



Donation after circulatory death heart procurement strategy impacts utilization and outcomes of concurrently procured abdominal organs

Jason Thomas, BS,^{a,#} Qiudong Chen, MD,^{a,#} Amy Roach, MD,^a
Stanley Wolfe, MD,^b Asishana A. Osho, MD, MPH,^{a,b} Vinay Sundaram, MD,^c
Steven A. Wisel, MD,^c Dominick Megna, MD,^a Dominic Emerson, MD,^a
Lawrence Czer, MD,^d Fardad Esmailian, MD,^a Joanna Chikwe, MD,^a
Irene Kim, MD,^c and Pedro Catarino, MD^a

From the ^aDepartment of Cardiac Surgery, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California;

^bDivision of Cardiac Surgery, Corrigan Minehan Heart Center, Massachusetts General Hospital, Boston, Massachusetts;

^cComprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, California; and the ^dDepartment of Cardiology, Smidt Heart Institute, Los Angeles, California.

KEYWORDS:

donation after
circulatory death;
heart transplantation;
organ procurement;
normothermic regional
perfusion

INTRODUCTION: The impact of donation after circulatory death (DCD) heart procurement techniques on the utilization and outcomes of concurrently procured DCD livers and kidneys remains unclear.

METHODS: Using the United Network for Organ Sharing database, we identified 246 DCD donors whose heart was procured using direct procurement and ex-situ machine perfusion and 128 DCD donors whose heart was procured using in-situ thoracoabdominal normothermic regional perfusion (12/2019-03/2022). We evaluated the transplantation rate of concurrently procured DCD livers and kidneys (defined as the number of organs transplanted/total number of organs available for procurement) and their post-transplant outcomes.

RESULTS: The transplantation rate of concurrently procured DCD livers was higher with in-situ perfusion compared to direct procurement (67.1% vs 56.5%, $p = 0.045$). After excluding pediatric, multiorgan, and repeat transplant recipients, there was no difference in 6-month liver graft failure rate (direct procurement 0.9% vs in-situ perfusion 0%, $p > 0.99$). Recipients of kidneys procured with in-situ perfusion had less delayed graft function (11.3% vs 41.5%, $p < 0.0001$) shorter length of stay, and lower serum creatinine at discharge (both $p < 0.05$). Six-month recipient survival in the direct procurement and in-situ perfusion group were similar after DCD liver and kidney transplantation ($p = 0.24$ and 0.79 respectively).

CONCLUSIONS: Compared to direct procurement, DCD heart procurement with in-situ thoracoabdominal normothermic regional perfusion was associated with increased utilization of DCD livers and a lower incidence of delayed graft function in concurrently procured DCD kidneys. Broader implementation of DCD heart transplantation must maximize the transplant potential of concurrently procured abdominal organs and ensure their successful outcomes.

J Heart Lung Transplant 2023;42:993–1001

© 2023 International Society for Heart and Lung Transplantation. All rights reserved.

[#]These authors have contributed equally to this work.

Reprint requests: Pedro Catarino, MD, Department of Cardiac Surgery, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, #A3600,

Los Angeles, CA 90048. Telephone: +1 310-423-3851. Fax: +1 310-423-0246.

E-mail address: Pedro.Catarino@cshs.org

Donation after circulatory death (DCD) heart transplantation has the potential to significantly increase the heart donor pool.¹⁻³ Encouraging results from international experiences and the US DCD Heart Trial (NCT03831048) provided further evidence to support its increased adoption.⁴⁻⁷ When both the heart and other abdominal organs are procured from a DCD donor, questions remain about the potential impact of DCD heart procurement strategies on abdominal organ utilization and outcomes.^{8,9} In contemporary practice, heart procurement in DCD donors has utilized 1 of the 2 techniques: direct procurement with machine perfusion or thoracoabdominal normothermic regional perfusion.¹⁰ With direct procurement, the donor heart is expeditiously explanted and placed on an ex-situ heart perfusion machine for reanimation and further assessment. This requires approximately 1.2-1.5 liters of donor blood to be drained to prime the ex-situ heart perfusion system before donor aortic cross-clamping and heart explanation. In some situations, this constitutes an additional 1-2 minutes of warm ischemia for the abdominal organs, as the initiation of the abdominal organ perfusion could be delayed until donor blood collection is completed by the heart team. In comparison, when thoracoabdominal normothermic regional perfusion is used, in-situ reperfusion is rapidly established after circulatory death through extracorporeal circulatory support via central aortic and right atrial cannulation. This approach leads to more rapid reperfusion of all transplantable donor organs and allows recovery from the initial warm ischemic insult.^{10,11} It follows the same principles as abdominal normothermic regional perfusion that has been used in DCD liver procurement.¹²

Successful adoption of DCD heart transplantation must also maximize the transplant potential of other organs from the same DCD donor. In this context, it remains unclear whether different DCD heart procurement strategies affect the utilization and early recipient outcomes of concurrently procured DCD abdominal organs. Therefore, we analyzed the United Network for Organ Sharing (UNOS) database to evaluate the differences in utilization and short-term outcomes of DCD livers and kidneys that are procured concurrently with DCD donor hearts.

