0003-4975 https://doi.org/10.1016/j.athoracsur.2025.08.044

Transplant & Mechanical Support: Research

Cardiac Allograft Vasculopathy After Donation After Circulatory Death Heart Transplantation

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ABSTRACT

BACKGROUND Use of donation after circulatory death (DCD) heart transplantation (HT) has dramatically expanded, with survival comparable to donation after brain death/standard recovery (DBD/SR). As cardiac allograft vasculopathy (CAV) remains a leading cause of post-HT morbidity, we sought to analyze CAV incidence among DCD recipients.

METHODS We used the Organ Procurement and Transplantation Network to tabulate adult (≥18 years) HT recipients between December 2019 and January 2024. DCD recipients were further stratified into the direct procurement with normothermic machine perfusion (DCD/DP-NMP) and thoracoabdominal normothermic regional perfusion (DCD/TA-NRP). The primary outcome of interest was the incidence of CAV over the first posttransplant year.

RESULTS Of 12,060 transplants, 11,262 (93.4%) used DBD/SR allografts, 566 (4.7%) used DCD/DP-NMP allografts, and 232 (1.9%) used DCD/TA-NRP allografts. The overall incidence of CAV at 1 year was 4.0% for the DBD/SR group, 3.8% for DCD/DP-NMP, and 7.1% for DCD/TA-NRP. After comprehensive risk adjustment, transplantation with DCD/TA-NRP allografts remained associated with greater hazard of CAV over the first posttransplant year, relative to DBD/SR (hazard ratio [HR] 1.83; 95% CI, 1.08-3.10). However, DCD/DP-NMP procurement was linked with comparable CAV hazard as DBD/SR (HR, 1.51; 95% CI, 0.92-2.50). Considering recipients at high-volume centers, DCD/TA-NRP remained significantly associated with increased hazard of CAV (HR, 2.22; 95% CI, 1.27-3.89; reference: DBD/SR).

CONCLUSIONS In this national analysis of CAV incidence among DCD HT recipients, DCD/TA-NRP, but not DCD/DP-NMP, was associated with greater risk of CAV.

(Ann Thorac Surg 2025;■:■-■)

In 1967, Dr Christiaan Barnard performed the world's first heart transplant using an allograft procured from a donor whose heart had stopped beating.[1] This groundbreaking operation preceded the Uniform Determination of Death Act in 1981, which shifted practice toward using hearts after donation after brain death (DBD).[2] Consequently, interest in donation after circulatory death (DCD) rapidly declined. However, the ongoing organ shortage has reignited interest in DCD allografts, culminating in the reemergence of DCD heart transplantation in the United States (US).[3,4]

In fact, the volume of DCD transplantations has steadily increased since 2019. Studies have demonstrated comparable posttransplant survival between DCD and traditional DBD allografts, both in the short-term and up to 5 years.[5-9] Importantly, advances in surgical techniques and perfusion methods have significantly advanced

Accepted for publication Aug 18, 2025.

Presented at the Sixty-first Annual Meeting of The Society of Thoracic Surgeons, Los Angeles, CA, Jan 24-26, 2025.

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Abbreviations and Acronyms

CAV = cardiac allograft vasculopathy
DBD = donation after brain death
DCD = donation after circulatory death
DP-NMP = direct procurement with normothermic machine perfusion
HR = hazard ratio
HVC = high-volume center
ISHLT = International Society for Heart and Lung Transplantation
IQR = interquartile range
TA-NRP = thoracoabdominal normothermic regional perfusion
OPTN = Organ Procurement and Transplantation Network
US = United States

DCD transplantation since its origins in 1967. As DCD transplantation expands in the US and more data emerge, there is a growing need to evaluate the field beyond survival alone.

In particular, the risk of cardiac allograft vasculopathy (CAV) has not been examined at the large scale. CAV is a progressive condition characterized by vascular remodeling, which ultimately disrupts perfusion of the transplanted heart allograft.[10] Among the general cardiac transplant population, CAV affects more than one-third of patients at 5 years[11,12] and contributes to 30% of posttransplant deaths.[13] Although the precise etiology of CAV remains incompletely understood, immune-mediated mechanisms are believed to play a central role.[14]

This relationship is especially critical in DCD transplantation, where exposure to warm ischemia and repeated ischemia-reperfusion injury may amplify immune activation and inflammatory signaling, key drivers in CAV pathogenesis. Despite this biologic plausibility, the incidence of CAV in DCD recipients remains poorly defined. Clarifying this link is essential to advancing our understanding of graft longevity and improving long-term outcomes in this expanding transplant population.

The present study characterized the contemporary incidence of CAV after DCD heart transplantation in the US. We hypothesized that DCD heart transplantation is associated with a higher incidence of CAV compared with DBD.

PATIENTS AND METHODS

This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN gathers and reports information on all donors, patients on the waiting list, and transplant recipients in the US, provided by its member organizations. Oversight of the OPTN is managed by the Health Resources and Services Administration and the US Department of Health and Human Services. This study was exempt from full review by the University of California, Los Angeles Institutional Review Board.

