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Cardiac allograft vasculopathy outcomes among donation after circulatory death heart transplant recipients

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KEYWORDS:
cardiac allograft vasculopathy;
donation after circulatory death;
intravascular ultrasound;
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heart transplant outcomes

BACKGROUND: Cardiac allograft vasculopathy (CAV) accounts for significant long-term morbidity and mortality in heart transplant recipients; limited data exist for donation after circulatory death (DCD). Intravascular ultrasound (IVUS) assessment is a gold standard for early diagnosis of CAV and has strong prognostic power.
METHODS: We evaluated all consecutive circulatory and brain death heart transplant recipients from January 2020 to March 2022. Patients were followed for need for percutaneous coronary intervention (PCI), development of severe allograft vasculopathy, or death. Among 143 heart transplant recipients, 39 received circulatory death and 104 received brain death hearts.
RESULTS: Baseline characteristics were similar between groups: median age (56.3 vs 53.7 years, $p = 0.290$), female sex (15% vs 26%, $p = 0.265$), and sirolimus use (69% vs 53%, $p = 0.116$). At 1 year, there were no significant differences in maximal intimal thickness (0.49 vs 0.46 mm, $p = 0.861$) or Stanford classification. During a median follow-up of 793 days [interquartile ranges 618, 1003], there was no difference in the unadjusted or adjusted primary composite outcome of death, PCI, or International Society of Heart and Lung Transplantation cardiac allograft vasculopathy maximal intimal thickness ≥0.6 mm (unadjusted hazard ratio (HR) 0.42, 95% confidence interval (CI): 0.05, 3.48, $p = 0.42$), event rate 9.6% vs 2.6%, $p = 0.29$, nor was there a difference in death, PCI or severe IVUS disease (HR 1.44, 95% CI 0.81, 2.56, $p = 0.21$).
CONCLUSION: In DCD heart transplant recipients, circulatory death donors did not have a significantly higher risk for coronary allograft vasculopathy by IVUS or related complications at 1 year following transplantation.
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Background

Cardiac allograft vasculopathy (CAV) is a highly morbid disease that causes graft dysfunction and death in heart transplant (HTx) recipients.[1-3] According to the International Society of Heart and Lung Transplantation (ISHLT) registry, the prevalence of CAV in HTx recipients has increased to 8% and 50% at 1 and 10 years, respectively.[4] As transplant survival continues to improve, there will be a growing population of HTx recipients at increased risk of long-term morbidities associated with CAV. Few interventions have been shown to mitigate CAV; therefore, early recognition and risk factor identification remain the mainstay of treatment.

Early and severe CAV noted on surveillance angiography serves as a strong prognostic indicator of future death and need for retransplantation.[5-8] Since its earliest description in postmortem allografts, obliterative intimal proliferation of the coronary arteries has been detectable as early as 9 days post-transplant and is present in most allografts surviving more than 1 month after transplantation.[1] Recent studies comparing CAV outcomes between donation after brain death (DBD) donors donation after circulatory death (DCD) found no difference between CAV severity on angiography.[9,10] Nonetheless, while a positive angiographic assessment is highly informative, a negative study does not ensure absence of disease, whereby CAV is detectable by angiography in only 8% of survivors within the first year and 32% within the first 5 years after HTx. Conversely, intravascular ultrasound (IVUS) is both a sensitive and specific technique for the presence of CAV and preferred in the early stages of CAV.[11-13] St Goar et al and Mehra et al found evidence of severe intimal thickening by IVUS assessment in greater than 60% of studied patients with normal angiographic studies, highlighting the hallmark feature of "angiographically silent" disease, and reason for late diagnosis.[8,14] Maximal intimal thickness (MIT) of greater than 0.5 mm is associated with a higher risk of long-term CAV-related morbidity and mortality.[6,8,14-16] Risk factors associated with the development and progression of CAV include donor and recipient cardiometabolic factors (diabetes, hypertension, age), infections (cytomegalovirus, hepatitis C), and peri-operative attributes (left ventricular hypertrophy, graft ischemic time).[2,5,7,17,18] Ischemia reperfusion injury can lead to development of CAV through coronary endothelial cell damage and inflammatory cascade mechanisms that trigger detrimental innate and adaptive immune responses promoting the development of CAV.[18-20] Timely identification is imperative for optimization of medical therapy, including lipid lowering therapy, use of proliferation signal inhibitors, aggressive risk factor modification as well as increased surveillance for rapidly progressive lesions.[21-23]

The utilization of DCD pathway for transplantation has significantly reduced waitlist time and increased HTx rate with early studies demonstrating good short-term graft function and survival; however, the impact of DCD status on development of CAV remains unknown.[24,25] DCD involves unique periods of ischemic time where the graft experiences functional warm ischemia due to the requirement of circulatory death. Concerns regarding warm ischemic time and reperfusion injury remain an area of active study and raise the question whether serial ischemia-reperfusion events in the DCD pathway increase the risk of CAV development.[26-28] The goal of this study is to compare early CAV outcomes, as detected by IVUS between DCD and DBD HTx recipients.

Methods

This single-center, retrospective, cohort study includes all sequential DCD and DBD HTx recipients at University of California, San Diego (UCSD) from January 2020 to March 2022. Patients were included if they were alive 1 year after HTx and had undergone at least one coronary angiogram during follow-up. Patients were followed for clinical outcomes through April 2023 including heart dysfunction, defined by a left ventricular ejection fraction < 50%, clinically significant rejection (≥2R) or treated rejection, death, listing or performance of retransplantation and need for percutaneous coronary intervention (PCI). Heart allograft pathology specimens were graded according to the ISHLT classifications. Laboratory and echocardiographic data were collected from annual visits. This study was approved by the institutional review board of UCSD. All authors agree with and confirm that this study adheres to the principles of the World Medical Association Statement on Organ and Tissue Donation, the Declaration of Helsinki, and the Declaration of Istanbul as stated in the ISHLT statement on transplant ethics.