Materials and methods

Data source

This retrospective analysis was performed using the UNOS Standard Transplant Analysis and Research files as of April 5, 2022, which included information on organ donation, transplants, and new listings occurring through March 31, 2022. We identified 421 DCD donors whose heart was procured between December 2019 and March 2022. They were stratified by the heart procurement technique into in-situ thoracoabdominal normothermic regional perfusion (herein referred to as “in-situ perfusion”, $n=128$) and direct procurement with ex-situ machine perfusion ($n=246$). Because the DCD heart procurement technique was not directly captured in the UNOS database, we identified this based on the time interval between death confirmation and aortic cross-clamping during procurement. Since direct procurement requires expeditious sternotomy and cross-clamping of the donor aorta after death

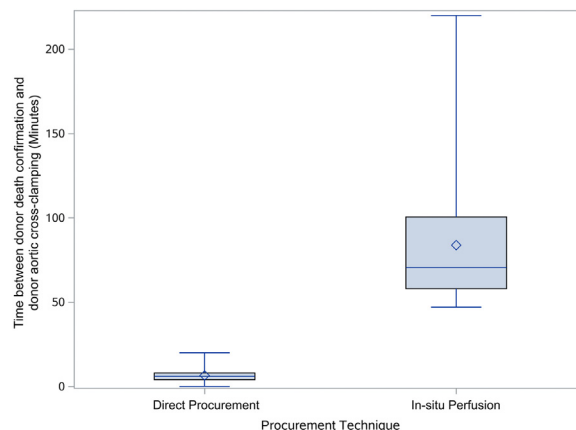


Figure 1 Time between donor death confirmation and donor aortic cross-clamping stratified by DCD heart procurement technique. The median time interval was 6 (range 1-20) minutes with direct procurement and 71 (range 48-220) minutes with in-situ perfusion.

to minimize warm ischemia, an interval ≤ 20 minutes was considered to involve its use. Conversely, a greater than 20-minute interval was considered to indicate the use of in-situ perfusion, as it typically involves a period of in-situ reanimation and functional assessment of the donor heart prior to aortic cross-clamping and heart explantation (Figure 1). Forty-seven DCD heart donors could not be classified due to missing time of either declaration of death or aortic cross-clamping and were excluded.

Among the 374 DCD heart donors included, a total of 265 livers and 734 kidneys were procured for transplant, and 225 livers and 681 kidneys were successfully transplanted. To create a secondary cohort for the analysis of recipient outcomes, we excluded pediatric, multiorgan, repeat transplant recipients, and recipients with unvalidated records (Figure 2). This study was approved by the Institutional Review Board at Cedars-Sinai Medical Center (with a waiver of informed consent) and is in compliance with the International Society for Heart and Lung Transplantation ethics statement.

Primary and secondary outcomes

The primary outcomes included organ transplantation rates and 6 month post-transplant survival. Organ transplantation rate was defined as the number of organs transplanted divided by the total number of organs available for procurement. We also considered using the number of organs transplanted divided by the total number of organs procured to reflect transplantation rate. However, because in-situ perfusion allows in-situ assessment of donor organ function so that poor-quality organs can be potentially rejected without recovery, we elected to not use this approach.

Median follow-up times for the entire liver and kidney recipient cohorts were 6.2 (interquartile range [IQR] 0.5-12.2) and 6.4 (IQR 1.2-12.1) months respectively. To avoid informative censoring due to the use of very recent UNOS data, only recipients transplanted before October 1st, 2021 were included in the time-to-event analysis of survival. Secondary outcomes included in-hospital episodes of acute rejection, hospital length of stay, and 30-day mortality. For kidney recipients, we also evaluated the incidence of delayed graft function, defined as dialysis requirement during the first week after kidney transplantation.

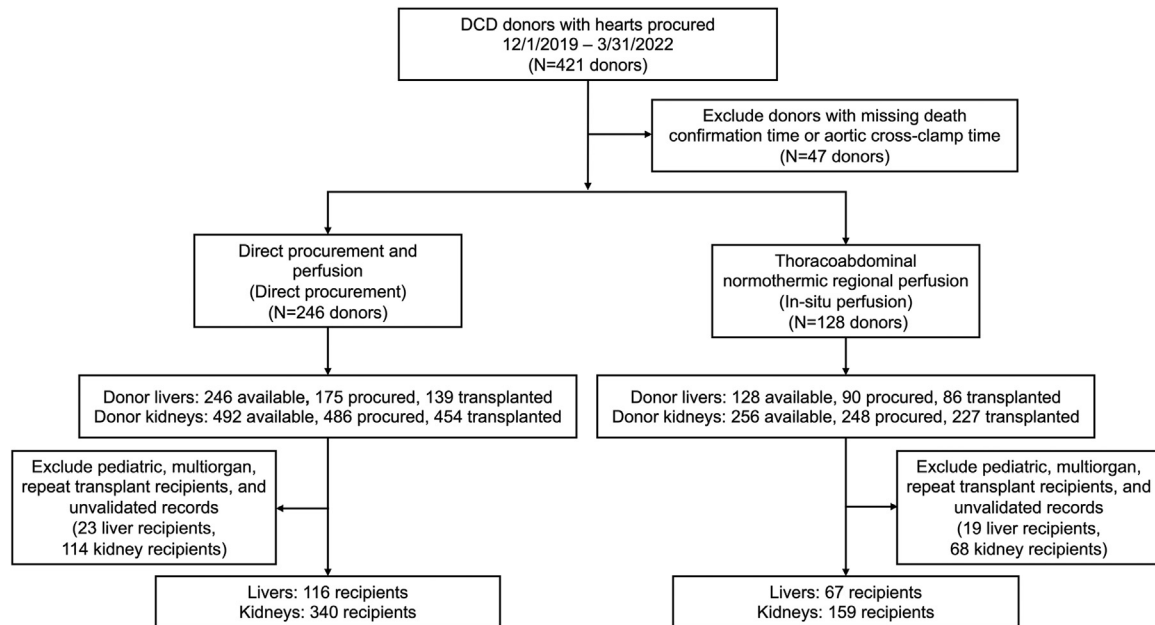


Figure 2 Cohort identification DCD, donation after circulatory death.

