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Outcomes of Donation After Circulatory Death Heart Transplantation in Australia

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ABSTRACT

BACKGROUND Transplantation of hearts retrieved from donation after circulatory death (DCD) donors is an evolving clinical practice.

OBJECTIVES The purpose of this study is to provide an update on the authors' Australian clinical program and discuss lessons learned since performing the world's first series of distantly procured DCD heart transplants.

METHODS The authors report their experience of 23 DCD heart transplants from 45 DCD donor referrals since 2014. Donor details were collected using electronic donor records (Donate Life, Australia) and all recipient details were collected from clinical notes and electronic databases at St. Vincent's Hospital.

RESULTS Hearts were retrieved from 33 of 45 DCD donors. A total of 12 donors did not progress to circulatory arrest within the pre-specified timeframe. Eight hearts failed to meet viability criteria during normothermic machine perfusion, and 2 hearts were declined due to machine malfunction. A total of 23 hearts were transplanted between July 2014 and April 2018. All recipients had successful implantation, with mechanical circulatory support utilized in 9 cases. One case requiring extracorporeal membrane oxygenation subsequently died on the sixth post-operative day, representing a mortality of 4.4% over 4 years with a total follow-up period of 15,500 days for the entire cohort. All surviving recipients had normal cardiac function on echocardiogram and no evidence of acute rejection on discharge. All surviving patients remain in New York Heart Association functional class I with normal biventricular function.

CONCLUSIONS DCD heart transplant outcomes are excellent. Despite a higher requirement for mechanical circulatory support for delayed graft function, primarily in recipients with ventricular assist device support, overall survival and rejection episodes are comparable to outcomes from contemporary brain-dead donors. (J Am Coll Cardiol 2019;73:1447–59)

Since our report of the first series of successful heart transplants utilizing distantly procured hearts from donation after circulatory death (DCD) donors in 2015 (1), >80 DCD heart transplants have now been performed across 5 units: St. Vincent's Hospital, Sydney, Australia; and 4 centers in the United Kingdom (Papworth Hospital, Cambridge; Harefield Hospital, London; Wythenshawe Hospital, Manchester; and Newcastle). The initial heart transplants performed by Barnard (2) and other surgical pioneers were also from DCD donors (3). However, in this early innovative stage, organ donors and transplant recipients were collocated in the same hospital, often in adjacent

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ABBREVIATIONS AND ACRONYMS

DBD = donation after brain death

DCD = donation after circulatory death

EMBx = endomyocardial biopsy

ICU = intensive care unit

NMP = normothermic machine perfusion

OCS = Organ Care System

WIT = warm ischemic time

WLS = withdrawal from life support

operating theatres, to minimize donor-organ ischemic times. The availability of artificial respiration and the precedence of heart and kidney transplants led to a period of profound ethical controversy regarding the definition of death. A simultaneous definition of death by the Declaration of Sydney (4) and that of irreversible coma by a Harvard Medical School Consensus Committee (5) paved the way for the subsequent Uniform Determination of Death Act in 1981 (6). This medicolegal document, together with the adoption of safe long-distance procurement using static cold preservation (7–10), the ethics of transporting donors to the recipient hospital, and the valid concern over the detrimental influence on cardiac function and recipient morbidity resulting from the obligatory warm ischemia following withdrawal of life support, led to the abandonment of DCD heart transplantation.

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For the past 5 decades with rare exceptions (11), heart transplant donors have been heart-beating donors who had met brain death criteria. The persistent shortage of donor organs has stimulated research into the use of machine perfusion to enhance preservation of the donor heart and extend procurement distance. The successful use of this technology for hearts from donation after brain death (DBD) donors and concomitant laboratory advances in myocardial protection from ischemic reperfusion injury led to renewed interest in the possibility of transplanting hearts from DCD donors. Following a series of preclinical studies examining the pathophysiological changes that occur in the DCD hearts during withdrawal of life support and the role of normothermic machine perfusion (NMP) in a porcine model of DCD heart transplantation (12–14), our unit undertook the first distant procurement DCD heart transplantation in July 2014 (1). Since then, we have performed a total of 23 DCD heart transplants with 1 early mortality. The aim of this study is to provide an update on our clinical program and discuss the lessons that have been learned.

METHODS

Based on the findings of our large animal laboratory experiments and clinical experience of utilizing marginal DBD hearts with prolonged cold ischemia and/or cardiac function, we developed a recipient-protective clinical protocol for DCD heart retrieval. Details of the protocol have been published previously, and a brief description is provided here (1).

DONOR SELECTION CRITERIA. We accepted male or female DCD donors under the age of 40 years with no known history of cardiac disease. Echocardiography was not routinely available as it was considered an unacceptable antemortem intervention in some institutions. Hearts were retrieved if the warm ischemic time (WIT) defined as the interval between commencement of withdrawal of life support (WLS) and cardioplegia was <30 min (Online Table 1).

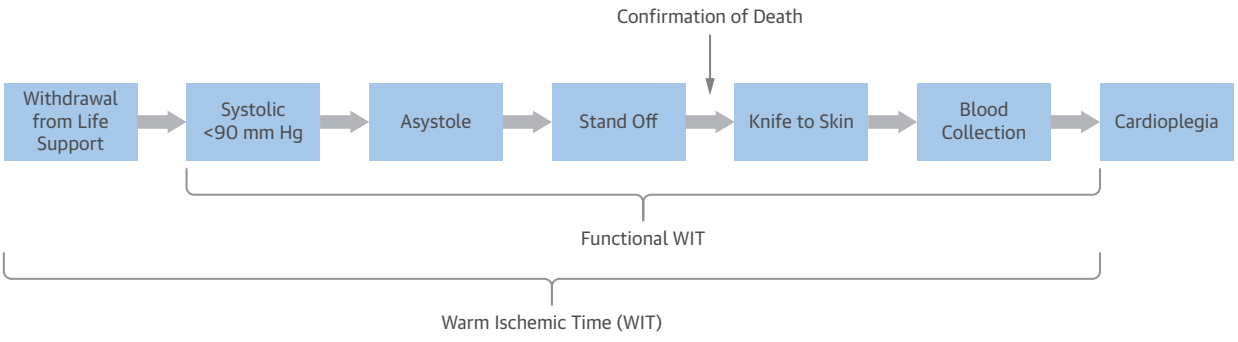
RECIPIENT SELECTION. Recipient selection was based on blood group and cross-matching outcomes, heart mass matching (<15% mismatch) (15), and clinical urgency. Recipients with low measured transpulmonary gradient were selected whenever feasible to reduce the risk of right ventricular dysfunction post-transplantation (13). All recipients provided written informed consent at the time of transplant listing and again on the day of transplantation. The use of DCD donors for human heart transplantation was approved by the St. Vincent's Hospital Human Research and Ethics Committee (HREC/13/SVH/68).

