Donation After Circulatory Death Donor Use

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Abstract

Strategies for procurement of the heart from brain dead donors (DBD) have been standardized over the past 3 decades and limited by the period of warm and cold ischemic time with acceptable total ischemic time of 4–5 h. This landscape has remained largely unchanged until relatively recent development of pumping systems for continued warm perfusion of

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the heart during transport. Although these technologies for ex-vivo perfusion were initially used for improved organ preservation, recent trials have evaluated the use of this type of technology for resuscitating hearts that would otherwise not be accepted for transplantation to increase the availability of the heart organ. An extension of this methodology has been the quest to reevaluate the potential for recovering hearts from donors who have neurologic function, and therefore are not legally brain dead, but in whom because of an irreversible condition the decision has been made to withdraw life support until circulation ceases; this group of donors are referred to as Donation after Circulatory Death (DCD). Although this strategy has now been widely applied to lungs, livers, and kidneys increasing the availability of these organs by about 10%, applicability to cardiac allograft donation has been limited. This chapter will discuss the process of DCD donation, the pathologic concerns related to the heart, and current existing technologies that have been used for DCD heart transplantation.

Keywords

DCD heart · Donation after circulatory death · Warm ischemia · Reperfusion injury · OCS · Ex-vivo heart perfusion · Organ care system · Normothermic regional perfusion · NRP · Heart postconditioning

Introduction

Strategies for procurement of the heart from brain dead donors (DBD) have been standardized over the past 3 decades. In all instances, with minor variations, the aorta is cross clamped, cardioplegia is administered directly into the aortic root, and the incisions in the inferior vena cava and left atrium are simultaneously performed to minimize ventricular distension and the potential for subendocardial ischemia. Following complete cardiac arrest and delivery of 1–2 L of cardioplegia, the heart is harvested (this time is known as the first phase of warm ischemic time which can take 15–20 min depending on whether the lungs are being procured simultaneously). The heart is then stored in a cold solution of either normal saline, Lactated Ringers, or the cardioplegia solution and immersed on ice with the goal of maintaining a temperature of around 4 degrees centigrade during the transport period. The period of time that the heart is in cold storage is referred to as cold ischemic time. Subsequently, the period during which the heart is actually sewn in but not reperfused is the second period of warm ischemia.

This methodology which has largely remained unchanged over the last 3 decades has proven to be successful and primary graft dysfunction (PGD) requiring temporary mechanical support is less than 5% of transplants in the USA. However, depending on the definition used, PGD may occur in as many as 20% of donated hearts requiring significant inotropic support during the post-transplant phase. The search for better preservation solutions has largely failed in terms of clinical applications and the period of warm and cold ischemic time have largely confined the acceptable total ischemic time for hearts to 4 h as a comfortable period and up to 5 h in selected cases. This landscape has remained largely unchanged despite efforts to develop better methodology for organ procurement with using improved preservation solutions and more recently development of pumping systems for continued warm perfusion of the heart with donor blood during transport. Although these technologies for ex-vivo perfusion were initially used for improved organ preservation, to increase the availability of hearts recent trials have evaluated the use of this type of technology for resuscitating hearts that would otherwise not be accepted for transplantation. An extension of this methodology has been the quest to reevaluate the potential for recovering hearts from donors who have neurologic function, and therefore not legally brain dead, but in whom because of an irreversible condition the decision has been made to withdraw life support until circulation ceases; this group of donors are referred to as donation after circulatory death (DCD). Although this strategy has now been widely applied to lungs, livers, and kidneys and has increased the availability of these organs by

about 10% (Cypel et al. 2015; Jay et al. 2011; Klein et al. 2010; Summers et al. 2010), applicability to cardiac allograft donation has been limited. This chapter will discuss the process of DCD donation, the pathologic concerns related to the heart, and current existing technologies that have been used in the United Kingdom and Australia to use DCD donors for heart transplantation (Boucek et al. 2008; Dhital et al. 2015; Garcia Saez et al. 2016; Garcia Saez et al. 2014; Messer et al. 2016).