Statistical analysis

Baseline characteristics were described either as means $\pm$ standard deviation or as medians and IQR for continuous variables depending on the overall distribution. Categorical variables were described as frequencies and percentages. Differences between groups were analyzed using Student's *t*-test or Wilcoxon signed-rank test for continuous variables depending on the overall distribution. Pearson's chi-square or Fisher Exact was performed for categorical variables where appropriate. Post-transplant 6 month survival was analyzed using the Kaplan Meier method and compared using the log-rank test.

To determine the independent effect of DCD heart procurement on delayed kidney graft function in DCD kidney recipients, we constructed a multivariable logistic regression model. Variables included for adjustment were selected based on clinical relevance and included both recipient characteristics (age, body mass index, race, Cytomegalovirus [CMV] status, etiology of renal disease) and donor characteristics (kidney donor profile index [KDPI], gender, cocaine use, and ischemic time). Patients with missing values ($n=19$) were excluded in this regression analysis. All tests were 2 tailed and an alpha level of 0.05 was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Organ utilization

Hearts were procured from 246 DCD donors using direct procurement and from 128 DCD donors using in-situ perfusion. Among these donors, livers were procured from 175 donors (71.1%, 175/246) in the direct procurement group and from 90 donors (70.3%, 90/128) in the in-situ perfusion group ($p = 0.87$). Direct procurement was associated with a donor liver transplantation rate of 56.5% (139/246) while in-situ perfusion resulted in a liver transplantation rate of

67.1% (86/128) ($p = 0.045$, Figure 3A). In the direct procurement group, 36 donor livers were discarded after procurement, and top reasons included prolonged warm ischemic time ($n=12$) and poor flushing ($n=4$) (Supplementary Table 1). In the in-situ perfusion group, 4 livers were discarded after procurement due to prolonged warm ischemic time ($n=2$), recipient deterioration ($n=1$), and an exhausted waitlist ($n=1$). In DCD livers that are successfully transplanted, there was no difference in the utilization of liver ex-situ machine perfusion between the direct procurement and in-situ perfusion group (2.9% vs 3.5%, $p > 0.99$).

In the direct procurement group, 486 out of the 492 available donor kidneys (98.5%) were procured, and in the in-situ perfusion group, 248 out of 256 available donor kidneys (95.5%) were procured ($p = 0.07$). Direct procurement was associated with a kidney transplantation rate of 92.3% (454/492), and in-situ perfusion was associated with a kidney transplantation rate of 88.7% (227/256) ($p = 0.10$, Figure 3B). Detailed reasons for organ discard after procurement are outlined in Supplementary Table 2. In DCD kidneys that are successfully transplanted, there was no difference in the utilization of kidney ex-situ machine perfusion between the direct procurement and in-situ perfusion group (74.7% vs 74.2%, $p = 0.91$).

Recipient and donor characteristics

Recipients of directly procured DCD livers were more frequently White (87.1% vs 73.1%, $p = 0.03$) and had type O blood (70.7% vs 53.7%, $p = 0.02$). They also had a greater prevalence of gross ascites compared to recipients of livers procured using in-situ perfusion (35.3% vs 13.4%, $p = 0.001$). Other differences in baseline DCD liver recipient characteristics are reported in Table 1. Regarding donor