RETRIEVAL PROTOCOL. Upon acceptance and recipient-matching for a potential DCD donor, the cardiothoracic retrieval team, comprising 2 surgeons, a perfusionist, an anesthetist, and a transplant coordinator, traveled to the donor hospital. Prior to departure, donor hemoglobin (Hb) was assessed and transfusion was requested (where possible) if Hb <100 g/dl to ensure a hematocrit >25% during NMP. As the successful procurement of DCD heart is time sensitive, comprehensive pre-operative briefing with the donor coordinators and the abdominal retrieval team was undertaken to minimize unnecessary delays and to streamline the transfer process into the operating theatre. Expedient setup of surgical instruments, cardioplegia giving set, and back-table preparation were performed prior to initiation of WLS.

DCD process. An outline of the steps involved in the DCD retrieval process from WLS to cardioplegia is presented in **Figure 1**.

Instability of donor hemodynamics results in considerable variation in the time to reach circulatory arrest, after which a mandatory "stand-off" period is observed. The "stand-off" period is 2 min in New South Wales and 5 min in all other Australian states and territories. Once death was confirmed and certified, the donor was rapidly transferred to the operating theater for the retrieval procedure. Multiple modifiable time components have been identified to maximize the likelihood of successful retrieval in our experience (Online Table 2).

FIGURE 1 Sequential Steps in the DCD Retrieval Process



This flowchart demonstrates the process during donation after circulatory death (DCD) retrieval, specifically the direct procurement protocol (DPP). Earlier protocols adopted a 30-min warm ischemic time (WIT) after which the donor heart is deemed unsuitable; however, increasing experience has shown that a functional warm ischemic time (beginning from a systolic <90 mm Hg) more accurately reflects myocardial injury during the withdrawal process. Stand-off period varies between 2 or 5 min depending on the location of retrieval due to local legislations that differ between different state governments.

SURGICAL PROCEDURE. On arrival to the operating room, the donor was reintubated and transferred onto the operating table. Rapid antiseptic skin preparation and draping was followed by a coordinated surgical procedure between the surgeon and his assistant (Online Table 3).

Blood collection was performed through the right atrial appendage, using a 2-stage venous cannula, with assisted drainage by placing the patient in the Trendelenburg position. Approximately 1.2 to 1.5 l of blood was collected in <2 min into a sterile heparin-primed collection bag. The collected blood was passed through a blood-leukocyte filter into the Organ Care System (OCS) reservoir. Arterial blood gas analysis was performed followed by administration of sodium bicarbonate for metabolic acidosis and insulin for hyperglycemia as required prior to installation of the heart on the OCS.

Once adequate blood volume was collected, the venous cannula was removed and an aortic cross-clamp was applied followed by commencement of cardioplegic flush via an aortic root cannula. All hearts were flushed with modified St. Thomas' solution supplemented with glyceryl trinitrate (100 mg/l) and erythropoietin (5,000 U/l) (16). The heart was kept cold with topical ice slush and cold saline during cardioplegia delivery. Venting of the heart was achieved by transecting the inferior vena cava and the left superior pulmonary vein. Once the cardioplegic flush solution was completed, the aortic root cannula was removed, and the cannulation site closed. The heart was rapidly excised leaving the pulmonary block in situ and was prepared for installation on the OCS. When the lungs were also to be procured, then the left-sided vent was achieved by transection of the tip of the left atrial appendage.

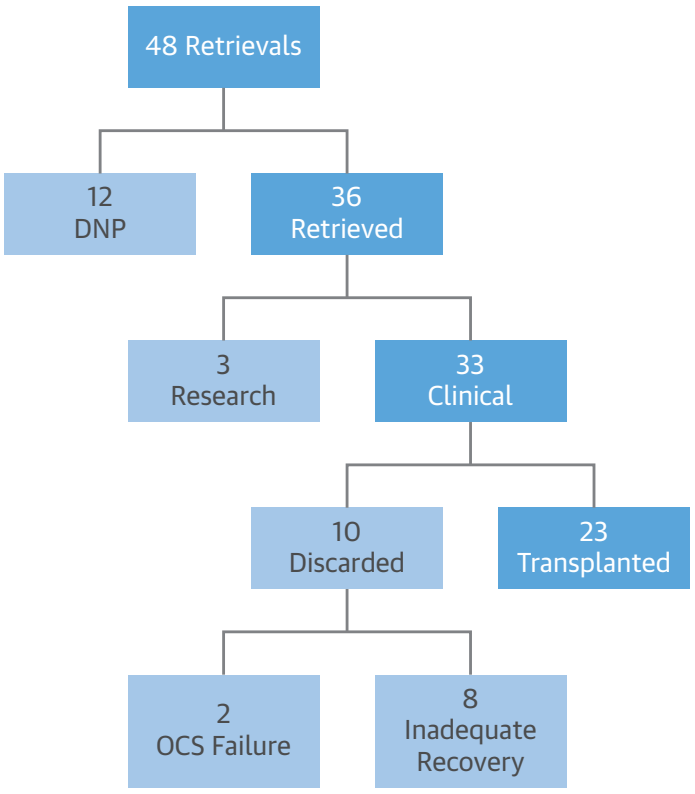
BACK-TABLE PROCEDURE AND OCS MANAGEMENT. The aorta and pulmonary arteries were cannulated on the back-table, and the heart was then instrumented on the OCS device as previously described (17,18). A left ventricular (LV) vent was inserted via the open left atrium, ventricular pacing leads were connected, and the inferior vena cava/superior vena cava closed with running sutures after the heart was placed on the OCS. Target OCS parameters are shown in Online Table 4.