Methodology of DCD Organ Donation

DCD organ donation protocol in the USA (UNOS) is very specific given the significant ethical concerns surrounding the donation process. Potential donors are considered suitable candidates if they have nonrecoverable, irreversible neurologic injury resulting in ventilator-dependency, do not fulfill brain death criteria, and have no other contraindications as assessed by the Organ Procurement Organization (OPO) and the primary health care team. Also assessed is the likelihood that the donor will expire within the allotted time frame once withdrawal of support has occurred. This time frame may vary from one OPO to another. Once the candidate is identified, the second step involves consent/approval for every procedure or medication that will be administered for the purposes of organ donation (heparin administration, line placement, ECMO, etc.) and making an alternative plan in case circulatory death does not occur within the allotted time for organ donation (logistics and provisions for continued end-of-life care, including immediate notification of the family). The process of withdrawal of artificial life support to allow for cessation of circulation can be complex as well. During the period of withdrawal, none of the members of the transplant team are allowed to be present, a timeout period is recommended to verify patient identification, the respective roles and responsibilities of the patient care team, OPO staff, and organ recovery team personnel. After proper verification and withdrawal of life support, the declaration of death must comply in all respects with the legal definitions and needs to be done by a member of a patient care team who is not a member of the OPO or the transplant team. Time required from asystole to declaration of death depends on each OPO but usually spans from 2 to 5 min interval.(Bernat et al. 2006) If circulatory death is confirmed within the allotted time period, then organ procurement is commenced. This complex set of rules is in place to ensure that the procedure is done with high medical, ethical, and judiciary standards.

Pathophysiology of Myocardial Acute Ischemic Injury and Reperfusion Injury

In DCD organs, the inherent interval period with reduction in heart rate, blood pressure, and gradual blood deoxygenation compounded by the mandatory wait time to declare death invariably leads to an extended period of warm ischemia which causes more damage to the heart. Energy in myocardial tissue is predominantly generated via oxidative phosphorylation. Oxidative phosphorylation is a highly efficient aerobic metabolic pathway that takes place at the mitochondrial membrane. After normothermic cessation of coronary blood flow and oxygen delivery to myocardial tissue, the oxygen reserves (dissolved in the myocardium and bound to myoglobin) are first utilized which can last for about 8 s or 8 heart contractions (Kubler and Spieckermann 1970). This is followed by a shift from aerobic to anaerobic myocardial metabolism (Pasteur-effect). Anaerobic metabolism (anaerobic glycolysis) is significantly less effective in energy production and is therefore unable to produce the minimal ATP needed to prevent irreversible myocardial damage (Reimer and Jennings 1981). This process is characterized by lactate production, depletion of adenosine stores, and intracellular acidosis (Reimer and Jennings 1981). Acidosis and ischemic metabolites lead to reduction of intracellular potassium and increase in intracellular sodium via membrane transporters (Na^+/H^+, K^+/H^+, Na^+/K^+) (Pridjian et al. 1987). Increase in cytosolic sodium in turn causes increases of cytosolic calcium which activates multiple pathways that lead to apoptosis, microscopically evident in myocytes

as death through hypercontracture (Cooley et al. 1972; Pridjian et al. 1987; Ronchi et al. 2017). The mechanism of increased sodium and calcium in cytosol during acute ischemia is not easily explainable by membrane exchange transports alone but is likely also contributed by a complex redistribution of ions between intracellular compartments specifically mitochondria which is a significant calcium ion reservoir (Ronchi et al. 2017).

Myocardial Damage during Reperfusion Injury

It is believed that up to 50% of the total damage to the DCD heart occurs in the period of initial reperfusion. The main mechanism of reperfusion injury is due to increased electrolyte gradient, primarily hydrogen gradient that causes increased sodium influx by the Na^+/H^+ exchange transporter (Sanada et al. 2011). Subsequent loss of the sodium gradient causes large increase in calcium cytosol concentration and calcium overload, due to Na^+/Ca^{++} exchange transporter working in reversed mode (Sanada et al. 2011). The calcium overload then further worsens damage done to the cell by ischemia.

