Review of Heart Transplant Recipient Outcomes: Donation After Circulatory Death (DCD) versus Donation After Brain Death (DBD)

by

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Abstract

Heart transplantation remains the gold standard therapy for end-stage heart failure. Although the number of donors has increased in recent years, there continues to be a critical shortage of organs where demand significantly exceeds supply. The upward trend of available donors has been attributed to several factors. In recent years, there has been an increased availability of donors from drug overdoses and the acceptance of hepatitis C positive donors because of effective antiviral therapy. In addition to an increase in donors from these two groups, donation after circulatory death (DCD) has emerged as a potential solution to augment the donor pool alongside the traditional donation after brain death (DBD) pathway.

Unlike DBD organs, which allow for a beating heart retrieval, DCD donor hearts experience warm ischemic time that can impact heart functioning and recovery. The development of normothermic regional perfusion (NRP) and the recent FDA approval of the Transmedics Organ Care System (OCS) have revolutionized the process of heart retrieval for DCD donors. This literature review aimed to critically evaluate and compare the outcomes of heart transplantation between DBD and DCD donors, focusing on recipient survival, complications, and clinical outcomes, as well as some of the new technology being used in DCD procurements. By synthesizing existing evidence, this review aims to inform clinical practice and guide future research efforts aimed at optimizing heart transplant outcomes and addressing the persistent challenges in organ shortage.

The literature review revealed comparable survival outcomes across all studies analyzed. There were no significant differences in 30-day or one-year survival between DBD and DCD cohorts. Some studies revealed higher rates of extracorporeal membrane oxygenation (ECMO) requirements in DCD heart recipients, although these hearts demonstrated rapid recovery of function and the need for short-term ECMO did not negatively impact survival. Some studies also showed potentially higher rates of severe primary graft dysfunction in DCD hearts, again with similar rapid recovery. These findings suggest that further research may need to be done regarding the post-operative management of DCD hearts, as their requirements may differ from DBD hearts unaffected by warm ischemic time.

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Nomenclature

Abbreviations

AAN	American Academy of Neurology
AAP	American Academy of Pediatrics
AKI	Acute Kidney Injury
A-NRP	Abdominal Normothermic Regional Perfusion
APP	Advanced Practice Provider
AST	American Society of Transplantation
BD/DNC	Brain Death/Death by Neurologic Criteria
BIVAD	Biventricular Assist Device
CAD	Coronary Artery Disease
CAV	Cardiac Allograft Vasculopathy
CNS	Child Neurology Society
CPB	Cardiopulmonary Bypass
DAA	Direct Acting Antiviral
DBD	Donation After Brain Death
DCD	Donation After Circulatory Death
DCDD	Donation After the Circulatory Determination of Death
ECMO	Extracorporeal Membrane Oxygenation
FDA	The Food and Drug Administration
HCV	Hepatitis C Virus
HTK	Histidine-tryptophan-ketoglutarate
IABP	Intra-aortic Balloon Pump

ICU	Intensive Care Unit
LVAD	Left Ventricular Assist Device
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MTS	Measured Toxicology Score
NAT	Nucleic Acid Test
NRP	Normothermic Regional Perfusion
OCS	Organ Care System
PCR	Polymerase Chain Reaction
PGD	Primary Graft Dysfunction
RVAD	Right Ventricular Assist Device
SBP	Systolic Blood Pressure
SCCM	Society for Critical Care Medicine
SCS	Static Cold Storage
TAH	Total Artificial Heart
TA-NRP	Thoracoabdominal Normothermic Regional Perfusion
UNOS	United Network of Organ Sharing
UTS	United Network for Organ Sharing Toxicology Score
UW	University of Wisconsin (solution)
VAD	Ventricular Assist Device
VA-ECMO	Veno-arterial Extracorporeal Membrane Oxygenation
VV-ECMO	Veno-venous Extracorporeal Membrane Oxygenation
WLST	Withdrawal of Life-Sustaining Therapy

1.0: Introduction

The landscape of organ donation and transplantation is constantly evolving and the critical shortage of donor hearts has inspired innovative approaches to improve outcomes for recipients and to expand the donor pool. The utilization of hearts from donation after circulatory death (DCD) has emerged as a promising avenue in recent years. DCD donors have cessation of circulatory function and are a source of potential organs, but before the organs can be recovered, they suffer warm ischemic time that can cause cell damage and pose significant challenges for successful transplantation [1]. The acceptable duration of warm ischemic time varies depending on the organ, with the heart being particularly susceptible to damage after removal [1]. The function of the organ may be compromised due to activation of the inflammatory response, cellular damage, mitochondrial dysfunction, and reperfusion injury, which can cause impaired heart function and may lead to an increased risk of rejection and poor transplant outcomes [1]. The negative effects of warm ischemic time can be mitigated through the integration of normothermic regional perfusion (NRP), which restores blood flow to the donor heart. This technology creates a transformative bridge between procurement and transplantation, and allows for comprehensive assessment along with potential rehabilitation of the donor heart prior to removal [2].

The goal of this paper is to evaluate and compare the outcomes of DCD and DBD heart recipients by reviewing the literature surrounding clinical outcomes and various procurement strategies. By delving into the clinical, scientific, and ethical considerations for the evolving technology in DCD procurements, this paper summarizes the potential for DCD heart transplants to expand the donor pool. To address this topic, transplant data

were first analyzed, followed by recent changes in donor and recipient profiles, organ preservation methods including the use of the Organ Care System (OCS), ethical considerations, and a thorough literature review of studies pertaining to DCD recipient outcomes when compared to traditional DBD recipients.

2.0: Background

2.1: Organ Donation Data

The development of organ transplants has been a breakthrough for treatment in individuals with organ failure, but lack of donor organs still represents a major cause of mortality for these individuals worldwide [3]. Without a transplant, end stage heart failure severely impacts quality of life and carries a poor prognosis. In the United States, the number of heart transplants performed per year has continued to rise, with a 7.6% increase from 2021 to 2022 [4]. The number of available donors has increased in recent years as well, yet the need for donor hearts continues to significantly exceed supply (Figure 1) [5]. The upward trend of available donors has been attributed to several factors. Some of these include the acceptance of hepatitis C positive donors because of effective antiviral therapy, increased availability of donors from drug overdoses, and greater public awareness of donation needs. The introduction of NRP and the recent FDA approval of the TransMedics Organ Care System (OCS) in 2021 has allowed for the acceptance of DCD hearts, which has also helped to increase the donor pool [2]. Despite the increase in available donor hearts, about 20% of patients on the waitlist expire before they are able to receive a transplant, or are removed from the list because of a worsening chance of post-transplant survival [5].

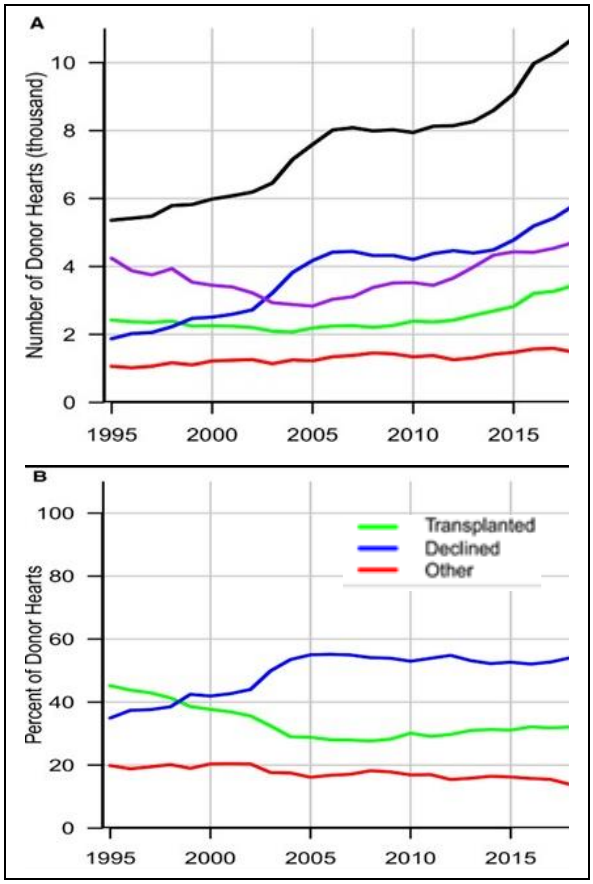

Figure 1: Trends in Donor Hearts from 1995 to 2018 [5]. Graph A shows the total number of donor hearts (black line), transplant waitlisted individuals (purple), transplants (green), and declined donor hearts (blue), which all show an increasing trajectory from 1995 to 2018. Graph B represents the data as a percentage of donor hearts.

Healthcare professionals must consider multiple factors when deciding to accept or reject a donor heart, with the goal of maximizing the chances of a successful transplant while minimizing the risk of complications. For a heart transplant to be successful, several specific requirements must be met. Over half of all potential donor hearts are declined for transplant, but new emerging technology has the potential to improve the utilization rates [5].

2.2: Recent Changes in Donor Characteristics

Tragically, the onset of the opioid epidemic in the early 2000s led to an increase in accidental and premature deaths in younger populations [6]. A recent study published by Baran *et al.* analyzed post heart transplant outcomes of more than 23,000 hearts from donors with illicit drug use between January 1, 2007 and December 31, 2017 [6]. The study analyzed trends in donor drug use based on the United Network for Organ Sharing Toxicology Score (UTS) as well as a Measured Toxicology Score (MTS). The purpose of this dual analysis was to determine if there was a significant difference between the UTS, which is based on drug use history, and the MTS, which is based on actual drug test findings from the donor organ [6]. The study found that the United Network of Organ Sharing (UNOS) reported drug history, or the UTS score, roughly correlated with actual toxicology results. These data were relevant because a reported history of drug use may not indicate current use at the time of donor death and may have had influence on the reliability of the results.

Another outcome of interest in the study was patient survival post-transplant, which was recorded at 1, 5, and 10 years. As shown in Figure 2, donor toxicology was not associated with inferior survival outcomes with any drug, or combinations of drugs [6]. This has clinical significance because the acceptance of hearts from deceased donors with a history of drug use has largely been adopted, yet some institutions still do not use these hearts due to concerns over perceived donor high risk behavior.

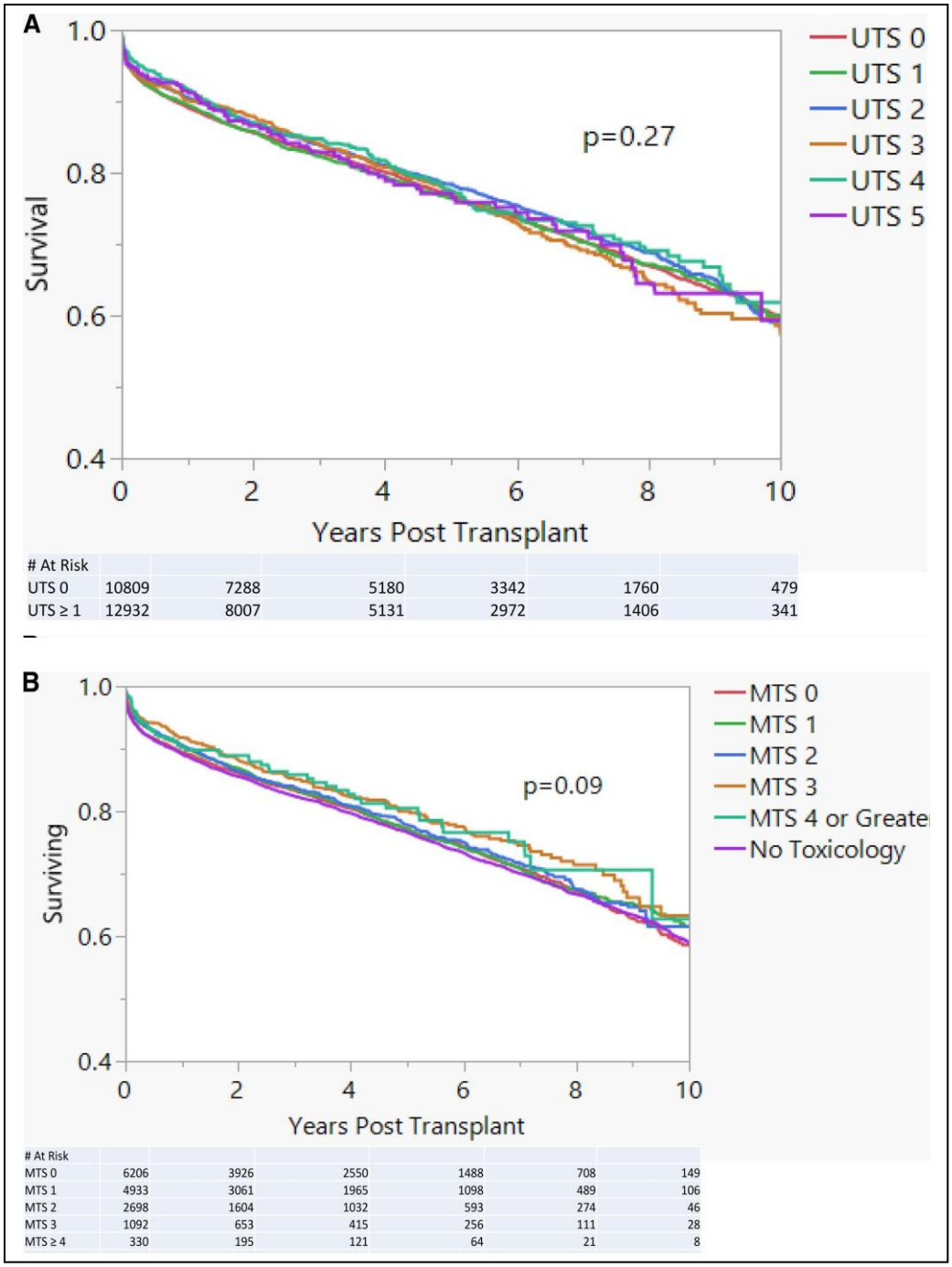

Figure 2: Kaplan-Meier Plots of Survival by UTS and MTS of the Donor [6]. (A) Kaplan-Meier survival plot by value of UTS. No statistically significant difference is detected (p=0.27). (B) Kaplan-Meier survival plot by value MTS. No statistically significant difference is detected (p=0.09).