Our criteria for donor heart viability for transplantation is based on a combination of lactate profile, stability of the hemodynamic and physiological parameters on the OCS, and serial visual assessment. Visual assessment is based on individual ventricular chamber contractility. However, the assessment of the left ventricle is limited as it is actively vented during OCS perfusion in resting mode.

Increasing clinical experience has led to less stringent adherence to our initial requirement for a lactate target <5 mmol/l in favor of an essential overall downward trend of lactate levels during reperfusion with evidence of lactate extraction.

DONOR AND RECIPIENT DATA COLLECTION. All donor data including organ management details during normothermic machine perfusion (i.e., OCS flow, coronary flow, aortic pressure, lactate concentrations in coronary arterial and coronary sinus samples) were collected prospectively. Recipient data were obtained post-operatively, and after discharge from hospital. All recipients were followed up at the Heart Transplant Clinic in St. Vincent's Hospital,

FIGURE 2 All DCD Retrievals Performed at Single Unit Since July 2014



All donation after circulatory death (DCD) donations where a retrieval team was dispatched are presented in this table. The outcome of all DCD retrievals during the period between July 2014 and January 2018 has demonstrated a 75% progression rate, of which 70% of retrieved hearts were successfully transplanted. In retrospect, 3 of the 8 hearts that were discarded due to "inadequate recovery" would have been transplanted, and our clinical protocol has since been updated as a result of increasing experience in managing and assessing DCD hearts. DNP = did not progress; OCS = Organ Care System.

Sydney, and underwent surveillance endomyocardial biopsies (EMBx) as per our standard institutional protocol for heart transplant recipients or as required based on clinical concern regarding possible rejection. Transthoracic echocardiography was performed 1 week post-operatively, prior to discharge, at 1 year, or more often if there was concern regarding graft function. Recipient outcomes, including New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) on transthoracic echocardiography, and International Society of Heart and Lung Transplant grading of rejection on EMBx, were collected periodically.

STATISTICAL ANALYSIS. Normally distributed continuous data are expressed as mean ± SD. Nonparametric continuous data are presented as median and range. Data analysis was performed using Microsoft Excel and Prism (Microsoft, Redmond, Washington). Donor and recipient data were compared using Student's *t*-test (parametric), Mann-Whitney analysis (nonparametric), and chi-square test (categorical).

RESULTS

DONOR CHARACTERISTICS. Between July 2014 and April 2018, we attended 45 DCD heart retrievals from which 33 hearts were procured and 23 transplanted (Figure 2). All donors were Maastricht Category III. Twelve potential DCD donors did not progress to circulatory arrest within 30 min from WLS. A total of 33 donors progressed to circulatory arrest within the acceptable WIT and were recovered on the OCS.

Donor location varied widely. Three donors were located in our institution, 8 were in other metropolitan hospitals in Sydney and were retrieved via road ambulance, and 9 were in regional or interstate hospitals with distances ranging from 300 to >3,000 km from our center. These donor hearts were retrieved using a combination of air and road transport. All but 4 donors underwent WLS in the intensive care unit (ICU): 3 underwent WLS in the anesthetic bay or adjacent operating theatre, and 1 underwent WLS within the retrieval operating theatre.

A total of 23 DCD hearts were transplanted from 19 male and 4 female donors with an average age of 29 ± 6 years (range 20 to 38 years). The indication leading to the decision to WLS was traumatic brain injury in 10 cases, cerebrovascular accident in 3 cases, and hypoxic brain injury in 6 cases (including 4 donors after suicide by hanging). Echocardiography was available in 13 donors in whom the mean donor LVEF was 62 ± 5%. These are detailed in Table 1, which includes the entire cohort, including donor hearts that were subsequently declined.

Recipient characteristics. Matched donor and recipient data are presented in Table 2, and recipient demographics are presented in Table 3.

There were 17 male and 6 female recipients with an average age of 52 ± 13 years (range 19 to 66 years). The underlying causes of heart failure were nonischemic dilated cardiomyopathy in 61% (n = 16), ischemic heart disease in 20% (n = 4), and valvular heart disease in 2 patients, including 1 patient with Marfan syndrome and previous aortic valve replacement. One patient underwent orthotopic heart transplantation for severe restrictive cardiomyopathy in association with AL amyloidosis. Eleven recipients required redo sternotomy: 7 cases of ventricular assist device explantation (6 left ventricular assist devices [LVAD] and 1 bi-ventricular assist device) and 4 cases of previous cardiac surgery. Furthermore, an

TABLE 1 Donor Characteristics (All Retrievals)

DNP (n = 12)				Declined (n = 9)				Transplanted (n = 23)			
Age, yrs	Sex	LVEF, %	COD	Age, yrs	Sex	LVEF, %	COD	Age, yrs	Sex	LVEF, %	COD
16	M	55	ICH	23	M	65	HBI	26	Male	65	Hanging
41	M	55	HBI	17	M	N/A	Hanging	26	Male	N/A	TBI
30	M	60	Hanging	19	M	N/A	ICH	27	Male	N/A	TBI
27	F	N/A	ICH	35	F	65	TBI	21	Male	60	CVA
18	M	59	Hanging	23	M	70	Hanging	31	Male	N/A	TBI
21	M	65	Hanging	27	M	N/A	TBI	30	Female	N/A	TBI
39	M	65	ICH	17	M	55	TBI	28	Male	50	TBI
32	M	55	Hanging	43	F	N/A	Hanging	38	Female	60	CVA
33	F	63	HBI	21	M	N/A	Hanging	37	Male	60	Aspiration
41	M	55	TBI					32	Male	52	Hanging
28	M	60	TBI					38	Male	65	TBI
31	M	55	ICH					22	Male	65	TBI
								20	Male	65	TBI
								33	Female	59	TBI
								37	Female	65	HBI
								24	Male	N/A	ICH
								39	Male	65	Burns
								22	Male	N/A	TBI
								24	Male	N/A	Hanging
								32	Male	70	Hanging
								33	Male	65	ICH
								21	Male	68	Hanging
								28	Male	65	Hanging

All referrals where the donor retrieval team was sent for organ retrieval. Donor echocardiogram is not routinely performed and is not considered a mandatory assessment in Australia.

