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Review

Machine Perfusion of Donor Hearts – The Recovery and Transplantation of Previously Unrecoverable Hearts

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Abstract

Heart transplantation remains the gold standard treatment for end-stage heart failure. With an increasing population and improving medical therapy there is an increasing number of patients who would benefit from heart transplantation but are unable to receive one due to a shortage of suitable donor organs. This ongoing need, and significant limitations with traditional cold static storage (CSS), have driven the development of machine perfusion technology that have expanded the donor pool. Machine perfusion is divided into hypothermic and normothermic, with both technologies perfusing the heart with oxygenated solution to reduce the degree of ischaemia-reperfusion injury that occurs. Both technologies have allowed for the safe retrieval and transplantation of hearts with prolonged ischaemic times or following donation after circulatory determination of death and have significantly

increased the potential donor pool and number of transplants able to be safely performed. The aim of this review is to summarise the current options available to clinicians for donor heart organ preservation, with a focus on how the development of machine perfusion technology has allowed for the recovery of hearts previously considered unrecoverable using CSS.

Keywords
Heart transplantation; donor organ preservation; hypothermic machine perfusion (HMP); normothermic machine perfusion (NMP); ischaemia-reperfusion injury

1. Chapter 1 - Introduction

The development of machine perfusion technology has allowed for the retrieval, recovery and subsequent transplantation of hearts that would previously have been considered unrecoverable with traditional cold static storage techniques. This review will provide an overview of the current machine perfusion techniques available within the cardiac transplantation field, along with background information on the development and successful use of this technology.

2. Background

Heart transplantation remains the gold standard treatment of symptomatic end-stage heart failure refractory to medical therapy, and provides a mortality and morbidity benefit to patients [1]. From the first human allotransplantation performed by Christiaan Barnard in 1967 [2], there are now over 8,900 heart transplants performed globally each year [3]. Despite the increasing numbers of heart transplants, a key limitation remains the supply of donor organs, with only 117 heart transplants performed in Australia in 2022 despite there being between 73-86 patients who would be transplantable at any point in time if a suitable organ was available [4, 5].

To increase the number of donor organs available for transplantation, research efforts have focussed on ways to broaden the pool of potential donors by including marginal donors who previously may not have been deemed suitable for organ donation. Marginal donors include those of advanced age, donors with poor left ventricular (LV) function, and donors with a predicted prolonged ischaemic time. Concerns regarding the use of organs from marginal donors predominantly relates to development of primary graft dysfunction (PGD) and failure post-operatively, which remains the leading cause of early mortality following heart transplantation, accounting for 39.5% of early post-transplant deaths [6-8]. These research efforts have led to improved organ preservation, allowing for the refinement of current storage techniques and the development of machine perfusion technologies, that have enabled the transplantation of organs previously considered unsafe to use.

There are three different approaches currently used for organ preservation in clinical practice – cold static storage (CSS), hypothermic machine perfusion (HMP), and normothermic machine perfusion (NMP). CSS is the mainstay of donor organ preservation, involving the use of hypothermic cold storage in combination with a preservation solution. While traditionally CSS has been performed using an insulated portable cooler and ice, technology has been developed to improve

the temperature stability of hearts during storage [9]. Machine perfusion devices typically refer to devices that perfuse the myocardium with an oxygenated solution (comprised of blood supplemented with various buffer and additive agents) to help diminish the risk of ischaemia-reperfusion injury (IRI), either in combination with hypothermia (HMP) or at a more physiologic temperature (NMP). Each of these preservation approaches has their own strengths and weaknesses, and as more trials are performed showing the benefits of machine perfusion, it is anticipated that the usage of CSS will decrease in future years.

3. Cold Static Storage (CSS)

To fully understand the benefits that machine perfusion offers, it is important that the premise and rationale of CSS is also discussed. CSS represents the most widely used technique for preserving retrieved donor hearts [10, 11], and is the current standard of care for donation following neurological determination of death (DNDD) at our institution. CSS relies on the use of hypothermia to slow down the rate of cellular metabolism, as well as the use of specially formulated preservation solutions designed to limit the impact of ischaemia-reperfusion injury to the donor heart.

Donor hearts retrieved using CSS are flushed with cold preservation solution *in-vivo* to induce rapid diastolic arrest and facilitate cooling of the organ. The heart is then rapidly explanted and stored within a sterile plastic bag containing either cold saline or preservation solution, followed by two further sterile plastic bags containing cold fluid and ice slush. The organ is then placed within an insulated portable cooler filled with ice and transported to the implanting hospital, where the heart is removed from the plastic bags and implanted into the transplant recipient.

