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Original Article

DCDD heart transplantation with thoraco-abdominal normothermic regional perfusion and static cold storage: The experience in Spain

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Abbreviations: A-NRP, abdominal normothermic regional perfusion; CIT, cold ischemic time; DCDD, donation after the circulatory determination of death; DNDD, donation after the neurologic determination of death; DPP, direct procurement and preservation; ECMO, extracorporeal membrane oxygenation; FWIT, functional warm ischemic time; ICU, intensive care unit; MAiD, medical assistance in dying; NRP, normothermic regional perfusion; ONT, Organización Nacional de Trasplantes; PGF, primary graft failure; SCS, static cold storage; TA-NRP, thoraco-abdominal normothermic regional perfusion; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; WLST, withdrawal of life-sustaining therapies.

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ABSTRACT

Heart transplantation from donors after the circulatory determination of death is expanding worldwide. Thoraco-abdominal normothermic regional perfusion (TA-NRP) allows the validation and recovery of the donation after the circulatory determination of death (DCDD) heart, but there is limited evidence on the results of heart transplants performed with this approach. This multicenter, nationwide, prospective study describes the short-term outcomes of adult patients receiving a DCDD heart transplant obtained via TA-NRP followed by static cold storage in Spain. Recipients of hearts from donors after the neurologic determination of death were used as controls. The primary outcome was a composite of 1-year all-cause death or severe primary graft failure. During 2020-2023, 98 adult DCDD and 347 donations after the neurologic determination of death (DNDD) heart transplants were performed across 11 centers. The primary outcome was met by 21 (21.4%) and 77 (22.2%) patients, respectively ($P = .87$). Thirty-day and 1-year survival were 94.9% and 88.8% in the DCDD vs 93.7% and 87.3% in the DNDD group ($P = .70$), respectively. Severe primary graft failure was observed in 13 (13.3%) vs 52 (15.0%) patients ($P = .67$). By inverse probability weighting, the DCDD heart was not associated with the primary outcome (hazard ratio, 0.97; 95% confidence interval, 0.58-1.62; $P = .91$). In conclusion, adult DCDD heart transplantation based on TA-NRP and static cold storage provides similar short-term outcomes than DNDD heart transplants.

1. Introduction

Heart transplantation is a life-saving therapy for patients diagnosed with end-stage heart failure. The transplantation of hearts from donors after the circulatory determination of death is a surgical innovation that aims at increasing the access of patients to this therapy. According to the Global Observatory on Donation and Transplantation, 823 DCDD heart transplants were performed in 9 countries (Australia, Austria, Belgium, Italy, Spain, Switzerland, the Netherlands, United Kingdom and United States) during 2023, which confirms the recent expansion of this procedure.[1]

There are 2 methods for the recovery of the donation after the circulatory determination of death (DCDD) heart. The direct procurement and preservation (DPP) technique is based on the rapid recovery of the heart ie, subsequently subject to ex situ machine perfusion. Metabolic parameters and the visual assessment of

ventricular contractility allow the validation of the heart. Recipients of DCDD hearts obtained through DPP exhibit similar outcomes than recipients of hearts from donors after the neurologic determination of death.[2,3] The Papworth team was the first to introduce thoraco-abdominal normothermic regional perfusion (TA-NRP) for the recovery of the DCDD heart.[4] Once the donor was declared dead, the chest and the abdomen were perfused with oxygenated blood in normothermia by use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO). The heart recovered its functionality, allowing the weaning from VA-ECMO and the in situ validation of the heart before organ recovery. Most procedures performed in Cambridge were still followed by ex situ machine perfusion,[5] though the group also reported the first cases of DCDD heart transplants obtained via TA-NRP and static cold storage (SCS).[6] Since then, TA-NRP, either combined with ex situ machine perfusion or SCS, has gained acceptance in Europe and the United States.[7-11]

In Spain, DCDD heart transplantation was initiated in January 2020 at the Hospital Universitario Puerta de Hierro, Madrid.[12] The protocol was approved by the Organización Nacional de Trasplantes (ONT) and the National Transplant Committee. The emergence of similar protocols in other centers, all subject to the same centralized approval, led to the development of a unified national protocol incorporating the common elements included in local approaches. The Spanish protocol was based on the use of TA-NRP followed by SCS.[13] Herein, we describe the national experience with this unified approach, analyzing the short-term outcomes of DCDD heart recipients, as compared with the standard, donation after the neurologic determination of death (DNDD) heart transplantation.

2. Patients and methods

2.1. Patients and data source

This is a multicenter, nationwide, prospective study, with a retrospective evaluation of DCDD heart transplants performed from January 2020 to December 2023 in adult recipients (age at transplantation ≥18 years) in Spain. For each center, the DNDD heart transplants performed since the initiation of the DCDD program were selected as controls. Follow-up was censored as of March 2024. Data were gathered from the Spanish Registry of Heart Transplantation (Registro Español de Trasplante Cardiaco)[14] and the ONT database (CORE).

2.2. Donor selection criteria

DCDD was considered in patients with a devastating brain injury or other diseases in whom the decision of withdrawal of life-sustaining therapies (WLST) had been made. Since July 2021, when the corresponding law entered into force,[15] DCDD was also considered in patients with approved medical assistance in dying (MAiD). Heart recovery was considered in potential DCDD donors aged ≤55 years without cardiovascular risk factors, history of heart disease, or previous sternotomy. Hemodynamic stability prior to the WLST (mean arterial pressure ≥60 mmHg and urine output ≥0.5 mL/kg/h with low inotrope support) and normal echocardiogram (left ventricular ejection fraction ≥50% and interventricular septum ≤13 mm) were required. Acceptable functional warm ischemic time (FWIT) was <30 minutes.