COD = cause of death; CVA = cerebral vascular accident; HBI = hypoxic brain injury; ICH = intracranial hemorrhage; LVEF = left ventricular ejection fraction; TBI = traumatic brain injury.

additional recipient underwent explantation of an infected LVAD that had been implanted minimally invasively via combined left and right thoracotomies. Two of the LVAD recipients had driveline infection pre-operatively. All recipients were NYHA functional class 3 or 4, with LVEF of 23 ± 5% and measured transpulmonary gradient 9 ± 4 mm Hg within 6 months of heart transplantation.

Withdrawal timings. Total WIT and its components (Figure 1) for all 23 donors are shown in Figure 3. As expected, the greatest variability during the period of WIT was the time taken for the donor to progress to circulatory arrest (10 ± 4 min). This was followed by the transportation time required for the donor to arrive in the operating theatre, with the necessary preparation and draping before commencement of organ retrieval. The average time from "knife to skin" to cardioplegia was 5 ± 3 min, which included a period of up to 2 min for donor blood collection.

The mean back-table time, which includes the time from cardioplegia until the establishment of normothermic perfusion using the OCS Heart (TransMedics, Andover, Massachusetts) was 28 ± 6 min. The mean time for organ perfusion on OCS was 276 ± 67 min.

ASSESSMENT OUTCOMES ON OCS. With 2 exceptions, all 23 transplanted hearts exhibited a favorable lactate trend (declining lactate over time) with evidence of venous extraction; however, in 6 hearts (DCD

TABLE 2 Donor and Recipient Characteristics, and Characteristics in Standard Criteria Brain-Dead Cohort Over the Same Period (n = 106)

	Donor	Recipient
DCD		
Age, yrs	29 ± 6	52 ± 13
Sex, M:F	19:4	17:6
Height, cm	176 ± 10	175 ± 8
Weight, kg	80 ± 14	73 ± 13
LVEF, %	62 ± 5*	23 ± 5
DBD		
Age, yrs	33 ± 10	51 ± 14
Sex, M:F	70:34	65:39
Height, cm	174 ± 9	171 ± 11
Weight, kg	79 ± 15	75 ± 14

Values are mean ± SD or n. *n = 16 (echocardiography was not available in 7 patients). Donor and recipient characteristic in DCD and DBD cohort during the same period were similar.

DBD = donation after brain death; DCD = donation after circulatory death; LVEF = left ventricular ejection fraction.

TABLE 3 Recipient Baseline Characteristics

DCD #	Age	Sex	Diagnosis	Redo	VAD	LVEF (%)	TPG (mm Hg)	Creatinine (μmol/l)
1	57	F	Familial DCM	N	N	20	6	114
2	43	M	Viral cardiomyopathy	N	N	25	5	133
3	57	M	ARVD	N	N	20	7	130
4	65	M	Idiopathic DCM	Y	N	30	7	146
5	60	M	Sarcoid	N	N	0	8	127
6	57	F	Idiopathic DCM	N	N	25	10	84
7	57	M	Familial DCM	Y	Y	30	8	101
8	22	F	Familial DCM	Y	Y	20	11	64
9	54	F	Idiopathic DCM	Y	N	20	17 (6)	210
10	50	M	Idiopathic DCM	Y	N	30	6	112
11	65	M	Ischemic cardiomyopathy	Y	Y	15	7	172
12	44	M	Ischemic cardiomyopathy	Y	Y	N/A	13 (8)	109
13	65	M	Idiopathic DCM	Y	N	25	7	141
14	40	F	Ischemic cardiomyopathy	N	N	n/a	10	96
15	63	F	Idiopathic DCM	N	N	25	16	106
16	27	M	Idiopathic DCM	N	N	20	6	110
17	41	M	Idiopathic DCM	N	Y	15	12	76
18	56	M	Ischemic cardiomyopathy	Y	Y	25	11	115
19	47	M	Amyloidosis	N	N	30	11	94
20	66	M	Idiopathic DCM	N	N	20	8	105
21	19	M	Danon disease—cardiomyopathy	N	N	60	7	95
22	66	M	Idiopathic DCM	Y	Y	15	7	138
23	61	M	Idiopathic DCM	Y	Y	25	20	91

Baseline characteristic of all DCD heart transplant recipients between June 2014 and January 2018 including diagnosis, redo-sternotomies, and left ventricular assist device details.

ARVD = arrhythmogenic right ventricular dysplasia; DCM = dilated cardiomyopathy; N/A = not available; TPG = transpulmonary gradient; other abbreviations as in Tables 1 and 2.

10, 12, 18, 19, 20, and 22), lactate values in the perfusate remained above 5 mmol/l. All of these hearts exhibited adequate right ventricular contraction without obvious evidence of wall motion abnormality. Visual assessment of LV contraction is inherently limited on the OCS platform in a resting mode configuration. In contrast, procured DCD hearts that were not transplanted exhibited unfavorable lactate profiles combined with poor cardiac contraction on visual inspection. Combined lactate data in the utilized and discarded groups are presented in Figure 4.

Two machine failures of the OCS occurred in our cohort: the first involved a faulty electrical contact between the disposable module and the base unit leading to pump shutdown while the heart was being reperfused; the second involved extensive clotting of the perfusion circuit, which led to pump stoppage. A total of 6 hearts were declined during NMP due to poor lactate profile, and 1 heart was declined due to inadequate blood volume collection for reperfusion with a resultant low hematocrit of 0.18.

INTRAOPERATIVE OUTCOME. DCD hearts that met pre-defined viability criteria were recardiopleged with supplemented St. Thomas' solution while on OCS Heart, and topically cooled during the process of implantation. Key intraoperative outcomes are presented in Table 4.

IMMEDIATE GRAFT FUNCTION. Intraoperative transesophageal echocardiography (TEE) was performed in all cases to assess graft function post-reperfusion. A retrospective review of TEE reports (n = 18) showed severe biventricular failure in 7 patients and isolated LV failure in 1 patient. Five patients' intraoperative TEE reports were missing, but none of these patient proceeded to require MCS postoperatively. A total of 7 patients proceeded to require extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump in 1 case to wean off bypass. Of the patients who did not require ECMO support, LV failure was observed in 4 patients (27%), but they were successfully managed with higher doses of inotropic support postoperatively.