DCD heart transplant protocol

Two organ procurement techniques, which are consistent with standard protocols, are used for DCD heart procurement at UCSD: (1) direct procurement protocol (DPP) with normothermic machine perfusion and (2) thoraco-abdominal normothermic regional perfusion (TA-NRP). After withdrawal of life-sustaining therapy, we accept donor organs up to 120 minutes for TA-NRP and up to 30 minutes for DPP as determined on a case-by-case basis. All allografts were orthotopically transplanted using bicaval techniques.

Coronary angiography and intravascular ultrasound protocol

The CAV surveillance protocol included coronary angiography with standard views of the right and left coronary system as well as IVUS imaging. IVUS was performed from the mid to distal left anterior descending to the left main ostium using an automatic pullback rate of 1 mm/sec. All studies were performed annually unless prohibitive due to stroke or renal function.

For all lesions on IVUS, the largest intimal thickness (IT) and minimal luminal area was measured and recorded

by the performing interventional cardiologist. Matched section assessment was performed in serial exams. CAV was graded by Stanford classification and ISHLT score. Class 1: Minimal, IT < 0.3 mm, Plaque < 180°; Class 2: Mild < 0.3 mm IT, > 180° arc; Class 3: Moderate 0.3 to 0.5 mm IT, > 0.5 mm and < 180° arc; Class 4: Severe: > 1.0 mm IT, or 0.5 mm > 180° arc.[8] ISHLT score was determined by 2010 guidelines: CAV0, not significant: no detectable angiographic lesions; CAV1, mild stenosis; CAV2, moderate stenosis; CAV3, severe stenosis left.[29]

Outcomes

The primary outcome was a composite outcome of all-cause mortality (conditional on 1 year survival), need for PCI, or development of ISHLT class ≥2.[13] Patients excluded from the study due to death prior to 1 year or death prior to IVUS were not included in the primary outcome analysis. Analysis of an additional IVUS focused composite outcome of death, PCI, or presence of severe CAV by IVUS (defined as MIT ≥ 0.6 mm) was performed. Additional outcomes included Stanford CAV class 4 disease and episodes of heart dysfunction with left ventricular ejection fraction < 50%.

Statistical analysis

Continuous variables were presented as means and standard deviations (SD) and compared using Student's *t*-tests. Pearson's chi-square test or Fisher's exact test was performed for normally distributed variables. Non-normally distributed continuous variables were presented as medians and interquartile ranges (IQR) and compared using Kruskal-Wallis test or Wilcoxon rank sum test as appropriate. Kaplan Meier plots were constructed for illustrative purposes for time to the composite event and compared using a log-rank test. Event-free patients were censored at the time of last follow-up. A multivariable Cox model was constructed to assess predictors and confounders of the composite outcome. Model covariates were chosen based on univariable association with composite outcome at a predetermined *p*-value cut off < 0.20. Clinically relevant variables were selected based on expert opinion, literature, and biologic plausibility. All statistical analyses were conducted using R version 4.1.3 (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA). A two-tail *p*-value ≤0.05 was considered significant for all other analyses.

Results

A total of 180 patients received HTx between January 2020 and March 2022, 50 of which were DCD and 130 of which were DBD. After excluding patients who died or did not have angiography at 1 year post transplant (n = 19), 143 patients remained in our cohort with 39 (27.3%) DCD and 104 (72.7%) DBD (Figure 1). Only 6 of the 19 patients excluded underwent autopsy, 4 DBD and 2 DCD, with CAV noted in 2 DBD and 1 DCD patient. The causes of death were primarily related to infection. The median follow-up time after HTx was 793 days [IQR 618, 1003]. Recipient characteristics were similar between DCD and DBD groups with regards to age (p = 0.290), sex (p = 0.265), and race (p = 0.695). DCD HTx recipients were less likely to have a panel reactive antibody (PRA) > 10% (18.3 vs 2.6, p = 0.03) and had lower rates of intra-aortic balloon pump (IABP) use at time of transplant (30% vs 2.6%, p = 0.002). DCD HTx recipients had significantly lower United Network of Organ Sharing status, 45.2% of DBD recipients were listed Status 2 or higher compared to 7.7% of DCD (p < 0.001) (Table 1). At 1 year, there were no significant differences in use of proliferation signal inhibitors (52.9% vs 69.2%, p = 0.116) or rejection episodes defined as acute cellular rejection ≥2 or treated episodes of antibody-mediated rejection (14.4% and 23.1%, p-value 0.326). Donor characteristics, including cardiometabolic risk factors, were similar between DBD and DCD cohorts except a higher prevalence of hypertension in the DBD donor cohort (23.1% vs 2.6%, p = 0.016).