This chain of events is important as strategies are being researched to minimize the ischemic-reperfusion injury, such as solutions with low calcium concentrations or Na^+/H^+ or Na^+/Ca^{++} exchanger inhibitors that may be added to the initial reperfusion solution (Ferrari et al. 1986; Sanada et al. 2011; Shine and Douglas 1983; Tani and Neely 1990; White et al. 2017).

History of DCD Heart Transplant

The concept of DCD donation actually predates the current accepted policies related to donation after brain death (DBD) given that the laws defining death as neurologic death did not go into effect until 1981 when the Uniform Determination of Death Act (UDDA) was enacted in the USA. In fact, the first heart transplant performed by Christian Barnard in Cape Town, South Africa, in 1967 was a DCD heart transplant from a young woman who sustained a massive head injury from a motor vehicle accident and was diagnosed with a lethal brain injury without a chance for recovery (Barnard 1967). She underwent withdrawal of life support as a prerequisite to officially be pronounced dead. Both donor and recipient were already in the operating room prepped and draped for transplant. The donor chest was opened immediately after she was pronounced dead and extracorporeal reperfusion was initiated with cooling of the heart. The heart was then explanted, subsequently implanted, and reperfused in the recipient. For this initial transplant, care was taken to minimize the ischemic time (warm and cold ischemic time) including measures such as rapid initiation of hypothermia and reperfusion of the donor, rapid transfer from the donor to the recipient by being collocated, and continued perfusion during implantation.

Following the establishment of clear brain death criteria in 1981, the need for withdrawal of life support was eliminated, thus avoiding the extended warm ischemic time. This subsequently led to predominant use of DBD organs as a simpler and a safer option. However, the unbalanced schism between available and needed organs has continued to grow exponentially, forcing increased renewed interest in DCD organs and exploration of new methods for heart preservation. In 2008, Boucek published their experience with transplanting three DCD hearts in pediatric population which in general has a higher wait list mortality (25%), as compared to adults (Boucek et al. 2008). Their protocol was similar to Bernard's in that the donor and recipient were both located at the same hospital, the donor was prepped and draped and ready for surgery with venous and arterial cannulas inserted. If death occurred within 30 min from withdrawal of life support, a patient would be considered a donor candidate. Immediately after withdrawal of donor's life support, and pronunciation of death, complete sternotomy was performed along with instillation of cold preservation fluid through a balloon arterial catheter in the ascending aorta, and topical cooling. All of

these measures were again performed to minimize ischemia time, especially warm ischemia time. New interest in adult DCD heart transplants is evident by the clinical Australian experiences published in 2015, and the UK series in 2016 (Dhital et al. 2015; Messer et al. 2016; Tsui and Oniscu 2017). The Australian experience is based on ex-vivo heart perfusion using the Organ Care System™ (OCS), while the UK group also used the strategy of normothermic regional perfusion (NRP) to assess heart function prior to procurement.

Ex-Vivo Heart Perfusion and Normothermic Regional Perfusion

After initial reperfusion, secondary focus is maintenance perfusion until transplantation of the heart into the recipient. This has not been possible until ex-vivo perfusion devices became available. The first commercially available normothermic ex-vivo perfusion device, the TransMedics Organ Care System (OCS), was used in the UK and Australian DCD protocols (Fig. 1). OCS was developed as a solution to reduce cold ischemia time. Cold ischemia time as well as warm ischemia time are both directly correlated with 30-day mortality after heart transplant (Banner et al. 2008). Cold storage also limits the distance that the recipient heart team can travel between donors and recipients, reducing the ability for optimal matching between the two. This also means discarding viable hearts at locations such as Hawaii where the distance from recipients may be too far. Therefore, the primary goal of OCS is to reduce the cold ischemia time, improve organ preservation, allow longer distance transplants, and possibly allow better matching. In the PROCEED II trial (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation, NCT00855712), OCS showed noninferiority compared to cold storage, but with longer total preservation times (324 mins vs. 195 mins) and at the same time shorter ischemia times (113 mins vs. 195 mins). (Ardehali et al. 2015). In addition, OCS allows procurement and resuscitation of high risk DCD hearts (Garcia Saez et al. 2014). One of the potential advantages of this system is that while on OCS perfusion, the heart's viability and therefore transplant suitability can be evaluated. At present, the main method of evaluation consists of repeated measures of lactate levels in the coronary sinus to determine tends. In addition, coronary flow and visual assessment of the empty contacting heart is possible (Dhital et al. 2015). OCS has been successfully used for high risk and DCD hearts, however, despite reports from Hamed and Deng showing significantly higher lactate levels in the graft failure group or "turned down organ" group as compared to successful transplants, concerns about reliability of using lactate levels for evaluation of the heart viability still exist (Deng et al. 2013; Hamed et al. 2009). One of the added features of this system, which has not yet been thoroughly evaluated, involves the possibility of loading the heart to assess contractile function by echocardiography which may also add to a better assessment of high risk marginal donors.