A total of 8 of 23 recipients (35%) required initial ECMO support to wean from cardiopulmonary bypass, 7 of which were for delayed graft function. In the eighth case, the heart was initially weaned from cardiopulmonary bypass (CPB) but then returned to CPB due to surgical bleeding around the aortic anastomosis resulting in the decision for ECMO support on second weaning from CPB. ECMO support was instituted for an average of 5 ± 2 days with return of normal biventricular function documented on hemodynamic monitoring and TEE prior to ECMO decannulation.

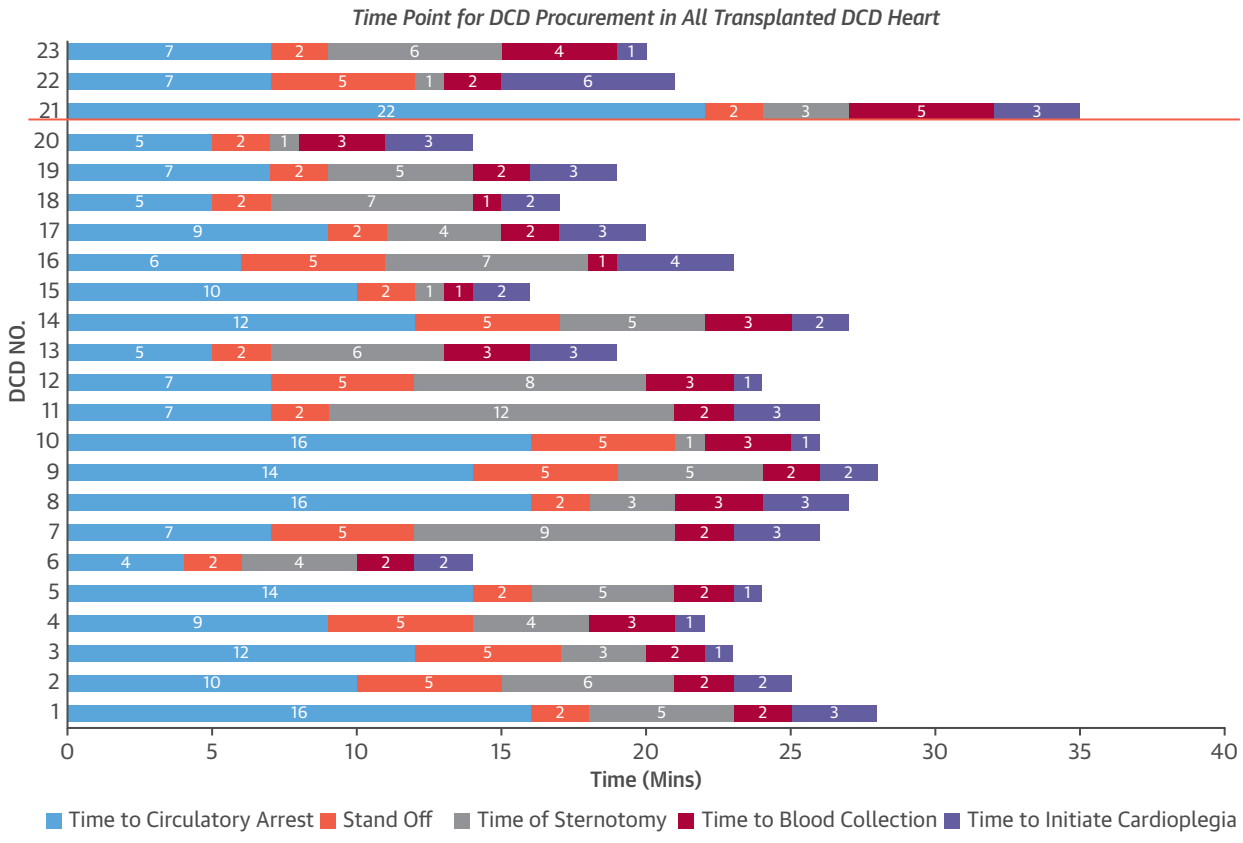
A total of 8 patients had in situ LVADs, 1 of which had been placed through a minimally invasive approach via bilateral mini thoracotomies. ECMO requirement was statistically higher in the LVAD explant recipients (5 of 8) compared with those without pre-transplant mechanical support ($p = 0.03$). Redo sternotomy alone (12 of 23) did not lead to a higher rate of ECMO use ($p = 0.2$).

A comparison between withdrawal times for DCD heart transplant recipients who required immediate ECMO support compared with those who did not is provided in Table 5. The only time interval that differed significantly between the 2 groups was the asystole to cardioplegia time, which was significantly longer in the ECMO group: 15 ± 3 min versus 12 ± 2 min ($p = 0.002$).

Despite higher rates of immediate graft dysfunction and ECMO requirement within the DCD cohort, all hearts recovered to normal biventricular function at 1-week post-transplantation (excluding the single mortality in the series).

PRIMARY OUTCOMES. Survival outcomes. There has been one early mortality (22nd recipient) at 6 days post-transplant in our DCD cohort due to primary