2.3. Recipient selection criteria

All patients on the elective or urgent waiting list were deemed eligible for DCDD heart transplantation. Preferably, patients should have low fixed pulmonary vascular resistance (≤ 2.5-3 Wood units and transpulmonary gradient ≤8-12 mmHg).

2.4. Information on DCDD heart transplantation for donors and recipients

Authorization for antemortem interventions was obtained from the donor or their surrogates. Specific informed consent was needed for the recovery of the heart after the provision of information about in situ perfusion.

Eligible waitlisted patients were informed of the possibility of receiving a DCDD heart, which would not exclude them from receiving a DNDD graft. Specific consent was obtained for DCDD heart transplantation based on a common informative document.

2.5. DCDD heart recovery by TA-NRP

Heparinization and cannulation of femoral vessels, where appropriate, were undertaken prior to the WLST. The WLST (or MAiD, where applicable) was performed in the operating theater by the treating team, according to national guidance.[15,16] Death was declared after a no-touch period of 5 minutes. Then, a median sternotomy was performed and the aortic arch vessels were dissected and cross-clamped to exclude the brain. Additional safety measures were required to deviate any potential collateral circulation to the brain.[17] In the first cases, the 3 arch vessels were cannulated and the drained blood was returned to the normothermic regional perfusion (NRP) circuit, though this measure turned out to be lengthy and complex. Therefore, since March 2023, the requirement was to cut the arch vessels and open the cephalad ends to atmospheric pressure. The drained blood was aspirated and returned to the NRP circuit. This refinement imposed the need for an open circuit (extracorporeal circulation or modified extracorporeal membrane oxygenation [ECMO] device with a reservoir). Afterward, TA-NRP was commenced. Neuromonitoring of the donor was performed during each procedure with bispectral index and transcranial Doppler, which could be replaced by intracranial arterial pressure monitoring in centers conducting a specific research project described elsewhere.[18]

As an alternative to the direct initiation of TA-NRP, NRP could be initially limited to the abdomen after occluding the supraceliac aorta with a balloon that was inflated after the determination of death. Once the supraaortic vessels were clamped and vented, the balloon was deflated and NRP extended to the thoracic organs.

After the heart recovered a satisfactory function, TA-NRP was gradually weaned-off. The assessment of heart function was performed by echocardiography and visual inspection. The heart

was considered viable if the left ventricular ejection fraction was >50% without segmental motion abnormalities and maintained mean arterial pressure values of 50 to 60 mmHg with low dose inotropes (dopamine <5 mcg/kg/min and/or norepinephrine <0.1 mcg/kg/min). If a right heart catheter was in place, a central venous pressure <12 mmHg, pulmonary wedge pressure <12 mmHg and cardiac index >2.5 L/min/m^2 were also required. Cardiectomy was performed following standard surgical procedures. The type of cardioplegia was variable across centers. The explanted heart was subjected to SCS, as the availability of ex situ machine perfusion was limited.

During 2020-2021, donors and recipients were colocated in the same hospital. Since 2022, after establishing the safety of the first procedures, transplant centers were authorized to consider organ offers from donors located at other centers and variable distances. In such cases, under the coordination of ONT, the transplant center ensured the provision of human and material resources required for heart recovery, if not available at the donor center.[19]

2.6. Outcomes and definitions

The primary outcome was a composite of 1-year all-cause death or severe primary graft failure (PGF). Secondary outcomes were each of the components of the composite primary outcome and total mortality. The length of stay in the intensive care unit (ICU), the duration of ventilatory support posttransplant and the number of rejection episodes needing treatment within the first year posttransplant were analyzed as well.

Acute rejection was defined as any clinical event (endomyocardial biopsy findings, echocardiogram indicating ventricular dysfunction, or abnormal hemodynamics) leading to temporary augmentation of immunosuppression.[20]

PGF was defined according to the International Society of Heart and Lung Transplantation Consensus.[21] Severe PGF was defined by the need for mechanical circulatory support (except for intraaortic balloon pump) for left or right ventricular dysfunction within the first 24 hours after transplantation without any other discernible cause for graft dysfunction (rejection, surgical complications, or pulmonary hypertension).

The agonal time was defined as the time from the WLST to asystole. The asystolic time was measured from asystole to the initiation of TA-NRP. The FWIT was defined as the time between systolic blood pressure <60 mmHg and the start of TA-NRP. The TA-NRP time was measured from the time the heart beat to the weaning of TA-NRP. Finally, the cold ischemic time (CIT) was measured from donor cross-clamp to reperfusion of the heart in the recipient.

2.7. Statistical analysis

Categorical variables were summarized as counts and percentages, and quantitative variables as median and interquartile range. Differences between the DCDD and the DNDD groups were analyzed by the chi-square test for categorical variables and the Wilcoxon rank-sum test for quantitative variables.

Missing data accounted for 0.4% of the total, involving pulmonary vascular resistance (53 patients) and recipient cytomegalovirus serology (2 patients). The missing data were handled through sequential imputation using chained equations. Pulmonary vascular resistance was imputed using linear regression, whereas logistic regression was employed for recipient cytomegalovirus serology, incorporating all study variables and the outcome in the models. Fifteen complete imputed data sets were generated, and the adjusted associations with the outcome were estimated for each data set and subsequently combined using Rubin's rules.