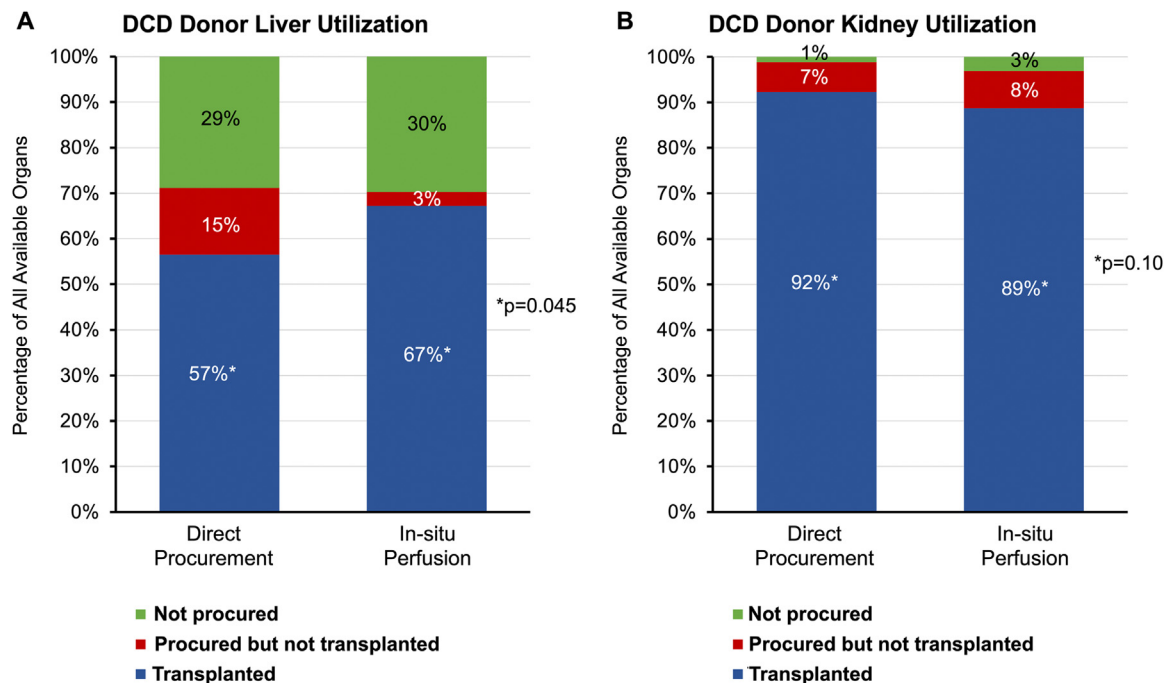


Figure 3 Donor liver (A) and kidney (B) utilization based on DCD heart procurement strategy. Stacked bar chart outlining DCD donor organ utilization. The percentages shown are calculated using the total number of available organs as the denominator.

characteristics, directly procured DCD livers were less frequently from Hispanic donors (6.9% vs 17.9%) ($p = 0.001$, Table 1).

Recipients of directly procured DCD kidneys were older (48 [IQR 37-58] vs 42 [IQR 32-55] years, $p = 0.005$) and less frequently positive for Cytomegalovirus (CMV) (59.4% vs 69.2%, $p = 0.04$) compared to those in the in-situ perfusion group. Directly procured DCD kidneys were also from older donors (30 [IQR 24-36] vs 27 [21-34] years, $p = 0.02$) with a higher KDPI (0.23 [IQR 0.13-0.39] vs 0.19 [IQR 0.10-0.33], $p = 0.02$). Other kidney donor characteristics are outlined in Table 2.

Post-transplant outcomes

After DCD liver transplantation, the rate of acute rejection before discharge was 2.6% with direct procurement and 4.5% with in-situ perfusion ($p = 0.67$). Thirty-day mortality was 1.1% with direct procurement and 0.0% with in-situ perfusion ($p = 0.53$, Table 3). During the 6-month follow-up, graft failure occurred in one (0.9%) recipient in the direct procurement group (due to primary graft non-function on post-transplant day 2), and in no recipients in the in-situ perfusion group ($p > 0.99$). Six-month survival was 95.6% (95% confidence interval [CI] 87.5%-98.6%) with direct procurement and 100% with in-situ perfusion ($p = 0.24$, Figure 4). The 4 deaths in recipients of directly procured livers were due to hemorrhagic stroke, renal failure, lower gastrointestinal hemorrhage, and unknown causes.

After DCD kidney transplantation, there were 4 episodes of in-hospital acute rejection in the direct procurement group and none in the in-situ perfusion group (1.2% vs 0%,

$p > 0.99$). Thirty-day mortality was 0.6% ($n=2$) with direct procurement and 0.6% ($n=1$) with in-situ perfusion ($p > 0.99$) (Table 3). Recipients of directly procured kidneys were significantly more likely to experience delayed graft function (41.5% vs 11.3%, $p < 0.001$) and had longer hospital lengths of stay with higher creatinine at discharge (Table 3). In the multivariable analysis adjusting for baseline recipient and donor characteristics, direct procurement was independently associated with an increased risk of delayed graft function (adjusted odds ratio 3.69, 95% CI 1.94-7.03, Supplementary Table 3). Six-month survival in kidney recipients was 97.9% (95% CI 94.8%-99.1%) with direct procurement and 96.9% (95% CI 85.2%-99.4%) with in-situ perfusion ($p = 0.79$, Figure 4). Six deaths occurred in recipients of directly procured kidneys, and causes included cardiac arrest, cardiopulmonary failure, natural causes, chronic myelogenous leukemia, and lung cancer. Two deaths occurred in recipients of kidney procured with in-situ perfusion, 1 due to hemorrhagic shock and the other died of intracranial hemorrhage. Graft failure occurred in 6 recipients of directly procured kidneys (thrombosis [post-operative day (POD) 2], nephrectomy secondary to bleed [POD 47], pseudoaneurysm [POD 116], primary nonfunction [POD 91 and 144], acute rejection [POD 161]) and 1 recipient in the in-situ perfusion group (mycotic aneurysm [POD 125]).

Discussion

This analysis of the national UNOS database compares the utilization and outcomes of transplantable abdominal organs procured concurrently with DCD donor hearts in the United States. Our data suggest that when both the heart and abdominal organs are procured from the same DCD

Table 1 Baseline Liver Recipient and Donor Characteristics Stratified by DCD Heart Procurement Strategy