The acceptance of hepatis C (HCV) positive donor hearts has been a change that has also increased the donor pool in recent years. Treatment for HCV was transformed in 2011, when the first direct-acting antiviral agents (DAAs) were discovered and approved [7]. Prior to the introduction of DAAs, studies reported reduced survival and accelerated cardiac allograft vasculopathy (CAV) among recipients of HCV-infected donor hearts [7]. Today, with the initiation of oral DAAs and proper management, the cure rates are greater than 95%, and therapy is generally well-tolerated [7]. Treatment in the heart recipient depends on the donor's nucleic acid test (NAT) status, as determined by polymerase chain reaction (PCR), and antibody status at the time of donation. Donors who are HCV antibody positive but PCR negative have a much lower risk of transmission to the recipient, as these donors may have been previously exposed to the virus but they do not have an active infection at the time of organ procurement [7]. Donors who are PCR positive represent those with an active infection and have the greatest risk of transmitting the disease to the organ recipient. UNOS analysis of heart recipients of HCV (both NAT positive and NAT negative) donors from 2015 to 2020 found similar 30-day and one-year mortality with no difference in the frequency of graft failure when compared to those who received hearts that were not infected [7]. Heart transplant recipients of HCV-positive donors who were treated with antiviral therapy for the first month post-transplant have comparable graft function and early mortality to those who have received organs from donors without the virus [5].

Despite promising early data, the long-term outcomes of HCV-positive donor hearts remain to be seen. Treatment of HCV using DAAs is an added cost, ranging from $30,000 to $60,000 for a 12-week course of treatment, and may not be tolerated by all

recipients due to side effects or significant drug-drug interactions [8]. Proper evaluation of potential risks versus benefits to the recipient should be weighed when offering acceptance of HCV donor hearts. Although there has been major improvement in the management of HCV, in 2020, only 28% of transplant centers were utilizing HCV-positive hearts [8]. Greater acceptance of these donor hearts would increase the donor pool, especially as treatment and management of HCV continues to improve.

2.3: Heart Recipient Characteristics and Allocation

A heart transplant may be recommended for individuals who have severe heart disease that cannot be treated with other therapies and who are at high risk of death due to their condition. Advances in medical management of heart failure and improvements in mechanical circulatory support (MCS) devices have changed heart recipient profiles in recent years. The most common indications for transplant in adults who received transplants from 2010 to 2020 was non-ischemic dilated cardiomyopathy, which represented 60% of cases, and ischemic cardiomyopathy, which represented around 30% [9].

When comparing early heart transplant recipient data from the 1990s to the current era, recent transplant recipients are more likely to have other high-risk comorbidities such as obesity and/or diabetes, a history of malignancy, and are more likely to be older, an ethnic minority, or female [10]. These changes, particularly multiple comorbidities, pose additional challenges in post-transplant management and may place the individual at a higher risk of complications.

The process of organ allocation for transplant is highly regulated and periodically reviewed to adjust for the continuously evolving patient profiles. The most recent change to the heart allocation policy occurred in October of 2018, where the previous three-tier system was converted to a six-tier system (Table 1) [7]. The intended effect of the policy change was to give clearer guidelines regarding patients on MCS devices, provide a broader sharing of donor organs, and reduce waitlist mortality [11].

Table 1: Status Tiers in the Modified 2018 Heart Allocation Guidelines [7].

Status 1	• Veno-arterial extracorporeal membrane oxygenation (VA-ECMO). • Non-dischargeable, surgically implanted, nonendovascular biventricular support device. • MCS device with life-threatening ventricular arrhythmias.
Status 2	• Nondischargeable, surgically implanted, nonendovascular left ventricular assist device (LVAD). • Percutaneous endovascular MCS device. • Ventricular tachycardia/ventricular fibrillation, MCS device not required. • MCS with device malfunction/mechanical failure. • Total artificial heart (TAH), biventricular assist device (BIVAD), right ventricular assist device (RVAD), or ventricular assist device (VAD) for single-ventricular patients.
Status 3	• Dischargeable LVAD for discretionary 30 days. • Multiple inotropes or single high-dose inotrope with continuous hemodynamic monitoring. • VA-ECMO after 7 days; percutaneous endovascular circulatory support device or intra-aortic balloon pump (IABP) after 14 days. • Nondischargeable, surgically implanted, nonendovascular LVAD after 14 days. • MCS device with one of the following: device infection, hemolysis, pump thrombosis, right heart failure, mucosal bleeding, aortic insufficiency.
Status 4	• Dischargeable LVAD without discretionary 30 days. • Inotropes without hemodynamic monitoring. • Retransplantation. • Diagnosis of one of the following: congenital heart disease, ischemic heart disease with intractable angina, hypertrophic cardiomyopathy, restrictive cardiomyopathy, amyloidosis.
Status 5	• On the waitlist for at least one other organ at the same hospital.
Status 6	• All remaining candidates.

The main 2018 policy modification was the prioritization of patients receiving extracorporeal membrane oxygenation (ECMO) [11]. The development and advancement of MCS devices such as ECMO can be effective in serving as a temporary bridge to transplant, but without a transplant, these individuals with severe heart failure typically do not survive [3]. Moving those individuals to the top of the transplant waiting list increases their chances of receiving a transplant, therefore reducing overall waitlist mortality [11]. The second change in the 2018 policy update was lowering the priority of stable patients that are on left ventricular assist devices (LVADs) [11]. Advances made in LVAD technology and maintenance have improved the survival rates of these individuals, which is close to 80% two years after implantation [11]. By moving these patients lower on the waitlist, the organs can be distributed to include more in the higher risk groups.

Preliminary analysis of the impact of the policy change has revealed a decrease in waitlist duration and mortality, but has unfortunately reduced one-year post-transplant survival by 4.6% [11]. The decrease in post-transplant survival is an expected consequence, since sicker recipients are often bridged with ECMO, which carries an increased risk of primary graft dysfunction (PGD) and reduced rates of early and late survival [11]. Organ allocation is a dynamic process, and advancements in medical knowledge and technology lead to adjustments in allocation policies over time. The ultimate goal is to save and improve as many lives as possible through successful organ transplantation while maintaining the principles of fairness and medical necessity.

2.4: Organ Preservation Methods

Organ procurement for organ transplant is a complex and multifaceted process. Each type of organ presents its own set of unique challenges and requirements for successful implantation into the recipient. The heart in particular is very sensitive to ischemia and has one of the shortest acceptable out of body times out of all the organs. In general, it is recommended that ischemic times for donor hearts should be kept below four to six hours [1]. Cold ischemic time beyond six hours in donor hearts has been associated with impaired cardiac function and an increased rate of post-transplant mortality in heart recipients [3, 12]. When donor heart cold ischemic time is increased from three to six hours, the recipient mortality at one-year post transplant doubles in adult patients [3].

Organ preservation aims to reduce the harmful effects of hypoxia and ischemia while the organ is in transport, as well as reduce reperfusion injury once it is implanted in the recipient [1]. Total ischemic times and organ transport distances have increased since the 2018 allocation policy change, and on average, hearts are received from older donors [12]. Studies have shown that hearts obtained from older donors are more sensitive to prolonged ischemic times when compared to hearts from younger donors, so there has been much clinical interest in improving organ preservation techniques to further extend acceptable ischemic time [12].

The traditional and most commonly utilized method for heart preservation involves the static placement of the heart on ice to reduce oxygen consumption and cellular metabolism [3]. Cooling the organ helps to prevent release of autolytic enzymes that can cause cell death through reducing the rate of lysis of intracellular organelles [1].

In static cold storage (SCS), once the heart is inspected for transplant viability, the aorta gets cross-clamped and the heart is flushed with a cardioplegia preservation solution to induce a diastolic arrest [13]. The heart is cooled and removed from the donor's body, placed in a bag containing ice and preservation solution, then placed in a cooler for transport to the heart recipient facility. Over the years, multiple heart preservation solutions have been developed, each with different concentration of electrolytes, metabolites, buffering agents, nutrients, and antioxidants [1]. Currently, the three most commonly used solutions for heart preservation are the University of Wisconsin (UW) solution, histidine-tryptophan-ketoglutarate (HTK) solution, and the Celsior solution [1]. Each of these solutions contain specific compounds that attempt to minimize the effects of ischemia on the heart, and they are summarized in Table 2. The solution used depends on each individual institution's protocol and surgeon preference.

Table 2: Components and Properties of Commonly Used Heart Preservation Solutions [1].

Component (g/L)	University of Wisconsin (UW)	Celsior	Histadine-tryptophan-ketoglutarate (HTK)
Pentafraction	50	-	-
Lactobionic acid	35.8	28.7	-
Potassium phosphate monobasic	3.4	-	-
Magnesium sulfate heptahydrate	1.2	-	-
Raffinose pentahydrate	17.8	-	-
Adenosine	1.3	-	-
Glutathione	0.9	0.9	-
Potassium hydroxide	5.6	-	-
Mannitol	-	10.9	5.5
Glutamic acid	-	2.9	-
Sodium hydroxide	Adjust to pH 7.4	4	-
Calcium chloride dihydrate	-	0.04	0.002
Potassium chloride	-	1.1	0.7
Magnesium chloride hexahydrate	-	2.6	0.8
Histidine	-	4.7	27.9
Histidine monohydrochloride monohydrate	-	-	3.8
Hydrochloric acid	Adjust to pH 7.4	-	-
Sodium chloride	-	-	0.9
Potassium hydrogen 2-ketoglutarate	-	-	0.2
Tryptophan	-	-	0.4
Physical Properties			
pH	7.4	7.3	7.2
Osmolarity (mosmol/kg)	320	320	310

In addition to improved preservation solutions, advancements have also been made with organ transport devices. The SherpaPak system was developed in 2018 to create a more controlled cold environment for transport, and keeps the organ in a single use container that maintains the organ temperature between 4 and 8°C [14]. When compared to standard SCS, early studies show that the use of the SherpaPak system increases recipient one-year survival rates, reduces the incidence of post-transplant severe PGD, and reduces post-transplant use of MCS devices [14]. Although this new

technology may be beneficial, it has not been shown to be effective in extending organ viability beyond the standard six hour maximum cold ischemic time [3].

2.5: The Organ Care System (OCS)

The TransMedics Organ Care System (OCS) was developed in an attempt to extend the organ preservation window, and was approved by the FDA for use in heart transplants in 2021 [3]. The OCS keeps the donor heart close to the physiological state during transport in a beating, perfused chamber [3]. The Organ Care System is a complex device that requires highly trained personnel to operate effectively. After the donor is declared deceased, the chest is opened and around 1500 mL of blood is removed from the donor to a heparinized bag to be used as the perfusate solution in the OCS [2]. In studies comparing ex-vivo perfusion with blood to other types of solution, the hearts perfused with blood performed significantly better [3]. Blood use in the OCS allows for oxygen and nutrient delivery to the tissue and mimics the native environment. Blood also functions as a strong buffer against acidosis, metabolic toxicity, and acts as a free radical scavenger [3]. After blood removal, the heart is flushed with cardioplegia, removed from the donor, and is shifted to the back table.

