

We performed 1:1 propensity-score matching to identify DPP donor-recipient pairs that were similar to the NRP donor-recipient pairs. After examining baseline characteristics potentially influencing organ procurement practice and/or post-transplant survival (see Supplement for alternative propensity-score models), we selected the 5 to maximize the number of matches between DPP and NRP transplants while maximizing comparability between the 2 cohorts. We included the recipient's age and recipient's treatment at the time of transplantation to control for confounding by transplant center candidate selection practices. We included donor age, donor BMI, and time from withdrawal of life support to declaration of death (WDT) to control for differences in transplant center donor utilization practices. We compared nearest neighbor, optimal pair, and optimal full match methods to identify the method that produced the best covariate balance. In optimal pair matching, each NRP organ recipient is paired with one or more DPP recipients to minimize the sum of the absolute pair distances in the matched sample. We considered the propensity-score match successful if the standardized mean difference of each covariate was under 10% after matching. As a sensitivity analysis, we fitted multiple alternative

propensity-score matching models, including one using all variables in the IMPACT score and donor risk index, both of which are validated prediction scores for post-transplant survival.[20,23]

We estimated survival during the first year after transplant for the NRP and DPP heart recipients with the Kaplan-Meier method for both the unmatched and propensity score-matched cohorts. We also computed restricted mean survival time (RMST) using a time limit (tau) of 365 days (average days survived in the first year) for both groups. After computing the ratio of RMST between NRP and DPP groups, we determined whether the ratio is statistically different from 1 using Z test.

Next, we estimated the hazard ratio of NRP versus DPP with a Cox proportional hazards model on the entire unadjusted cohort, and on the propensity score-matched cohort stratified by matching pairs.[24]

All analyses were performed using RStudio 4.3.2 (R Foundation for Statistical Computing). Significance tests were 2-sided with a p-value threshold of <0.05. The complete statistical code necessary to reproduce the study results is available online.[25]

Results

Donor and recipient characteristics by procurement type

During the study period, there were 319 DCD heart transplants performed in the United States. Among DCD donors, DPP was used for 216 (68%) procurements and NRP for 102 (32%, $p < 0.001$). Table 1 compares the donor and recipient characteristics between heart transplants performed using these 2 procurement techniques. Recipients of NRP organs were older, with 51% being over 60 years of age compared to 37% in DPP recipients ($p = 0.01$). NRP recipients were more likely to have a waitlist status of 4, 5, or 6 (73% vs 57%, $p = 0.01$) and have better functional status (50% with limited impairment vs 25% in DPP, $p < 0.001$).

With a few exceptions, donors had similar demographic and clinical characteristics regardless of the procurement technique used ($p > 0.05$). As expected, there was a large discontinuity in death to cross-clamp times (Figure 1A), with no values between 9 and 39 minutes recorded. While the median time from WDT did not differ significantly between DPP and NRP cases by the Wilcoxon rank-sum test (Table 1), maximum WDT tended to be longer among donors of NRP organs, with the maximum time being 90 minutes in NRP cases and 79 minutes in DPP cases. (Figure 1A).

Patterns in the use of NRP and DPP procurement

The use of NRP and DPP for DCD heart procurement varied greatly across transplant centers (Figure 2). Among 22 transplant centers that performed DCD heart transplantation during the study period, 5 used a mixture of DPP and NRP, 14 used DPP exclusively, and 3 used NRP exclusively. As shown in Figure 3, DPP organs were transported across a greater distance (mean = 457NM) than NRP organs (273NM) (p-value < 0.001).

Post-transplant survival by procurement type

In unmatched cohorts (Figure 4), the unadjusted 1-year KM estimated survival rate was not significantly different between procurement types (93.5% for NRP vs 93.2% for DPP, $p = 0.8$ by 2-sample Z test for proportions).