From the moment of cessation of circulation in the donor to removal of cross-clamp in the recipient the donor heart is suffering ischaemic insult, with cellular and biochemical changes occurring within cells. The cooling of the myocardium via cold preservation solution and storage in ice results in the slowing of biochemical reactions within the cells, decreasing the rate of degradation of essential cellular components, in addition to slowing the lysis of lysosomes that release autolytic enzymes [12]. Multiple cardiac preservation solutions exist that contain differing concentrations of electrolytes and additive agents, each with their own strengths and weaknesses compared to the other solutions. Regardless of the solution, all are based on the same key principles. They all induce rapid diastolic arrest (when used for DNDD) via a reduction in the transmembrane gradient, minimising the use of high-energy phosphate compounds such as adenosine triphosphate. Secondly, the solutions help provide myocardial protection against injury caused by global ischaemia and the subsequent reperfusion injury, creating a biochemical environment that helps to maintain the structural components of myocardial cells during arrest [12, 13]. Cardiac preservation solutions should also have a degree of reversibility, allowing for quick resumption of cardiac activity when appropriate, as well as having no toxic effects on the heart or other organ systems when used [13].

The use of CSS has significant benefits which has led to its ongoing use as the standard of care for DNDD organ retrievals. CSS is relatively cheap with minimal resources and disposable equipment required to use, nor does it require any specialised equipment or training. CSS has been shown to have consistent outcomes and is a reliable method of organ procurement, particularly when there is no concern or suspicion of organ marginality.

However, there are drawbacks to the use of CSS, with the development of progressive ischaemic injury to the organ an inevitable consequence of an increasing duration of preservation. Limited

ischaemic times restrict the distance from where organs may be safely procured, with increasing ischaemic periods associated with worse short- and long-term survival, as well increasing rates of organ rejection [7, 14]. While the degree of organ injury increases with each minute of ischaemic time [15], there appears to be an inflection point at four hours with significant differences in overall survival and graft failure found on both univariate and multivariate analysis after this timepoint [16]. The influence of prolonged organ ischaemic time on recipient outcomes is especially noticeable in organs from older donors, as these organs demonstrate a reduced capacity to withstand ischaemic stress compared to those from younger donors [7, 14].

CSS also results in thermal injury to the organs themselves, worsening the impact of ischaemic damage. After four hours of storage the temperature in the myocardium can be below 0°C, well below the recommended guidelines of 5-10°C [17], with histological evidence of mitochondrial injury and disruption of myofilaments in a canine model [18]. Even when stored at temperatures within the recommended guideline, damage to endothelial cells can still occur, with significant rises in cytosolic calcium and sodium levels found after even brief periods of hypothermia [19, 20], leading to increased endothelial cell swelling [21]. Longer periods of cold storage result in significant damage to the endothelial cells, with cellular blebbing and formation of intercellular gaps seen in cells stored in hypothermic conditions for over 3 hrs [22]. CSS also has limited use in the scenario of extended criteria or donation after circulatory determination of death (DCDD) donors, with animal studies showing poor results with most hearts unable to be weaned off cardiopulmonary bypass (CPB). Hearts that were able to be weaned off bypass had significantly reduced cardiac output (CO) (compared to hearts perfused via machine perfusion), and increased degree of cell death [23-27]. As such CSS is not felt to be a viable method of preserving organs following DCDD.

3.1 Modern CSS Technology

While traditional CSS has been accomplished using ice and an insulated portable cooler, new CSS devices have been developed to improve the cold preservation of organs. The SherpaPak (Paragonix Technologies, MA, USA) was designed to provide an environment that maintains a stable optimal temperature between 4-8°C, with the donor heart affixed to a connector and temperature probe before being suspended within a cannister containing cold cardioplegia. The cannister is then surrounded by disposable cooling packs and is designed to be easily transported while maintaining a stable temperature (Figure 1) [17, 28].

Figure 1 SherpaPak. (Image courtesy of Paragonix Technologies, Inc. All rights reserved.). A – Paragonix SherpaPak, showing all components of the system. B – Heart suspended in cardioplegia-containing cannister.