Procurement variables were comparable between DBD and DCD cohorts (Table 2). In the DCD cohort, there was a

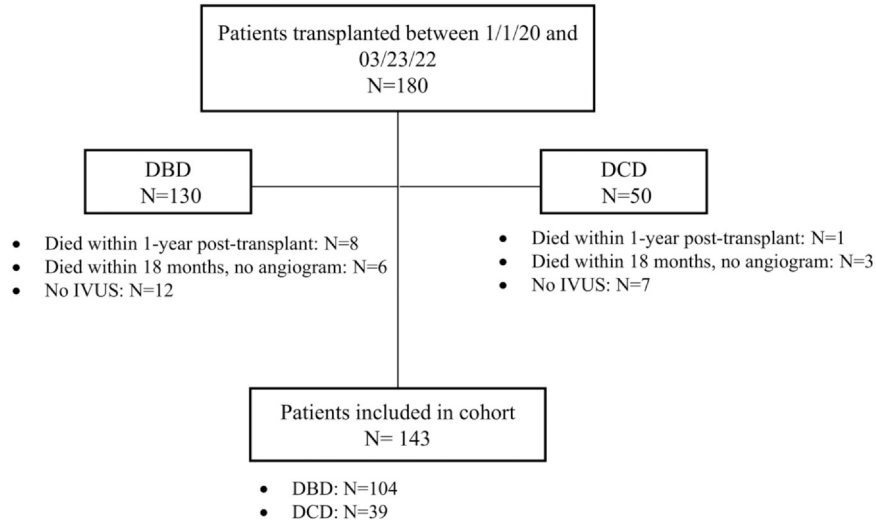

Figure 1 Study flow diagram. DBD, donation after brain death; DCD, donation after circulatory death; IVUS, intravascular ultrasound.

Table 1 Baseline Characteristics of Transplant Recipients and Donors

Baseline characteristics	DBD (N = 104)	DCD (N = 39)	*p*-value
Recipient			
Age – mean (SD)	53.7 (12.9)	56.3 (11.8)	0.290
Female – *n* (%)	27 (26)	6 (15.4)	0.265
Body mass index, kg/m^2 – mean (SD)	26.2 (5.0)	27.9 (4.4)	0.067
Race – *n* (%)			0.695
Non-Hispanic White	38 (36.5)	19 (48.7)	
Black	16 (15.4)	6 (15.4)	
Hispanic	28 (26.9)	7 (17.9)	
Asian or Pacific Islander	14 (13.5)	4 (10.3)	
Other	8 (7.7)	3 (7.7)	
Blood type – *n* (%)			0.069
A	39 (37.5)	12 (30.8)	
AB	6 (5.8)	4 (10.3)	
B	17 (16.3)	1 (2.6)	
O	42 (40.4)	22 (56.4)	
Etiology – *n* (%)			0.787
Non-ischemic	61 (58.7)	22 (56.4)	
Ischemic	35 (33.7)	15 (38.5)	
Congenital	8 (7.7)	2 (5.1)	
Hypertension – *n* (%)	53 (51.0)	22 (56.4)	0.694
Diabetes – *n* (%)	39 (37.5)	10 (25.6)	0.257
Tobacco use – *n* (%)	45 (43.3)	19 (48.7)	0.693
LVAD present – *n* (%)	22 (21.2)	9 (23.1)	0.983
HeartMate II	2 (10.0)	0 (0.0)	
HeartMate III	12 (60.0)	4 (50.0)	
HeartWare	6 (30.0)	4 (50.0)	
PRA > 10% – *n* (%)	19 (18.3)	1 (2.6)	**0.032**
Multiple-listing – *n* (%)	17 (16.3)	8 (20.5)	0.561
Heart-kidney	9 (8.7)	7 (17.9)	
Heart-lung	5 (4.8)	0 (0.0)	
Heart-liver	3 (2.8)	1 (2.6)	
CMV status, positive – *n* (%)	68 (65.4)	27 (69.2)	0.775
CMV viremia – *n* (%)	14 (13.4)	3 (7.7)	0.537
HCV NAT status, positive – *n* (%)	10 (9.6)	3 (7.7)	0.976
UNOS status at time of transplant – *n* (%)			**< 0.001**
Status 1	5 (4.8)	0 (0.0)	
Status 2	42 (40.4)	3 (7.7)	
Status 3	25 (24.0)	7 (17.9)	
Status 4	18 (17.3)	21 (53.8)	
Status 5	4 (3.8)	2 (5.1)	
Status 6	10 (9.6)	6 (15.4)	
ACR ≥ 2/AMR at 1 year – *n* (%)	15 (14.4)	9 (23.1)	0.326
AMR, treated[a] – *n* (%)	15 (14.4)	3 (7.7)	0.425
ACR, ≥2R[a] – n (%)	17 (16.3)	7 (17.9)	1
mTOR inhibitor use, at 1 year – *n* (%)	55 (52.9)	27 (69.2)	0.116
Statin use, at 1 year – *n* (%)	104 (100)	38 (97.4)	0.608
ECMO at time of transplant – *n* (%)	3 (2.9)	0 (0.0)	0.677
IABP at time of transplant – *n* (%)	30 (28.8)	1 (2.6)	**0.002**
Inotropes at time of transplant – *n* (%)	24 (23.1)	7 (17.9)	0.664
Donor			
Age – median [IQR]	33.5 [24.7, 40.2]	32.0 [24, 30.4]	0.134
Female – *n* (%)	21 (20.2)	4 (10.3)	0.673
BMI kg/m^2 – mean (SD)	27.8 (6.3)	27.5 (4.1)	0.735
Hypertension – *n* (%)	24 (23.1)	1 (2.6)	**0.016**
Diabetes – *n* (%)	3 (2.9)	0 (0.0)	0.438
High-risk donor– *n* (%)	35 (33.7)	13 (33.3)	1.0
Donor cause of death – *n* (%)			0.266
Anoxia	46 (44.2)	22 (56.4)	
Cerebrovascular event/Stroke	15 (14.4)	1 (2.6)	

(*continued on next page*)

Table 1 (*Continued*)