Time-to-event was analyzed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Hazard ratios and their robust 95% confidence intervals were estimated using Cox regression. Proportionality assumption was tested by the Schoenfeld residuals test.

To account for the unbalanced distribution of certain characteristics between the groups, regression models were adjusted using inverse probability weighting. For this purpose, the probability of receiving a DCDD heart was calculated after multivariate logistic regression using as predictors: donor age, donor sex, use of ECMO or ventricular assist devices prior to transplantation, recipient-to-donor weight ratio, prior sternotomy, infection prior to transplantation, CIT, and donor hepatitis C virus positivity. A limited number of covariates were selected to avoid overparameterization of the model and were chosen based on their unbalanced distribution between treatment groups and/or their association with the primary outcome. Stabilized weights with truncation at first and 99th percentiles were used.[22] Additionally, multivariate adjustment was performed by including in the final model those variables that had a P value $< .1$ in their association with the outcome.

For sensitivity analysis, the analysis was reproduced using the complete-case sample and after calculating stabilized truncated weights through a nonparsimonious logistic regression model, including all the study variables.

Two-tailed test was used throughout the study and the level of significance was established at a P value $< .05$. Statistical analysis was performed with the Stata 16.0 package (StataCorp LLC, College Station, TX).

This study adheres to the STROBE statement (Supplementary material).

2.8. Ethical approval

All recipients consented to the utilization of their data for investigational purposes. The research ethics committee of each center approved the DCDD heart transplant protocol. This study was approved by the research ethics committee of the University Hospital Virgen de la Arrixaca (2024-5-1-HCUVA).

3. Results

During the study period, 98 DCDD heart transplants with TA-NRP and SCS were performed across 11 centers, each conducting between 2 and 25 procedures. During the same period, these centers also performed 347 DNDD heart transplants. The main characteristics of recipients are summarized in Table 1.

Table 1
Recipient characteristics by donor type.

	DCDD (n = 98)	DNDD (n = 347)	*P* value
Age (y), median (IQR)	54.5 (47.0-61.0)	56.0 (47.0-62.0)	.35
Sex (female), n (%)	23 (23.5)	88 (25.4)	.70
Weight (kg), median (IQR)	74.5 (64.0-88.0)	74.0 (64.6-84.0)	.50
Primary etiology, n (%)			.22
Dilated	34 (35.7)	119 (34.3)	
Ischemic	36 (36.7)	118 (34.0)	
Valvular	0 (0.0)	17 (4.9)	
Hypertrophic	11 (11.2)	23 (6.6)	
Congenital	2 (2.0)	13 (3.8)	
Retransplant	2 (2.0)	11 (3.2)	
Restrictive	5 (5.1)	30 (8.6)	
Myocarditis	3 (3.1)	9 (2.6)	
Other	5 (5.1)	9 (3.6)	
Hypertension, n (%)	36 (36.7)	111 (31.7)	.36
Diabetes, n (%)	24 (24.7)	83 (23.9)	.75
Hypercholesterolemia, n (%)	45 (45.9)	156 (44.6)	.81
Peripheral artery disease, n (%)	11 (11.5)	18 (5.2)	.03
GFR (mL/min/1.73 m^2), median (IQR)	69.2 (51.0-93.1)	68.0 (53.0-98.4)	.66
Bilirubin (mg/dL), median (IQR)	0.9 (0.6-1.3)	0.9 (0.6-1.3)	.56
Respiratory disease, n (%)	11 (11.2)	23 (6.7)	.13
Pulmonary vascular resistance (Wood unit), median (IQR)	1.71 (0.98-2.45)	1.69 (1.11-2.36)	.73
CMV positive serology, n (%)	79 (80.6)	267 (77.4)	.50
Infection, n (%)	9 (9.2)	55 (15.9)	.10
Malignancy prior to HTx, n (%)	3 (3.1)	21 (6.0)	.25
Prior sternotomy, n (%)	18 (18.4)	149 (42.9)	.001
Mechanical ventilation, n (%)	3 (3.1)	26 (7.5)	.12
Circulatory support prior to HTx, n (%)			<.001
No	84 (84.6)	204 (58.8)	
IABP	1 (1.0)	2 (0.6)	
VA-ECMO	8 (8.3)	31 (8.9)	
Ventricular assist device	4 (4.1)	110 (31.7)	

CMV, cytomegalovirus; DCDD, donation after the circulatory determination of death; DNDD, donation after the neurologic determination of death; GFR, glomerular filtration rate; HTx, heart transplantation; IABP, intraaortic balloon pump; IQR, interquartile range; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

Significant differences were observed in the use of circulatory support prior to transplantation and in the history of previous cardiac surgery, which were less common in recipients of DCDD hearts.

Figure 1 shows the progression of the DCDD hearts offers. DCDD heart recovery was undertaken in 31 centers, of which 20 did not have a heart transplant program. In 34 (35%) DCDD heart transplant procedures, donors and recipients were located in different hospitals, either in the same (n = 16) or in a different city (n = 18).

The characteristics of donors, recipient-donor interaction, and heart transplant procedures are displayed in Table 2. The median FWIT in the DCDD cohort was 13.0 minutes. CIT was shorter in the DCDD group (median 99.5 vs 191.0 min; $P < .001$). Of note, most DCDD heart transplant procedures were performed in elective recipients (89.8% vs 57.7%; $P < .001$).