SherpaPak has shown potential to improve organ preservation in clinical practice. In a single-centre retrospective study examining short-term outcomes in 34 patients following use of the SherpaPak, a 0% incidence of severe PGD was found, with 25/34 patients (74%) having no evidence of any PGD. In this study, however, there was no comparison made to transplants performed with regular CSS [29]. Results published from the GUARDIAN-Heart registry, an industry-funded retrospective review of patients undergoing heart transplantation using either CSS or SherpaPak, showed mixed results for its use. Recipients of hearts preserved with SherpaPak were less likely to have severe PGD (both in the overall and propensity-matched cohort), however there was no difference in 30-day or 1-year survival following transplantation. For recipients of transplants where

the ischaemic time was longer than 4 hours the use of SherpaPak resulted in a decreased rate of severe PGD and increased 30-day survival, however there was no difference in one-year survival [30]. These findings indicate there may be a role for SherpaPak for organs with longer ischaemic times, however its benefit in day-to-day practice remains uncertain and it has not yet achieved widespread use in place of traditional CSS.

4. Hypothermic Machine Perfusion

Hypothermic Machine Perfusion (HMP), most commonly referring to Hypothermic Oxygenated Perfusion (HOPE) or non-ischaemic hypothermic perfusion (NIHP), involves the perfusion of the organ at cold temperatures with an oxygenated perfusate, aiming to combine the known protective benefit of hypothermia while reducing the obligatory ischaemic insult that occurs during the organ retrieval and transport process. The use of HMP has allowed for the recovery and use of donor hearts with significantly prolonged ischaemic times, longer than would have been possible through standard CSS [31, 32]. Another variant of HMP involves the use of deoxygenated perfusate and this is referred to as hypothermic deoxygenated (nitrogenated) perfusion (HNPE), however this is not used in clinical cardiac preservation.

4.1 XVIVO Heart Assist Transport (XHAT)

Currently the only available option for HMP is the XHAT, previously known as the XVIVO Heart Perfusion System (XVIVO Perfusion AB, Gothenburg, Sweden), seen in Figure 2. This consists of the XVIVO Heart Assist Transport, XVIVO Heart Assist Transport Perfusion Set (XHATPS), XVIVO Heart Solution (XHS), and XVIVO Heart Solution Supplement (XHSS) [31]. The perfusion system is automatic with pressure-controlled flow, an automatic gas exchange system supplied by a 95% oxygen/5% carbon dioxide gas cylinder, a leukocyte arterial filter, cooler unit, batteries, and software to run the system and provide user feedback on perfusion [33, 34]. The perfusion solution used within the XHAT is an albumin-based, hyper-oncotic, cardioplegia solution that is supplemented with a cocktail of brain death hormones (XHSS) and meropenem. The system is primed with 2.5 litres of this perfusion solution, along with 300 to 500 mL of donated packed red blood cells aiming for a haematocrit between 10-15% [31]. The packed red blood cells may either be blood group O-negative, or recipient-matched blood group if this is known at the time of preparing the system.