Normothermic regional perfusion (NRP) , will be described in next sections in more detail, is an extracorporeal membrane oxygenation system that provides circulatory and respiratory support until return of heart function. Once the heart is able to take over the circulation, NRP is weaned. This allows for restoration of the donor's circulatory system and in a way converts a DCD to a DBD donor. Once the NRP is weaned, heart function can be assessed via standard TEE and pulmonary catheter measurements in addition to lactate levels. The benefit of this strategy is the ability to evaluate the heart in vivo (Fig. 2) (Messer et al. 2016; Tsui and Oniscu 2017).

It is worth mentioning that there are also other methods in development for DCD heart preservation, most notably hypothermic ex-vivo heart perfusion. Hypothermic ex-vivo heart perfusion principle is similar to the one of OCS but perfusion is being maintained around 4 °C and usually with lower flows. Caenegem et al. compared heart preservation between hypothermic (4 °C) ex-vivo heart perfusion using HeartPort System (Modified

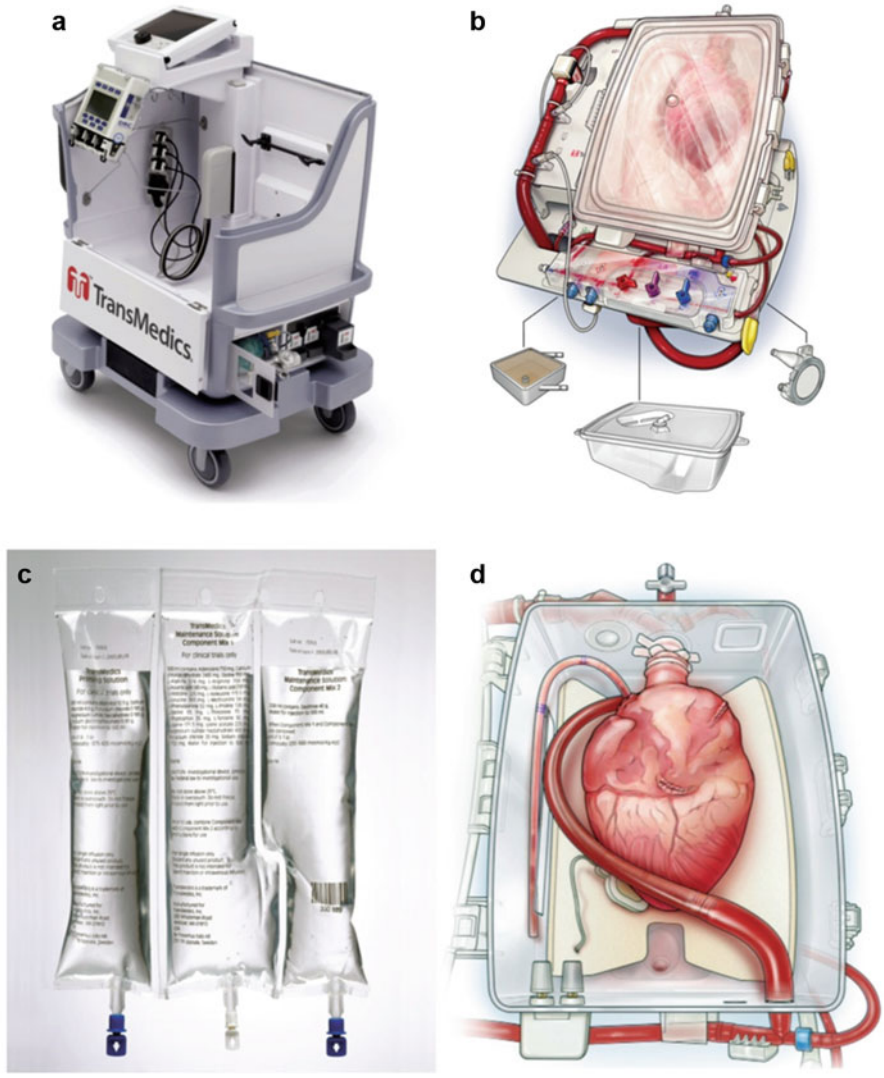

Fig. 1 The Organ Care System is composed of a portable console with heart console (**a**), heart perfusion set (**b**), and heart solution set (**c**). The system is designed for ex-vivo heart perfusion with warm, oxygenated, nutrient-enriched donor blood (**d**). (This figure is reprinted from Ardehali et al. 2015 (PROCEED II trial))

LifePort System, Organ Recovery Systems) and traditional cold storage on 16 pig hearts (Fig. 3) (Van Caenegem et al. 2016). They found that compared to cold storage, cold perfusion has improved preservation and functional recovery of the heart. The cold perfusion group had lower lactate levels, lower adenosine monophosphate/adenosine triphosphate ratio, and higher phosphocreatine/creatine ratio. Using the same cold perfusion system in a canine model ($N = 18$) and measuring several metabolic parameters, Ozeki et al. concluded that cold perfusion reduces tissue injury and improves myocardial recovery when compared with cold storage despite mild transient tissue edema (Fig. 4) (Ozeki et al. 2007). In both studies, coronary flow was 80 mL/min and aortic root pressure was 15 mm Hg, which is about ten times lower than OCS