The OCS cannulas are attached to the pulmonary artery and the aorta, and a left ventricular vent is placed to prevent distension (Figure 3A) [2]. The heart is then re-perfused with the normothermic solution containing the donor's own heparinized blood, antibiotics, sodium bicarbonate, methylprednisolone, electrolytes and insulin [15]. The solution is pumped into the aorta, which perfuses the coronary arteries. The return flow

from the coronary sinus passes from the right atrium to the right ventricle through the tricuspid valve, and is ejected into the attached pulmonary artery cannula [16]. This blood is deposited into a reservoir, where it gets propelled through a pulsatile pump which leads to the oxygenator and warmer. Eventually the blood returns back to the heart through the aortic line, and the process repeats [16]. After a few minutes, the heart usually starts beating independently but may require defibrillation [3]. Ventricular pacing wires are sutured and the heart is paced if necessary [3]. The heart is then covered with a sterile film and cover to protect it from damage during transport (Figure 3B) [3].

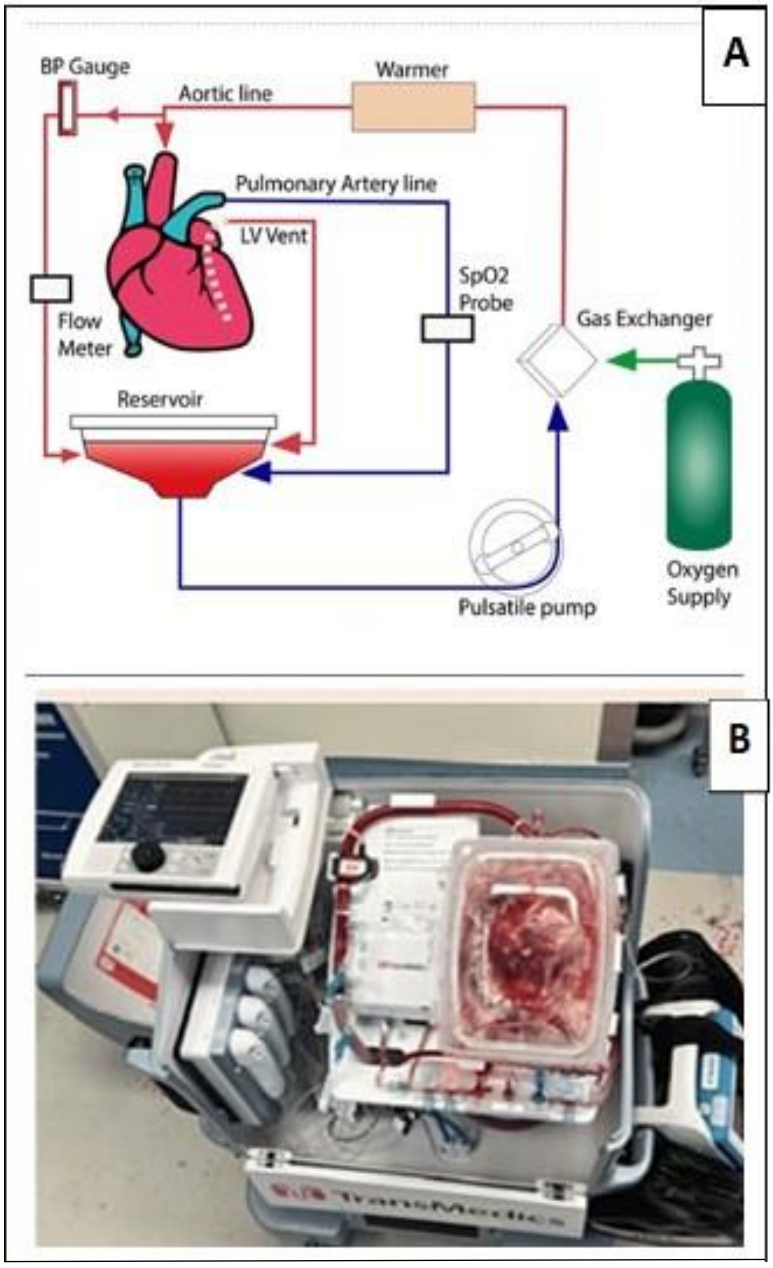

Figure 3: OCS Cannulation of Donor Heart Diagram (3A) and Application (3B) [3].

The cold ischemic time the heart experiences in the OCS is only during the initial and final phases, which significantly reduces the total cold ischemic time and allows for longer duration of heart preservation when compared to SCS [3]. The PROCEED II trial

was a large, multicenter, prospective study that compared outcomes between heart transplant recipients who received an organ preserved with the OCS compared to traditional SCS [16]. Overall survival outcomes of patients who received donor hearts from the OCS were similar to the SCS method, even with a longer total out of body time [16]. The study also showed no significant differences in the length of intensive care unit (ICU) stay or incidence of high-grade rejection in OCS patients [16]. Recipients of OCS hearts who were on LVAD support before transplant actually showed slightly better outcomes in some studies when compared to similar populations who received SCS hearts [17]. Only one center that was a part of the PROCEED II trial published two-year outcomes that showed a lower, albeit not significant (72.2% versus 81.6%, respectively, $p = 0.38$), difference in survival rates in the OCS group when compared to the SCS group [18]. The secondary outcomes from this center revealed no significant differences in biopsy-proven cellular rejection, antibody mediated rejection, CAV, or non-fatal major cardiac events between the two cohorts [18]. Early data indicate that the OCS safely lengthens total out of body time and allows for donor hearts to be transported farther than the SCS method, which has potential to expand the donor pool and improve donor matching [3].

Another potential benefit achieved through the OCS may be further optimization and evaluation of previously unacceptable or unused hearts [16]. Extended criteria, or higher risk donor hearts, may have a reduced left ventricular ejection fraction, previous cardiac arrest, left ventricular hypertrophy, prolonged ischemic time, or unknown coronary artery disease status because of a lack of coronary angiography [19]. The OCS allows for heart recovery in near physiological conditions where real-time system and

organ measurements are displayed [19]. Expanded structural evaluation of the donor heart can be achieved through the OCS as well, and offers the benefit of ex-vivo medication administration to optimize function [19]. One study showed successful recipient outcomes of higher risk donor hearts through ex-vivo optimization with the Organ Care System [19]. As organ management on the OCS continues to evolve, the utilization rate of formerly discarded "marginal" hearts may improve, therefore reducing waste and increasing the number of transplants performed without negatively impacting outcomes.

As the OCS has increased in popularity in the United States, there have been some challenges associated with its use. The OCS is expensive to run, it is estimated that each use costs around $80,000, not including the additional cost of the hospital stay [3]. For the heart to remain viable during transport, the staff operating the machine must be highly skilled and trained in the management and troubleshooting of the device. TransMedics initially attempted to train individual hospital staff on the use of the OCS, but currently utilizes an internalized team that gets dispatched to each site as needed in most regions. By using this method, the company can ensure the proper training and confidence of the staff in running the high-risk device. In addition, the OCS machine must be plugged into an outlet and connected to Wi-Fi, so it must be transported in upgraded cars and/or airplanes [3]. Since the device only received FDA approval in 2021, long-term patient outcomes outside of preliminary clinical trials have yet to be revealed. Current data supports that the OCS appears to be a safe and effective alternative for donor heart transport, and as its use continues to expand it holds the potential to expand the donor pool through more efficacious use of marginal hearts and to allow for longer

distance procurements [3]. The OCS may be used to transport hearts from both DBD and DCD donors.

2.6: Organ Donation After Brain Death (DBD)

Currently, donor hearts are retrieved primarily from donors who have been declared brain dead. These donors have irreversible, permanent brain damage and must meet several strict criteria. In the United States, there is some variation in the physician and/or advanced practice provider's (APP) eligibility to perform a brain death examination depending on the state and institution [20]. Some states only allow neurosurgeons, neurologists, and ICU specialists to perform brain death exams, while other states allow declaration from any physician or APP [20]. Until recently, adult brain death/death by neurologic criteria (BD/DNC) determination was based on the American Academy of Neurology (AAN) guidelines from 2010 [21]. In 2023, an evidence-based, updated guideline for BD/DNC was released by the AAN formulated through consensus-based collaboration with the Society for Critical Care Medicine (SCCM), Child Neurology Society (CNS), and the American Academy of Pediatrics (AAP) [21]. The 2023 document combines adult and pediatric guidelines, which are largely similar, but feature some age specific variations due to physiologic differences [21].

The guidelines detail prerequisite conditions for BD/DNC, and are summarized in Table 3 [22]. The etiology of the brain injury must be known, and conditions (hypothermia, hypotension, abnormal lab values, etc.) that could confound the interpretation or assessment of the BD/DNC evaluation are excluded [22]. The guidelines

state how to perform a meticulous neurologic exam and describe the responses to expect in a patient with brain death. This includes the absence of the pupillary light reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex, cough and gag reflex, and no motor responses that occur spontaneously or through noxious stimuli, with the exception of spinal motor reflexes [22].

Table 3: Prerequisite Conditions for Brain Death/Death by Neurologic Criteria Evaluation [22].

Age ≥ 37 week corrected gestational age
Etiology of brain injury must be known • Neuroimaging should be consistent with the mechanism and severity of brain injury. • Primary posterior fossa injury: ensure concurrent catastrophic supratentorial injury.
Observe for sufficient time to determine the severity and permanency of the brain injury. • < 24 months old: wait >48 hours independent of brain injury etiology. • ≥ 24 months old: wait > 24 hours after hypoxic-ischemic brain injury. • After medical or surgical interventions to treat intracranial hypertension, wait sufficient time to ensure no recovery of brain function.
Core body temperature • ≥ 36° C • If temperature ≤ 35.5° C, wait >24 hours after rewarming to ≥ 36° C.
Blood pressure • Adults: Systolic blood pressure (SBP) ≥ 100mmHg and mean arterial pressure (MAP) ≥ 75 mmHg • Children: SBP and MAP ≥ fifth percentile for age. • VV-ECMO: same as for non-ECMO. • VA-ECMO: MAP ≥ 75mmHg (adults) or ≥ fifth percentile for age (children).
Toxicology • Ensure toxicology (urine and blood) screening is negative. • Alcohol blood level ≤ 80 mg/dL.
Medications • Confirm medication levels (when available) are in therapeutic or subtherapeutic range. • Allow at least five half-lives to pass. • Consider age-dependent metabolism. • Consider a longer elimination period if the patient has renal or hepatic dysfunction. • Consider a longer elimination period if the patient is obese or hypothermic.
Exclude severe metabolic, acid-base, and endocrine derangements • Sodium: <130 mmol/L or >160 mmol/L • Glucose: <70 mg/dL or >300 mg/dL • Blood urea nitrogen: >75 mg/dL • Calcium (iCa): <7 mg/dL or >11 mg/dL (<1 mmol/L or >1.3 mmol/L) • Magnesium: <1.5 mg/dL or >4 mg/dL • pH: <7.3 or >7.5 • Total T4: <3 mg/dL or >30 mg/dL; free T4: <0.4 ng/dL or >5 ng/dL • Ammonia: >75 μmol/L

Apnea testing is a requirement for BD/DNC evaluation, and the guidelines also provide a protocol for providers on how to safely perform this test (Figure 4) [22]. The updated version includes specific modifications needed for patients on ECMO. If the patient is an organ donor, once BD/DNC is confirmed, planning for organ procurement

can begin. Scheduled organ evaluation and procurement in DBD patients is controlled and well established and allows for a "beating heart" retrieval of the donor organs.

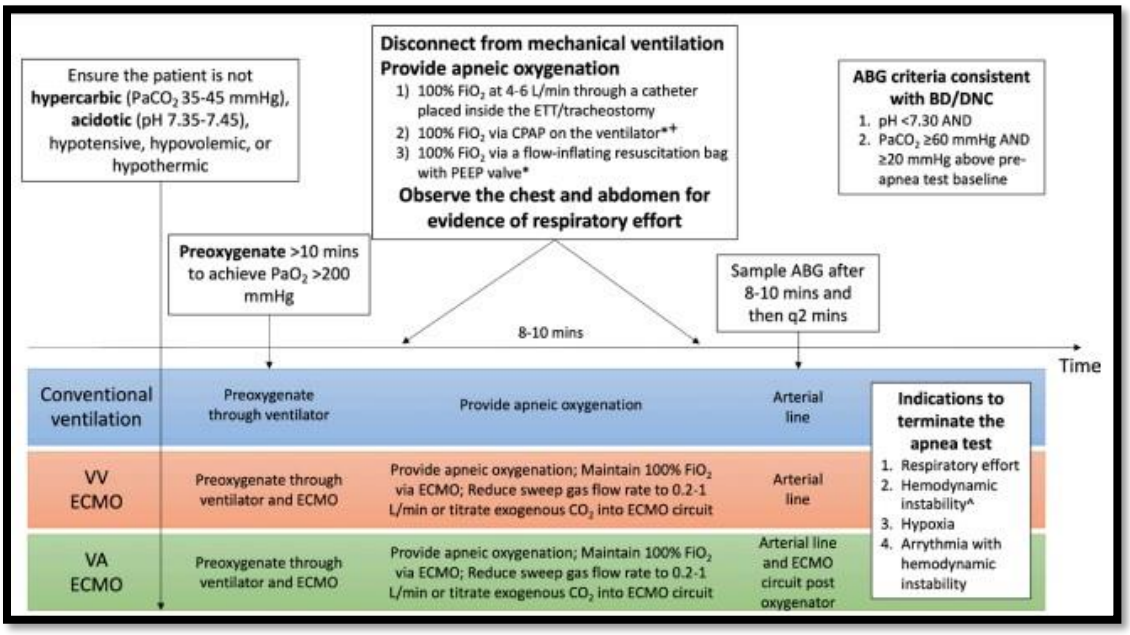

Figure 4: Clinical Guidance for Conducting Apnea Testing in BD/DNC Evaluation [22].