FIGURE 3 **Components of Warm Ischemic Time Period During DCD Withdrawal**

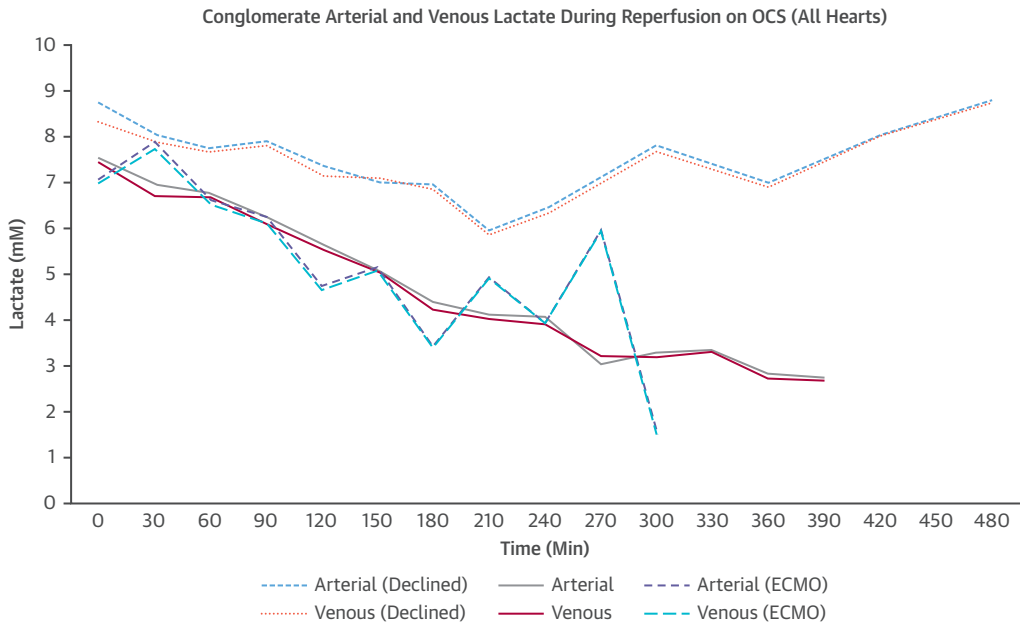


This graph provides a breakdown of individual time periods of all transplanted donation after circulatory death (DCD) hearts from withdrawal of life support until the administration of cardio-preservation solution. Each time period represents a continuous time frame. In 2018, we updated our protocol, commencing warm ischemic time after the systolic blood pressure is <90 mm Hg. This change in practice is represented by the **orange line** in the bar graph.

graft failure. The 21-year-old male donor was located interstate and had experienced severe anoxic brain injury after attempted suicide by hanging. An echocardiogram performed prior to withdrawal of life support was reported as showing a normal-sized left ventricle with an LVEF of 68%. The total WIT (from commencement of withdrawal to cardioplegia) was 23 min, which encompasses time to circulatory arrest (10 ± 5 min) and time from asystole to cardioplegia (13 ± 3 min). The time period from asystole to cardioplegia, also known as the agonal phase (AP time) encompasses the mandatory stand-off period, transport time, and subsequent operative time required before cardioplegia can be delivered. This is presented in **Figure 3**. The DCD heart was transported and supported on the OCS for 270 min. The initial perfusate lactate concentration was 7.17 with evidence of lactate extraction. After an initial fall in lactate concentration to 5.73 over the first 30 min, subsequent lactate concentrations over the next 240 min remained at or above this concentration with favorable A-V lactate differential until the final measurement of 5.88 for arterial lactate and 6.01 for coronary sinus lactate, indicating myocardial lactate production. However, based on initially favorable measurements the recipient surgery had already commenced with cardiac and LVAD explantation.

The recipient was a 66-year-old man who had previously undergone LVAD placement for end-stage heart failure. Following implantation, the heart showed inadequate function without aortic valve opening and required ECMO as well as insertion of an LV vent. The heart function improved over the next few days, but a significant thrombus developed in the aortic root with subsequent akinesia of the anterior and apical segments. Despite surgical clot extraction, the heart failed to recover on continued mechanical support and the patient was subsequently palliated on the sixth post-operative day.

FIGURE 4 Conglomerate Lactate Profile of All Retrieved DCD Hearts



Serial lactate measurements were sampled from the arterial and venous ports, and the overall lactate trend of 3 groups of donation after circulatory death (DCD) hearts are presented here. The **colored lines** represent hearts procured and transplanted without the use of mechanical circulatory support (MCS) post-transplant. The **blue lines** represent hearts that were recovered and transplanted but required MCS post-operatively. The **teal lines** represent hearts that were recovered but not transplanted due to inadequate recovery.

Overall survival for our DCD cohort was 95% at 1 month (n = 23), 1 year (n = 14), and 2 years (n = 9) post-transplant, with 4 patients having passed 3 years from their transplant. The total follow-up time for the 22 survivors is 15,500 days. Comparative survival for our DCD cohort compared with our concurrent standard criteria DBD cohort is presented in Figure 5.

SECONDARY OUTCOMES. Hospital outcomes. Median ICU and hospital stay in the DCD cohort was 7 days (range 2 to 22 days) and 24 days (range 7 to 60 days), when compared with 7 days (range 1 to 65 days) and 27 days (range 3 to 292 days) in our contemporary DBD cohort. There was no significant difference between hospital and ICU length of stay between the DCD and DBD cohorts.

Post-operative complications. Post-operative acute kidney injury was defined as a 2-fold increase of pre-operative renal creatinine within the initial 24 h post-transplant or requirement for hemodialysis. A total of 7 patients had early acute kidney injury (30%), 4 of whom required short-term hemodialysis (17%). All 7 patients had full recovery of renal function.

There was 1 case of deep sternal wound infection, which was in an LVAD explant with driveline site infection tracking to his mediastinum. The patient was managed postoperatively with negative pressure wound therapy (V.A.C.) and had delayed closure of sternum, which healed without further complications. There was no incidence of cerebrovascular injury in our series.

Functional outcomes and rejection rates. Post-discharge, all recipients were followed regularly as per standard protocol in the Heart Transplant Clinic. Currently, all recipients demonstrate NYHA functional class I level of activity with normal biventricular function on most recent transthoracic echocardiogram. EMBx grading of rejection (using ISHLT grading) and LVEF at different time intervals post-transplant

TABLE 4 Intraoperative Outcomes of All Transplanted DCD Hearts

Cross clamp time, min	81 ± 33
Bypass time, min	181 ± 67
Mechanical support	9/23
ECMO	8/23
IABP	2/23

Values are mean ± SD or n/N. Key intraoperative details for all donation after circulatory death (DCD) heart transplants (n = 23). Nine cases required temporary support with mechanical support, of which 1 case required intra-aortic balloon pump (IABP) only; and 1 case required both IABP and VA-extracorporeal membrane oxygenation (ECMO) support post-transplantation.