	Direct Procurement (n = 116)	In-situ Perfusion (n = 67)	p-value
Recipient characteristics			
Age (years)	58 (49-65)	59 (50-63)	0.90
Body mass index (kg/m ²)	28.3 (24.5-32.2)	29.9 (26.1-32.4)	0.24
Male sex	81 (69.8)	50 (74.6)	0.49
Race			0.03
White	101 (87.1)	49 (73.1)	
Black	3 (2.6)	1 (1.5)	
Hispanic	11 (9.5)	13 (19.4)	
Other	1 (0.9)	4 (6.0)	
Diabetes	36 (31.0)	23 (34.3)	0.65
Cytomegalovirus positivity ^a	64 (56.1)	36 (54.6)	0.84
Liver disease etiology			0.73
Alcoholic cirrhosis	41 (35.3)	23 (34.3)	
Hepatocellular carcinoma & cirrhosis	33 (28.5)	14 (20.9)	
Non-alcoholic steatohepatitis	21 (18.1)	13 (19.4)	
Autoimmune ^b	8 (6.9)	5 (7.5)	
Viral hepatitis	6 (5.2)	4 (6.0)	
Cryptogenic	3 (2.6)	5 (7.5)	
Other	4 (3.5)	3 (4.5)	
Days on waitlist	136 (30-306)	114 (21-281)	0.56
Blood type O	82 (70.7)	36 (53.7)	0.02
Mechanical ventilation	1 (0.9)	0	>0.99
Portal vein thrombosis	17 (14.7)	5 (7.5)	0.15
Encephalopathy Grade 3 or 4 at Transplant	12 (10.2)	7 (10.5)	0.98
Gross ascites	41 (35.3)	9 (13.4)	0.001
Albumin (mg/dL)	3.3 (2.9-3.6)	3.2 (2.8-3.7)	0.74
Bilirubin (mg/dL)	2.8 (1.7-5.6)	3.0 (1.9-5.7)	0.70
INR	1.6 (1.3-1.8)	1.6 (1.4-1.9)	0.62
INR >2	27 (23.3)	14 (20.9)	0.71
Creatinine (mg/dL)	0.98 (0.75-1.35)	0.97 (0.80-1.25)	0.97
MELD Score	19 (14-26)	19 (13-24)	0.94
Location prior to transplant			0.68
Home	101 (87.1)	58 (86.6)	
Hospital, non-ICU	13 (11.2)	9 (13.4)	
Hospital, ICU	2 (1.7)	0	
Donor characteristics			
Age (years)	28 (23-33)	28 (21-34)	0.62
Body mass index (kg/m ²)	25.4 (22.9-28.5)	26.2 (23.8-29.1)	0.37
Male gender	102 (87.9)	61 (91.0)	0.52
Creatinine (mg/dL)	0.80 (0.66-1.02)	0.73 (0.60-0.90)	0.19
Race			0.001
White	91 (78.5)	54 (80.6)	
Black	14 (12.1)	0 (0.0)	
Hispanic	8 (6.9)	12 (17.9)	
Other	3 (2.6)	1 (1.5)	
Diabetes	1 (0.9)	1 (1.5)	>0.99
Hypertension	10 (8.6)	4 (6.0)	0.52
Smoking	11 (9.5)	3 (4.5)	0.22
Cocaine use ^c	26 (22.6)	19 (28.4)	0.39
Cancer	2 (1.7)	2 (3.0)	0.62
Cause of death			0.92
Head trauma	58 (50.0)	35 (52.2)	
Anoxic brain injury	49 (42.2)	29 (43.3)	
Stroke	4 (3.5)	1 (1.5)	
Other	5 (4.3)	2 (5.4)	
Ischemic time (hours)	5.0 (4.5-6.1)	4.8 (3.9-6.2)	0.34

DCD, donation after circulatory death; ICU, intensive care unit; MELD, model for end-stage liver disease.

Values are in n (%) or median (interquartile range).

^aMissing in 3 recipients.^bAutoimmune liver disease also included primary biliary sclerosis and primary sclerosing cholangitis.^cMissing in 1 donor.

Table 2 Baseline Kidney Recipient and Donor Characteristics Stratified by DCD Heart Procurement Strategy

	Direct Procurement (n = 340)	In-situ Perfusion (n = 159)	p-value
Recipient characteristics			
Age (years)	48 (37-58)	42 (32-55)	0.005
Body mass index (kg/m ²)	28.9 (25.2-34.2)	28.6 (23.7-33.5)	0.20
Male sex	190 (55.9)	90 (56.6)	0.88
Race			0.06
White	114 (33.5)	44 (27.7)	
Black	141 (41.5)	59 (37.1)	
Hispanic	62 (18.2)	46 (28.9)	
Other	23 (6.8)	10 (6.3)	
History			
Diabetes mellitus	88 (25.9)	36 (22.6)	0.44
Hepatitis C antibody ^a	10 (3.0)	4 (2.6)	>0.99
Cytomegalovirus positivity ^b	200 (59.4)	108 (69.2)	0.04
Pretransplant dialysis	312 (91.8)	147 (92.5)	0.79
Creatinine (mg/dL) ^c	8.4 (5.7-11.7)	8.6 (6.4-11.7)	0.15
Etiology			0.17
Hypertensive nephropathy	84 (24.7)	43 (27.0)	
Diabetic nephropathy	75 (22.1)	31 (19.5)	
Focal segmental glomerulosclerosis	30 (8.8)	19 (12.0)	
Polycystic kidney disease	37 (10.9)	6 (3.8)	
Systemic lupus erythematosus	25 (7.4)	11 (6.9)	
IgA nephropathy	17 (5.0)	11 (6.9)	
Other	72 (21.2)	38 (23.9)	
Days on waitlist	505 (115-1315)	609 (99-1427)	0.86
ABO match level			0.34
Exact	326 (95.9)	156 (98.1)	
Compatible	10 (2.9)	1 (0.6)	
Incompatible	4 (1.2)	2 (1.3)	
Donor characteristics			
	Direct Procurement (n = 212)	In-situ Perfusion (n = 100)	p-value
Age (years)	30 (24-36)	27 (21-34)	0.02
Body Mass Index (kg/m ²)	26.7 (24.1-31.1)	26.6 (24.0-29.9)	0.30
Male Sex	186 (87.7)	94 (94.0)	0.09
Kidney Donor Profile Index	0.23 (0.13-0.39)	0.19 (0.10-0.33)	0.02
Creatinine (mg/dL) ^d	0.80 (0.66-1.09)	0.79 (0.61-0.90)	0.12
Race			0.007
White	172 (81.1)	79 (79.0)	
Black	23 (10.9)	3 (3.0)	
Hispanic	15 (7.1)	15 (15.0)	
Other	2 (0.9)	3 (3.0)	
Hypertension	28 (13.2)	7 (7.0)	0.10
Diabetes	5 (2.4)	1 (1.0)	0.67
Smoking ^e	20 (9.4)	6 (6.1)	0.32
Cocaine use ^f	46 (22.4)	30 (30.6)	0.12
Cause of Death			0.69
Head Trauma	100 (47.2)	50 (50.0)	
Anoxic Brain Injury	97 (45.8)	40 (40.0)	
Stroke	10 (4.7)	6 (6.0)	
Other	5 (2.4)	4 (4.0)	
Ischemic Time (hours) ^g	17.6 (13.5-21.9)	18.3 (14.7-22.5)	0.11