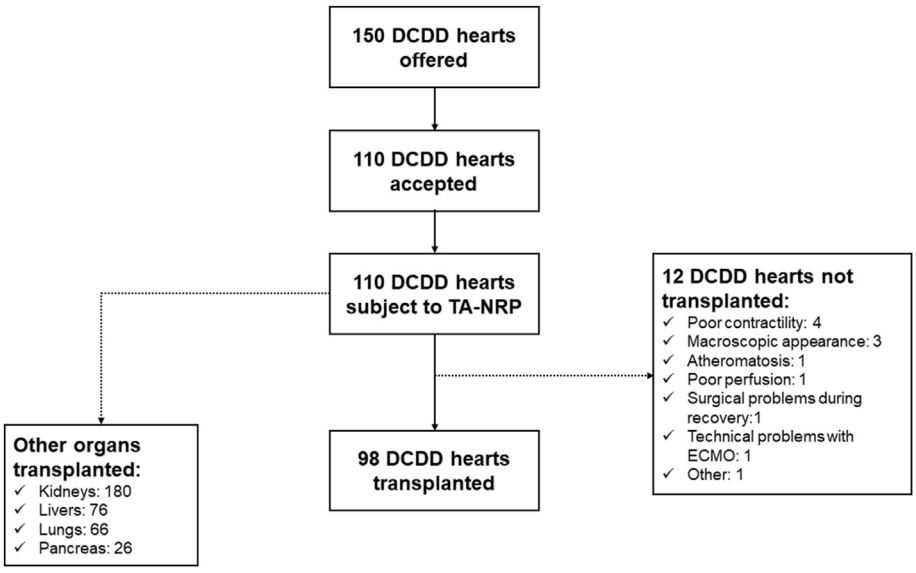

Figure 1. Flowchart of donation after the circulatory determination of death (DCDD) heart transplants offered to transplant teams during the study period. ECMO, extracorporeal membrane oxygenation; TA-NRP, thoraco-abdominal normothermic regional perfusion.

3.1. One-year all-cause mortality and severe PGF

Table 3 summarizes posttransplant outcomes. The primary composite outcome was met by 21 (21.4%) and 77 (22.2%) patients in the DCDD and the DNDD groups, respectively ($P = .87$). No significant differences were observed between the 2 cohorts in the Kaplan-Meier for the primary composite outcome (Fig. 2). Univariate associations with 1-year all-cause mortality or severe PGF are summarized in Supplementary Table 1. In the adjusted analysis by inverse probability weighting, the DCDD heart was not significantly associated with the primary composite outcome (hazard ratio, 0.96; 95% confidence interval, 0.61-1.52; $P = .87$). Associated variables included infection ($P = .01$), support with ECMO ($P < .001$), and cardiac surgery ($P = .01$) prior to transplantation, as well as urgent transplantation ($P < .001$). CIT and donor hepatitis C virus seropositivity showed a nonsignificant trend toward a higher incidence of the primary composite outcome ($P = .09$ and .7, respectively). Figure 3 shows the results of the adjusted models. Sensitivity analyses did not alter the magnitude of the treatment effect (Supplementary Table 2).

3.2. DCDD heart transplants

Table 4 provides information on recipients of DCDD hearts, with no differences observed between recipients who met and those who did not meet the primary composite outcome regarding donor and procedural factors. Notably, the CIT was over 180 minutes in 14 (14.3%) DCDD heart transplant cases, 2 (9.5%) in the group meeting the composite primary endpoint, and 12 (15.6%) in the group with no events ($P = .48$). Similarly, the incidence of the primary composite outcome was not higher in cases where donors and recipients were located in different hospitals. As expected, urgent status prior to transplantation was more frequent among recipients of DCDD hearts who met the primary composite outcome. The experience of the center, assessed by the date the DCDD heart transplant program started and the number of DCDD heart transplant procedures performed, was not associated with a higher occurrence of 1-year all-cause mortality or severe PGF.

3.3. Secondary outcomes

First-year survival posttransplant, severe PGF, and total mortality did not differ between the DCDD and the DNDD groups (Fig. 4 and Table 3). Survival at 30 days and 1 year posttransplant was 94.9% and 88.8% in DCDD vs 93.7% and 87.3% in the DNDD group ($P = .70$), respectively. Severe PGF was observed in 13 patients (13.3%) in the DCDD group and 52 (15.0%) in the DNDD cohort ($P = .67$). All severe PGF cases were managed with VA-ECMO, with 2 cases additionally requiring an intraaortic balloon pump. Among the 65 patients with severe PGF, 22 (33.9%) died within the first year posttransplant: 3 out of 13 patients (23.1%) in the DCDD group, and 19 out of 52 patients (36.5%) in the DNDD group ($P = .36$ for interaction). The duration of ventilatory support posttransplant was shorter in the DCDD group; however, the length of ICU stay did not differ between the 2 cohorts.

4. Discussion

DCDD heart transplantation is expanding to provide further opportunities for patients in need. To the best of our knowledge, this is the first nationwide prospective study describing the outcomes of recipients of DCDD hearts obtained via TA-NRP and SCS, based on a common protocol and with details on specific aspects of the TA-NRP procedure that can affect posttransplant outcomes.