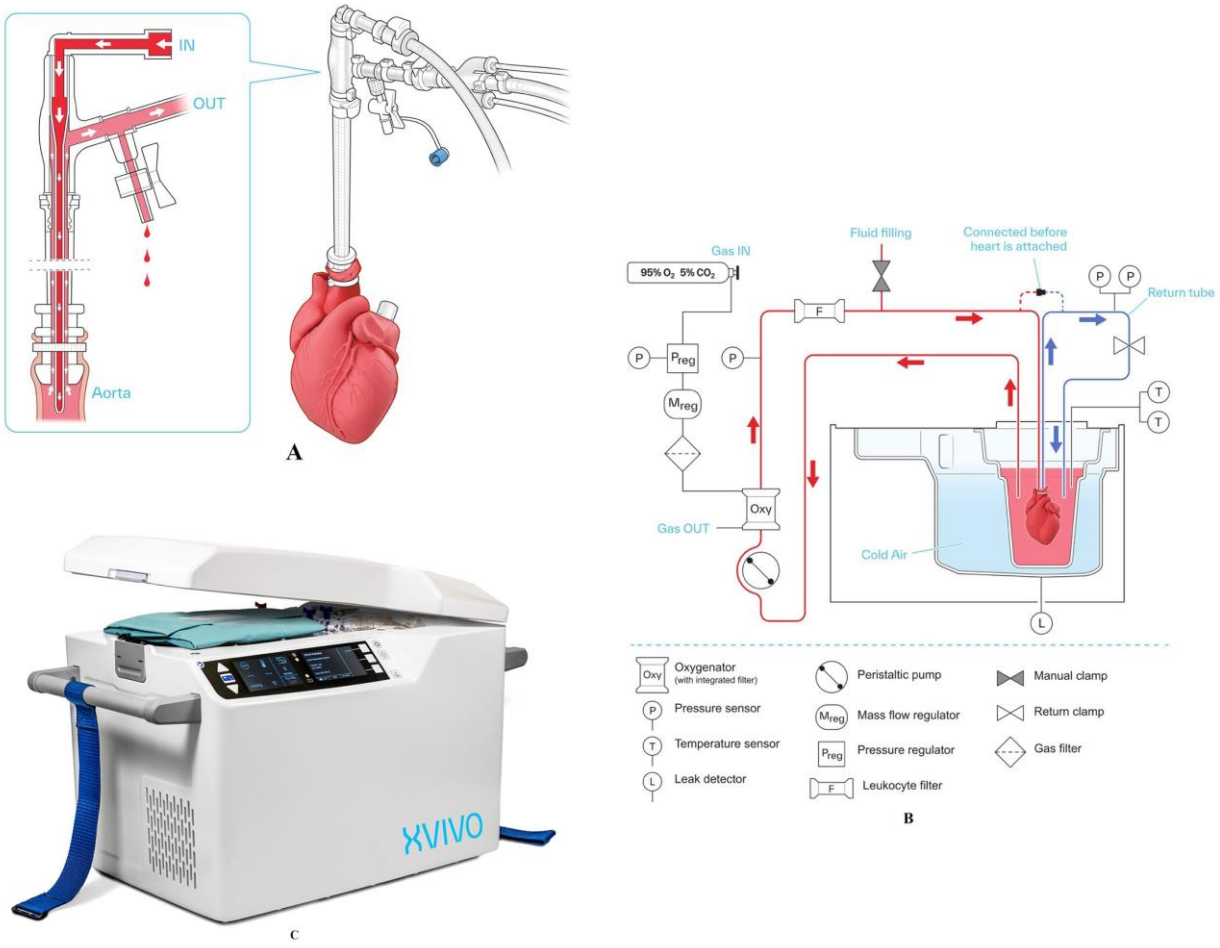

Figure 2 XVIVO Heart Assist Transport (XHAT) (Images courtesy of XVIVO Perfusion AB). A – XVIVO self de-airing cannula with circuit connections and de-airing port. The cannula is inserted and secured in the ascending aorta, and a silastic tube placed through the mitral valve. B – XHAT circuit. Red arrows indicate the perfusion circuit with the blue arrows indicating circuit used for priming, flushing and de-airing. C – XVIVO Heart Assist Transport.

The donor heart is arrested via infusion of the supplemented heart solution into the aortic root, with cardiectomy as would be performed for any routine organ retrieval. Following this, the ascending aorta is cannulated with a self de-airing XVIVO aortic cannula, and a split silastic tube is placed through the mitral valve into the left ventricle and secured to the left atrial wall (to prevent distension of the left ventricle during perfusion) [31]. The heart is then submerged into a reservoir containing the perfusion solution and the aortic cannula is connected to the perfusion circuit, and following de-airing of the circuit perfusion is commenced. The donor heart is then perfused at a pressure of 20 mmHg, resulting in a flow of 150–200 mL/min, at a temperature of 8°C [31, 33, 34].

4.1.1 Development of HMP

Research efforts into the development of HMP have been taking place for many years, with a research group from The Alfred Hospital (Melbourne, Australia) showing the protective benefits of

continuous perfusion of a cold crystalloid oxygenated solution in a greyhound DCDD model in 2011 [35], as well as in a human DCDD heart model in 2014 [36].

Further work into the development of HMP was published in 2016 and was performed using a porcine model of brain death and heart transplantation with an early version of the XHAT. After the establishment of brain death, the porcine heart was excised, connected to the perfusion circuit, and perfused for 24 hours. The protocol for perfusion in these early experiments involved 15 minutes of perfusion, followed by 60 minutes of non-perfusion (i.e., perfused for 20% of the time). Following perfusion the heart was then transplanted into a recipient pig, with all 10 animals in the experiment able to be weaned from CPB. A control group was included with three hearts preserved via CSS (preserved at 4°C with St Thomas solution for 24 hours). None of these three hearts were able to be weaned from CPB, with the animals dying after one hour despite high dose vasoactive support [33]. Subsequent work from the same research group found that there was preservation of endothelium-dependent relaxation and contraction, as well as preservation of coronary smooth muscle contraction following a perfusion time of 8 hours [37].