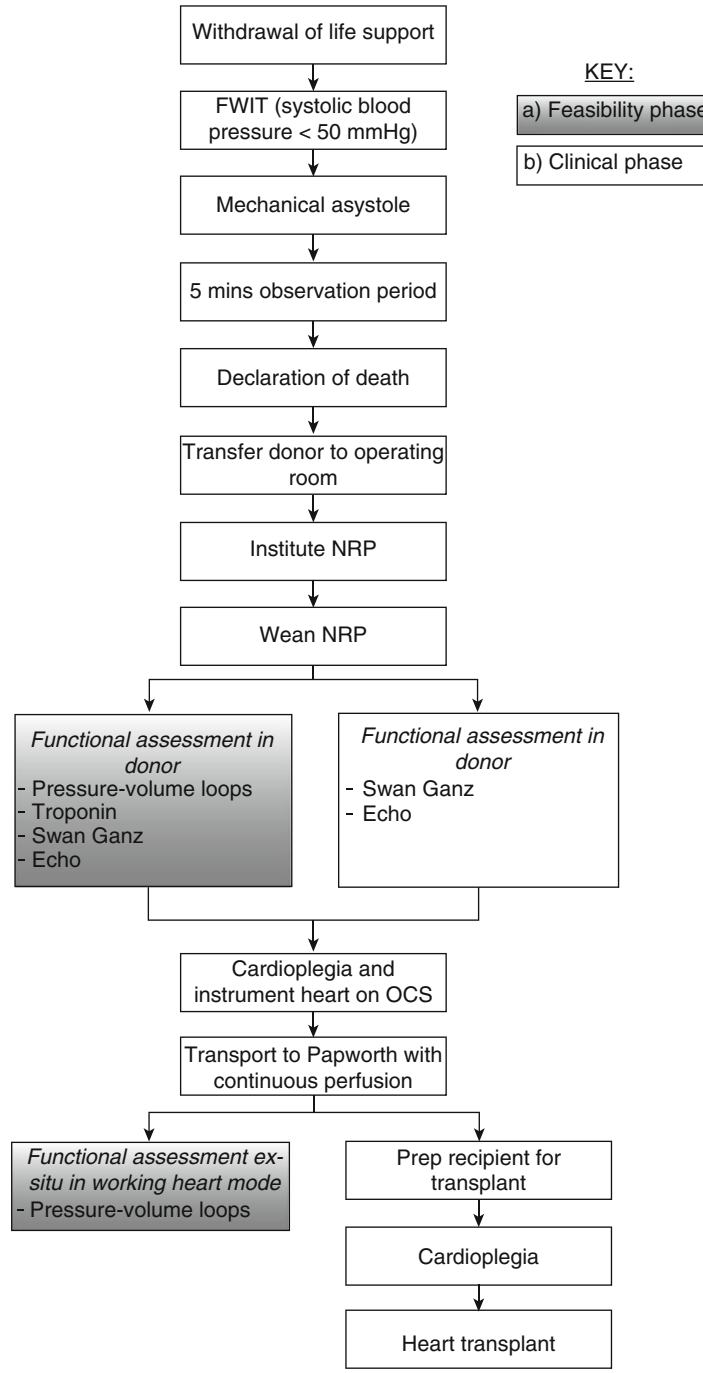

Fig. 2 Flow diagram of DCD heart assessment, protocol, from withdrawal of donor life support to the transplant. (This figure is reprinted from Messer et al. 2016)

normothermic ex-vivo perfusion. Ou et al. and Choong et al. used custom hypothermic low flow perfusion device in canine modes also to compare hypothermic perfusion to cold storage and arrived to the same conclusion. They used 4–12 °C temperature range of perfusion and pressure of 8–10 mm H2O (Choong et al. 2016; Ou et al. 2014).

Fig. 3 Portable perfusion pump. The HeartPort© System is a modified version of the LifePort© System (Organ Recovery Systems©, Itasca, IL, USA), designed for kidney graft perfusion and preservation. The heart grafts were suspended inside a sterile cassette and subjected to retrograde perfusion with 1 L asanguineous preservation solution (KPS-1©, Organ Recovery Systems©, Itasca, Il, USA). The perfusate was cooled to 4 °C by a heater exchanger, oxygenated by oxygenator (Minimax Oxygenation System©, Medtronic, Inc., Minneapolis, MN, USA), and recirculated by means of a pulsatile roller pump. (This figure is reprinted from Caenegem et al. 2016)

Fig. 4 Heart Transporter™, a lithium-powered, ultra-lightweight apparatus equipped with temperature and perfusion pressure controls, as well as a bubble oxygenator (Organ Recovery Systems; Des Plains, IL, USA). (This figure is reprinted from Ozeki et al. 2007)