There are some notable changes in terminology used in the new guidelines, including the use of the term "permanent" rather than "irreversible" to describe the severity of brain injury [21]. Permanent brain injury is defined as "(1) will not resume spontaneously and (2) medical interventions will not be used to attempt restoration of function" [21]. The term was changed because the term "irreversible" reflects the ethical obligation that everything should be done to revive a patient, which is not always appropriate for patients that display severe brain injury where further care would not lead to meaningful recovery.

2.7: Organ Donation After Circulatory Death (DCD)

Donation after circulatory death (DCD), or donation after the circulatory determination of death (DCDD), usually occurs when a patient suffers devastating neurologic injuries where further care is futile, but does not fully meet all brain death criteria [2]. Death according to neurological criteria and death according to circulatory criteria share a thread of loss of all brain function, as the loss of circulation from WLST in DCD donors causes permanent destruction of brain function [23]. Patients who are considered for DCD are in the ICU dependent on circulatory and ventilatory support, and have little to no hope for meaningful recovery. The first successful heart transplant, performed by Christiaan Barnard in 1967, utilized a heart from a DCD donor [7]. The legalization and recognition of brain death a few years later shifted the focus of heart transplants to DBD donors, where the donor heart can be retrieved without damage due to warm ischemia. In contrast to DBD hearts, which are beating up until procurement, the functional status of DCD hearts cannot be directly observed without revival [3]. Revival of the heart in the DCD donor can be done two ways: first through the use of the OCS, or secondly with normothermic regional perfusion (NRP), which utilizes a modified cardiopulmonary bypass (CPB) circuit [3].

NRP is a technique that was developed to improve the function and quality of the organs recovered from DCD donors [24]. Once the decision is made to withdraw care and donate, just as in DBD donation, the patient is brought to the operating room with all medications and life sustaining devices remaining in place. Once in the operating room, all hemodynamic supportive medications and devices are stopped or removed. If the patient does not expire within an institution’s allotted time frame (usually 30 minutes) the

organs are declined and the patient returns to the unit on hospice care [3]. If the patient expires in the operating room, a grace period of 2 to 5 minutes (depending on the institution protocol) is given to ensure no spontaneous recovery of cardiac function [2]. The grace period is important because autoresuscitation, as defined as unassisted return of circulation after declaration, is very rare after an interval of 60 to 75 seconds and has never been reported by any institution after withdrawal for NRP at this time [25]. Determining the exact time of death for DCD patients after withdrawal of life-sustaining therapy (WLST) is an important distinction, because ischemic time is closely related to the quality and viability of transplantable organs. The "dead donor rule" also states that the removal of organs for transplantation must not precede the death of the organ donor [25]. After the grace period, organ procurement begins. Vascular cannulas are placed and the cerebral vessels are ligated to exclude brain circulation during revival [24]. CPB is then initiated, which perfuses the organs (excluding the brain) with oxygenated blood. Usually the heart recovers within an hour, and CPB is weaned allowing for formal assessment of heart function [2]. If the heart is deemed satisfactory, the heart is re-arrested with cardioplegia and transported.

There are two types of NRP: abdominal NRP (A-NRP) and thoracoabdominal NRP (TA-NRP) [26]. TA-NRP, as described above, allows for the greatest potential use of all recoverable organs from the DCD donor. TA-NRP supports the heart, lungs, and abdominal organs [26]. In A-NRP, the thoracic aorta is occluded at the level of the diaphragm and cannulas are inserted into either the iliac artery/vein or into the abdominal aorta and inferior vena cava (Figure 5) [23]. A-NRP only supports the abdominal organs, including the liver, kidneys, and pancreas, but does not support the heart or lungs [26].

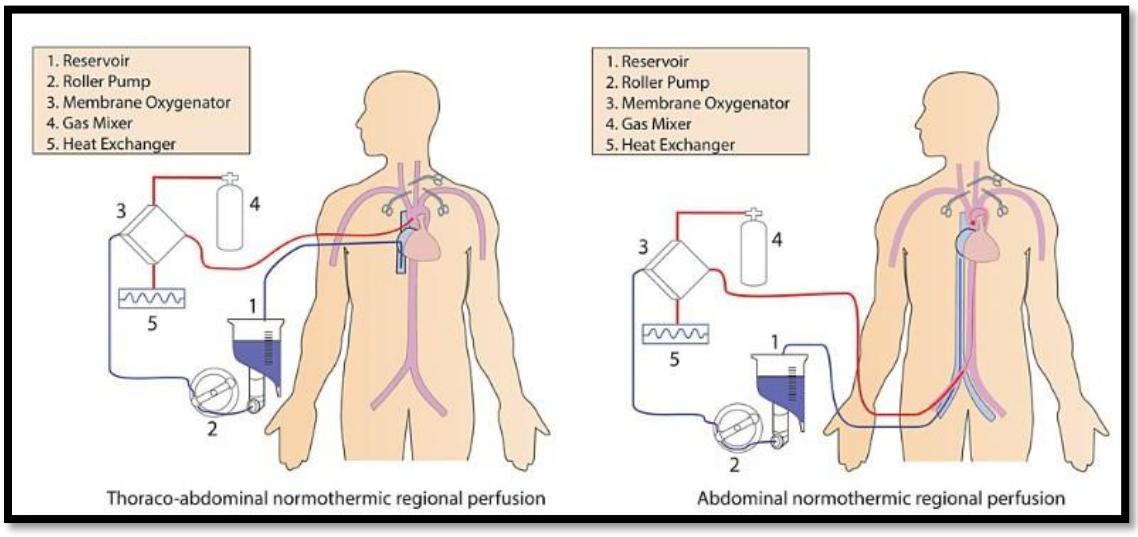

Figure 5: Cannulation and Circuit for TA-NRP and A-NRP [23]. In both TA-NRP (left) and A-NRP (right) the circuit is the same. In TA-NRP, typically the aorta and right atrium are cannulated. In A-NRP, the femoral artery and femoral vein are cannulated.

Studies comparing the outcomes of DCD hearts procured with NRP versus direct procurement with the OCS have shown similar survival rates [27]. The choice to use in-situ or ex-situ recovery for DCD hearts is complicated, and depends on multiple factors. Geographical distance between donor and recipient, patient condition, the anticipated procurement of additional donor organs, as well as logistical factors may influence which method is utilized [28]. Although both the OCS and NRP allow for assessment of heart function, NRP is currently associated with higher rates of donor heart utilization [27]. Limited studies show long-term outcomes for abdominal organ recipients from the DCD donor are improved when NRP is utilized, compared to direct procurement perfusion and rapid recovery [27].

Financial analysis of DCD heart transplants compared to DBD heart transplants has revealed similar direct costs and contribution margins for the hospitals [28]. In

comparing the two procurement strategies for DCD donors, TA-NRP had a direct cost of $155,955 versus direct procurement with the OCS costs $223,399 (p=0.21) [28]. This difference was not statistically significant, although it translated into a clinically meaningful greater contribution margin for TA-NRP [28]. While cost alone should not determine the plan of care, it is a factor that may be considered as the cost of healthcare continues to escalate in the U.S.

2.8: Ethical Considerations

In the United States, through the Uniform Anatomical Gift Act, a person has the right to make a donation decision before death and for donated organs to be recovered on that basis [25]. The laws do not specify how death is declared (DBD versus DCD), although some argue that this distinction should be made. This is called “first person consent,” and is often declared by individuals while obtaining a driver’s license through the Department of Motor Vehicles donor registry. It can also be done via a durable power of attorney, through an online donor registry, or by stating their preferences to donate in an advance directive or living will [25]. If first person consent is present, surrogates are not legally allowed to override the patient’s decision to donate. However, in cases of DCD, the patient’s clinical condition renders them unable to communicate their preferences, so families play an integral role because generally their consent is required for WLST even if the patient has authorized donation through first person consent prior to injury [25]. Decision makers also provide consent for providers to perform interventions prior to withdrawal such as placement of arterial lines and various tests that

are necessary before proceeding with DCD donation. Medications and treatments the physician would normally order in any end-of-life scenario, such as pain medications and appropriate sedation, are still provided regardless of whether or not the patient is a DCD donor. Some argue that any interventions performed prior to death in DCD donors are not appropriate because they are not intended to benefit the patient, but rather the potential organ recipients. Others feel that these interventions are necessary to honor the patient's wishes to donate their organs.

Another ethical issue regarding NRP that concerns some healthcare providers is the potential for donor awareness during procurement. Even though the head vessels are ligated prior to the initiation of NRP, there is no test performed to confirm absolute brain death before procurement begins. Studies show complete lack of blood flow to the brain causes death of neurons after only five minutes, and is one of the reasons the stand-off period is required [29]. However, the possibility of collateral circulation could result in a potential restoration of blood flow to the brain, even with the ligation of the arch vessels. A small multicenter study by Royo-Villanova *et al.* addressed this concern by measuring intracranial arterial blood pressure directly at the circle of Willis during NRP [30]. They found that while the thoracic aortic pressure increased during TA-NRP with the clamping of the arch vessels, the intracranial blood pressure did not change [30]. This study confirmed there is true lack of blood flow to the brain during NRP procurements, but larger studies are needed to confirm these findings.

Currently, there is no universal protocol for DCD procurement, so each individual hospital relies on their own institution specific policies that have been formulated based on recommendations from regulatory agencies and their transplant organizations. The

Joint Commission and the Centers for Medicare and Medicaid Services currently require all hospitals to establish and implement protocols for recovering organs through DCD [25]. Smaller hospitals may not be as well equipped to manage this complex, multidisciplinary process as well as large hospitals. This is consistently one of the main criticisms against the use of DCD, and represents an area for improvement. Development of a universal protocol/guideline, similar to what is referenced when formulating DBD policies, is necessary to ensure proper standardization of care. This could help alleviate some of the ethical ambiguity that some healthcare providers face regarding DCD procurements, particularly with NRP.

2.9: Challenges with NRP

The American Society of Transplantation (AST) supports the use of NRP and the development of associated strategies that promote its broader clinical implementation [24]. In 2022, there were 4,776 DCD organ donors, which represents an increase of nearly 14% from the previous year [4]. Specifically, heart transplants from DCD donors increased by 68% from 2021 to 2022 [4]. During the first six months of 2023, more than 254 DCD hearts were recovered, which accounted for approximately 13.3% of all heart transplants performed in the U.S. (compared to 8.7% in 2022, 5.7% in 2021, and 3.3% in 2020) [31]. The wider use of NRP can lead to even greater transplant rates and the expansion of the donor pool, but there have been some barriers to its success. Some of the largest barriers to widespread NRP use in the U.S. include cost, training, complexity of use, and staffing shortages. A study done in 2019 showed a predicted 12.3% vacancy rate

among perfusionists in the U.S. [32]. This is considered high when compared to other professions, but vacancy rates of registered nurses, cardiothoracic surgeons, and other healthcare personnel have been reported to be similarly high, if not even higher [32]. The study found that the primary factor in current vacancies in perfusion was not clinicians leaving the workforce, but rather an increase in clinical workload [32]. Advances in medical technology, such as TA-NRP, significantly increases the workload of the entire cardiac surgery team and increases demand for perfusionists and other healthcare providers. Although published reports have demonstrated that NRP use can lead to expansion of the donor organ pool and increased transplant rates, the current staffing models at most hospitals will not adequately support the extra demand.

2.10: Project Statement

Normothermic regional perfusion is a concept that has great potential for improving the lives of many. Although it is not a novel concept, its interest for use in heart transplants has recently been reignited as a response to an increasing heart failure population and a largely stable, yet inadequate number of suitable donor organs [1]. NRP used alone or in conjunction with the OCS has emerged as a promising strategy to mitigate the effects of warm ischemia on DCD donor hearts. The first DCD heart transplant performed in the U.S. was completed in late 2019 at Duke University Hospital, which sparked a subsequent surge in such transplants nationwide. Because it is a new technology, healthcare providers are still learning about the risks and benefits of this application. The goal of this paper is to evaluate and compare the outcomes of DCD and

DBD heart recipients by reviewing the literature surrounding clinical outcomes and procurement strategies for DCD donors, including NRP.