HMP also appears to induce a degree of donor heart immunodepletion, in addition to the immunodepletion provided by the leukocyte arterial filter present in the XHAT. In six pig hearts that were perfused with HMP for eight hours, there was decreased phosphorylation of six proteins linked to IRI – STAT2, STAT5a/5b, STAT6, CREB, and WNK1. There was also a decreased level of nine proteins known to be linked to cell death pathways, including p53, TNF receptor 1, and pro-caspase 3, and on histological examination there was no evidence seen of ischaemic or endothelial disruption. Following transplantation of the hearts preserved with HMP, there was also found to be reduced recipient leukocyte recruitment into the graft compared to organs preserved with CSS [38].

Further animal studies performed using an ovine model of heart transplantation showed that organs preserved using HMP were more likely to be weaned from bypass, required less vasoactive support, and had lower blood lactate levels compared to transplants performed using CSS. In these studies the period of CSS was two hours compared to two separate HMP groups – two hours HMP and eight hours HMP [34], demonstrating the protective benefit HMP had in hearts preserved for longer periods than would usually be accepted in clinical practice.

4.1.2 Evidence for Use of HMP

The first in-human clinical use of HMP was published in 2020 as a non-randomised trial comparing the outcomes following heart transplantation of 6 patients who received a heart preserved with XVIVO HMP compared to 25 patients who received a heart preserved with routine CSS. The median total preservation time in the HMP group was 223 minutes, with a median perfusion time of 140 minutes, compared to a median ischaemic time of 194 minutes in the CSS group. The primary composite outcome was defined as freedom from severe PGD within 24 hours post-transplant, freedom from use of extracorporeal membrane oxygenation (ECMO) within seven days post-transplant, and freedom from acute cellular rejection (ACR) greater or equal to Grade 2R. All six patients in the HMP group remained free of the primary composite outcome, compared to 18 patients (72%) in the CSS group. While the patients in the HMP group were more likely to require renal replacement therapy immediately following transplantation, no patients had persisting renal impairment at later follow-up [39].

The recently published HOPE Study provided strong clinical evidence for the benefit of HMP for donor hearts with long preservation times [31]. This was a single-arm, multicentre non-randomised trial on donor hearts with a projected preservation time of 6-8 hours. It was deemed to be unethical to randomise patients to transplantation with CSS with an ischaemic time >6 hours, so patient outcomes were compared to historical International Society of Heart and Lung Transplantation (ISHLT) Registry data. Thirty-six patients were included in the study, of which 29 had a long preservation time >6 hours. The median preservation time in this long preservation cohort was 414 minutes, with the longest preservation time being 527 minutes [32] and 4 hearts travelling greater than 3,000 km (1864 miles) from donor hospital to recipient hospital. The primary outcome was severe PGD and secondary graft dysfunction (SGD), defined by the need for post-transplant mechanical circulatory support (MCS). Three patients required post-op MCS, 2 in the long-preservation arm and 1 in the short preservation arm. One of the cases in the long-preservation arm was deemed to have severe PGD requiring a temporary right ventricular assist device (VAD), with 1 patient from each arm developing severe SGD (1 due to mechanical right ventricular outflow tract obstruction, the other due to pre-existing non-obstructive right coronary artery disease). There was no 30-day mortality of any patients enrolled in the trial, which contrasted strongly to the comparison ISHLT Registry data showing increasing rates of 30-day all-cause mortality with increasing preservation time.

4.2 Benefits

The use of HMP offers significant benefits to both transplant recipients and the transplant surgical team. As shown in the HOPE study [31, 32] preservation of donor hearts can be extended beyond 8 hours without the development of fatal PGD allowing for the acceptance, transport, and transplantation of hearts that previously would be unable to be retrieved with CSS due to the risk of development of PGD. A recently published case report described the successful transplantation of a heart retrieved in the French West Indies and transplanted in Paris, with a total preservation time of 12 hours and 6 minutes [40]. This means that despite the significant distances present between cities in Australia and New Zealand, as well as in North America including Canada and the United States of America (USA), there is no longer a donor heart that cannot be transported to a transplant centre and even raises the possibility of trans-Atlantic organ retrieval and transplantation occurring.

The use of HMP may also allow for friendlier surgical operating times, allowing for the heart to be “parked” at the recipient hospital on the machine and for the implant to occur during daylight hours. The ability to have long preservation times also provides a buffer to surgeons in the case of complex congenital or re-do transplant surgeries, as well as VAD-explant transplant surgeries. HMP was also used in the world-first xenotransplantation of a genetically modified porcine heart [41]. More recently, a world-first report of three successful human heart transplants from DCDD donors using HMP following direct procurement of the DCDD heart has been reported [42].