DCD, donation after circulatory death.

Values are in n (%) or median (interquartile range).

^aMissing in 6 recipients.^bMissing in 6 recipients.^cMissing in 2 recipients.^dMissing in 5 donors.^eMissing in 1 donor.^fMissing in 9 donors.^gMissing in 4 recipients.

Table 3 Short-term Outcomes in DCD Liver and Kidney Recipients Stratified by DCD Heart Procurement Strategy

Liver Recipient Outcomes			
	Direct Procurement (n = 116)	In-situ Perfusion (n = 67)	p-value
In-hospital acute rejection episodes	3 (2.6)	3 (4.5)	0.67
Length of stay (days) ^a	8 (6-13)	7 (6-11)	0.17
30-day mortality	2 (1.7)	0	0.53
Kidney Recipient Outcomes			
	Direct Procurement (n = 340)	In-situ Perfusion (n = 159)	p-value
In-hospital acute rejection episodes	4 (1.2)	0 (0)	0.31
Delayed graft function ^b	141 (41.5)	18 (11.3)	<0.001
Creatinine at discharge (mg/dL)	5.8 (3.3-8.5)	2.0 (1.3-4.3)	<0.001
Length of stay (days) ^c	5 (3-6)	4 (3-5)	0.002
30-day mortality	2 (0.6)	1 (0.6)	>0.99

DCD, donation after circulatory death.

Values are in n (%) or median (interquartile range).

^aMissing in 11 liver recipients.^bDelayed graft function was defined as requiring dialysis within the first week after kidney transplantation.^cMissing in 13 recipients.

donor, in-situ thoracoabdominal normothermic regional perfusion was associated with an increased transplantation rate of DCD livers and a lower incidence of delayed kidney graft function. Short-term post-transplant survival among DCD liver and kidney recipients was not different irrespective of the DCD heart procurement strategy.

As the utilization of DCD heart transplantation in the United States increases, it is important that the transplant potential of abdominal organs in DCD donors is also maximized. In this context, the use of in-situ thoracoabdominal regional perfusion provides the advantages of faster warm reperfusion of abdominal organs and reduced warm ischemia. The reinstitution of circulatory support also allows the abdominal procurement operation to proceed like that of donation after brain death donors, thereby eliminating the need for rapid dissection under the pressure of minimizing warm ischemic time. Previous studies have demonstrated that the use of in-situ abdominal regional perfusion in DCD liver procurement resulted in reduced postoperative biliary complications and graft

loss compared to direct procurement.^{12,13} Similarly, the use of in-situ abdominal regional perfusion in DCD kidney procurement was shown to result in lower rates of delayed graft function compared to direct procurement, which is consistent with our observations.¹⁴ These differences are likely a result of the transition from warm ischemia directly to cold ischemia in direct procurement, as opposed to the warm reperfusion following warm ischemia in in-situ perfusion. Previous experimental studies have demonstrated that post-mortem normothermic perfusion can restore metabolic processes and repair cellular injury secondary to warm ischemia.¹⁵ Additionally, it is important to note that in-situ abdominal regional perfusion primarily relies on retrograde perfusion via the femoral arteries and aortic interruption via balloon occlusion, while thoracoabdominal regional perfusion used in DCD heart procurement is typically performed with central cannulation. This can potentially provide more physiological antegrade perfusion of the abdominal organs as well as improved venous decompression.

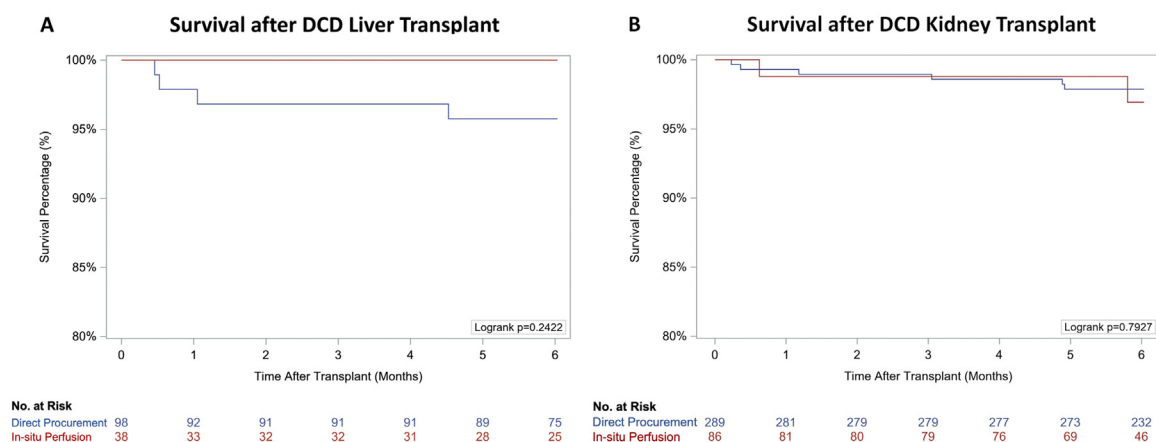


Figure 4 Six-month survival in DCD liver and kidney recipients stratified by DCD heart procurement strategy To allow sufficient follow-up and minimize informative censoring, only recipients transplanted before October 1st, 2021 (6-months prior to study end), were included in the analysis of 6-month survival.