3.0: Methods

This project involved a detailed literature review aimed at identifying and summarizing all evidence related to DCD heart transplant outcomes. To identify relevant papers for this review, several terms were entered into the PubMed search engine. Searches were conducted on the following combination of terms: “heart transplant” combined with terms such as “normothermic regional perfusion,” “donation after circulatory death,” “outcomes,” “pathophysiology,” and “ethical considerations.” Additional papers were identified based on reference lists of articles identified in the search.

The articles were reviewed for study quality and level of applicability to the research topic. Only articles that studied exclusively adult populations were included. The primary outcome of interest was post-transplant survival of DCD compared to DBD heart transplant recipients, so articles that did not include a DBD comparison group were excluded. Given that the use of hearts from DCD donors is relatively new, most articles were noted to be published within the past few years, but newer articles were given precedence over those that were older and covered similar topics. If there were multiple published papers with the same primary author, the study period of each publication was evaluated to ensure no data redundancy.

Articles were first grouped by study design. The strongest methodologies were large scale, multicenter studies, comprising four out of the 11 articles. The remaining seven articles were retrospective observational cohort studies conducted at single centers. Subsequently, studies were prioritized according to the size of the DCD group, arranged from the largest number of participants to the smallest.

4.0: Results

4.1: Overall Review of Outcomes

In total, 11 articles were reviewed for analysis. One article was eliminated because its outcomes after TA-NRP focused primarily on organs other than the heart. Although some data on DCD hearts were presented, they were vague and did not provide adequate description of study design. Of the 11 articles reviewed, the primary outcome of interest was post-transplant survival of DCD compared to DBD heart transplant recipients. Secondary outcomes varied but included topics such as: PGD, graft failure, cardiac performance, MCS device use, inotrope requirements, ventilator support, length of stay in the ICU and hospital, acute kidney injury (AKI) requiring dialysis, rejection, and utilization rates. Main article findings are summarized in Table 4, arranged by strength of study design and sample size from greatest to least.

Table 4: Summary of Articles Included in Review.

Article Title and Authors	Outcomes	Summary of Findings
Early Outcomes of Heart Transplantation Using Donation After Circulatory Death Donors in the United States, Kwon *et al.* [33]	Primary: 1-year post transplant survival of DCD (n=229) and DBD (n=7267) heart recipients Secondary: Acute rejection, AKI requiring dialysis, stroke, pacemaker requirement, length of stay	» 1-year survival was not significantly different between DCD and DBD heart recipients (92.5% vs. 90.3%; p=0.44). » Acute rejection requiring treatment occurred significantly more among DCD recipients compared with DBD recipients (14.7% versus 10.1%, p=0.03). » There were no differences in stroke, rates of dialysis, hospital length of stay or pacemaker implantation between DBD and DCD recipients.
The International Experience of in-situ Recovery of the DCD Heart: A Multicenter Retrospective Observational Study, Louca *et al.* [34]	Primary: Recipient 30-day survival of DCD (n=157) and DBD (n=673) heart recipients Secondary: 1-year and 5-year survival, ventilation hours, ICU/hospital length of stay, RV and LV function short and long term.	» Overall survival did not significantly differ between heart transplants with NRP or DBD (p=0.273). » More patients in the NRP group required an IABP (p<0.001), but more patients in the DBD group required a VAD (p<0.001). ECMO usage was similar in both groups (p=0.854).
Transplantation Outcomes with Donor Hearts After Circulatory Death, Schroder *et al*. [35]	Primary: 6-month survival of DCD (n=80) and DBD (n=86) heart recipients Secondary: 30-day survival, 1-year survival, utilization rates, primary graft dysfunction/failure	» 6-month survival did not differ significantly between the two groups (94% DCD vs. 90% DBD). » 30-day and 1-year survival were not significantly different between the two groups. » Higher incidence of PGD among recipients of DCD hearts.
A National Pilot of Donation After Circulatory Death (DCD) Heart Transplantation Within the United Kingdom, Messer *et al.* [36]	Primary: 90-day recipient survival of DCD (n=50) and DBD (n=179) hearts Secondary: Rejection episodes, ICU and hospital length of stay, AKI requiring dialysis, ventilator requirements, MCS, 30-day and 1 year survival	» The 90-day survival rate between DCD and DBD was the same (90%), and there was no significant difference in 30-day survival rates (94% vs 93%) or 1-year survival rates. »Higher rate of ECMO use post-DCD compared to DBD (40% vs 16%, p = 0.0006), and DCD hearts in the pre-pilot era, (17%, p = 0.002). » No difference in length of ICU stay (9 DCD vs 8 days DBD, p = 0.13) or hospital stay (28 DCD vs 27 DBD days, p = 0.46). » No difference in rejection episodes, dialysis, or ventilator requirements.

Table 4: Summary of Articles Included in Review (continued).

Article Title and Authors	Outcomes	Summary of Findings
Outcomes of Heart Transplant Donation After Circulatory Death, Siddiqi *et al.* [31]	Primary: 6-month and 1-year post-transplant survival rates between DCD (n=122) and DBD (n=263) heart recipients Secondary: Primary graft dysfunction, cardiac allograft vasculopathy, rejection	» No significant difference in 1-year survival between DCD and DBD recipients (94.3% DCD and 92.4% DBD, p=0.54). » No significant difference between groups for likelihood of cardiac allograft vasculopathy at 1-year after transplant, treated rejection, or incidence of severe PGD.
A 5-year Single-Center Early Experience of Heart Transplantation from Donation After Circulatory-Determined Death Donors, Messer *et al.* [37]	Primary: 30-day and 1-year survival between DCD (n=79) and DBD (n=79) heart recipients Secondary: Duration of ICU/hospital stay, MCS requirements, cardiac performance, inotropic support, dialysis, ventilation times	» No difference in 30-day survival (97% for DCD vs 99% for DBD, p = 1.00) or 1 year (91% for DCD vs 89% for DBD, p = 0.72). » No difference in the length of stay in the ICU (7 for DCD vs 6 for DBD days, p = 0.24) or in the hospital (24 for DCD vs 25 for DBD days, p = 0.84). » Similar findings for recipient's need for ventilatory support, dialysis, and inotropic support, and MCS post-op between DCD and DBD.
Improved Outcomes in Severe Primary Graft Dysfunction After Heart Transplantation Following Donation After Circulatory Death Compared with Donation After Brain Death, Ayer *et al.* [38]	Primary: Incidence of primary graft dysfunction among DCD (n=65) and DBD (n=394) heart recipients Secondary: MCS use, length of stay, 60-day, and 1-year post-transplant survival	» Moderate/severe PGD in DCD and DBD recipients was 34% and 23%, respectively (p = 0.070). DCD recipients were more likely to experience severe biventricular PGD than DBD recipients (19% vs 7.4%; p = 0.004). » Among patients with severe PGD, DCD recipients had shorter duration of post-transplant MCS and a shorter post-transplant hospital length of stay. » DCD and DBD recipients had similar 60-day survival rates (100% vs 80% p = 0.17) and overall survival (p= 0.078).
Hemodynamic and Clinical Performance of Hearts Donated After Circulatory Death, D'Alessandro *et al.* [39]	Primary: Allograft function at week 1 and 4 post-transplant for DCD (n=47) and DBD (n=166) heart recipients Secondary: PGD, MCS use, hospital length of stay, inotrope scores, readmission rates, mortality	» Right heart function was impaired in DCD recipients compared with DBD recipients 1-week post-transplant (higher median right atrial pressure (10 mmHg vs 7 mmHg; p<0.001), higher right atrial pressure to pulmonary capillary wedge pressure ratio (0.64 vs 0.57; p=0.016), and lower pulmonary arterial pulsatility index (1.66 vs. 2.52; p< 0.001), but was similar between groups by 3 weeks post-transplant. » DCD and DBD recipient mortality was similar at 30 days (p=0.29) and 1-year post-transplant (p=0.16). » Hospital/ICU length of stay and readmission rates were not significantly different between groups.

Table 4: Summary of Articles Included in Review (continued).

Article Title and Authors	Outcomes	Summary of Findings
DCD Donations and Outcomes of Heart Transplantation: the Australian Experience, Dhital *et al.* [40]	Primary: 1-year recipient survival of DCD (n=32) and DBD (n=32) heart recipients Secondary: 3-year survival, 5-year survival, ECMO use, rejection rates	» The 1-, 3-, and 5-year survival was 96%, 94%, and 94% for DCD hearts compared with 89%, 83%, and 82% for DBD hearts. » The immediate ECMO support requirements for delayed graft function in DCD recipients was 31%, but was reduced to 22% over the last 9 recipients as familiarity with management improved. » No difference in rejection rates when compared with standard criteria DBD hearts.
Outcome After Heart Transplantation from Donation After Circulatory-Determined Death Donors, Messer *et al.* [41]	Primary: Recipient 90-day survival of DCD (n=26) and DBD (n=26) heart recipients Secondary: MCS requirements, ventilatory support, cardiac performance, inotropic requirements, rejection episodes, hospital/ICU length of stay	» 90-day survival was not significantly different between DCD and matched DBD recipients (DCD, 92%; DBD, 96%; p=1.0). » 1-year survival, MCS, ventilatory support, and number of treated rejection episodes between the groups were not significantly different. » The DCD hearts had better early cardiac performance and a higher mean cardiac index than the DBD group on similar support (2.5 vs 2.0 L/min/m^2, p=0.04).
Outcomes of Donation After Circulatory Death Heart Transplantation in Australia, Chew *et al.* [42]	Primary: Survival outcomes at 1 month, 1 year, and 2 years for DCD (n=23) and DBD (n=106) heart recipients Secondary: AKI, length of stay, rejection, MCS use, functional outcomes	» Overall DCD survival was 95%, with one case of early mortality. » DCD hearts had higher rates of immediate graft dysfunction and ECMO requirements, but all hearts recovered to normal biventricular function at 1-week post-transplant. » No significant difference in ICU/hospital length of stay or rejection rates between DCD and DBD.

The main finding of this review is that none of the currently published studies found a significant difference in survival rates between DCD and DBD heart transplant recipients. Seven articles published Kaplan-Meier survival rates at thirty-days post-transplant (Figure 6), and nine articles published one-year post-transplant survival rates (Figure 7). The thirty-day survival rates for DCD recipients ranged from 94 to 100%,

compared to 92 to 100% in the similar DBD groups. The one-year survival rates for DCD recipients ranged from 84 to 97%, and in the DBD comparison groups rates ranged from 84 to 92.4%. Of the articles that published ICU and hospital length of stay, there were no significant differences between DCD and DBD heart recipients.

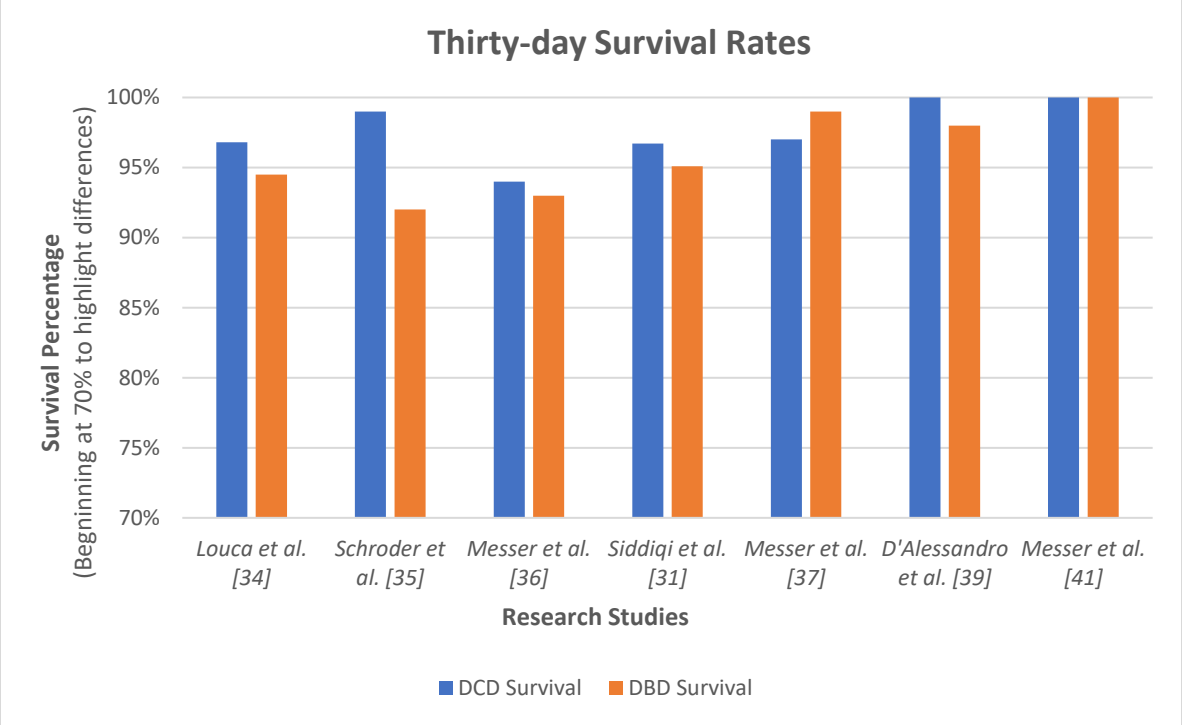

Figure 6: Thirty-day Post-transplant Kaplan-Meier Survival Rates of DCD and DBD Heart Recipients.