We used DNDD heart recipients transplanted during the same period as the control group. The DCDD and the DNDD cohorts significantly differed in variables that could have an impact on 1-year all-cause mortality or severe PGF. Initially, to prove the safety of the procedure, the centers used to select low-risk

Table 2
Characteristics of donors, recipient-donor interactions, and surgeries by donor type.

	DCDD (n = 98)	DNDD (n = 347)	*P* value
Donor			
Age (y), median (IQR)	44.0 (34.0-49.0)	46.0 (35.0-53.0)	.08
Sex (female), n (%)	21 (21.4)	109 (31.4)	.06
Weight (kg), median (IQR)	75.0 (68.0-87.0)	80.0 (70.0-88.0)	.12
Active smoking, n (%)	25 (25.1)	111 (32.0)	.22
Cocaine use, n (%)	6 (6.1)	26 (7.5)	.64
Alcohol $\geq$ moderate, n (%)	11 (11.2)	48 (13.8)	.50
Hypertension, n (%)	14 (14.3)	54 (15.6)	.76
Diabetes, n (%)	2 (2.0)	13 (3.8)	.41
Positive HCV serology, n (%)	0 (0.0)	9 (2.6)	.11
Positive CMV serology, n (%)	62 (63.3)	251 (72.3)	.08
Cause of death, n (%)			<.001
Cranial trauma	22 (22.4)	97 (27.9)	
Hemorrhagic CVA	22 (22.4)	144 (41.5)	
Ischemic CVA	9 (9.2)	26 (7.5)	
Cerebral anoxia	18 (18.4)	51 (14.7)	
MAiD	10 (10.2)	-	
Others[a]	17 (17.4)	29 (8.4)	
Recipient-donor interaction			
Recipient/donor weight, median (IQR)	0.99 (0.86-1.09)	0.94 (0.80-1.08)	.07
Recipient male/donor female, n (%)	12 (12.2)	55 (15.8)	.38
CMV serology recipient negative/donor positive, n (%)	14 (14.3)	53 (15.3)	.80
Surgical procedure and ex situ preservation			
Functional warm ischemic time (min), median (IQR)	13.0 (11.0-17.0)	-	
Cold ischemic time (min), median (IQR)	99.5 (74.0-157.0)	191.0 (129.0-236.0)	<.0001
Ex situ heart preservation			.41
Static cold storage	97	335	
Advanced static cold storage	1	8	
Hypothermic oxygenated perfusion	-	4	
Surgical technique (bicaval), n (%)	93 (94.9)	271 (78.6)	<.0001
High priority (urgent), n (%)	10 (10.2)	148 (42.3)	<.001

CMV, cytomegalovirus; CVA, cerebrovascular accident; DCDD, donation after the circulatory determination of death; DNDD, donation after the neurologic determination of death; HCV, hepatitis C virus; IQR, interquartile range; MAiD, medical assistance in dying.

[a] Central nervous system neoplasia, central nervous system infections, neurodegenerative disorders, and rare diseases.

recipients. Therefore, recipients of DCDD hearts had less often a previous history of cardiac surgery and were usually in elective status at the time of transplant. DCDD hearts also underwent shorter CIT, because only donors located at the transplant center were considered at the beginning of the program. However, DCDD donors did not significantly differ from DNDD donors, except for the cause of death. After adjusting for variables associated with the primary composite endpoint in univariate analysis, the DCDD donor was not associated with a higher likelihood of 1-year all-cause death or severe PGF. In terms of secondary outcomes, DCDD heart recipients exhibited similar 1-year survival, incidence of severe PGF, overall survival, ICU length of stay, and incidence of acute rejection during the first year. However, the duration of posttransplant mechanical ventilation was shorter in the DCDD group, which may relate to the better baseline condition of these recipients.

We assessed factors that could relate to the occurrence of the primary composite outcome among recipients of DCDD hearts.

Table 3
Outcomes after transplantation by donor type.

Outcome	DCDD (n = 98)	DNDD (n = 347)	*P* value
Death within the first year after transplant/severe primary graft failure, n (%)[a]	21 (21.4)	77 (22.2)	.87
Death within the first year after transplant, n (%)	11 (11.2)	44 (12.7)	.70
Severe primary graft failure, n (%)	13 (13.3)	52 (15.0)	.67
Total deaths, n (%)	11 (11.2)	47 (13.5)	.55
Cause of death, n (%)			.20
Infection	4 (36.4)	10 (21.3)	
Primary graft failure	2 (18.2)	16 (34.4)	
Sudden death	1 (9.1)	-	
Multiorgan failure	1 (9.1)	1 (2.1)	
Cerebrovascular accident	1 (9.1)	5 (10.6)	
Acute rejection	-	5 (10.6)	
Allograft vasculopathy	-	2 (4.3)	
Surgical complications	1 (9.1)	1 (2.1)	
Cardiovascular	-	1 (2.1)	
Respiratory	-	2 (4.3)	
Noncompliance	-	1 (2.1)	
Other	1 (9.1)	3 (6.4)	
Primary graft failure, n (%)	18 (18.4)	83 (23.9)	.25
No. of first-year acute rejection episodes, mean (SD)	0.49 (0.76)	0.51 (0.84)	.91
Ventilatory support (h), median (IQR)	12.0 (6.0-24.0)	24.0 (12.0-96.0)	<.001
ICU length of stay (d), median (IQR)	7.0 (5.0-13.0)	7.0 (5.0-14.0)	.69
Survival (%)			.70
1 month	94.9	93.7	
6 months	90.8	89.0	
12 months	88.8	87.3	
Survival free of severe primary graft failure or death (%)			.86
1 month	83.7	83.0	
6 months	80.6	79.5	
12 months	78.6	77.8	

ICU, intensive care unit; IQR, interquartile range.