Baseline characteristics	DBD (N = 104)	DCD (N = 39)	*p*-value
Head trauma	41 (39.4)	16 (41.0)	
Other	2 (2.0)	0 (0.0)	
LV ejection fraction – mean (SD)	62.2 (7.1)	61.9 (5.5)	0.838
Angiography performed – *n* (%)			**0.001**
Not performed	52 (50)	33 (84.6)	
Performed, normal	49 (47.1)	6 (15.4)	
Performed, abnormal	3 (2.9)	0 (0)	

Abbreviations: ACR, acute cellular rejection; AMR, antibody-mediated rejection; BMI, body mass index; CMV, cytomegalovirus; DBD, donation after brain death; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygenation; HCV, hepatitis C virus; IABP, intra-aortic balloon pump; IQR, interquartile ranges; LV, left ventricle; LVAD, left ventricular assist device; mTOR, mammalian target of rapamycin; NAT, nucleic acid test; PRA, panel reactive antibody; SD, standard deviation; UNOS, United Network of Organ Sharing.

Bolded values represent significant *p*-values < 0.05.

[a]All rejection episodes from transplant to record review 03/2023.

Table 2 Ischemic Times and Procurement Characteristics

Organ procurement	DBD (N = 104)	DCD (N = 39)	*p*-value
Cardiopulmonary bypass time, minutes – median [IQR]	193 [165, 215]	176 [155, 210]	0.232
Cold ischemic time, minutes – median [IQR]	-	158 [62, 196]	
Warm ischemic time, minutes – median [IQR]	-	49 [45, 52]	
Functional warm ischemic, minutes – median [IQR]	-	24 [20.5, 33.5]	
Total ischemic time, minutes – median [IQR]	211 [183, 267]	206 [167, 242]	0.342
Procurement strategy			
DPP, *n* (%)	-	10 (25.6)	
TA-NRP, *n* (%)	-	29 (74.4)	
Storage and transport			
Cold static storage	104 (100)	29 (74.4)	
OCS	-	10 (25.6)	
Donor hospital to recipient (miles) – median [IQR]	260 [78, 383]	270 [244, 712]	0.073

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; DPP, direct procurement protocol; IQR, interquartile ranges; NMP, normothermic machine perfusion; OCS, Organ Care System; TA-NRP, thoraco-abdominal normothermic regional perfusion.

median functional warm ischemic time (FWIT) of 24 minutes [IQR 20.5, 33.5 minutes] with a median cold-ischemic time of 158 minutes [IQR 62, 196 minutes]. Total ischemic time was not significantly different between groups (211 vs 206 minutes, $p = 0.342$). The majority of DCD heart procurement was performed via TA-NRP strategy (74.4%) and transported in cold-static storage (74.4%).

IVUS and angiography

IVUS was performed on 140 patients (103 DBD and 37 DCD) 1 year post transplant, mean time from transplant to IVUS was 376.6 days (±73). There was a high prevalence of disease noted on IVUS with 67.8% of all HTx recipients having Stanford class 3 or higher. There was no significant difference in prevalence of moderate CAV, defined as Stanford class ≥3 (66% vs 72.9%, $p = 0.567$) or MIT between groups (median 0.46 mm vs 0.49 mm, $p = 0.662$) in the DBD and DCD cohorts, respectively (Figures 2A and 2B, Table 3). Overall, there was no statistically significant difference in angiographic CAV severity between DBD and DCD HTx recipients at year 1 (Figure 2B). There was a higher prevalence of severe ISHLT disease, CAV grade 3, in the DBD compared to the DCD group (3 vs 0, p-value = 0.56). Year 2 studies were available for 82 patients (21 DCD and 61 DBD). While year 2 MIT was numerically higher in the DBD patients, median MIT was not statistically different, 0.59 mm [IQR 0.31, 1.05] vs 0.50 mm [IQR 0.37, 0.99] (Figure 3A and B). Most patients had CAV progression with a median increase of 6.6% [IQR −14.8, 46.7]; however, 43% (35/81) patients demonstrated regression (negative percent change). Progression occurred in 46 (57%) patients, with numerically higher rates of progression in the DCD group vs the DBD group, 76% vs 51% (relative risk (RR) 1.5, p-value = 0.10).

Outcomes

A total of 5 deaths were observed with 1 belonging to the DCD cohort and 4 from DBD. Six patients underwent PCI with all belonging to the DBD group (Table 4). On univariable analysis 2R rejection in year 1 and recipient gender were the only variables to demonstrate an association (p-value ≤ 0.2) with the composite outcome of death, PCI, or ISHLT class ≥2 (Table 5). In the final multivariable model, type of transplant (DBD or DCD) was not associated with reduced event free survival, controlling for recipient diabetes, recipient gender, donor age, 2R rejection, and proliferation signal inhibitor use