During the multiorgan recovery process in DCD donors, collaboration between different procurement teams is critical, and is particularly relevant when direct procurement is used. When a DCD donor heart is directly procured, the collection of donor blood under warm ischemia by the thoracic team to prime the ex-situ heart perfusion machine typically takes place before the abdominal team starts infusing antegrade flush into the abdominal organs. This creates potential conflicting priorities between the thoracic and abdominal teams and may have contributed to the decreased transplant rate we observed in DCD livers when direct procurement is used. Technical nuances and potential pitfalls during this step have been previously described.¹⁶ Preemptive control of the supra celiac or thoracic aorta and inferior vena cava during multi-organ DCD recovery has also been proposed to allow the perfusion of abdominal organs without delay.^{17,18} Nevertheless, careful preparation, coordination, and communication are essential to avoid jeopardizing the viability of the abdominal organs during DCD heart procurement. Our findings also underline the potential need for standardized multi-organ procurement protocols at the Organ Procurement Organization or national level in DCD donors.

Comparisons of direct procurement and in-situ perfusion must also take cost, resource utilization, and ethical implications into consideration. Although not evaluated in our study, direct procurement is associated with significantly higher costs due to the use of the ex-situ heart perfusion console. In contrast, in-situ perfusion typically requires greater expertise and an additional team member to initiate the extracorporeal perfusion. Ethical controversies also surround the use of in-situ perfusion due to the in-situ restoration of perfusion after circulatory death, and consequently, this approach may not be accepted or available at all procurement hospitals. For example, in a recent analysis of the UNOS database, only 7 out of the 22 U.S. centers performing DCD heart transplantation between 2019 and 2022 have utilized in-situ perfusion for donor heart procurement.¹⁹ Consensus guidelines from major stakeholders from all disciplines, including patients, family representatives, and organ procurement organizations, will be necessary to overcome the ethical challenges surrounding in-situ perfusion.²⁰

Our study has several limitations. First, the technique of DCD heart procurement was classified using a surrogate measure. Although this could result in misclassification, there was a natural break in the time interval between death confirmation and donor aortic cross-clamping at 20 minutes (Figure 1). This cutoff is also consistent with real-world clinical practice of DCD heart procurement. In most cases of direct procurement, it takes less than 5 minutes to complete sternal entry and aortic cross-clamping, although this can be longer based on experience. Second, when in-situ perfusion is used, the exact time of donor organ reperfusion is not recorded in the UNOS database. Therefore, we could not determine the warm ischemic time with in-situ perfusion and compare them to directly procured donors. Third, we were unable to identify donors who underwent in-situ perfusion for intended heart procurement, but the heart was not procured. This may occur due to technical

complications during cannulation (e.g., iatrogenic aortic dissection) or poor graft function/quality that is discovered after sternal entry. Consequently, the abdominal organ utilization rates may be different if these cases were included. However, a previous single-center report described that in DCD donors who underwent heart recovery using in-situ perfusion, despite technical complications such as iatrogenic aortic dissection resulting in abandonment of donor hearts, these donors were still cannulated and systemic perfusion initiated for abdominal organs, which resulted in their successful transplantations.³ Fourth, although we performed a logistic regression to adjust for baseline recipient and donor risk factors when evaluating delayed kidney graft function, similar risk adjustments were not done with other outcomes due to the low event rates and insufficient sample size to create a robust regression model. We also considered a propensity-matched analysis but elected to not do so due to the potential loss of patients in the matching process. Therefore, selection bias exists and may have confounded our results. Fifth, given the limited number of DCD heart donations thus far in the United States, our study may be underpowered to detect subtle differences in outcomes. Lastly, follow-up was too short to draw meaningful conclusions regarding the longer-term effects of concurrent DCD heart procurement on outcomes after DCD liver and kidney transplantation.

Conclusions

This national registry analysis suggests that among DCD donors, the donor heart procurement strategy could have an impact on the utilization and outcomes of concurrently procured abdominal organs. The use of thoracoabdominal normothermic regional perfusion for DCD heart procurement was associated with increased utilization of DCD livers, equivalent liver recipient outcomes, and a lower incidence of delayed graft function in DCD kidneys compared to direct procurement. These findings have important implications for the selection of heart procurement techniques in joint DCD procurements. As the practice of DCD heart transplantation continues to expand, it is crucial to maximize the transplant potential and optimize outcomes of concurrently procured abdominal organs in DCD donors.