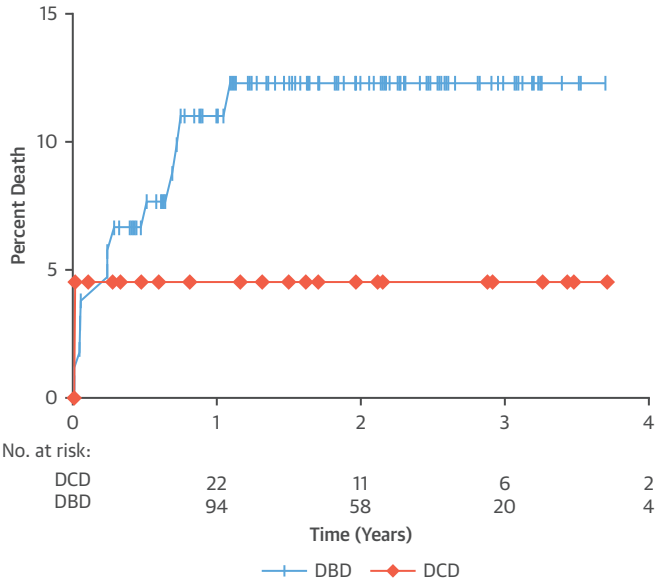
TABLE 5 Comparison of Withdrawal Times Between DCD Heart Transplant Recipients Who Did or Did Not Require Initial ECMO Support

Time Interval	No ECMO (n = 15)	ECMO (n = 8)	p Value
Warm ischemic time, min	23 ± 6	24 ± 3	0.34
Time to asystole, min	11 ± 4	8 ± 4	0.08
Asystole to cardioplegia, min	12 ± 2	15 ± 3	0.002
Cold ischemic time, min	28 ± 5	26 ± 6	0.17
OCS, min	266 ± 68	293 ± 59	0.18

Values are mean ± SD, comparing the withdrawal times between DCD heart transplants that required ECMO post-operatively versus those that did not. There is no significant difference in warm ischemic time, cold ischemic time, or NMP time for the organ. Time to delivery of cardioplegia after asystole is the only significant time point with a positive correlation to ECMO requirement post-transplant.

OCS = Organ Care System; other abbreviations as in Table 4.

FIGURE 5 Survival Outcomes of DCD Versus DBD Heart Transplant Recipients



Kaplan-Meier survival curve for all donation after circulatory death (DCD) and donation after brain death (DBD) hearts between 2014 and 2018 are presented here. All DCD recipients are followed up in the Heart Lung Clinic regularly, and there has been no loss to follow-up within this group to date. The **values beneath the graph** presents the number of patients at risk in relation to the mortality curve. There was only 1 case of early mortality in our DCD cohort.

are presented in Figure 6. Rejection rates in DCD cohort were comparable to DBD in the same period. Antibody-mediated rejection within the first 12 months of transplant was DCD 0.2 ± 0.7 vs. DBD 0.1 ± 0.4 episodes ($p > 0.1$); acute cellular rejection (ISHLT ≥2R), DCD 0.8 ± 1.6 vs. DBD 1.0 ± 1.6 episodes ($p > 0.1$); and mild acute cellular rejection (ISHLT 1R), DCD 5.3 ± 3.4 vs. DBD 4.0 ± 3.0 episodes ($p > 0.1$).

DISCUSSION

Current DCD heart transplantation experience remains limited despite excellent short-term outcomes reported here and recently by Messer et al. (19). Currently, 2 procurement techniques are practiced between 5 centers in Sydney and the United Kingdom: The Sydney Direct Procurement Protocol (DPP), as described previously (1) and in this report, has also been adopted by all of the current DCD heart transplant centers. The other method of Normothermic Regional Perfusion (NRP) championed by the Papworth group utilizes central-ECMO after declaration of death. This allows in situ cardiac reanimation and reperfusion of all donor organs with the exclusion of cerebral flow by clamping the head and neck vessels prior to initiation of ECMO. The Papworth group, which utilizes both methods as dictated by retrieval logistics and location of the procurement hospital, have reported excellent outcomes with both techniques (19). Both protocols utilize NMP for transportation of the donor heart to the recipient hospital.

The main disadvantages of the current clinical protocols include the increased manpower and costs associated with the use of NMP, which also requires an experienced team in facilitating the assessment of DCD hearts during reperfusion. The determination of functional recovery and cardiac viability for transplantation remains limited in the absence of a working heart modality on the OCS platform as well as the reliance on serum lactate as the only available biomarker at present. Currently, the protocols use arterial and venous perfusate lactate levels as a surrogate of organ health; however, we are aware of its limitations in reflecting functional outcomes post-transplantation. As reported in this study, we have transplanted 5 DCD hearts with perfusate lactate concentration >5 mmol/l with good outcome. Based on this experience, our current practice is to accept a DCD heart for transplantation if it demonstrates a decreasing lactate concentration in the perfusate with evidence of myocardial lactate extraction without requiring the absolute lactate concentration to be <5 mmol/l. Also, based on our experience to date, we regard a DCD heart with an increasing lactate concentration in the perfusate with evidence of myocardial lactate generation (coronary sinus lactate > coronary arterial lactate) as unsuitable for transplantation. The single mortality case in our series occurred in a recipient of a DCD heart from a young donor who, despite a short WIT and an initial favorable trend in perfusate lactate concentration, demonstrated myocardial lactate generation by the end of machine perfusion.

FIGURE 6 **EMBx ISHLT Rejection Grading and TTE LVEF Function Chart in all DCD Recipients (n = 23)**

DCD	Pre-D/C	1 Month	3 Months	6 Months	12 Months	24 Months
1	65	65	45	50	55	55
2	70	70	70		70	45
3	60	60			Normal	65
4	65	65	70	65		80
5	70	70			65	65
6	75	80	80	65	65	65
7	70	70			65	65
8	65	65	65	65	65	
9	60	55	55			
10	65	65	65	65	65	
11	65	65	60	65	65	
12	75	65	45	55	65	
13	55	55			60	
14	75			65	65	
15	65	65	65	65		
16	65	65				
17	65	65				
18	65					
19	65	65				
20	65	70				
21	70	65				
22	0					
23	65					