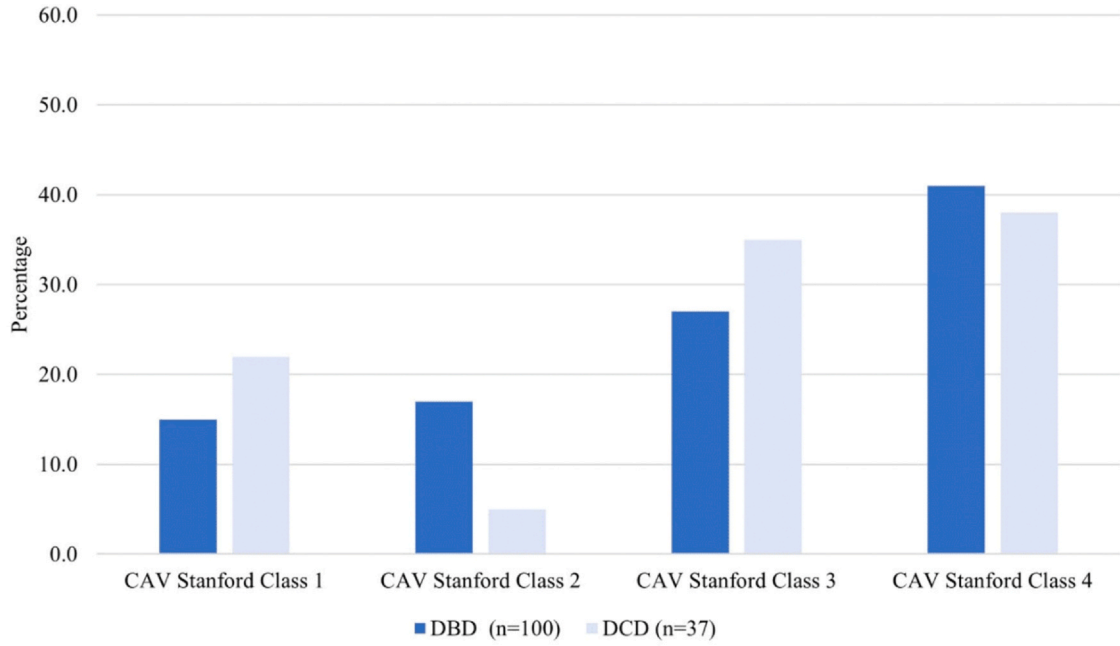

Figure 2A Prevalence of CAV by Stanford classification in DBD vs DCD heart transplant recipients 1 year following transplant. DBD, donation after brain death; DCD, donation after circulatory death; CAV, cardiac allograft vasculopathy.

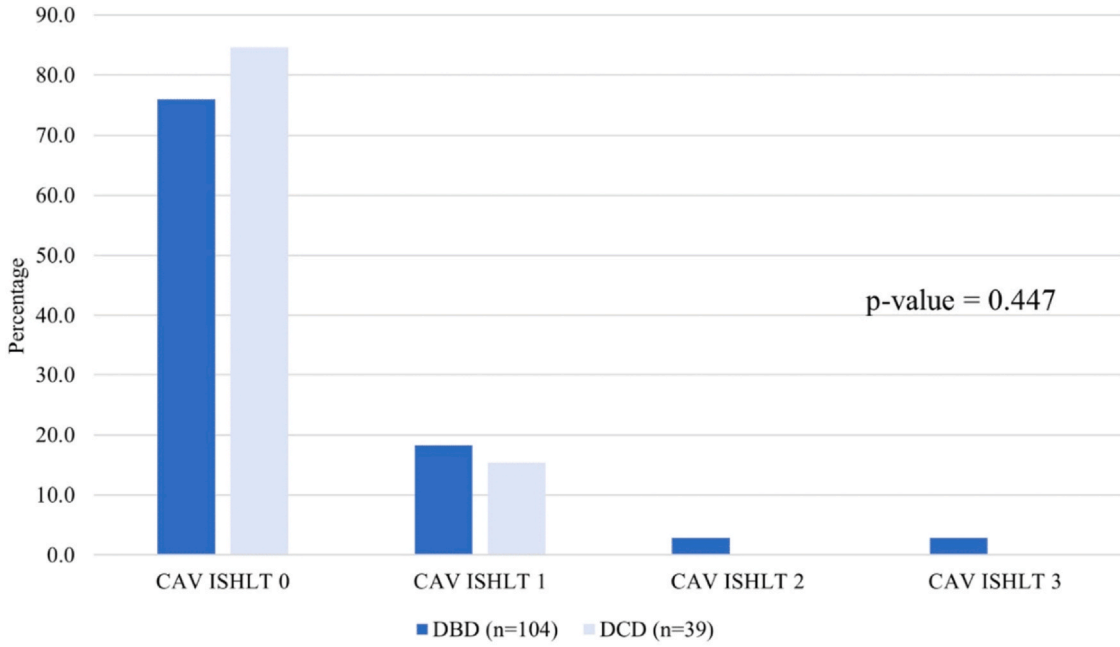

Figure 2B Prevalence of CAV by ISHLT classification in DBD vs DCD heart transplant recipients 1 year following transplant. DBD, donation after brain death; DCD, donation after circulatory death; CAV, cardiac allograft vasculopathy, ISHLT, International Society of Heart and Lung Transplant.

(hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.04-2.78, $p = 0.31$). The event rate was 9.6% vs 2.6% for DBD vs DCD recipients, $p = 0.29$. 2R rejection had the strongest association with composite outcome on multivariable analysis, HR 6.25 (CI 1.5, 25.5), p-value = 0.01 (Table 5, Figure 4A). In an IVUS focused analysis, DCD did not confer a statistically increased risk of death, PCI or severe IVUS disease, defined by MIT ≥0.6 mm (adjusted HR 1.44, CI 0.81, 2.56, p-value = 0.21). Event rate of IVUS composite 51.9 vs 48.7%, $p = 0.87$, respectively (Figure 4B).