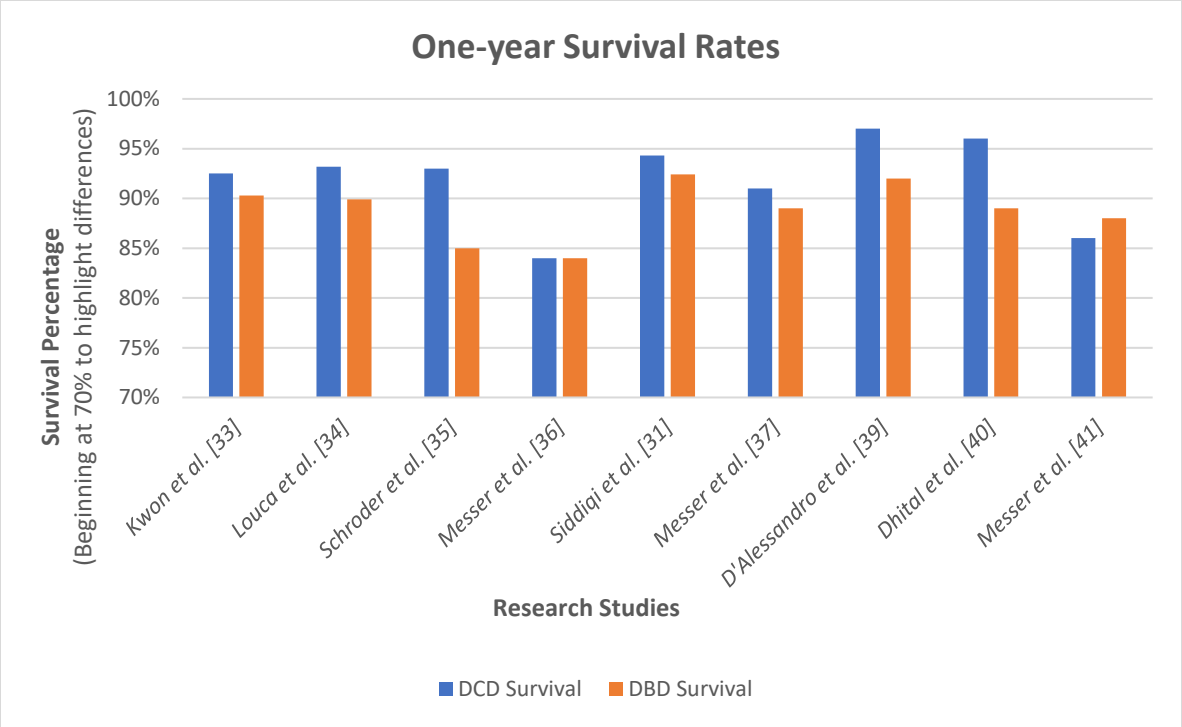

Figure 7: One-year Post-transplant Kaplan-Meier Survival Rates of DCD and DBD Heart Recipients.

4.2: Summary of Findings

A single-center observational matched cohort study by Messer *et al.* revealed better early cardiac performance measured by median cardiac output in DCD hearts when compared to DBD hearts on similar support [41]. One possible explanation for this finding is some ischemic pre-conditioning that may occur during WLST in DCD donors, although the data to support this are limited [41]. Another possibility is the avoidance of the detrimental effects of brain death on heart function in DCD donors. Brain death can cause a significant catecholamine release, which may result in increased peripheral resistance that can cause a sudden increase in oxygen consumption, potentially leading to myocardial infarction, ischemia, and elevation of cardiac troponin levels [43]. However, with the exception of one individual's cause of death listed as "other", all DCD donors in

this study had a neurologically based cause of death listed as a hypoxic brain injury, intracerebral hemorrhage, or traumatic brain injury [41]. These injuries would likely cause a catecholamine release as well, although perhaps not to the extent seen with true DNC. Despite the significant finding of better early cardiac performance in DCD hearts, this had no significant impact on survival rates, MCS use, ventilatory requirements, rejection episodes, or length of stay between the DCD and DBD cohorts included in this study [41].

Cardiac allograft vasculopathy (CAV) is a form of accelerated coronary artery disease (CAD) that can be a significant long-term complication of heart transplantation, leading to graft failure and mortality [44]. A single-center study by Birs *et al.* compared early CAV outcomes, as detected by intravascular ultrasound, between DCD and DBD heart transplant recipients [44]. This study found no significant differences in the markers used to diagnose CAV between the two cohorts, indicating that DCD donors do not have a higher risk for CAV or related complications [44]. This study only analyzed outcomes at one-year post-transplant, and although it is possible CAV can develop early, it typically does not occur until at least a few years after a transplant. However, the findings of this study were valuable, as there were some initial concerns that the warm ischemic time the hearts procured from DCD donors sustained would predispose them to developing CAV.

Two studies that were analyzed showed higher, statistically significant differences in ECMO use with post-DCD hearts compared to DBD. The first was a national, multicenter retrospective cohort study in the United Kingdom that revealed ECMO use in post-DCD heart transplants at 40%, compared to 16% in the DBD group ($p=0.0006$) [36]. Of note, after further analysis, three of the centers included in this study who had low

experience with DCD transplants had 100% post-transplant ECMO utilization rates, which likely skewed the data [36]. A separate single center, retrospective analysis of DCD heart transplant outcomes in Australia found similar findings, and reported ECMO use in their DCD cohort at 35% compared to 10% in the DBD group [42]. Despite the higher rates of ECMO in the DCD cohort, all hearts (with the exception of one early mortality) recovered to normal biventricular function at one-week post-transplant [42]. In both studies, the higher rates of ECMO in DCD hearts had no significant impact on survival outcomes. Although these two studies showed significant differences in ECMO use, the remaining five articles that included ECMO use published non-significant differences in ECMO use between groups. Dhital *et al.* reported DCD ECMO requirements of 31%, Messer *et al*. reported 12% and 15% over two separate time periods, Louca *et al.* reported 5.7%, and D'Alessandro *et al.* reported 10.6%, none of which were significantly different from the data in their DBD groups [34, 37, 39, 40, 41] (Figure 8).

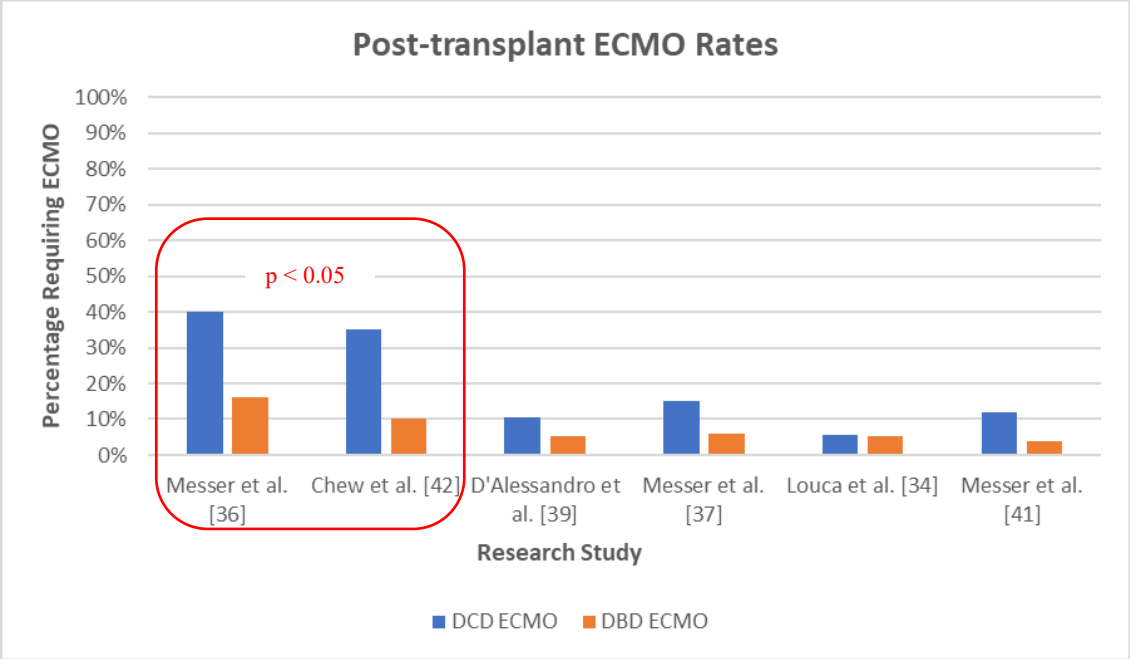

Figure 8: Post-transplant ECMO Rates of DCD and DBD Heart Recipients.

D'Alessandro *et al.* found DCD heart utilization was associated with transient right heart dysfunction [39]. DCD recipients had significantly higher median right atrial pressures, higher right atrial pressure to pulmonary capillary wedge pressure ratios, and a lower pulmonary arterial pulsatility index (all $p<0.05$) [39]. These findings normalized within three weeks post-transplant and had no significant effects on mortality when compared to DBD hearts. This study also revealed a trend towards higher incidence of severe PGD in DCD hearts, although not statistically significant (DCD 10.6% versus DBD 3.6%, $p=0.07$) [39]. PGD diagnosis is defined by the International Society of Heart Lung Transplant criteria, and is based on assessments of dose of vasoactive medications, MCS requirements, and ventricular function assessment using transesophageal echocardiogram post-transplant [38]. Interestingly, this single center study found that as

their center gained more experience with DCD transplants, the rates of severe PGD decreased over time (Figure 9) [39].

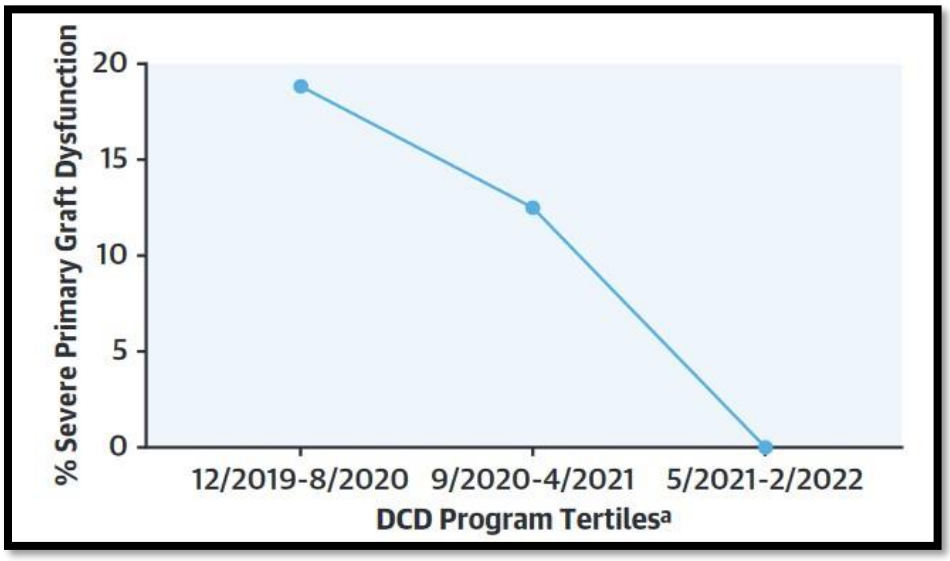

Figure 9: Trends of Severe PGD in DCD Hearts Over Time [39].