[a] Primary composite outcome.

None of the different ischemic times, the preservation sequence (abdominal normothermic regional perfusion [A-NRP] first vs TA-NRP first), or other procedural aspects were associated with such occurrence. This was surprising for the CIT, revealing that DCDD hearts obtained via TA-NRP and subject to SCS may tolerate longer cold ischemia than initially thought. Indeed, 25% of the DCDD hearts in our series exhibited CIT over 157 minutes (75th percentile), including 14 grafts with more than 180 minutes of cold ischemia, of which most (n = 12) resulted in appropriate short-term outcomes. However, the safety of increasing CIT in this setting needs to be confirmed in future studies. In this regard, there may be room for increasing CIT by using advanced cold heart preservation or hypothermic oxygenated perfusion.[23,24] These new preservation modalities were exceptionally used in our DCDD donors, with only 1 DCDD heart subject to advanced cold storage because of an anticipated long CIT. This technique may improve the cardiomyocytes and cellular adenosine triphosphate stores, decreasing the incidence of PGF and allowing a safer use of these complex hearts.[25]

Two other multicenter studies have been published on DCDD heart transplantation based on the use of TA-NRP.[10,11] Louca et al[11] reported the outcomes of 157 DCDD heart transplants

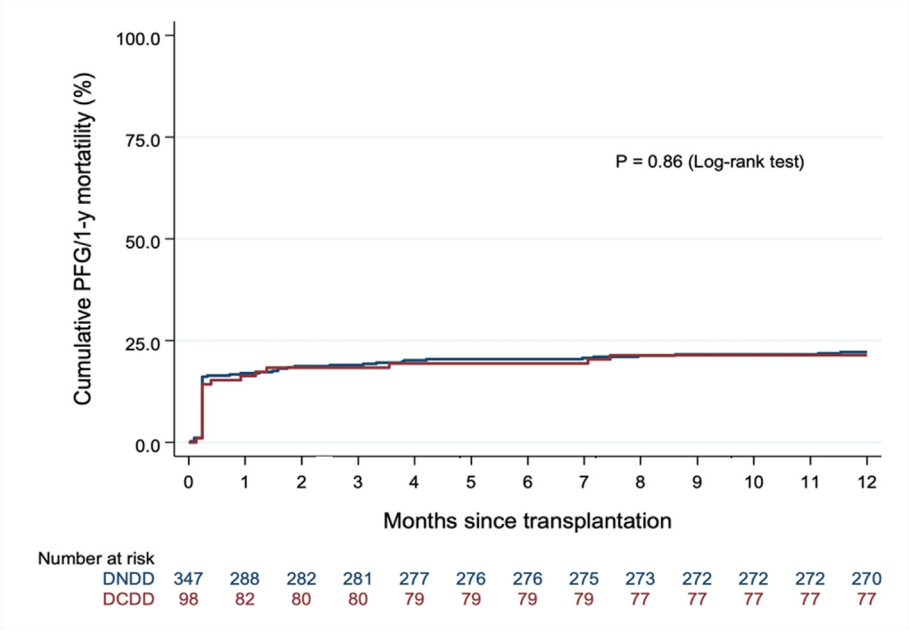

Figure 2. Cumulative all-cause mortality within the first year posttransplant/severe primary graft failure (PGF) (Kaplan-Meier), by donor type. DCDD, donation after the circulatory determination of death; DNDD, donation after the neurologic determination of death.

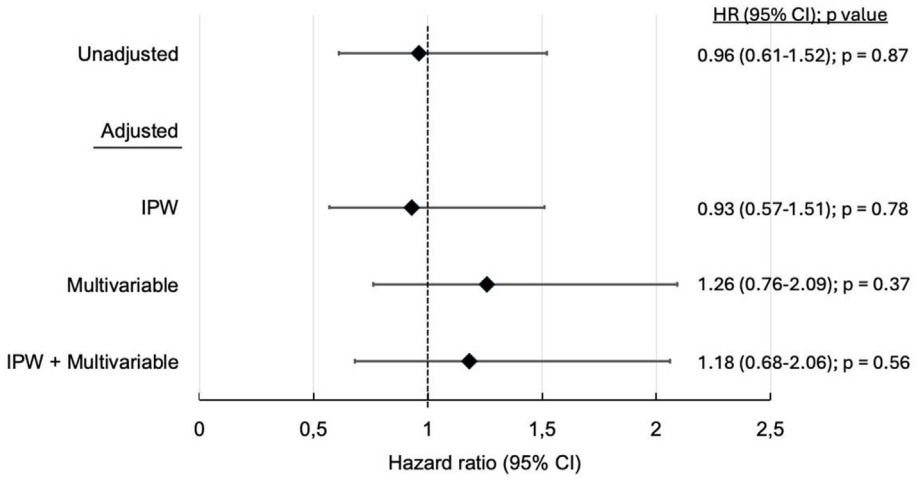

Figure 3. Unadjusted and adjusted risk of all-cause mortality within the first year posttransplant/severe primary graft failure for donation after the circulatory determination of death donor type. IPW, inverse probability weighting. Multivariate adjustment includes infection prior to transplantation, use of extracorporeal membrane oxygenation prior to transplantation, previous cardiac surgery, urgent transplantation, and cold ischemic time. CI, confidence interval; HR, hazard ratio.