We considered all adult (≥18 years) heart transplant recipients from December 1, 2019, to January 1, 2024, with follow-up through March 31, 2025. Recipients were classified by donor type as identified within the OPTN: DBD or DCD, with DCD donors adhering to controlled Maastricht category III criteria. To distinguish between DCD procurement techniques, we defined thoracoabdominal normothermic regional perfusion (TA-NRP) as a circulatory death to aortic cross-clamp time of ≥40 minutes and rapid aortic cross-clamping with direct procurement (DP) as ≤30 minutes, excluding cases between 30 and 40 minutes, as previously described.[6,15] Consequently, our final study cohort included DBD with standard recovery (DBD/SR), DCD with thoracoabdominal normothermic regional perfusion (DCD/TA-NRP), and DCD with rapid aortic cross-clamping, direct procurement, and ex situ normothermic machine perfusion (DCD/DP-NMP).[16] To enable meaningful comparisons between procurement techniques and perfusion strategies, allografts that underwent subsequent NMP were excluded from the DBD/SR and DCD/TA-NRP groups, whereas those in the DCD/DP group that did not undergo subsequent NMP, were also excluded. Records involving previous transplantation (2.9%) or those missing follow-up data (6.1%) were excluded (Figure 1).

The primary outcome was the development of CAV in the first posttransplant year. In line with prior work, we defined CAV as any evidence of angiographic coronary disease recorded upon transplant program follow-up.[17,18] Within the OPTN registry, CAV status is reported by each participating center. Once patients were reported to have CAV at 1 follow-up appointment, we assumed them to have CAV upon subsequent visits. We considered donors to have a history of coronary artery disease if a coronary angiogram was performed with documented abnormal findings or stenosis.

Cumulative cardiac transplant volume was computed for each transplant program, across the study period. Centers in the top quartile of average annual volume (≥37 transplants per year), were considered high-volume centers (HVCs), with others deemed non-HVCs.

Continuous variables are presented as means with standard deviations (SDs) for normally distributed data or as medians with interquartile ranges (IQRs) for nonnormally distributed features. Categorical variables are shown as percentages. The

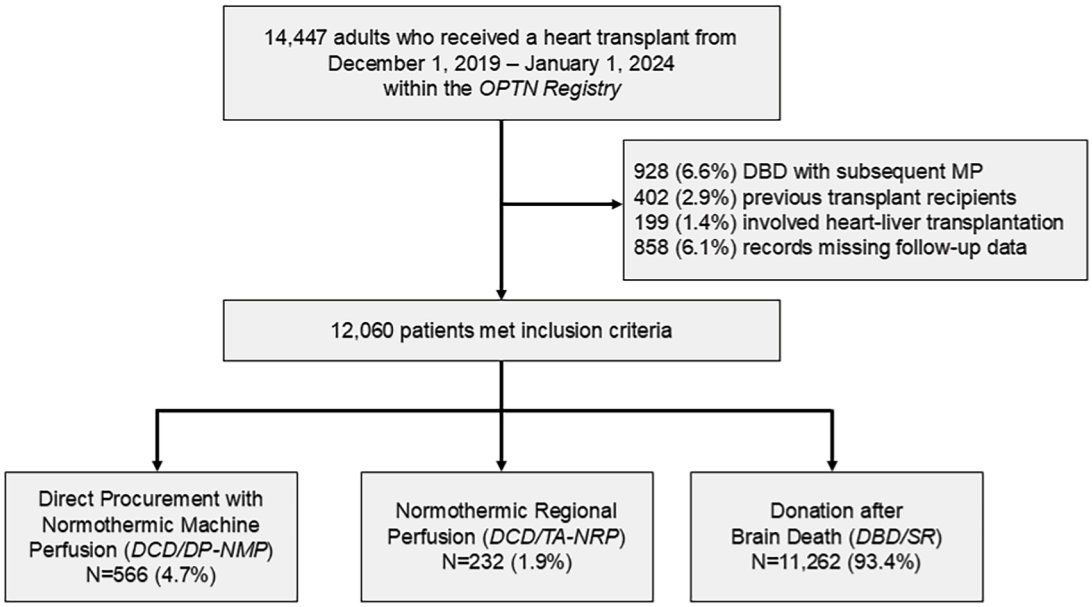

FIGURE 1 Study Consolidated Standards of Reporting Trials (CONSORT) diagram. Among 12,060 adult heart transplant patients meeting study criteria, 11,262 (93.4%) received cardiac allografts procured by donation after brain death/standard recovery (DBD/SR), 566 (4.7%) by donation after circulatory death (DCD)/direct procurement with normothermic machine perfusion (DCD/DP-NMP), and 232 (1.9%) by DCD/thoracoabdominal normothermic regional perfusion (DCD/TA-NRP). (MP, machine perfusion; OPTN, Organ Procurement and Transplantation Network.)