4.3 Limitations

Despite the benefit of perfusing donor organs with an oxygen-rich perfusate, there is no ability to assess the functionality of organs following retrieval with HMP. Thus, there remains a “leap of faith” that must be taken when implanting an organ into a patient following DCDD that has not had its functionality assessed.

HMP has been used for DCDD kidney transplantation successfully, with kidneys preserved with HMP showing decreased rates of delayed graft failure and higher creatinine clearance 1-month post transplantation compared to kidneys preserved with CSS [43]. Oxygenated perfusate has also shown benefit in DCDD kidney transplants, with kidneys preserved with HOPE showing increased function and lower rates of graft failure 12-months post-transplant compared to kidneys preserved with HNPE [44].

Animal studies have been performed examining the impact of HMP for DCDD heart transplantation. In a murine model simulating DCDD, hearts were preserved for 30 minutes with either CSS, HOPE or HNPE, before being reperfused *ex-vivo*. The hearts preserved via HOPE were found to have higher CO compared with CSS and HNPE [45], with further work from the same group showing there appears to be preservation of endothelial nitric oxide production in heart preserved with HOPE [46]. A porcine DCDD transplant model has been used to assess the impact of the XVIVO Heart Perfusion System, comparing 2 hrs CSS to 3 hrs HMP. Following transplantation all hearts were able to be weaned from CPB (excluding hearts that suffered technical issues), however it was noted the hearts preserved with HMP were able to be weaned quicker than those preserved with CSS. The HMP group was found to have preserved contractile function after storage and transplantation, particularly in hearts retrieved via a direct procurement protocol [27]. Further animal studies are also being carried out within our own research group regarding the feasibility of using HMP for DCDD heart transplantation.

Early work with HMP has shown significant benefit in allowing the retrieval and transplantation of hearts previously unable to be accepted, and within our own institution participation in the HOPE trial has changed our clinical practice and led to an increase in the number of transplants able to be performed. It remains unclear if there would be any benefit in using HMP instead of CSS in cases where short ischaemic times are anticipated, however, given known issues with cold static storage further research is warranted to answer this question.

The financial impact of using currently commercially available HMP systems, along with NMP systems must also be considered and may pose a significant challenge to uptake of the technology worldwide. All machine perfusion technologies will cost more than CSS in terms of consumables required, however as the technology becomes more developed it is hoped the overall costs will reduce. In addition, there is likely a financial benefit in allowing staff to operate during normal working hours (so no overtime rates are required to be paid), and by increasing the number of transplantations performed the burden on the healthcare system of recurrent hospitalisations of patients with heart failure will likely be reduced.

5. Normothermic Machine Perfusion

NMP involves the perfusion of the heart with warm oxygenated perfusate, and allows for not only the reduction of ischaemic insult that occurs during CSS but also the opportunity to assess the organ *ex-vivo* prior to organ transplantation. Evaluation of donor hearts for viability occurs via visual assessment of contractility of the right ventricle, and lactate profile over the duration of perfusion. While initially an absolute lactate concentration of <5 mmol/L was required for transplantation, it appears the concentration does not correlate to clinical outcomes and need for post-transplantation MCS [47]. In our own centre's clinical practice with DCDD we now accept hearts showing a reduction in overall lactate levels as well as lactate extraction (venous lactate level being less than the arterial

lactate level) [48], with post-transplantation MCS rates in our recent experience of 7%. Other additional biomarkers may have a role in assessing donor heart viability (such as cardiac troponin I/T, tumour necrosis factor-α, brain natriuretic peptide) however currently there is limited research into the clinical utility of these markers [49].

5.1 TransMedics Organ Care System

NMP is currently performed via the use of the Organ Care System (OCS) Heart System (TransMedics, Andover, Massachusetts, USA), the only commercially available device (Figure 3). This is composed of a portable heart console with wireless controller and pulsatile perfusion pump, a disposable single-use heart perfusion set, and heart solution that is used to prime the circuit along with 1.2-1.5 L of donor blood [48, 50-52]. The OCS functions by pumping warm oxygenated blood retrogradely into the aorta, perfusing the coronary arteries, and coronary sinus effluent flow is ejected via the right ventricle into a catheter secured into the pulmonary artery, with blood returned to the reservoir. The flow of warm blood allows the heart to be reanimated *ex-vivo* on the OCS, preserving the heart in the warm, near-physiologic state during transportation. The wireless controller displays system information during the preservation period including aortic pressure, coronary flow rate, temperature, and oxygen saturations. The controller allows for alterations to the rate of infusions of adrenaline and OCS Maintenance Solution to help ensure flow parameters remain in the recommended ranges (mean aortic pressure 65–90 mmHg, mean coronary flow 650-850 mL/min) [52-54].