Balance diagnostics identified optimal pair matching as the highest-performing method, and the final propensity-matched cohorts consisted of 102 NRP transplants and 102 DPP transplants with standardized differences of $<10\%$ for all covariates (Figure S1, Table S1). One-year post-transplant survival was similar (93.1% for NRP vs 91.1% for DPP, $p = 0.79$ by 2-sample Z test for proportions). The RMST of NRP recipients was 346 days (95% confidence interval: 332-361 days), and 339 in the DPP group (95% CI: 323-354 days, $p = 0.52$). There was no significant difference in risk of post-transplant death between procurement types in the unadjusted full cohort (HR = 0.9 for NRP, 95% CI: 0.37-2.19) or the propensity score-matched cohort (HR = 0.739, 95% CI: 0.31-1.79) after stratifying by matching pairs (Table 2, Tables S2-S3).

In our sensitivity analyses ($n = 204$, NRP = 102 and DPP = 102), where distance between donor and recipient hospitals, recipient functional status, components of the IMPACT, and the donor risk score is added to the propensity score model, there was no significant difference in 1-year survival between matched DPP and NRP cohorts (Figures S2-S7).[20,23]

Discussion

In this study, we directly compared 1-year survival estimates for NRP versus DPP procurement techniques for adult US DCD heart transplants performed during 2019-2021. Fewer transplant centers used NRP than DPP, and hearts procured via NRP travel shorter distances compared to those procured via DPP. After propensity-score matching on recipient characteristics (age and intensity of treatment before transplant) and donor characteristics (time between withdrawal of life support to circulatory death, age, and BMI), we found no significant association between choice of procurement technique and 1-year post-transplant survival.

Transplant centers historically used DCD to expand donor access to patients who had lower priority or access in the organ allocation system (e.g., higher BMI, blood type O, and durable LVAD support).[1,4,6,26] Our results confirm that from 2019 to 2021, the use of DCD hearts remained concentrated in this recipient population, but given recent results DCD heart transplantation will likely become a standard option for the average candidate. A recent multicenter, randomized control trial demonstrated similar 6-