significance of differences between groups was assessed using the Mann-Whitney *U* test, Pearson χ^2 test, and 2-sided Student *t* tests. Survival rates were illustrated using Kaplan-Meier survival curves. Cox proportional hazards models were then used to calculate risk-adjusted hazard ratios (HRs) for CAV. To reduce model bias, the least absolute shrinkage selection operator was used for automated variable selection.[19]

Covariates included in the analysis were recipient age, sex, body mass index, race/ethnicity, reliance on mechanical circulatory support (extracorporeal membrane oxygenation, ventricular assist device, or intra-aortic balloon pump), diabetes, serum creatinine and bilirubin, hospitalization or intensive care unit admission at transplant, calculated panel reactive antibodies, cytomegalovirus positivity status, transplant indication, multiorgan transplant status, and induction immunosuppression, as well as donor age, sex, race/ethnicity, body mass index, serum creatinine, history of diabetes, hypertension, coronary artery disease, cigarette use, cytomegalovirus status, and allograft cold ischemia time. Patients without CAV as of March 31, 2025, were censored at their last-known follow-up.

To complement the primary analysis, which accounted for various donor and recipient factors, we performed a sensitivity analysis using entropy balancing. This method addresses baseline intergroup differences by optimizing sample weights to balance the distribution of covariates across groups.[20]

All statistical analyses were performed using Stata 18.0 software (StataCorp LLC). Statistical significance was set at $\alpha = 0.05$.

RESULTS

Of 12,060 heart transplant recipients tabulated from the UNOS database with adequate follow-up data, 11,262 (93.4%) received DBD/SR and 798 (6.6%) received DCD allografts. Stratifying by procurement approach, 566 (70.9% of DCD organs) were obtained by DCD/DP-NMP and 232 (29.1%) by DCD/TA-NRP.

Recipient and donor characteristics are reported in Table 1 and 2, respectively. Compared with the DBD/SR group, the DCD/DP-NMP cohort was of a similar age and race distribution, but less commonly listed at status 1 (1.8% vs 5.8%, $P < .001$). DCD/TA-NRP patients (58 years; IQR, 48-64 years) were older than both DBD/SR (56 years; IQR, 46-63 years; $P = .04$) and DCD/DP-NMP (55 years; IQR, 44-63 years; $P = .04$).

TABLE 1 Recipient Characteristics, Stratified by Donor Type and Procurement Method

Recipient Characteristics	DBD/SR No. (%) = 11,262 (93.4)	DCD/DP-NMP No. (%) = 566 (4.7)	*P* Value (Ref: DBD/SR)	DCD/TA-NRP No. (%) = 232 (1.9)	*P* Value (Ref: DBD/SR)
Age, y	56 (46–63)		.04	58 (48–64)[a]	.04
Body mass index, mean (SD), kg/m^2	27.8 (4.9)	28.3 (4.8)	.04	28.6 (4.9)	.01
Sex			.009		<.001
Male	8258 (73.3)	443 (78.3)		203 (87.5)[a]	
Female	3004 (26.7)	123 (21.7)		29 (12.5)[a]	
Race/ethnicity					
Black	2978 (26.4)	128 (22.6)	.04	50 (21.6)	.09
Hispanic	1221 (10.8)	64 (11.3)	.73	23 (9.9)	.65
White	6451 (57.3)	356 (62.9)	.008	154 (66.4)	.006
Other	612 (5.4)	18 (3.2)	.02	5 (2.2)	.03
Diabetes	3441 (30.6)	174 (30.7)	.92	80 (34.5)	.20
On dialysis	691 (6.1)	26 (4.6)	.13	9 (3.9)	.16
Ventricular assist device	2879 (25.6)	196 (34.6)	<.001	57 (24.6)[a]	.73
Extracorporeal membrane oxygen	724 (6.4)	14 (2.5)	<.001	3 (1.3)	.001
Intra-aortic balloon counterpulsation	3105 (27.6)	79 (14.0)	<.001	42 (18.1)	.001
Prior cardiac surgery	4499 (40.0)	228 (40.3)	.87	90 (38.8)	.72
Hospital admission status					
Admitted in the hospital	1588 (14.1)	87 (15.4)	.40	35 (15.1)	.67
Admitted in the intensive care unit	6663 (59.2)	225 (39.8)	<.001	68 (29.3)[a]	<.001
OPTN status					
Adult 1	652 (5.8)	10 (1.8)	<.001	1 (0.4)	<.001
Adult 2	3586 (31.8)	136 (24.0)	<.001	41 (17.7)	<.001
Adult 3	1224 (10.9)	62 (11.0)	.95	17 (7.3)	.08
Adult 4	3227 (29.1)	181 (32.0)	.14	95 (41.0)[a]	<.001
Adult 5	195 (1.7)	10 (1.8)	.95	11 (4.7)[a]	.001
Adult 6	1747 (15.5)	136 (24.0)	<.001	59 (25.4)	<.001
Diagnosis					
Dilated myopathy	6403 (56.9)	332 (58.7)	.40	127 (54.7)	.52
Restrictive myopathy	511 (4.5)	20 (3.5)	.26	13 (5.6)	.44
Coronary artery disease	3192 (28.3)	152 (26.9)	.44	68 (29.3)	.75
Hypertrophic cardiomyopathy	386 (3.4)	23 (4.1)	.42	9 (3.9)	.71
Valvular disease	118 (1.1)	6 (1.1)	.98	4 (1.7)	.32
Adult congenital heart disease	362 (3.2)	16 (2.8)	.61	6 (2.6)	.59
Other	290 (2.6)	17 (3.0)	.53	5 (2.2)	.69
Induction immunosuppression					
Antithymocyte globulin	2564 (22.8)	88 (15.6)	<.001	37 (16.0)	.01
Basiliximab	2993 (26.6)	223 (39.4)	<.001	52 (22.4)[a]	.16
Characteristics at transplant					
Panel reactive antibody ≥80%	3220 (28.6)	165 (29.1)	.77	35 (15.1)[a]	<.001
Cytomegalovirus Positive	6247 (56.1)	285 (50.9)	.02	118 (51.5)	.17