Figure 3 TransMedics OCS Heart System [55].

Organ procurement techniques vary slightly between DNDD and DCDD donors. In DNDD procurement starts as usual with opening of the pericardium and visual assessment of biventricular function and palpation of the coronary arteries, however just prior to cross-clamp application and arrest of the donor heart, 1.2-1.5 L of donor blood is collected and used to prime the perfusion module. In DCDD donors, blood collection is performed as soon as possible after opening the sternum via a cannula inserted into the right atrium, with donor blood collected in a heparin-primed bag [52]. Since 2020 our institution has also added tirofiban to the bag (in addition to heparin) to help prevent platelet clotting of the leucocyte filter [48]. Following blood collection an aortic cross-clamp is applied and the heart flushed with cardioplegia solution, allowing for cessation of circulation in DNDD donors, and cooling and organ preservation in both DCDD and DNDD donors. Cardiectomy is performed and on a back table the aorta and pulmonary arteries are cannulated, an LV vent is inserted into the left atrium, and the superior vena cava and inferior vena cava are sutured closed. Following this, the heart is mounted on the OCS device and perfusion of warm blood is commenced [50].

5.1.1 History and Experience with NMP

The first clinical use of NMP was in the PROTECT I trial, a non-randomised trial in which 20 patients underwent transplantation with hearts preserved via the OCS system. All patients reached the primary endpoint of 30-day survival, and the 6 patients that were transplanted at Papworth Hospital (Cambridge, United Kingdom) were still alive 5 years following their transplant [54, 56]. The PROCEED II trial was the first randomised trial examining the OCS Heart System, with 130 patients randomly assigned 1:1 either to standard CSS or preservation with the OCS, and was designed as a non-inferiority trial with a 10% margin. The primary endpoint was 30-day patient and graft survival, which was reached in 94% of the OCS group and 97% of the CSS group, with non-inferiority shown. There was no difference found between the groups for secondary endpoints of severe organ rejection, cardiac-related serious adverse events, or median intensive care unit (ICU) stay [51]. Given the absence of clear superiority of OCS over CSS, along with the substantial cost, logistical and technical challenges associated with OCS, its ongoing use in standard-criteria donors was not pursued, and attention was instead turned to extended-criteria donors (ECD).

The OCS Heart EXPAND Trial was a prospective, multi-centre trial evaluating the OCS device with ECD. This included donors with an expected ischaemic time of $\geq$4 hours, or an expected total ischaemic time of $\geq$2 hours plus one of LV hypertrophy, ejection fraction 40-50%, downtime $\geq$20 min, or donor age >55 years. In the initial report, 75 of the 93 retrieved donor hearts were successfully transplanted (utilisation rate 81%), with 30-day survival and 6-month survival 94.7% and 88% respectively [57]. At 2-years, 116 of 138 donor hearts were transplanted (utilisation rate 84%) with a 2-year survival of 85.3% in these patients compared to 87.8% in patients transplanted with standard criteria hearts ($p = 0.8893$) [58]. The success of the OCS EXPAND trial has led to the publication of case series and reports of OCS being used successfully for multiple marginal donors and ECD worldwide, with hospitals reporting a 14% increase in the number of heart transplantations performed [59], and others having successful preservation times of 10 hours with patient survival to at least 1-year [60].

5.1.2 NMP in DCDD Donors

The biggest impact of NMP has been in supporting the development of distant procurement and recovery of donor hearts following DCDD. The first successful clinical heart transplantation was performed in 1967 by Christiaan Barnard and the team at Groote Schuur Hospital with a heart donated after circulatory death [2]. At that time, brain death criteria did not exist, and early transplantation was carried out with donors and recipients co-located in adjacent operating theatres [61]. Subsequent development of brain death legislation led to DNDD becoming standard for heart transplantation. However, the ongoing desire to increase the potential donor pool and number of patients able to be helped with heart transplantation, along with a progressive increase in the number of organs (kidney, liver, lungs) retrieved following DCDD, has led to ongoing efforts to make heart transplantation following DCDD viable.

Following extensive pre-clinical studies performed by our research group examining methods to improve cardioprotection [23, 62-65], the world's first heart transplants performed with distant procurement of hearts donated after circulatory death was performed in 2014 at St Vincent's Hospital Sydney (Sydney, Australia) [66]. Since that time, our group has published its experience and improvements in technique, and we most recently completed our 100th successful DCDD heart transplant [48, 50]. The successful development of heart transplantation following DCDD donation has led to a dramatic increase in the number of heart transplantations performed with excellent patient outcomes reported worldwide.