Table 1 DCD Heart Donor and Recipient Characteristic by Procurement Technique

Cohort characteristics	DPP ($n = 216$)	NRP ($n = 102$)	*P*-value
Recipient characteristics			
Recipient age over 60 (%)	77 (35.6)	52 (51.0)	0.01
Waitlist status at transplant (%)			0.01
Status 1	1 (0.5)	2 (2.0)	
Status 2	49 (22.7)	8 (7.8)	
Status 3	44 (20.4)	19 (18.6)	
Status 4	82 (38.0)	48 (47.1)	
Status 5	3 (1.4)	2 (2.0)	
Status 6	37 (17.1)	23 (22.5)	
Recipient Serum bilirubin (mg/dl)	0.70 [0.50, 1.10]	0.60 [0.46, 0.80]	0.019
Recipient on dialysis before transplant (%)	3 (1.4)	1 (1.0)	1
Recipient male sex (%)	166 (76.9)	81 (79.4)	0.667
Heart failure etiology (%)			0.22
Idiopathic cardiomyopathy	78 (36.1)	39 (38.2)	
Ischemic cardiomyopathy	57 (26.4)	36 (35.3)	
Congenital heart disease	6 (2.8)	2 (2.0)	
Other	75 (34.7)	25 (24.5)	
Recipient pretransplant infection (%)	9 (4.2)	1 (1.0)	0.240
Treatment received immediately before transplant (%)			0.012
ECMO	1 (0.5)	0 (0.0)	
Exception	55 (25.5)	12 (11.8)	
High-dose inotropes	3 (1.4)	1 (1.0)	
IABP	12 (5.6)	2 (2.0)	
Low-dose inotropes	6 (2.8)	9 (8.8)	
LVAD	76 (35.2)	37 (36.3)	
None	54 (25.0)	38 (37.3)	
Other MCS	9 (4.2)	3 (2.9)	
Recipient race (%)			0.058
American Indian or Alaska Native	1 (0.5)	0 (0.0)	
Asian	3 (1.4)	4 (3.9)	
Black or African American	54 (25.0)	15 (14.7)	
Hispanic/Latino	9 (4.2)	8 (7.8)	
Multiracial	1 (0.5)	0 (0.0)	
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.0)	
White	148 (68.5)	74 (72.5)	
Functional status (%)			< 0.001
Limited impairment, 100%-70%	56 (25.9)	50 (49.0)	
Moderate impairment, 50%-60%	43 (19.9)	23 (22.5)	
Severe impairment < 40%	113 (52.3)	29 (28.4)	
Unknown	4 (1.9)	0 (0.0)	
Recipient ABO blood type (%)			0.517
A	60 (27.8)	34 (33.3)	
AB	5 (2.3)	4 (3.9)	
B	22 (10.2)	11 (10.8)	
O	129 (59.7)	53 (52.0)	
Recipient BMI	29.39 [25.74, 32.82]	29.42 [26.59, 32.88]	0.592
Recipient cardiac output	4.28 [3.50, 5.25]	4.19 [3.58, 5.24]	0.893
Recipient PCWP	16.00 [10.00, 22.25]	15.00 [9.00, 20.00]	0.288
Donor characteristics			
Donor age (years)	29.50 [23.00, 35.00]	28.00 [22.00, 34.00]	0.206
Donor male sex (%)	27 (12.5)	10 (9.8)	0.576
Donor BMI (kg/m^2)	26.53 [23.94, 31.01]	26.81 [24.00, 29.99]	0.689
Donor LVEF	62.00 [60.00, 65.00]	61.00 [59.25, 67.75]	0.873
Donor cumulative smoking history exceeding 20 pack years (%)			0.617
Unknown	2 (0.9)	2 (2.0)	
Yes	20 (9.3)	7 (6.9)	
No	194 (89.8)	93 (91.2)	