[a]*P* < .05, comparing DCD/TA-NRP vs DCD/DP-NMP. Data are presented as n (%) or median (interquartile range), unless indicated otherwise as mean (SD). DBD, donation after brain death; DCD, donation after circulatory death; DP, direct procurement; NMP, normothermic machine perfusion; OPTN, Organ Procurement and Transplantation Network; SR, standard recovery; TA-NRP, thoracoabdominal normothermic regional perfusion.

Indications for transplant were similar between DBD/SR, DCD/DP-NMP, and DCD/TA-NRP recipients. Additionally, the DCD/DP-NMP (15.6%, $P < .001$) and DCD/TA-NRP groups (16.0%, $P = .01$) less frequently received antithymocyte globulin for induction compared with DBD/SR (22.8%). Relative to donors for the DBD/SR group, donors for the DCD/DP-NMP group were younger (30 years [IQR, 24-36 years] vs 32 years [IQR, 25-40 years], $P < .001$) and more commonly male (84.3 vs 71.4%, $P < .001$). Donors for DCD/DP-NMP (0.9%, $P < .001$) and DCD/TA-NRP (1.7%, $P = .04$) less often had known coronary artery disease relative to donors for DBD/SR (4.5%). Donors for DCD/DP-NMP (9.7%, $P = .03$), but not DCD/TA-NRP (12.3%, $P = .84$), less commonly had a history of cigarette use, relative to those for DBD/SR (12.8%).

The overall incidence of CAV at 1 year was 4.0% for DBD/SR, 3.8% for DCD/DP-NMP, and 7.1% for DCD/TA-NRP (Figure 2A). After multivariable risk

TABLE 2 Donor Characteristics, Stratified by Procurement Method

Donor Characteristics	DBD/SR (Ref) No. (%) = 11,262 (93.4)	DCD/DP-NMP No. (%) = 566 (4.7)	*P* Value (DCD/DP vs DBD/SR)	DCD/TA-NRP No. (%) = 232 (1.9)	*P* Value (DCD/TA-NRP vs DBD/SR)	*P* Value (DCD/DP-NMP vs DCD/TA-NRP)
Time from declaration of death to cross-clamp, min	…	7 (5-9)	…	78 (62-105.5)	…	<.001
Age, y	32 (25-40)	30 (24-36)	<.001	32 (25-39)	.50	.02
Body mass index, mean (SD), kg/m^2	28.1 (6.3)	27.7 (6.1)	.08	28.7 (6.7)	.15	.03
Sex			<.001		<.001	.31
Male	8043 (71.4)	477 (84.3)		202 (87.1)		
Female	3219 (28.6)	89 (15.7)		30 (12.9)		
Race/ethnicity						
Black	1908 (16.9)	57 (10.1)	<.001	18 (7.8)	<.001	.31
Hispanic	2138 (19.0)	51 (9.0)	<.001	36 (15.5)	.18	.007
White	6836 (60.7)	447 (79.0)	<.001	172 (74.1)	<.001	.14
Other	2138 (19.0)	51 (9.0)		36 (15.5)	.18	.007
Medical history						
Coronary artery disease	506 (4.5)	5 (0.9)	<.001	4 (1.7)	.04	.31
Cigarette use	1394 (12.8)	54 (9.7)	.03	28 (12.3)	.84	.28
Hypertension	1704 (15.1)	75 (13.2)	.22	34 (14.7)	.84	.60
Diabetes	454 (4.0)	17 (3.0)	.22	3 (1.3)	.03	.16
Donor creatinine, mean (SD), mg/dL	1.6 (1.8)	1.0 (1.4)	<.001	1.2 (1.4)	<.001	.24
Cold ischemia time, mean (SD), h	3.4 (1.0)	6.0 (2.0)	<.001	3.3 (1.2)	.02	<.001
Cytomegalovirus positive	6983 (62.6)	307 (55.1)	<.001	126 (55.3)	.02	.97
Donor cause of death						
Anoxia	5357 (47.6)	281 (49.7)	.33	98 (42.2)	.11	.06
Cerebrovascular/stroke	1349 (12.0)	33 (5.8)	<.001	20 (8.6)	.12	.15
Head trauma	4276 (38.0)	232 (41.0)	.15	105 (45.3)	.02	.27
Central nervous system tumor	41 (0.4)	1 (0.2)	.46	1 (0.4)	.87	.51
Other	239 (2.1)	19 (3.4)	.05	8 (3.4)	.17	.95