performed with TA-NRP vs 673 DNDD heart transplants in 15 centers worldwide. Survival for up to 5 years was similar in both groups. Importantly, the survival of recipients of DCDD hearts recovered with TA-NRP was not improved by the use of ex situ machine perfusion. Recently, Ran et al[10] described DCDD heart transplants performed in the United States during 2019-2021, based on data from the Scientific Registry of Transplant Recipients, where TA-NRP cases were identified based on cross-clamp times (the registry does not collect information on the type of DCDD heart recovery). The authors compared 216 hearts obtained via DPP with 102 grafts obtained via TA-NRP. After propensity-score matching, no significant differences were found in 1-year survival between the groups. These 2 experiences are limited by their retrospective design, absence of uniform protocols, and lack of relevant details on TA-NRP, which underscores the novelty of our study.

Compared with the 2 above-mentioned studies, DCDD heart donors in our series were older (median age 44 years vs 32[11] and 28 years[10]), which may explain the slightly inferior 1-year survival in our cohort. However, our DCDD donors showed a shorter agonal time. This may be explained by differences in donor selection strategies and end-of-life care practices between countries. Moreover, 10 DCDD heart donors in our series were subject to MAiD, which implies a very short agonal time.

This study confirms that DCDD heart transplants obtained via TA-NRP can produce satisfactory outcomes, even without ex situ machine perfusion. This groundbreaking technique has significant ethical implications, especially regarding the restoration of circulation and cardiac function while excluding cerebral blood flow to prevent restoration of brain functions.[26] Maintaining trust in death determination is essential, though commentators differ

Table 4
Characteristics of heart transplant procedures from donors after the circulatory determination of death, according to the incidence of death within the first year after transplant or severe primary graft failure (event).

Variable	Total	No event (n = 77)	Event (n = 21)	*P* value
Donor				
Age (y), median (IQR)	44.0 (34.0-49.0)	43.0 (34.0-48.0)	45.0 (37.0-51.0)	.34
Sex (female), n (%)	23 (23.5)	18 (23.4)	5 (23.8)	.97
MAiD as the cause of death, n (%)	10 (10.2)	7 (9.1)	3 (14.3)	.49
Use of inotropes, n (%)	39 (39.8)	33 (42.9)	6 (28.6)	.24
Location from recipient, n (%)				.88
Same center	64 (65.0)	50 (64.9)	14 (66.7)	
Different center	34 (35.0)	27 (35.1)	7 (33.3)	
Procedure				
Timing, median (IQR)				
Agonal time (min)	11.0 (8.5-16.0)	11.0 (8.0-16.0)	11.0 (9.0-15.0)	.99
Asystolic time (min)	7.0 (5.0-9.0)	7.0 (5.0-9.0)	7.0 (5.0-9.0)	.87
Functional warm ischemia (min)	13.0 (11.0-17.0)	13.0 (11.0-16.0)	14.0 (10.0-18.0)	.79
TA-NRP time (min)	30.0 (19.0-64.0)	32.0 (19.0-64.0)	29.0 (22.0-51.0)	.67
Cold ischemic time (min)	99.5 (74.0-157.0)	103.0 (74.0-157.0)	85.0 (76.0-130.0)	.35
Intraaortic balloon use, n (%)	43 (44.8)	32 (42.7)	11 (52.4)	.42
Preservation sequence, n (%)				.58
Thoraco-abdominal first	65 (66.3)	50 (64.9)	15 (71.4)	
Abdominal first	33 (33.7)	27 (35.1)	6 (28.6)	
Type of TA-NRP pump, n (%)				.92
Extracorporeal circuit	43 (43.9)	34 (44.2)	9 (42.9)	
ECMO	55 (56.2)	43 (55.8)	12 (57.1)	
Recipient				
Age (y), median (IQR)	54.5 (47.0-61.0)	55.0 (47.0-62.0)	53.0 (45.0-60.0)	.89
Sex (female), n (%)	21 (21.4)	15 (19.5)	6 (28.6)	.37
High priority (urgent), n (%)	10 (10.2)	5 (6.5)	5 (23.8)	.02
Prior sternotomy, n (%)	18 (18.4)	12 (15.6)	6 (28.6)	.17
Transplant center experience				
Start of the DCDD program				.70
Early (before July 2021)	41 (41.8)	33 (42.9)	8 (38.1)	
Late (since July 2021)	57 (58.2)	44 (57.1)	13 (61.9)	
Volume of DCDD heart transplant procedures				.88
$\geq$ 10	64 (65.3)	50 (64.9)	14 (66.7)	
$<$ 10	34 (34.7)	27(35.1)	7 (33.3)	

Event is defined as death within the first year posttransplant or severe primary graft failure.
DCDD, donation after the circulatory determination of death; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; MAiD, medical assistance in dying; TA-NRP, thoraco-abdominal normothermic regional perfusion.

on how TA-NRP protocols affect standards to diagnose death.[27-31] We believe that the effective prevention of brain flow makes TA-NRP compatible with these standards under a unified concept of death.[18,26,32]

Therefore, if legally and ethically permissible, TA-NRP could be considered the preferred approach to recovering the DCDD heart for several reasons. First, TA-NRP allows the simultaneous perfusion of all DCDD organs, with evidence of improved