(*continued on next page*)

Table 1 (*Continued*)

Cohort characteristics	DPP ($n = 216$)	NRP ($n = 102$)	*P*-value
Donor ABO blood type (%)			0.072
A	43 (19.9)	32 (31.4)	
B	12 (5.6)	6 (5.9)	
O	161 (74.5)	64 (62.7)	
Time from withdrawal of life support to death (min)	18.00 [14.00, 21.25]	19.00 [14.00, 25.00]	0.149
Donor HCV NAT serology positive (%)	11 (5.1)	3 (2.9)	0.56

Abbreviations: DPP, direct perfusion and procurement; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left-ventricular assistive device; LVEF, left-ventricular ejection fraction; NAT, nucleic acid amplification testing; NRP, normothermic regional perfusion; PCWP, pulmonary capillary wedge pressure.

Square brackets show median and interquartile range for continuous variables.

Round brackets show proportion for categorical variables.

P-values generated by Wilcoxon rank-sum test for continuous variables and Fisher exact test for all categorical variables except for treatment received before transplant, for which a 2-group ANOVA test was performed.

Values are mean (standard deviation) or *n*(%).

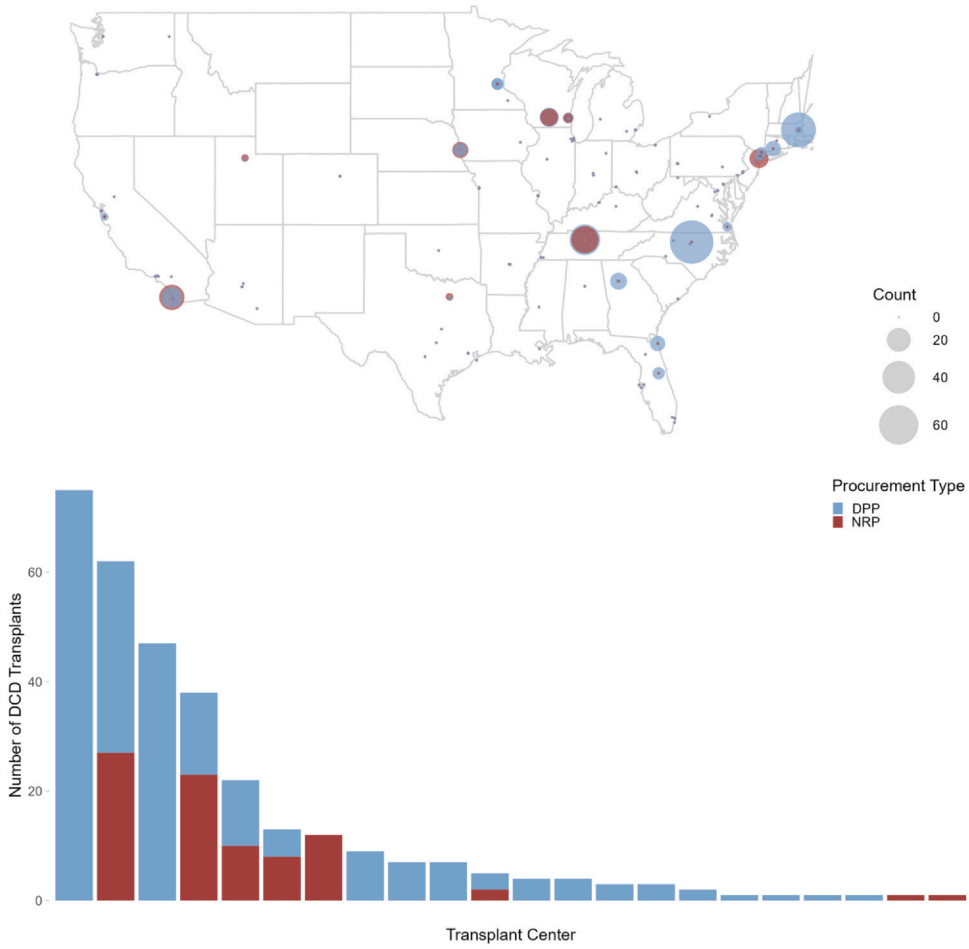

Figure 2 Center-level differences in the adoption of the NRP and DPP techniques for heart procurement. Map (A) and bar graph (B) show the volume of heart transplants from donated following circulatory death donors at centers around the country. Color indicates the procurement technique used in heart procurement from donated following circulatory death donor, deduced from death-to-cross-clamp time. The size of circle and height of bars indicate the number of transplants completed between January 1, 2019 and December 31, 2021 using each procurement technique. DPP, direct procurement and perfusion; NRP; normothermic regional perfusion.

month post-transplant survival between 80 DCD heart recipients and 86 DBD heart recipients but did not include any NRP procurements in the DCD arm.[26] Prior work specifically on the efficacy of NRP for heart transplantation consisted of case series and limited 6-month post-transplant survival registry analyses of only 47 NRP donor hearts.[3,27] Most recently, Siddiqi et al[28] published 1-year survival outcome from 1 transplant center where most DCD hearts are procured via NRP. While the authors found comparable survival between DCD and DBD heart recipients, they were unable to directly compare outcomes from NRP and DPP procurement techniques due to the limited number of DPP