Data are presented as n (%) or median (interquartile range), unless indicated otherwise as mean (SD). DBD, donation after brain death; DCD, donation after circulatory death; DP, direct procurement; NMP, normothermic machine perfusion; SR, standard recovery; TA-NRP, thoracoabdominal normothermic regional perfusion.

adjustment, transplantation with DCD/DP-NMP allografts was linked with comparable hazard of CAV at 1 year as DBD/SR (HR, 1.51; 95% CI, 0.92-2.50; $P = .10$). However, use of DCD/TA-NRP organs was associated with significantly increased CAV hazard (HR, 1.83; 95% CI, 1.08-3.10; $P = .024$) (Figure 2B).

Several other factors were identified to be linked with greater likelihood of CAV and included male sex (HR, 1.58; 95% CI, 1.18-2.13; $P = .002$; reference: female), Hispanic ethnicity (HR, 1.60; 95% CI, 1.22-2.08; $P = .001$; reference: White race), and reliance on an intra-aortic balloon pump preoperatively (HR, 1.34; 95% CI, 1.04-1.72; $P = .02$). Furthermore, increasing donor age (HR 1.03 per year; 95% CI, 1.02-1.04 per year; $P < .001$), donor male sex (HR, 1.58; 95% CI, 1.18-2.13; $P = .002$), and donor history of cigarette use (HR, 1.43; 95% CI, 1.11-1.83; $P = .005$) were similarly linked with increased CAV risk (Figure 3).

After entropy balancing and risk adjustment and with DBD/SR as the reference, DCD/DP-NMP remained associated with similar likelihood of CAV (HR, 1.22; 95% CI, 0.73-2.02; $P = .45$), whereas DCD/TA-NRP was linked with increased CAV hazard (HR, 2.26; 95% CI, 1.29-3.96; $P = .004$).

Considering only the 6955 patients who underwent transplant at an HVC, 6317 (90.8%) used DBD/SR, 449 (6.5%) used DCD/DP-NMP, and 189 (2.7%) used DCD/TA-NRP. The incidence of CAV at 1 year was 3.8% for DBD/SR, 3.9% for DCD/DP-NMP, and 8.0% for DCD/TA-NRP (Figure 4A). At these HVCs and relative to DBD/SR, DCD/TA-NRP transplantation was linked with increased CAV hazard (HR, 2.22; 95% CI, 1.27-3.89; $P = .005$), whereas DCD/DP-NMP transplantation yielded similar CAV risk (HR, 1.66; 95% CI, 0.93-2.96; $P = .089$) (Figure 4B).

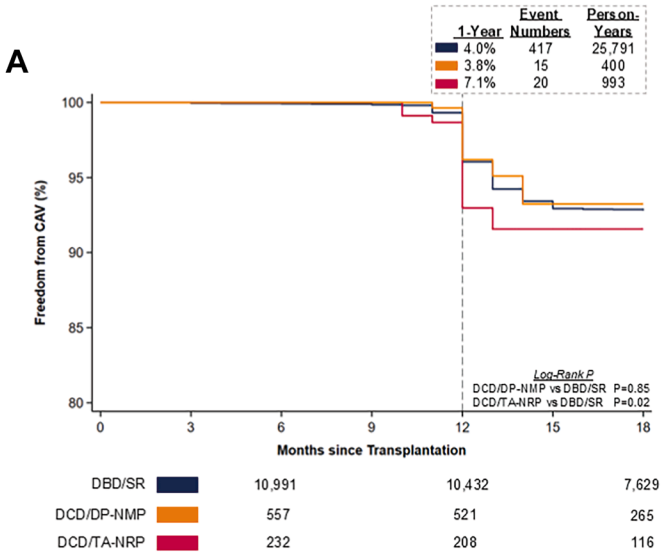

FIGURE 2 Incidence of cardiac allograft vasculopathy (CAV), stratified by procurement technique. (A) Kaplan–Meier time-to-CAV analysis. At 12 months, donation after circulatory death (DCD)/thoracoabdominal normothermic regional perfusion (DCD/TA-NRP) recipients demonstrated higher incidence of CAV, relative to donation after brain death/standard recovery (DBD/SR) and DCD/direct procurement with normothermic machine perfusion (DCD/DP-NMP). (B) After risk-adjustment, DCD/TA-NRP was associated with significantly greater CAV hazard at 1 year.