Discussion

DCD continues to gain momentum worldwide as a safe and effective method to expand the donor pool.[30-33] While early experience literature supports the use and short-term safety of DCD, long-term outcomes, such as development of CAV, remain unknown. In this study of HTx recipients, there was no significant difference in severity of CAV by angiographic or IVUS assessment between DCD and DBD donors at 12 months. In a modest follow-up time, there was no early signals of aggressive vasculopathy or adverse

Table 3 CAV MIT and Percent Change in DBD vs DCD Heart Transplant Recipients

IVUS and angiography results	DBD	DCD	*p*-value
Year 1	(*n* = 104)	(*n* = 39)	
Max intimal thickness, mm – mean (SD)	0.63 (0.49)	0.59 (0.38)	0.66
Max intimal thickness, mm – median [IQR]	0.46 [0.25, 0.90]	0.49 [0.34, 0.82]	0.86
Year 2	(*n* = 61)	(*n* = 21)	
Max intimal thickness, mm – mean (SD)	0.73 (±0.48)	0.63 (±0.33)	0.36
Max intimal thickness, mm – median [IQR]	0.59 [0.31, 1.05]	0.50 [0.37, 0.99]	0.29
Percent change	(*n* = 61)	(*n* = 21)	
Max intimal thickness, % – median [IQR]	4.65 [−17.04, 45.87]	17.69 [0.62, 64.11]	0.37

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; IQR, interquartile ranges; SD, standard deviation.

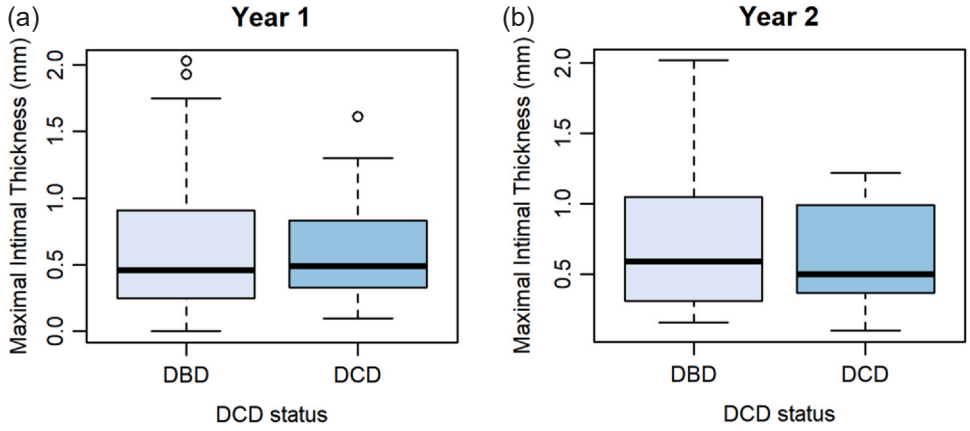

Figure 3 Maximal intimal thickness in DBD vs DCD heart transplant recipients 1 and 2 years following transplant. DBD, donation after brain death; DCD, donation after circulatory death.

cardiac outcomes in patients receiving organ donation following circulatory death.

Numerous donor, recipient, and peri-operative conditions have been instigated in the promotion and maintenance of CAV; however, factors unique to DCD have not been previously investigated. In contrast to donation following brain death, whereby perfusion to vital organs remains constant until time of procurement, organs in the DCD pathway withstand a period of FWIT beginning at time of withdrawal of life supporting therapies until cardiac arrest as well as a period of warm reperfusion during which graft assessment takes place. Cycles of ischemia and reperfusion have been identified as a key mechanism in the pathogenesis of vascular endothelial death and injury, resulting in deleterious downstream cellular

Table 4 Clinical Outcomes in DBD vs DCD Heart Transplant Recipients 1 Year Following Transplant and Total Follow-Up Time

Clinical outcomes at 1 year	DBD (*n* = 104)	DCD (*n* = 39)	*p*-value
PCI, N (%)	1 (1.0)	0 (0)	1
LVEF < 50%, N (%)	9 (8.7)	5 (12.8)	0.66
CAV ISHLT Class ≥2, N (%)	6 (5.8)	0 (0)	0.28
CAV Stanford Class 4, N (%)	41 (39.8)	14 (37.8)	0.84
Clinical outcomes, Total time			
Death, N (%)	4 (3.8)	1 (2.6)	0.98
PCI, N (%)	6 (5.8)	0 (0)	0.28
LVEF < 50%, N (%)	14 (13.5)	6 (15.4)	0.98
CAV ISHLT Class > 2, N (%)	6 (5.8)	0 (0)	0.28
MIT ≥0.6 mm, N (%)	50 (48.1)	18 (46.2)	0.98
CAV Stanford Class 4, N (%)	51 (49.5)	15 (38.5)	0.32
Composite 1 event rate, N (%)	10 (9.6)	1 (2.6)	0.29
Composite 2 event rate, N (%)	54 (51.9)	19 (48.7)	0.87

Abbreviations: CAV, cardiac allograft vasculopathy; DBD, donation after brain death; DCD, donation after circulatory death; ISHLT, International Society of Heart and Lung Transplant; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; MIT, maximal intimal thickness; PCI, percutaneous coronary intervention.

Composite 1: death, PCI, or ISHLT grade 2 disease; Composite 2: death, PCI, or severe IVUS disease (MIT ≥ 0.6 mm).