Multiple studies did show that rates of severe PGD were higher immediately post-op in the DCD cohorts. Ayer *et al.* found significantly higher rates of severe biventricular PGD in the DCD recipients when compared to DBD (19% versus 7.4%, p=0.004) [38]. Despite these findings, DCD recipients with severe PGD spent fewer days in the hospital and on MCS than comparable DBD patients, and it did not affect overall survival [38]. Schroder *et al.* also reported higher rates of moderate/severe PGD in the DCD groups (22% DCD versus 10% DBD) with similar rapid recovery of function in a multicenter, randomized control trial involving 15 transplant centers across the United States [35]. Similarly, Chew *et al.* also revealed higher rates of immediate graft dysfunction in their

DCD group, with normal recovery within one week [42]. The pathophysiology of PGD is not well understood, but it is thought to be driven by cold and warm ischemia, catecholamine surges, and reperfusion injuries [38]. The finding of higher rates of PGD in DCD donors is somewhat expected due to the period of warm ischemia that occurs from the beginning of the agonal phase to cardioplegia initiation. Although DCD hearts may be more prone to severe PGD, their rapid recovery and comparable short-term outcomes to DBD are reassuring.

There are limited studies analyzing the long-term outcomes of DCD hearts, but one study by Li *et al.* found that DCD recipients were more likely to have acute rejection prior to discharge and were more likely to be hospitalized for rejection at a follow-up of 15 months [45]. Implications of this study may have a significant impact on the future use of DCD hearts, but more studies are needed to confirm these findings.

4.3: Utilization Rates of Potential DCD Hearts

Another topic of interest with the growing use of DCD hearts is utilization rates. Unlike in DCD, DBD procurements involve retrieving organs while the heart is still beating, which eliminates the variable of waiting for the patient to progress to asystole before beginning organ recovery. It is difficult to predict when a patient will progress to asystole in DCD procurements, as it can be influenced by many factors. Additionally, since there is no universal protocol, hospitals vary on maximum time spent waiting for asystole after WLST and the duration of the standoff period before beginning procurement. This can influence the availability of the donor organ, and contributes to

higher rates of refusal for DCD hearts when compared to DBD hearts [46]. The UNOS registry does not specifically identify DCD donors who failed to progress to circulatory death after WLST, but it does report general refusal codes for potential donor hearts. An analysis of UNOS heart refusal codes by Dann *et al.* reported that DCD hearts were declined 3.37 times more often than DBD hearts [46].

Even though the variable of failure of progression to death after WLST in the allotted time frame is not included in the UNOS data, six of the studies analyzed provided this information (Figure 10). The defined maximum duration from WLST to asystole across the six studies ranged from 30 minutes to four hours. Chew *et al.* reported the largest percentage of these declined hearts, where 12/45 (26.7%) of potential DCD hearts in the study were discarded for failure to progress to asystole [42]. Of note, the maximum time frame allowed for progression to asystole in this study was 30 minutes, which was the shortest across all studies reviewed. Messer *et al.* allowed for a maximum time period of four hours to progress to asystole after WLST, and had the lowest percentage of unused hearts at 5/40 (12.5%) [41]. Combined data across all six studies revealed the total failure of 92/441 (20.9%) potential DCD hearts to progress to asystole after WLST, preventing their use [36, 37, 39, 40, 41, 42]. Despite this finding, even with rejection of a portion of the organs, the use of DCD hearts still holds the potential to significantly increase and expand the donor pool.

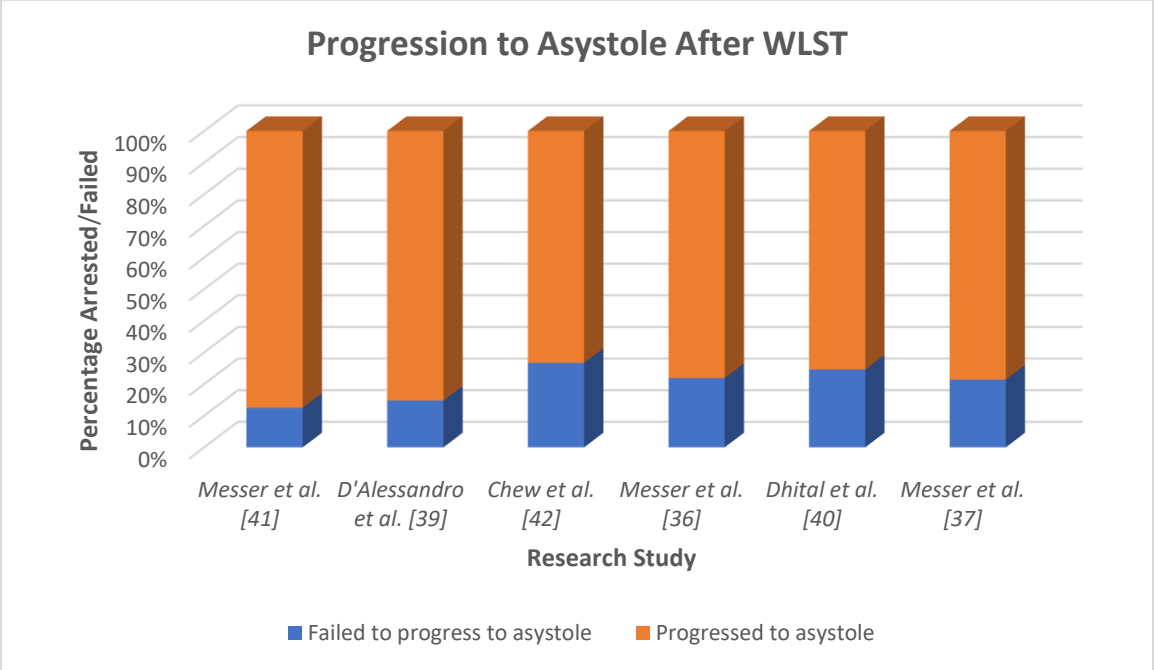

Figure 10: Progression to Asystole After WLST in Potential DCD Donors [36, 37, 39, 40, 41, 42]. The percentage of potential DCD hearts that failed to progress to asystole after WLST in the defined time frame (blue) compared to the percentage of potential DCD hearts that did progress to asystole (orange).

5.0: Discussion and Conclusion

The landscape of organ donation and transplants continue to evolve, with many changes occurring in the last decade. The recent adaptation of utilizing hearts from DCD donors has caused a shift in donor profiles and the retrieval process with the introduction of NRP. The American Society of Transplantation supports the use of NRP for DCD donors along with the development of associated strategies that promote its broader clinical implementation [24]. DCD heart transplants have significantly increased over the past few years, with an increase of 68% from 2021 to 2022 alone [4]. Around 16% of heart transplant centers in the U.S. utilized DCD donors in 2021, and the number is growing each year [33]. A universal protocol for DCD procurements should be introduced as more centers begin to accept these patients to ensure ethical compliance and to maintain standard of care.

The literature review revealed a substantial body of evidence comparing the outcomes of DCD heart transplants with DBD heart transplants. Across multiple studies, DCD hearts demonstrated comparable survival rates and patient outcomes to DBD heart transplants, even though there were sometimes differences in intermediate variables such as ECMO usage.

Although not a universal finding, a few studies showed differences in the early recovery of DCD heart recipients, which included the need for greater post-op ECMO use, higher rates of severe PGD, and transient right heart dysfunction. However, in these studies, the DCD hearts showed rapid recovery of function within one week after transplant and there was no significant impact on patient survival. This suggests that “the DCD process may predispose hearts to a period of delayed graft function with subsequent

rapid recovery, distinct from the more sustained graft dysfunction observed after some DBD heart transplants" [38]. The post-op management of DCD hearts compared to DBD hearts may need to be modified, as the DCD procurement results in warm ischemic time that can impact how the heart recovers. DCD hearts may require more aggressive management in the initial post-op period, particularly with supporting RV function through the early introduction of inotropes and pulmonary vasodilators [39]. More research is needed to optimize post-transplant management in the context of DCD heart transplantation, and as more centers gain experience with DCD heart transplants, the short-term outcomes may continue to improve. Similarly, as the timeframe following WLST until asystole in DCD donors is studied, the utilization rates for DCD hearts will likely improve with narrowed selection criteria for potential donors.

Overall, the findings suggest the outcomes from the utilization of hearts from DCD donors is comparable to DBD donors. Further studies are needed to assess long-term outcomes of DCD heart recipients, but the short-term outcomes appear to be promising. Its potential for substantial clinical impact may be limited by current staffing shortages and lack of materials/proper training, but it represents great potential for increasing the donor pool in the near future.

References

[1] N. R. Hess, L. A. Ziegler, and D. J. Kaczorowski, “Heart Donation and Preservation: Historical Perspectives, Current Technologies, and Future Directions,” *Journal of Clinical Medicine*, vol. 11, no. 19, pp. 5762-5778, September 2022, https://doi.org/10.3390/jcm11195762.

[2] C. Lee, C. Tsai, E. Adler, and V. Pretorius, “Emerging Frontier in Heart Transplantation: Donation After Circulatory Death,” *American College of Cardiology*. Expert analysis. November 1, 2022. Accessed: January 1, 2023. [Online]. Available: https://www.acc.org/Latest-in-Cardiology/Articles/2022/11/21/13/31/Emerging-Frontier-in-Heart-Transplantation.

[3] M. Alomari, P. Garg, J. Yazji, I. Wadiwala, E. Alamouti-fard, M. Hussain, M. Elawady, and S. Jacob, “Is the Organ Care System (OCS) Still the First Choice With Emerging New Strategies for Donation After Circulatory Death (DCD) in Heart Transplant?,” *Cureus*, vol. 14, no. 6, pp. [1]-[8], June 2022, https://doi.org/10.7759/cureus.26281.

[4] “National data - Organ Procurement and Transplantation Network.” *U.S. Department of Health and Human Services.* Accessed: January 1, 2023. [Online]. Available: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#.

[5] N. Dharmavaram, T. Hess, H. Jaeger, J. Smith, J. Hermsen, D. Murray, and R. Dhingra. “National Trends in Heart Donor Usage Rates: Are We Efficiently Transplanting More Hearts?,” *Journal of the American Heart Association*, vol. 10, no. 15, pp. [1]-[14], August 2021, https://doi.org/10.1161/JAHA.120.019655.

[6] D. Baran, J. Lansinger, A. Long, J. Herre, A. Yehya, E. Sawey, A. Badiye, W. Old, J. Copeland, K. Stelling, and H. Copeland, “Intoxicated Donors and Heart Transplant Outcomes: Long-Term Safety,” *Circulation: Heart Failure*, vol. 14, no. 8, pp. 849-858, August 2021, https://doi.org/10.1161/CIRCHEARTFAILURE.120.007433.

[7] E. DeFilippis, K. Khush, M. Farr, A. Fiedler, A. Kilic, and M. Givertz, "Evolving Characteristics of Heart Transplantation Donors and Recipients: JACC Focus Seminar," *Journal of the American College of Cardiology*, vol. 79, no. 11, pp. 1108–1123, March 2022, https://doi.org/10.1016/j.jacc.2021.11.064.

[8] P. Patel, N. Patel, F. Ahmed, and J. Gluck, "Review of Heart Transplantation From Hepatitis C-Positive Donors," *World Journal of Transplantation*, vol. 12, no. 12, pp. 394–404, December 2022, https://doi.org/10.5500/wjt.v12.i12.394.

[9] K. Khush, W. Cherikh, D. Chambers, M. Harhay, D. Hayes, E. Hsich, B. Meiser, L. Potena, A. Robinson, J. Rossano, A. Sadavarte, T. Singh, A. Zuckermann, and J. Stehlik, "The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth Adult Heart Transplantation Report — 2019; Focus Theme: Donor and Recipient Size Match," *The Journal of Heart and Lung Transplantation*, vol. 38, no. 10, pp. 1056–1066, October 2019, https://doi.org/10.1016/j.healun.2019.08.004.

[10] E. Akintoye, P. Alvarez, D. Shin, A. Egbe, A. Panos, F. Sellke, and A. Briasoulis, "Changing Demographics, Temporal Trends in Waitlist, and Posttransplant Outcomes After Heart Transplantation in the United States: Analysis of the UNOS Database 1991–2019," *Circulation: Heart Failure*, vol. 14, no. 11, pp.1223-1233, November 2021, https://doi.org/10.1161/CIRCHEARTFAILURE.121.008764.

[11] A. Kilic, M. Mathier, G. Hickey, I. Sultan, V. Morell, S. Mulukutla, and M. Keebler, "Evolving Trends in Adult Heart Transplant With the 2018 Heart Allocation Policy Change," *The Journal of the American Medical Association*: Cardiology, vol. 6, no. 2, pp. 159–167, February 2021, https://doi.org/10.1001/jamacardio.2020.4909.

[12] M. John, W. Shih, D. Estevez, T. Martens, L. Bailey, A. Razzouk, and D. Rabkin, "Interaction Between Ischemic Time and Donor Age on Adult Heart Transplant Outcomes in the Modern Era," *The Annals of Thoracic Surgery*, vol. 108, no. 3, pp. 744–748, September 2019, https://doi.org/10.1016/j.athoracsur.2019.03.042.