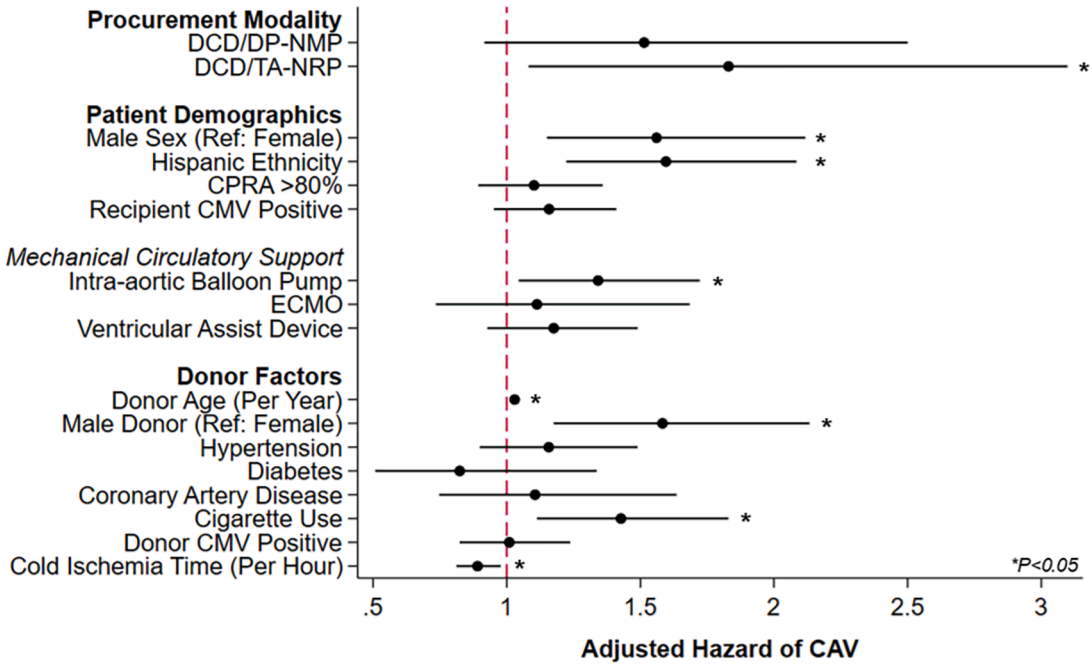

FIGURE 3 Recipient and donor factors linked with cardiac allograft vasculopathy (CAV). After risk adjustment, several recipient and donor factors were found to be linked with greater hazard of CAV. *P < .05 indicating statistical significance. (CMV, cytomegalovirus; CPRA, calculated panel reactive antibody; DCD, donation after circulatory death; DP-NMP, direct procurement with normothermic machine perfusion; ECMO, extracorporeal membrane oxygenation; TA-NRP, thoracoabdominal normothermic regional perfusion.)