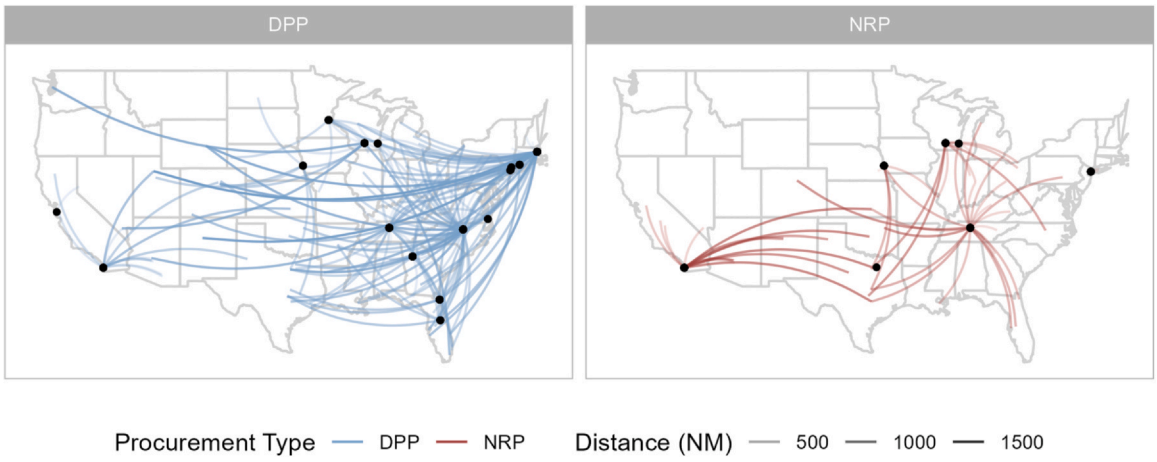

Figure 3 Distance of donated following circulatory death heart sharing by procurement type. Map of the distance between donor and recipient hospitals in donated following circulatory death heart transplantations, stratified by heart procurement technique. The length and thickness of the curve indicate the haversine distance in nautical miles between donor and recipient, if the 2 parties are located in different hospitals. No curve is drawn if donor and recipient are located at the same hospital before heart procurement. Color indicates the method of heart procurement deduced from death-to-cross-clamp time. DPP, direct procurement and perfusion; NRP; normothermic regional perfusion.

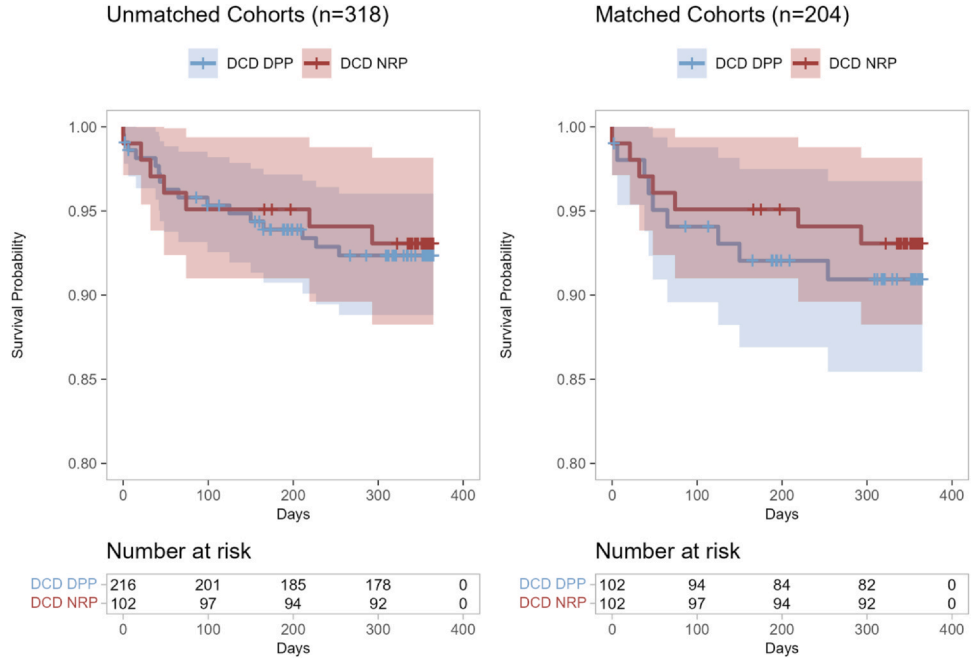

Figure 4 One-year post-transplant survival of DCD heart recipients by procurement type. Kaplan-Meier curves showing survival of DCD heart recipients within 1 year of transplantation. Administrative censoring is done for 365 days. Color indicates the method of heart procurement deduced from death-to-cross-clamp time. The shaded area indicates the 95% confidence interval around survival probability. The left panel compares all DPP and NRP-heart recipients in the study period. Right panel compares DPP- and NRP-heart recipients in a propensity-score matched cohort. The propensity score is calculated based on optimal matching on time from withdrawal of life support to death (quartiles), recipient age (above or below 60 years), treatment received by the recipient at the time of transplantation, donor age (in years), and donor body mass index. The table indicates the number of individuals still under observation at each time point. DCD, donated following circulatory death; DPP, direct procurement and perfusion; NRP; normothermic regional perfusion.

cases at the transplant center. Our nationwide registry analysis represents the largest direct comparison of NRP and DPP to our knowledge, finding both techniques lead to similar post-transplant outcomes.