[13] P. Camp, “Heart Transplantation: Donor Operation for Heart and Lung Transplantation,” *Operative Techniques in Thoracic and Cardiovascular Surgery*, vol. 15, no. 2, pp. 125–137, June 2010, https://doi.org/10.1053/j.optechstcvs.2010.04.003.

[14] D. Radakovic, S. Karimli, K. Penov, I. Schade, K. Hamouda, C. Bening, R. Leyh, and I. Aleksic, “First Clinical Experience With the Novel Cold Storage SherpaPak TM System for Donor Heart Transportation,” *Journal of Thoracic Disease*, vol. 12, no. 12, pp. 7227-7235, December 2020, https://doi.org/10.21037/jtd-20-1827.

[15] M. Tsukashita and Y. Naka, “Organ Care System for Heart Procurement and Strategies to Reduce Primary Graft Failure After Heart Transplant,” *Operative Techniques in Thoracic and Cardiovascular Surgery*, vol. 20, no. 3, pp. 322–334, September 2015, https://doi.org/10.1053/j.optechstcvs.2015.12.002.

[16] A. Ardehali, F. Esmailian, M. Deng, E. Soltesz, E. Hsich, Y. Naka, D. Mancini, M. Camacho, M. Zucker, P. Leprince, R. Padera, and J. Kobashigawa, “Ex-vivo Perfusion of Donor Hearts for Human Heart Transplantation (PROCEED II): A Prospective, Open-label, Multicentre, Randomised Non-inferiority Trial,” *The Lancet*, vol. 385, no. 9987, pp. 2577–2584, June 2015, https://doi.org/10.1016/S0140-6736(15)60261-6.

[17] R. Kaliyev, T. Lesbekov, S. Bekbossynov, Z. Nurmykhametova, M. Bekbossynova, S. Novikova, A. Medressova, N. Smagulov, L. Faizov, R. Samalavicius, and Y. Pya, “Heart Transplantation of Patients with Ventricular Assist Devices: Impact of Normothermic Ex-vivo Preservation Using Organ Care System Compared with Cold Storage,” *Journal of Cardiothoracic Surgery*, vol. 15, no. 1, pp. 323-329, October 2020, https://doi.org/10.1186/s13019-020-01367-w.

[18] J. Chan, J. Kobashigawa, H. Reich, D. Ramzy, M. Thottam, Z. Yu, T. Aintablian, F. Liou, J. Patel, M. Kittleson, L. Czer, A. Trento, and F. Esmailian, “Intermediate Outcomes with Ex-vivo Allograft Perfusion for Heart Transplantation,” *The Journal of Heart and Lung Transplantation*, vol. 36, no. 3, pp. 258–263, March 2017, https://doi.org/10.1016/j.healun.2016.08.015.

[19] D. Saez, B. Zych, A. Sabashnikov, C. Bowles, F. Robertis, P. Mohite, A. Popov, O. Maunz, N. Patil, A. Weymann, T. Pitt, L. McBrearty, B. Pates, R. Hards, M. Amrani, T. Bahrami, N. Bennel, and A. Simon, "Evaluation of the Organ Care System in Heart Transplantation with an Adverse Donor/Recipient Profile," *The Annals of Thoracic Surgery*, vol. 98, no. 6, pp. 2099–2106, December 2014, https://doi.org/10.1016/j.athoracsur.2014.06.098.

[20] M. Aboubakr, M. Yousaf, L.Weisbrod, and G. Alameda, "Brain Death Criteria," in *StatPearls*, Continuing Education Activity, Accessed: November 06, 2023. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK545144/.

[21] A. Lewis, M. P. Kirschen, and D. Greer, "The 2023 AAN/AAP/CNS/SCCM Pediatric and Adult Brain Death/Death by Neurologic Criteria Consensus Practice Guideline: A Comparison With the 2010 and 2011 Guidelines," *Neurology: Clinical Practice*, vol. 13, no. 6, pp. [1]-[15], December 2023, https://doi.org/10.1212/CPJ.0000000000200189.

[22] M. Kirschen, A. Lewis, and D. Greer, "The 2023 American Academy of Neurology, American Academy of Pediatrics, Child Neurology Society, and Society of Critical Care Medicine Pediatric and Adult Brain Death/Death by Neurologic Criteria Determination Consensus Guidelines: What the Critical Care Team Needs to Know," *Critical Care Medicine*, vol. 52, no. 3, pp. [1]-[11], https://doi.org/10.1097/CCM.0000000000006099.

[23] E. Alamouti-fard, P. Garg, I. Wadiwala, J. Yazji, M. Alomari, M. Walid, A. Hussain, M. Elawady, and S. Jacob, "Normothermic Regional Perfusion is an Emerging Cost-Effective Alternative in Donation After Circulatory Death (DCD) in Heart Transplantation," *Cureus*, vol. 14, no. 6, pp. [1]-[6], June 2022, https://doi.org/10.7759/cureus.26437.

[24] S. Covington and B. Applegate, “The American Society of Transplantation would like to Share its Statement Regarding Normothermic Regional Perfusion (NRP), a Technique Sometimes Used in Organ Donations,” *American Society of Transplantation*, Accessed: December 9, 2023. [Online]. Available: https://www.organdonationalliance.org/wp-content/uploads/2022/09/AST-KEY-POSITION-STATEMENT-ON-NORMOTHERMIC-REGIONAL-PERFUSION_final.pdf#:~:text=In%20order%20to%20improve%20the%20quality%20and%20function,on%20the%20spontaneous%20cessation%20of%20respiration%20and%20circulation.

[25] C. Gries *et al*., “An Official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: Ethical and Policy Considerations in Organ Donation after Circulatory Determination of Death,” *American Thoracic Society*, vol. 188, no. 1, pp. 103–109, July 2013, https://doi.org/10.1164/rccm.201304-0714ST.

[26] J. Basmaji, C. Weijer, A. Skaro, A. Healey, S. Shemie, and M. Slessarev, “Paving the Road for the Adoption of Normothermic Regional Perfusion in Canada,” *Critical Care Explorations*, vol. 3, no. 11, pp. [1]-[4], October 2021, https://doi.org/10.1097/CCE.0000000000000553.

[27] G. Ran, A. Wall, N. Narang, K. Khush, J. Hoffman, K. Zhang, W. Parker, “Post-transplant Survival After Normothermic Regional Perfusion Versus Direct Procurement and Perfusion in Donation After Circulatory Determination of Death in Heart Transplantation,” *The Journal of Heart and Lung Transplantation*, pp. [1]-[9], February 2024, https://doi.org/10.1016/j.healun.2024.02.1456.

[28] M. Urban, T. Ryan, J. Um, A. Siddique, A. Castleberry, and B. Lowes, “Financial Impact of Donation After Circulatory Death Heart Transplantation: A Single-Center Analysis,” *The Journal of Clinical and Translational Research*, vol. 38, no. 4, pp. 1-6, March 2024, https://doi.org/10.1111/ctr.15296.

[29] J. Lee, M. Grabb, G. Zipfel, and D. Choi, “Brain Tissue Responses to Ischemia,” *The Journal of Clinical Investigation*, vol. 106, no. 6, pp. 723–731, September 2000, https://doi.org/10.1172/jci11003.

[30] M. Royo-Villanova *et al.*, “Maintaining the Permanence Principle of Death During Normothermic Regional Perfusion in Controlled Donation After the Circulatory Determination of Death: Results of a Prospective Clinical Study,” *American Journal of Transplantation*, vol. 24, no. 2, pp. 213–221, February 2024, https://doi.org/10.1016/j.ajt.2023.09.008.

[31] H. Siddiqi *et al*., “Outcomes of Heart Transplant Donation After Circulatory Death,” *Journal of the American College of Cardiology*, vol. 82, no. 15, pp. 1512–1520, October 2023, https://doi.org/10.1016/j.jacc.2023.08.006.

[32] M. Colligan, “Results of the 2019 Survey on Perceptions of Vacancy and Turnover Among Perfusionists in the United States,” *The Journal of ExtraCorporeal Technology*, vol. 52, no. 1, pp. 27–42, March 2020, https://doi.org/10.1182/JECT-2000001.

[33] J. Kwon, A. Ghannam, K. Shorbaji, B. Welch, Z. Hashmi, R. Tedford, and A. Kilic, “Early Outcomes of Heart Transplantation Using Donation After Circulatory Death Donors in the United States,” *Circulation: Heart Failure*, vol. 15, no. 12, pp. 1114-1124, October 2022, https://doi.org/10.1161/CIRCHEARTFAILURE.122.009844.

[34] J. Louca *et al.,* “The International Experience of In-situ Recovery of the DCD Heart: A Multicentre Retrospective Observational Study,” *The Lancet*, vol. 58, pp. [1]-[12], April 2023, https://doi.org/10.1016/j.eclinm.2023.101887.

[35] J. Schroder *et al*., “Transplantation Outcomes with Donor Hearts After Circulatory Death,” *The New England Journal of Medicine*, vol. 388, no. 23, pp. 2121–2131, June 2023, https://doi.org/10.1056/NEJMoa2212438.

[36] S. Messer *et al.,* “A National Pilot of Donation After Circulatory Death (DCD) Heart Transplantation Within the United Kingdom,” *The Journal of Heart and Lung Transplantation*, vol. 42, no. 8, pp. 1120–1130, August 2023, https://doi.org/10.1016/j.healun.2023.03.006.

[37] S. Messer *et al*., "A 5-year Single-center Early Experience of Heart Transplantation From Donation After Circulatory-determined Death Donors," *The Journal of Heart and Lung Transplantation*, vol. 39, no. 12, pp. 1463–1475, December 2020, https://doi.org/10.1016/j.healun.2020.10.001.

[38] A. Ayer, L. Truby, J. Schroder, S. Casalinova, C. Green, M. Bishawi, B. Bryner, C. Milano, C. Patel, and A. Devore, "Improved Outcomes in Severe Primary Graft Dysfunction After Heart Transplantation Following Donation After Circulatory Death Compared With Donation After Brain Death," *Journal of Cardiac Failure*, vol. 29, no. 1, pp. 67–75, January 2023, https://doi.org/10.1016/j.cardfail.2022.10.429.

[39] D. D'Alessandro *et al*., "Hemodynamic and Clinical Performance of Hearts Donated After Circulatory Death," *Journal of the American College of Cardiology*, vol. 80, no. 14, pp. 1314–1326, October 2022, https://doi.org/10.1016/j.jacc.2022.07.024.

[40] K. Dhital, P. Ludhani, S. Scheuer, M. Connellan, and P. Macdonald, "DCD Donations and Outcomes of Heart Transplantation: The Australian Experience," *The Indian Journal of Thoracic and Cardiovascular Surgery*, vol. 36, no. 2, pp. 224–232, August 2020, https://doi.org/10.1007/s12055-020-00998-x.

[41] S. Messer *et al*., "Outcome After Heart Transplantation From Donation After Circulatory-Determined Death Donors," *The Journal of Heart and Lung Transplantation*, vol. 36, no. 12, pp. 1311–1318, December 2017, https://doi.org/10.1016/j.healun.2017.10.021.

[42] H. Chew *et al.,* "Outcomes of Donation After Circulatory Death Heart Transplantation in Australia," *Journal of the American College of Cardiology*, vol. 73, no. 12, pp. 1447–1459, April 2019, https://doi.org/10.1016/j.jacc.2018.12.067.

[43] S. Shemie and S. Dhanani, "The Physiology of Brain Death and Organ Donor Management," *Pediatric Critical Care Medicine*, pp. 497–518, January 2014, https://doi.org/10.1007/978-1-4471-6362-6_38.

[44] A. Birs *et al.*, “Cardiac Allograft Vasculopathy Outcomes Among Donation After Circulatory Death Heart Transplant Recipients,” *The Journal of Heart and Lung Transplantation*, vol. 4, pp. [1]-[11], May 2024, https://doi.org/10.1016/j.jhlto.2024.100065.

[45] S. Li *et al.*, “Acute Rejection in Donation After Circulatory Death (DCD) Heart Transplants,” *The Journal of Heart and Lung Transplantation*, vol. 43, no. 1, pp. 148–157, January 2024, https://doi.org/10.1016/j.healun.2023.09.004.

[46] T. Dann, B. Spencer, S. Wilhelm, S. Drake, R. Bartlett, A. Rojas-Pena, and D. Drake, “Donor Heart Refusal After Circulatory Death: An Analysis of United Network for Organ Sharing Refusal Codes,” *The Journal of Thoracic and Cardiovascular Surgery*, pp. [1]-[13], February 2024, https://doi.org/10.1016/j.xjon.2024.02.010.

Thesis Approval Form

Master of Science in Perfusion- MSP

Milwaukee School of Engineering

This thesis, entitled "Review of Heart Transplant Recipient Outcomes: Donation After Circulatory Death (DCD) versus Donation After Brain Death (DBD)," submitted by the student Ruthanne Havlichek, has been approved by the following committee:

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