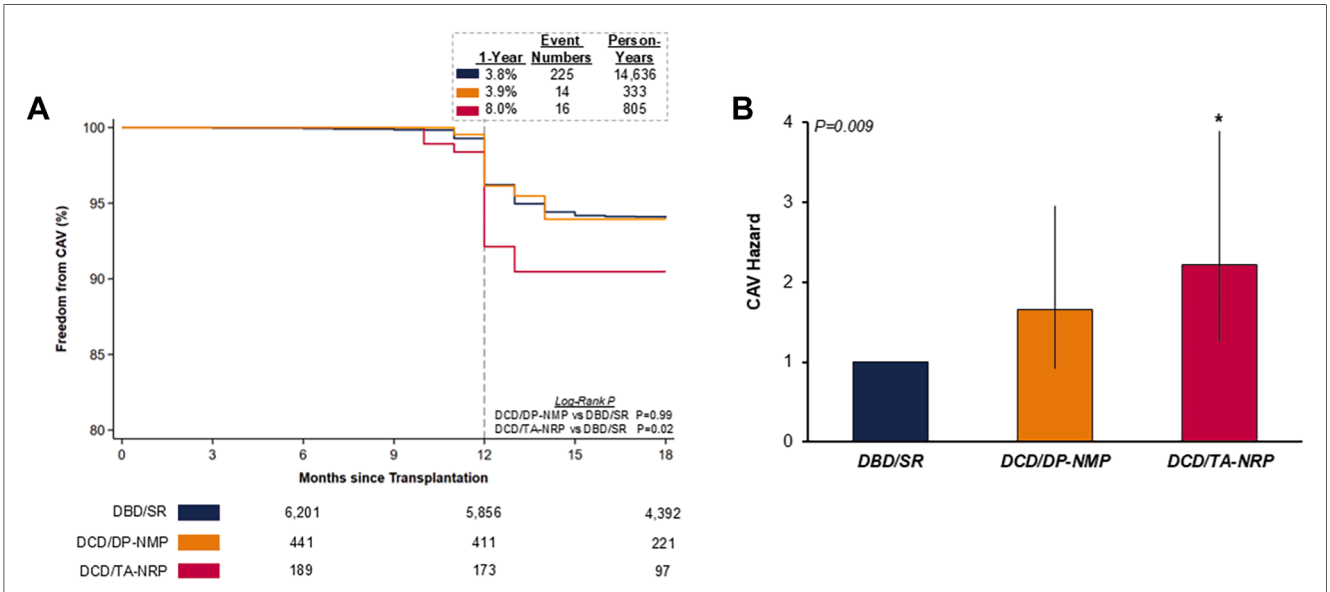

FIGURE 4 Cardiac allograft vasculopathy (CAV) at high-volume centers (HVCs), stratified by procurement technique. Centers performing ≥37 transplants per year were considered HVCs. (A) Kaplan-Meier time-to-CAV analysis. At 12 months, donation after circulatory death (DCD)/thoracoabdominal normothermic regional perfusion (DCD/TA-NRP) recipients demonstrated higher incidence of CAV, relative to donation after brain death/standard recovery (DBD/SR) and DCD/direct procurement with normothermic machine perfusion (DCD/DP-NMP). (B) After risk-adjustment, DCD/TA-NRP was associated with significantly greater CAV hazard at 1 year. *$P < .05$ indicating statistical significance.

COMMENT

In this national, retrospective cohort study, we identified a significantly higher incidence of CAV among adult heart transplant recipients of DCD allografts procured by normothermic regional perfusion compared with those receiving DBD organs. By contrast, this association was not observed among recipients of DCD allografts obtained by direct procurement and subsequent normothermic machine perfusion.

To better understand the significance of these findings, it is important to place our observed incidence within the context of existing literature. According to data from the International Society for Heart and Lung Transplantation (ISHLT) registry, the prevalence of CAV among heart transplant recipients is ~8% at 1 year, increasing to 29% at 5 years and 47% at 10 years after transplant.[21] Although it remains to be seen how the incidence of CAV will evolve as 5- and 10-year data from the US DCD experience become available, our 1-year incidence aligns with ISHLT-reported rates. Notably, our findings reflect a lower rate than that reported in single-center studies. For example, Birs and colleagues[22] observed a 31% incidence of CAV in a cohort of 39 DCD recipients. This discrepancy may be attributed to differences in diagnostic approaches. Whereas the ISHLT classification is based on angiographic evidence of disease, Birs and colleagues[22] used intravascular ultrasound, which may detect earlier or milder forms not typically captured by angiography.

Beyond incidence rates, our study also diverges from previous single-center reports that found no difference in CAV between DCD and DBD recipients, or among various DCD procurement techniques. These discrepancies are likely attributable to limited sample sizes, methodologic variation, and heterogeneity in institutional practices inherent to single-center reports. For example, Cheshire and colleagues[8] analyzed 230 heart transplant recipients (77 DCD and 153 DBD) at Royal Papworth Hospital, a large center in the United Kingdom, and found no difference in 1-year CAV incidence between groups. On subgroup analysis, they also observed no difference between DCD/DP-NMP (n = 55) and DCD/TA-NRP (n = 22). Similarly, Dulay and colleagues[7] reported no difference in 1-year CAV incidence between 44 DCD and 33 DBD recipients, although their DCD cohort did not include TA-NRP cases.

In the US, Siddiqi and colleagues[23] studied 263 DBD and 122 DCD recipients and reported comparable 1-year CAV rates (14% vs 15%). However, their DBD group included both static cold storage and ex situ perfusion, whereas the DCD

group combined NRP and ex situ perfusion, potentially obscuring distinctions between procurement techniques.[23] Nevertheless, several key observations from these early experiences merit further discussion.

CAV results from a complex interplay of factors, with immune-related mechanisms often cited as the primary underlying cause.[14] Although single-center studies have not fully defined the natural history of CAV in DCD recipients, their findings on graft rejection, which is also an immunologically mediated process, may provide valuable insights. Messer and colleagues,[24] from the Papworth group, published their experience with 26 consecutive DCD heart transplants, reporting 2 deaths from severe noncalcific coronary artery disease and antibody-mediated rejection, respectively. Similarly, investigators at St Vincent's Hospital in Sydney observed a higher incidence of rejection among DCD recipients, despite graft and patient survival comparable to DBD recipients. In their 4-year update, 18 of 23 DCD recipients experienced grade 2 or higher rejection before discharge, and 11 of 14 had grade 1 or higher rejection at 1 year.[25] Recently, Li and colleagues[26] analyzed 292 DCD recipients within the OPTN database and identified a significantly higher incidence of acute rejection compared with DBD recipients. Collectively, these findings suggest immune-related ramifications of DCD transplantation that cannot be ignored.