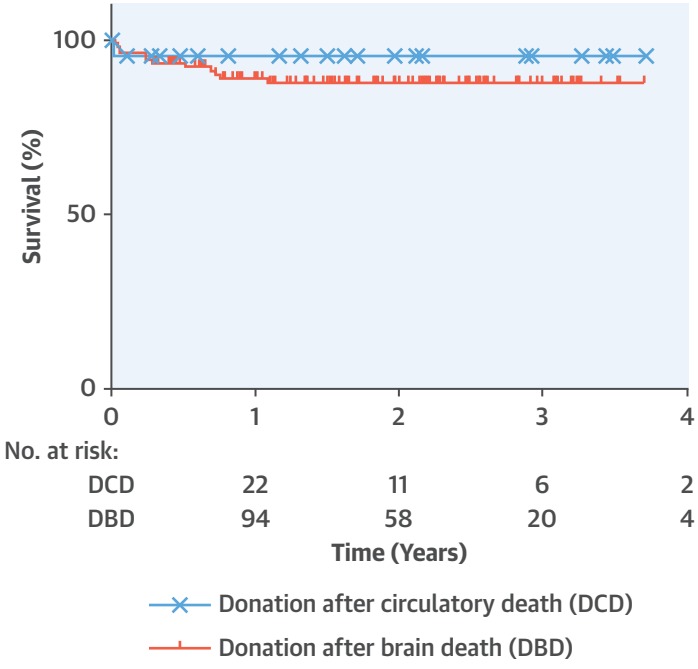
ISHLT Grading
0
1
2
3

Values are left ventricular ejection fraction in percent based on echocardiogram assessment and histological rejection score as per ISHLT grading system. All DCD heart recipients were followed up routinely in the Heart Transplant Clinic. Endomyocardial biopsy is not performed routinely after the first month if left/right ventricular functions are normal on echocardiogram and not dictated by clinical symptoms or signs. Where no biopsies were performed, the squares are left **white**. TTE = transthoracic echocardiogram.

Our experience of using post-transplant ECMO successfully in the marginal hearts from DBD donors, and in particular, for those donor hearts with cold ischemic times >6 h, was an important reassuring component in initiating a DCD heart transplant program (20). We had initially anticipated ECMO requirement following all DCD heart transplants. Despite the significantly higher rate of ECMO use in our DCD cohort of 35% in comparison to the 10% rate in our DBD series (21), the remarkable recovery of these hearts and the excellent short-medium term outcomes have allowed us to continue the program. The utilization of DCD hearts is now standard practice in our service accounting for an extra 15% of all heart transplants, which with inclusion of the marginal DBD hearts preserved on the OCS, account for a combined increase of 20% in heart transplant volume.

Current data suggests pre-transplant VAD support confers a significantly higher risk for ECMO requirement. Furthermore, our current experience also highlights the importance of some key temporal

CENTRAL ILLUSTRATION **Recipient Survival After Cardiac Transplantation Using Donation After Circulatory Death Versus Donation After Brain Death**



Chew, H.C. et al. J Am Coll Cardiol. 2019;73(12):1447–59.

This survival curve illustrates the excellent survival of donation after circulatory death (DCD) hearts at up to 4 years post transplantation when compared to the institutional donation after brain death (DBD) cohort over the same time period.

stages following withdrawal of life support, in particular, the interval between circulatory arrest and cardioplegia delivery (AP time) as being a determinant of delayed graft function and the need for short-term ECMO. This is particularly important as strategies to reduce transport delays can be implemented to reduce AP time (i.e., withdrawal in anesthetic bay or adjacent operating room, location of donor operating room and/or ICU). Furthermore, the availability of an experienced retrieval team to minimize delays during the donor retrieval operation is crucial. Other factors, including administration of antemortem heparin, which has been shown experimentally to improve organ outcome (22), may also affect early graft function. The antemortem administration of heparin is subject to state and institutional policies and therefore is only administered to the minority of DCD donors in Australia.

The co-retrieval and utilization of lungs and abdominal organs are also important considerations in the DCD setting. There have been concerns regarding the quality of coretrieved thoracic and abdominal organs from DCD donors, especially the liver due its susceptibility to warm ischemic injury resulting in ischemic cholangiopathy (23–25). In developing our direct procurement protocol, we have attempted to minimize the effect that heart retrieval has on the retrieval of other organs. The main modification required to permit retrieval of the heart from a DCD multiorgan donor is a delay in the administration of abdominal preservation solutions until after completion of blood collection via the right atrial cannulation. However, as this can be completed in <2 min, providing rapid and beneficial decongestion of the heart and abdominal organs, the actual DCD heart retrieval process has so far never delayed the start of abdominal perfusion, nor has there been any abandonment of an abdominal organ secondary to tissue compromise as a direct result of our heart procurement method. A total of 24 of 30 offered lungs were subsequently retrieved and transplanted with no adverse long-term sequelae. Six lungs were deemed medically unsuitable due to deteriorating arterial blood gas or lack of matching recipient. This highlights the DPP procurement technique as a safe method for multiorgan retrieval.

CONCLUSIONS

DCD heart transplantation is still in its infancy; however, early outcomes support DCD donor hearts as a safe source to address current organ shortages. In our current experience, despite a significant rate of early ECMO utilization, all hearts recovered normal function within 1 week of transplantation except for the 1 mortality (**Central Illustration**). The full recovery of DCD hearts after short-term support using ECMO is suggestive of delayed graft function as opposed to primary graft failure as has been described for DCD kidney transplants (26). We would, however, recommend caution for centers embarking on a new DCD heart transplant program, and for those without experience with post-transplant ECMO use to consider recipients with in situ VAD support as a relative contraindication. In addition, through analysis of withdrawal time points, we have identified that the AP defining the time between asystole and institution of cardioplegia is a predictive factor for ECMO utilization in our cohort when the AP time exceeds 15 min.

The utilization of DCD hearts in our unit has led to a 15% increase in heart transplant activity per annum since its implementation in 2014. This is based on our current DCD protocol, which will be updated to include older donors and a WIT timed to begin when systolic blood pressure <90 mm Hg following withdrawal of life support. These changes are expected to further increase the acceptable pool of DCD donors.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In the recovery of hearts for DCD, warm ischemic time is a crucial determinant outcome. The need for post-transplant mechanical circulatory support rises when the asystolic to cardioplegia (AP) time exceeds 12 min.

TRANSLATIONAL OUTLOOK: Additional research is required to improve the efficiency of donor heart harvesting and transport and to identify better methods to measure ventricular function in transplanted hearts.

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KEY WORDS DCD, ECMO, heart failure, heart transplant, OCS, outcomes

APPENDIX For supplemental tables, please see the online version of this paper.