Table 5 Univariable and Multivariable Predictors of Composite Outcome: Death, PCI, and Moderate or Severe Cardiac Allograft Vasculopathy

	Univariable				Multivariable		
Variable	HR	95% CI	*p*-value	LRT	HR	95% CI	*p*-value
DCD status	0.384	0.047, 3.092	0.36	1.03	0.333	0.039, 2.788	0.31
Age	0.996	0.951, 1.043	0.88	0.02			
Gender (M)	0.349	0.106, 1.147	**0.08**	2.79	0.269	0.074, 0.975	**0.04**
BMI	0.969	0.862, 1.089	0.59	0.28			
Diabetes	0.412	0.088, 1.923	**0.26**	1.5	0.274	0.054, 1.370	0.11
IABP	1.353	0.357, 5.112	0.65	0.19			
PRA prior to transplant	0.996	0.965, 1.031	0.81	0.06			
2R rejection in year 1	2.990	0.873, 10.24	**0.08**	2.66	6.250	1.530, 25.530	**0.01**
Sirolimus/everolimus use	0.459	0.121, 1.737	**0.25**	1.15	0.747	0.201, 2.768	0.66
Total ischemic time	1	0.991, 1.009	0.92	0.01			
Donor age	0.980	0.925, 1.039	0.50	0.46	0.981	0.928, 1.037	0.51
Donor gender (M)	0.531	0.139, 2.025	0.35	0.78			
Donor BMI	0.938	0.832, 1.056	0.29	1.24			
Donor HTN	0.836	0.180, 3.897	0.82	0.42			
Donor HCV NAT (+)	1.08	0.138, 8.450	0.94	0.01			
CMV high risk (+/+)	0.357	0.076, 1.661	0.189	2.09			

Abbreviations: BMI, body mass index (kg/m^2); CI, confidence interval; CMV, cytomegalovirus; DCD, donation after circulatory death, HCV, hepatitis C virus; HR, hazard ratio; HTN, HTN: hypertension; IABP, intra-aortic balloon pump; LRT, likelihood ratio test; NAT, nucleic acid amplification testing; PRA, panel reactive antibody.

Bolded values represent significant *p*-values < 0.05.

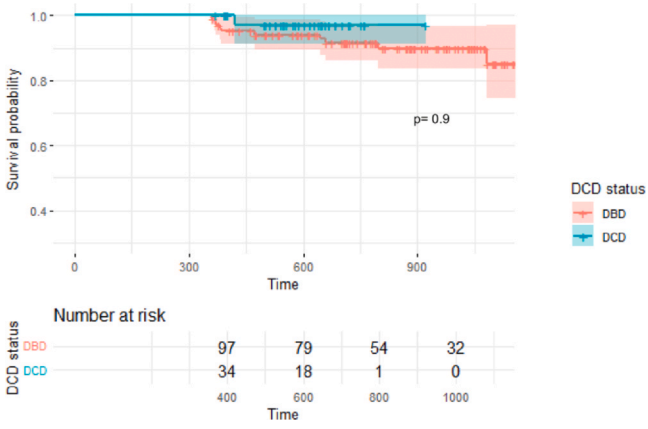

Figure 4A Kaplan Meier survival analysis of primary composite outcome in DBD vs DCD heart transplant recipients. DBD, donation after brain death; DCD, donation after circulatory death.

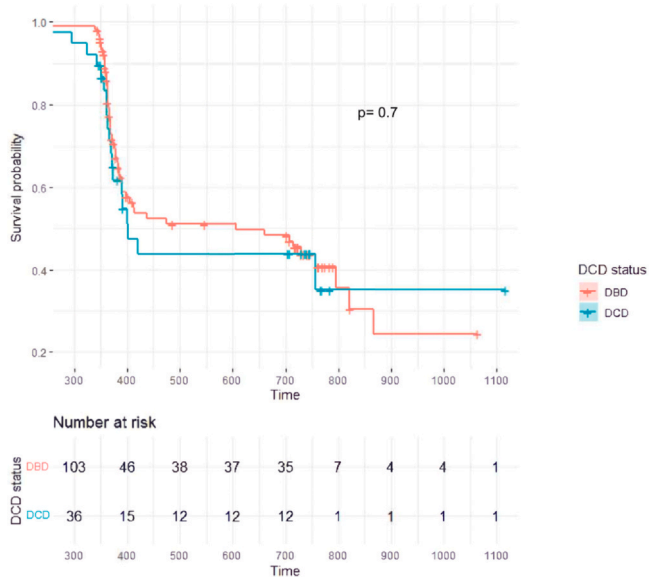

Figure 4B Kaplan Meier survival analysis of IVUS, Death, and PCI composite outcome in DBD vs DCD heart transplant recipients. DBD, donation after brain death; DCD, donation after circulatory death; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention.

changes, such as increased reactive oxygen species production, activation of the innate immune system, and enhanced proinflammatory signaling.[18,26,34] Adverse pathophysiologic changes have been demonstrated in porcine DCD models, beginning from the time of withdrawal of lifesaving therapy during which acidemia and hypoxia result in a progressive rise in blood lactate, troponin-T and right ventricular distension worsening with longer periods of hypoxia and acidemia.[28,34] Conversely, Sanchez-Camara et al utilized serial endomyocardial biopsies from 16 DCD noncardiac donors to study cellular function and myocyte viability during FWIT. Compared to baseline, they found no significant change in calcium homeostasis, mitochondrial function, or cellular function during withdrawal of lifesaving therapy to cardiac arrest (median time 9 minutes, range 4–19 minutes) and up to 10 minutes following cardiac arrest.[35] Notably, the ischemic times reported in the study were lower than those reported from multicenter experiences with DCD, a multicenter report of 157 TA-NRP DCD donors report a mean withdrawal to reperfusion time average of 26.7 minutes, comparable to a mean FWIT of 24 minutes in our study.[30] Differences in the ischemia and reperfusion signatures between DCD and DBD grafts were a major area of interest in our investigation, and we found no association between ischemic time nor DCD status and the occurrence of our composite outcome

or intimal thickening on IVUS. While our findings corroborate the in-vivo findings from Sanchez Camara et al, significant differences in outcomes may be under appreciated due to the smaller number of DCD patients relative to DBD in the final study population.[27,32,36] Lastly, differences in donor hypertension and recipient PRA, known risk factors associated with CAV, between the DBD and DCD groups may have contributed to the higher prevalence of CAV seen in the DBD patient cohort.