Our observed differences in CAV incidence may result from several contributing factors. One possibility is that DBD recipients, who are often more critically ill, may have suppressed immune systems and are therefore less likely to mount a strong immune response.[26] In our analysis, DBD recipients did appear slightly more ill at baseline compared with DCD recipients; however, these differences were modest. Although statistically significant, likely due to the large sample size, they are unlikely to fully explain the disparity in CAV outcomes observed in this study. Another factor may be the repeated episodes of ischemia-reperfusion injury associated with DCD transplantation, which can provoke a more intense inflammatory reaction.[27]

However, we propose that the choice of procurement method itself may also play a role in shaping the immunologic environment and contribute to the development of CAV. Indeed, recipients of DCD/TA-NRP allografts demonstrated a higher hazard of developing CAV, even though the DCD/TA-NRP and DCD/DP-NMP groups had comparable baseline clinical profiles, similar perioperative exposures to ischemia-reperfusion injury, and remained balanced after adjustment for key donor and recipient variables.

Therefore, a crucial question arises: Why does DCD/TA-NRP result in a higher incidence of CAV, whereas DCD/DP-NMP does not? We proffer that this difference may be partly due to the distinct methodologies of each technique. Although both methods involve external circuitry and perfusate, only DCD/TA-NRP reestablishes in situ circulation, allowing continued interaction with the donor's spleen, bone marrow, and broader lymphoid system. Stated differently, DCD/TA-NRP preserves the physiologic conditions of the donor's native immune system, potentially triggering immunologic changes in the circulating blood, and possibly within the allograft itself, in response to exposure to nonendogenous elements such as the perfusion solution, oxygenators, pumps, and tubing. In contrast, DCD/DP-NMP involves explantation of the organ before perfusion. As such, the process occurs entirely ex situ, eliminating any interaction between the graft and the donor's immune system. Consequently, the immunologic milieu surrounding the allograft in DCD/DP-NMP differs fundamentally from that of DCD/TA-NRP.

This rationale is supported by studies of analogous extracorporeal systems, such as cardiopulmonary bypass and extracorporeal membrane oxygenation, where the immunologic impact of circuits, flow rates, and shear stress has been well documented. Research has consistently shown changes in circulating lymphocyte counts, shifts in leukocyte phenotypes marked by increased expression of adhesion molecules, such as cluster of differentiation 11b and 18, and activation of endothelial cells, often accompanied by variable expression of adhesion molecules such as L-selectin.[28] This imbalance between innate and adaptive immunity may disrupt organ-specific self-tolerance, as shown by Ortega and colleagues,[29] who found increased T cell-mediated autoreactivity to the central nervous system in patients with acquired brain injury receiving extracorporeal membrane oxygenation support.[29] How this translates to transplantation remains uncertain. Nonetheless, DCD/TA-NRP may potentially induce shifts in donor blood components and vascular endothelial changes within the allograft. Future studies are required to determine whether these modifications affect the recipient's immune response and contribute to the observed increase in CAV incidence.

This study has several important limitations. First, the severity and extent of vasculopathy were

not recorded in the OPTN data set, and ISHLT CAV grades, intravascular ultrasound findings, and cardiac catheterization data were unavailable. Similarly, the registry lacks detailed information on perfusion devices and DCD/TA-NRP circuits, including flow rates, specific perfusate solutions, and perfusion duration, all of which may influence outcomes. Direct immunologic markers, cytokine profiles, and histopathologic data are also unavailable. Future studies using more granular data sets should aim to explore these variables across procurement strategies.

Although donor cause of death was recorded, we could not ascertain the rationale for selecting donors for DCD specifically. We inferred the use of TA-NRP or DP-NMP based on the time from death to aortic cross-clamp, an established but indirect method that carries a risk of misclassification.

Finally, our analysis focused on the 1-year CAV incidence, which may be limited by the relatively small number of events, particularly in the DCD/DP-MP group, potentially affecting statistical power. As a retrospective analysis, our findings reflect associations rather than causation; any suggestion of underlying immune mechanisms remains speculative, and further research is needed to assess whether procurement approach influences the development of CAV over longer-term follow-up.

Although adoption is increasing, DCD transplantation is still in its early stages. With this growth comes an opportunity to deepen our understanding of its clinical implications beyond 1-year survival alone, including immune responses and long-term outcomes. This study represents a comprehensive analysis of CAV incidence in a contemporary DCD heart transplantation cohort. Our findings demonstrate a higher incidence of CAV among DCD/TA-NRP allograft recipients, even after rigorous risk adjustment and across multiple analytic approaches. These results suggest that the choice of procurement technique may play a critical role in influencing immune modulation and subsequent outcomes. By shedding light on this association, our study provides a foundation to uncover mechanisms driving CAV in DCD/TA-NRP recipients and explore strategies to mitigate its impact.

FUNDING SOURCES

The authors have no funding sources to disclose.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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