Our own institution's experience of 74 DCDD transplants showed an overall survival of 94% at 1-year and 88% at 5-years post-transplantation, which was comparable to transplantations performed from DNDD donors over the same period (87% 1-year survival, 81% 5-year survival, $p = 0.31$). Overall, 16% of patients who underwent transplantation from DCDD donors required ECMO post-transplant for severe PGD, however this rate decreased to 8% in our contemporary transplant cohort [48].

A randomised trial in the USA comparing DCDD with OCS to DNDD transplantation with standard CSS showed a 6-month survival of 94% for DCDD compared to 90% in the DNDD group ($p < 0.001$ for non-inferiority) in the as-treated groups, with 80 patients in the DCDD group and 86 patients in the DNDD group. However, patients in the DCDD group were more likely to develop severe PGD compared to patients in the DNDD group (15% vs 5%) [67]. A United Kingdom retrospective cohort study of 50 DCDD transplants performed with the TransMedics OCS showed a 30-day survival of 94% compared to 93% for 179 DNDD transplants that occurred over the same period ($p = 0.72$), and a similar 1-year survival rate between the two groups (84% for both groups, $p = 0.91$). There was, however, a significantly higher rate of ECMO support post transplantation (40% DCDD vs 16% DNDD, $p = 0.0006$) [68].

5.2 Benefits

The impact NMP has had on the rate of transplantation has been sizeable, with the combination of published series and our institutional experience reporting nearly 500 DCDD transplantations performed with the OCS, offering a lifechanging transplantation to patients that would otherwise not be possible [48, 67-69]. This has led to an increase in the heart transplant donor pool by around 30% [48, 68, 70], in addition to hearts retrieved from DNDD donors that are recovered using NMP and subsequently transplanted.

5.3 Limitations

NMP, along with HMP, has a significant financial cost associated with it that is not present with routine CSS. In addition to the cost of consumables, staff require special training to mount hearts to the TransMedics OCS, and more staff are required to attend donor organ retrievals when NMP is being used. Hearts preserved with NMP also develop significant myocardial oedema as total perfusion time increases, however it is unclear if this impacts patient outcomes following transplantation.

6. Conclusion

The development of machine perfusion technologies has allowed for a significant number of donor hearts to be retrieved and recovered, enabling the successful transplantation of organs that would not have been possible with standard CSS. The use of HMP has shown clear benefit for DNDD donor organs where long ischaemic times would previously have resulted in an unacceptable risk to the recipient, and NMP has allowed for the development of DCDD heart transplantation, dramatically increasing the number of transplants able to be performed. Further research is needed to determine if there is a benefit in using HMP in DNDD donors with short ischaemic times, particularly given the cost of using these machines, as well as if HMP can be successfully used for DCDD donors. With ongoing research work into improving donor heart organ preservation, it is hoped that increased rates of donor heart utilisation will result in any patient who requires a heart transplantation being able to receive one a timely manner, decreasing wait-list times and improving patient quality of life.

Abbreviations

ACR	acute cellular rejection
CO	cardiac output
CPB	cardiopulmonary bypass
CRRT	continuous renal replacement therapy
CSS	cold static storage
DCDD	donation after circulatory determination of death
DNDD	donation following neurological determination of death
ECD	extended-criteria donors
ECMO	extracorporeal membrane oxygenation
HMP	hypothermic machine perfusion
HNPE	hypothermic deoxygenated (nitrogenated) perfusion
HOPE	hypothermic oxygenated perfusion
ISHLT	International Society of Heart and Lung Transplantation
ICU	intensive care unit
IRI	ischaemia-reperfusion injury
LV	left ventricle/left ventricular
MCS	mechanical circulatory support
NIHP	non-ischaemic hypothermic perfusion
NMP	normothermic machine perfusion

OCS	Organ Care System
PGD	primary graft dysfunction
SGD	secondary graft dysfunction
VAD	ventricular assist device
XHAT	XVIVO Heart Assist Transport
XHATPS	XVIVO Heart Assist Transport Perfusion Set
XHS	XVIVO Heart Solution
XHSS	XVIVO Heart Solution Supplement

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Competing Interests

Yashutosh Joshi and Peter Macdonald have been provided research modules for pre-clinical studies by both TransMedics and XVIVO Perfusion.

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