Author Contributions

JT, QC, and PC were involved in the study conceptualization and design. JT, QC, and AR conducted the data analysis. JT, QC, AR, and SW drafted the manuscript. AO, VS, SW, DM, DE, IK, and PC were involved in the data interpretation and manuscript writing/review. AO, LC, FE, JC, IK, SW, and PC were involved in the critical revisions and final approval of the article.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Funding

Jason Thomas is supported in part by the Office of Scholarly Engagement, Harvard Medical School. Qiudong Chen and Amy Roach are both supported by a grant from the National Institutes of Health for advanced heart disease research (T32HL116273). Stanley B. Wolfe's research fellowship is made possible through philanthropic funding from the Corrigan-Minehan and Martignetti families. This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.healun.2023.02.1497>.

References

- Jawitz OK, Raman V, DeVore AD, et al. Increasing the United States heart transplant donor pool with donation after circulatory death. *J Thorac Cardiovasc Surg* 2020;159:e307-9. <https://doi.org/10.1016/j.jtcvs.2019.09.080>.
- Madan S, Saeed O, Forest SJ, et al. Feasibility and potential impact of heart transplantation from adult donors after circulatory death. *J Am Coll Cardiol* 2022;79:148-62. <https://doi.org/10.1016/j.jacc.2021.10.042>.
- Hoffman JRH, McMaster WG, Rali AS, et al. Early US experience with cardiac donation after circulatory death (DCD) using normothermic regional perfusion. *J Heart Lung Transplant* 2021;40:1408-18. <https://doi.org/10.1016/j.healun.2021.06.022>.
- Chew HC, Iyer A, Conellan M, et al. Outcomes of donation after circulatory death heart transplantation in Australia. *J Am Coll Cardiol* 2019;73:1447-59. <https://doi.org/10.1016/j.jacc.2018.12.067>.
- Messer S, Page A, Axell R, et al. Outcomes after heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transplant* 2017;36:1311-8. <https://doi.org/10.1016/j.healun.2017.10.021>.
- Lomero M, Gardiner D, Coll E, et al. Donation after circulatory death today: an updated overview of the European landscape. *Transpl Int* 2020;33:76-88. <https://doi.org/10.1111/tri.13506>.
- Schroder JN, Shah A, Pretorius V, et al. Expanding Heart Transplants from Donors After Circulatory Death (DCD) — Results of the First Randomized Controlled Trial Using the Organ Care System (OCS™) Heart — (OCS DCD Heart Trial). *J Heart Lung Transplant* 2022;41:S72. <https://doi.org/10.1016/j.healun.2022.01.165>.
- Gauntt K, Carrico B, Klassen D. DCD Heart Donation: Impact on Organ Yield [abstract]. *Am J Transplant* 2021;21(Suppl 3). Available at <https://atcmeetingabstracts.com/abstract/dcd-heart-donation-impact-on-organ-yield/>. Accessed April 02, 2022.
- Feizpour CA, Gauntt K, Patel MS, et al. The impact of machine perfusion of the heart on warm ischemia time and organ yield in donation after circulatory death. *Am J Transplant* 2022;22:1451-8. <https://doi.org/10.1111/ajt.16952>.
- Copeland H, Hayanga JWA, Neyrinck A, et al. Donor heart and lung procurement: a consensus statement. *J Heart Lung Transplant* 2020;39:501-17. <https://doi.org/10.1016/j.healun.2020.03.020>.
- Messer S, Page A, Colah S, et al. Human heart transplantation from donation after circulatory-determined death donors using normothermic regional perfusion and cold storage. *J Heart Lung Transplant* 2018;37:865-9. <https://doi.org/10.1016/j.healun.2018.03.017>.
- Hessheimer AJ, Coll E, Torres F, et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019;70:658-65. <https://doi.org/10.1016/j.jhep.2018.12.013>.
- Watson CJE, Hunt F, Messer S, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant* 2019;19:1745-58. <https://doi.org/10.1111/ajt.15241>.
- Ramirez P, Vázquez D, Rodríguez G, et al. Kidney transplants in controlled donation following circulatory death, or maastricht type iii donors, with abdominal normothermic regional perfusion, optimizing functional outcomes. *Transplant Direct* 2021;7:e725. <https://doi.org/10.1097/TXD.0000000000001174>.
- Net M, Valero R, Almenara R, et al. The effect of normothermic recirculation is mediated by ischemic preconditioning in NHBD liver transplantation. *Am J Transplant* 2005;5:2385-92. <https://doi.org/10.1111/j.1600-6143.2005.01052.x>.
- Funamoto M, Pierson RN, Nguyen JH, et al. Surgical and logistical concerns for ex vivo-based perfusion strategies for “donation after circulatory death” multiorgan recovery. *JTCVS Tech* 2021;11:49-56. <https://doi.org/10.1016/j.xjtc.2021.11.005>.
- Croome KP, Daneshmand MA. Successfully sharing the sandbox: A perspective on combined DCD liver and heart donor procurement. *Am J Transplant* 2021;21:484-7. <https://doi.org/10.1111/ajt.16309>.
- Wisel SA, Thiessen C, Day R, et al. Setting rules for the sandbox: A response to “Successfully sharing the sandbox: A perspective on combined DCD liver and heart donor procurement”. *Am J Transplant* 2021;21:1981-2. <https://doi.org/10.1111/ajt.16426>.
- Chen Q, Emerson D, Megna D, et al. Heart transplantation using donation after circulatory death in the United States. *J Thorac Cardiovasc Surg* 2022. <https://doi.org/10.1016/j.jtcvs.2022.05.005>.
- Holm AM, Courtwright A, Olland A, et al. ISHLT position paper on thoracic organ transplantation in controlled donation after circulatory determination of death (cDCD). *J Heart Lung Transplant* 2022;41:671-7. <https://doi.org/10.1016/j.healun.2022.03.005>.