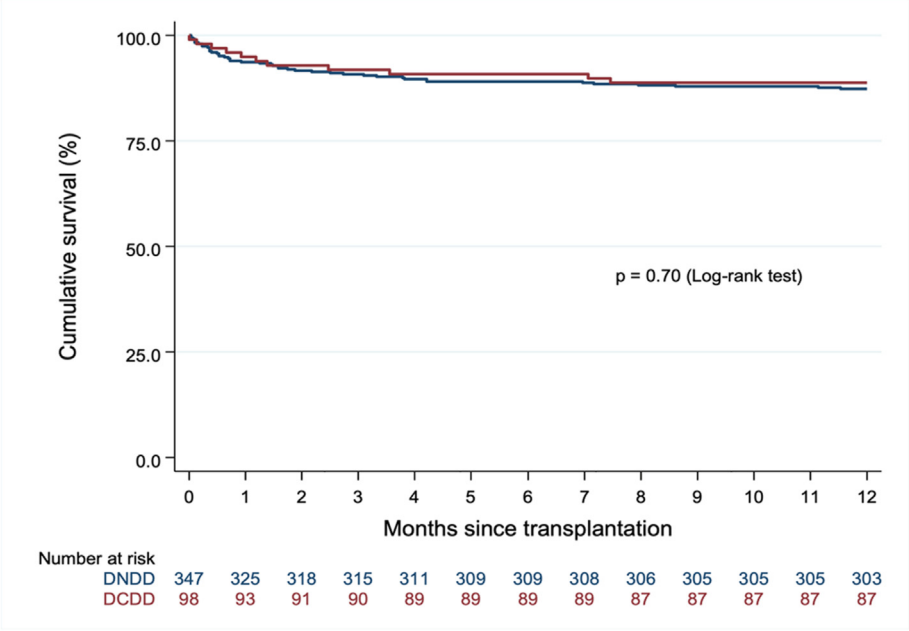

Figure 4. Survival (Kaplan-Meier), by donor type. DCDD, donation after the circulatory determination of death; DNDD, donation after the neurologic determination of death.

organ utilization compared with the standard rapid recovery technique.[33] Notably, a mean of 4.21 organs were transplanted per DCDD donor whose heart was used for transplantation, compared with 4.36 in the DNDD group (Supplementary Tables 3 and 4).[33-37] The existing literature suggests that lung recovery and posttransplant results are not negatively influenced by TA-NRP, though more data are needed.[38,39] Our strategies to make lung recovery possible in TA-NRP protocols have been described elsewhere.[39] NRP eliminates the need to resort to expensive organ-specific ex situ machine perfusion devices, reducing costs and allowing more patients to access high-quality organs. Second, and despite a higher donor age, the overall utilization of DCDD hearts obtained with TA-NRP was 89% in our experience, comparable to the 81% to 89% utilization rate described with DPP.[2,40] Third, recipients of DCDD hearts in our study exhibited a similar rate of severe PGF and rejection than recipients of DNDD hearts. Notably, DCDD hearts recovered via DPP seem to exhibit a higher incidence of PGF and rejection than DNDD hearts.[2,3,40] This is important as, although severe PGF can be treated with VA-ECMO, the outcomes of these patients are significantly worse than those without this event.[41]

Despite the complexity of the TA-NRP procedure, this could be reproduced in 31 donor centers, most without a heart transplant program. This was possible thanks to the engagement of the donor coordination network and the planning of each procedure in a manner that was tailored to the singularities of the centers concerned. Two key elements of the national protocol were to effectively exclude the brain during TA-NRP[26] and to prevent the loss of other organs. Regarding the first issue, the surgical refinements described in our protocol emerged from the ideas proposed by Manara et al,[17] who warned that the simple cross-clamping or ligation of the arch vessels might not be sufficient to isolate the brain. Based on these findings, our decision was to clamp the supraaortic arch vessels, cut and vent them to the atmosphere.[13] With this approach, Royo-Villanova et al[18] confirmed the absence of brain perfusion by the invasive monitoring of the intracranial blood pressure. Regarding the second element of the protocol, it is important to emphasize that controlled DCDD in Spain has historically relied on A-NRP with outstanding transplant outcomes.[33,34,42] The incorporation of the recovery of the heart into the well-established A-NRP procedure raised concerns about the impact on recovery rates and outcomes of abdominal grafts. This explains why in 34% of DCDD heart recoveries, A-NRP was initiated while the venting of the arch vessels, to reduce warm ischemia for abdominal organs. Although the direct initiation of TA-NRP was the predominant strategy, the placement of an intraaortic balloon was common practice to rapidly switch to A-NRP should the heart not be suitable for transplantation.

Our study is limited by its observational nature and a relatively short follow-up of DCDD heart recipients. Another limitation concerns the subanalysis of TA-NRP DCDD heart transplant cases, as the number of procedures is still modest. Lastly, comparisons within the DCDD group were not adjusted for other factors and should therefore be considered informative only and interpreted with caution.

In conclusion, DCDD hearts obtained via TA-NRP followed by SCS provide short-term outcomes similar to those of DNDD heart transplants. Our experience can help other countries to expand heart transplant opportunities and offer DCDD donors

the chance to contribute to the life-transforming therapy that heart transplantation is.

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Francisco González-Vilchez: Application of statistical, mathematical, computational to analyze study data. Substantial contributions to the conception of the work. First drafting and subsequent revisions of the manuscript for content, including medical writing for content. Data curation. Reviewing it critically for important intellectual content. Final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The authors of this manuscript have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2025.02.006.

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