Our findings have direct relevance to the ongoing ethical debate on NRP. NRP increases donor recovery and utilization rates compared with DPP and has benefits for both kidney and liver allografts procured from DCD heart donors.[7,29] Additionally, NRP uses resources readily available at transplant centers and does not require ex vivo machine perfusion technology which represents a large potential cost savings to transplant programs and the healthcare system overall. Therefore, if post-transplant survival for heart recipients is similar between NRP and DPP, as observed in our study, NRP should be the preferred DCD heart procurement technique to maximize recipient benefits from transplantation. Assuming consensus is

Table 2 Hazard ratio associated with the NRP procurement technique, compared to DPP

Procurement type = NRP	Unmatched	PS matched
Hazard ratio	0.90	0.78
Confidence interval	(0.37-2.19)	(0.28-1.94)
N	318	204
N events	23	16

Abbreviations: DCD, donated following circulatory death; NRP; normothermic regional perfusion; PS, Propensity Score.

All continuous predictors are mean-centered and scaled by 1 standard deviation.

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

achieved that NRP is ethically permissible and conforms to the dead donor rule, the benefits to the abdominal organ recipients obligate the procuring heart team to use NRP over DPP.

Limitations

Our manuscript has a few limitations. First, while we carefully selected variables for our propensity score model to eliminate major biases in choosing 1 organ procurement technique over the other, not all relevant donor and recipient variables were available. In particular, there is no accurate measurement for the extent of warm ischemic injury sustained by each organ at the time of procurement. We attempted to proxy the differences in the extent of organ function deterioration between NRP and DPP using the duration of time between withdrawal of life support and pronouncement of death due to the consistency in the recording of this variable. However, this is not an ideal measure because organ deterioration likely does not occur linearly over time following withdrawal of life support. Our propensity-score matching technique identified DPP transplants that were similar in donor and recipient characteristics to the NRP transplants. This approach means our result is only valid for recipients of NRP hearts, who tended to be younger and received organs with shorter travel distances. Our study does not rule out a potential advantage for DPP and ex vivo machine perfusion for organs with longer travel distances. Second, since we classified the procurement method using death-to-cross-clamp time, some cases may have been misclassified, therefore affecting the accuracy of our model outcome. Third, because only a few centers practice both DPP and NRP, we could not control for center-fixed effects with a stratified Cox model, and confounding from unmeasured center-level differences may bias our results. However, adoption of NRP versus DPP has happened somewhat randomly across the country at centers with excellent DBD outcomes (Figure S8): therefore, we believe it is unlikely that NRP centers are systematically better at other aspects of peri- and post-transplant care than DPP centers (or vice versa). Fourth, organ storage and transport practices can have a significant impact on graft function but are poorly captured in national registry data. Importantly, our analysis assigned organs a transportation distance of zero if the donor-recipient pair were located in the same hospital, including if the donor was co-located before withdrawal of life support. Co-location practices can have a significant impact on observed differences in the mean distance of organ transportation. Additionally, the introduction of NRP in the United States coincided with both the onset of the COVID-19 pandemic and the end of the Organ Care System Heart EXPAND Trial.[30] The unusualness of our observation period may have had a significant impact on the care and outcomes of patients. As a result, the efficacy of NRP relative to DPP may vary over time.

Conclusion

Among recipients of DCD hearts, 1-year post-transplant survival does not differ significantly between NRP and DPP procurement techniques after propensity-score matching to control for recipient and donor factors. These findings suggest that NRP should be used to expand access to heart transplantation and improve outcomes for abdominal organ recipients.

Data availability statement

The data used in this study are available from the Scientific Registry of Transplant Recipients. Restrictions apply to data availability, which were used under license for this study.

Author contributions

W.P conceived of the presented idea and secured funding for the project. G.R. performed the data cleaning and statistical analyses. A.W developed the key method of identifying procurement methods. N.N. reviewed and suggested important parameters to include in the propensity score model. A.W., K.K., and J.H. provided input on the clinical and ethical implications of our study. K.Z. provided input on the statistical soundness of the study. All authors discussed the results and contributed to the drafting of the final manuscript.

Disclosure statement

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2024.02.1456.

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