A strength of this study is the use of IVUS, which allows for early identification of subclinical disease that can prompt timely interventions and modify or slow progression of disease.[2,5,8,22,37,38] Prior reports demonstrating absence of angiographic disease lack the sensitivity to fully assess for differences in CAV which often manifests angiographically 5 to 10 years after transplant. Subangiographic evaluation of CAV is particularly important in DCD patients whereby the natural history has yet to be determined. In our study, we found no significant differences in MIT between DCD and DBD HTx recipients and the median MIT were < 0.5 mm at year 1 in all patients and no difference in severity of disease by Stanford grade. Use of proliferation signal inhibitor and statin therapy favorably modifies and slows CAV progression, in our cohort high conversion to mammalian target of rapamycin (mTOR) inhibitor therapy by year 1 and statin protocol contributed to the high percentage of patients demonstrating regression. DCD patients tended to have a numerically higher rate of intimal thickening compared to DBD patients and a higher hazard for severe IVUS disease overtime, however, due to incomplete year 2 data, ongoing longitudinal studies are needed to confirm and power these findings. Finally, multiorgan transplant is considered somewhat protective against CAV given prior studies demonstrating lower rates of CAV in these patients when compared to heart only recipients. In our cohort, there was no statistically significant interaction between multiorgan and DCD vs DBD for the composite outcome of death, PCI, and ISHLT or IVUS significant disease.[39,40]

Our incidence of CAV (ISHLT ≥ 1), present in 21.6% (31/143), 37.5% of DBD patients, and 30.8% in DCD, is higher than prior reports by the ISHLT registry which reports CAV incidence of 8% at year 1.[41] This difference is driven primarily by the high proportion of ISHLT 1 disease present in our cohort, accounting for 80% (25/31) of patients with angiographic CAV. Our incidence of moderate and severe ISHLT grade 2 or 3 disease is comparable to recent studies.[9,42] Despite higher rates of grade 1 disease, during a modest median follow-up time of 793 days, there was no early signal of adverse cardiac outcomes, including PCI or acute coronary syndrome in our population.

While the long-term outcomes of patients receiving DCD heart transplantation will not be fully appreciated for many years to come, utilization of IVUS as a diagnostic tool to identify early and subclinical disease is useful to inform risk and provide insight into future events. Our overall observed rate of high grade IVUS detected disease (Class 4) was high, present in 38.4% of our population, which may be reflective of the national trend toward transplanting higher risk donors and recipients.[43] Our results comparing DCD and DBD demonstrate no difference in year 1 CAV severity or CAV-related cardiovascular events. While limited, our year 2 data suggest DCD patients may have higher rates of IT progression compared to DBD. Our experience demonstrates good outcomes and adds to the growing evidence establishing safety with the use of DCD hearts. Further studies are required to determine if long-term CAV outcomes differ between groups. Commonly used ischemia thresholds and post procurement storage may also play a role in this disease and should be further investigated.

Limitations

This is a single-center, retrospective study which limits broad generalization of our findings. The number of DBD and DCD patients was not equal in this study due to novel uptake of DCD technique began in 2019. While most DBD donors underwent coronary angiography prior to procurement, few DCD donors did and without post-transplant baseline angiography (0-6 weeks post-transplant), the assessment of donor transmitted disease is limited. Our center did not use core lab blinded data or full volumetric IVUS data analysis. Our center has a high use of mTOR inhibitor with the goal of reducing CAV, which may not reflect the current practice of other institutions, and therefore limits the generalizability of these outcomes. Differences in donor hypertension and high-risk status between DCD and DBD groups may confound presence of donor derived CAD and CAV. While a large, recent retrospective cohort of 1918 HTx recipients found no significant difference in donor hypertension between those with nonsignificant, significant, or no donor-derived CAD, higher rates of donor hypertension and high-risk features may suggest differences in baseline CV risk factors which have been previously associated with CAV.[44] Lastly, as CAV is a slowly progressive disease process, several additional years of IVUS surveillance is necessary to monitor development.

Conclusion

In a large cohort of DCD HTx recipients, there were no significant differences in prevalence, severity, or clinically significant (death, PCI, ISHLT class ≥2) CAV at 1 year between DCD and DBD HTx recipients. Furthermore, there was no difference in MIT at 1 year between DCD and DBD recipients, this is the first report of IVUS assessment in this population. Further work is needed to confirm these findings, obtain long term follow-up, and investigate differences in donor characteristics.

CRediT authorship contribution statement

A.S.B, Q.B., and V.P., devised the main conceptual ideas and outline. A.S.B. and Q.B., performed statistical calculations and manuscript writing. A.S.B. designed the figures

and took the lead in writing the manuscript. E.A, M.U, M.J.K, Y.G., and N.W., provided critical feedback, shaped the research analysis and manuscript. J.D., K.P, L.K, L.A., and A.D., and participated in design and project concept, and carried out data acquisition. All authors provided critical feedback, review and competition of the project and manuscript.

Disclosure statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eric Adler reports a relationship with Medtronic that includes consulting or advisory. Eric Adler reports a relationship with Abbott that includes consulting or advisory. Victor Pretorius reports a relationship with Medtronic that includes consulting or advisory. Victor Pretorius reports a relationship with Abbott that includes consulting or advisory. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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