Comparisons of cold and normothermic ex-vivo perfusion techniques have not been performed yet. While cold ex-vivo perfusion still needs to prove itself clinically, it would be interesting to see whether cold or normothermic perfusion technique would be better for heart preservation and resuscitation.

Experimental and Animal Data on DCD Heart Donation and Resuscitation

Before clinical application, there were a number of experiments exploring the possibility of using DCD hearts. The studies mentioned here and others later in the chapter laid the ground work for the first clinical human transplant of a DCD heart.

Animal Data

Ali et al. compared DCD pig hearts ($N = 8$) resuscitated on CPB and DBD pig hearts ($N = 8$) and found that posttransplant cardiac function was similar between the two, concluding that DCD hearts could be used for transplant and that further research on reperfusion strategies needs to be done (Ali et al. 2011). Repse et al., using a DCD dog model ($N = 15$), determined that pre-reperfusion (acidic, mitochondrial protective cardioplegia) and continuous normothermic perfusion is superior to cold storage and more suitable for transplant (Repse et al. 2010). White et al. looked at cardioprotective strategies on a DCD pig model ($N = 17$) and found improved posttransplant function with initial use of tepid adenosine-lidocaine cardioplegia and continuous myocardial perfusion compared to cold hypokalemic cardioplegia (White et al. 2013). Lyer et al. based on seven DCD pig models found that OCS provides excellent platform for recovery and assessment of DCD hearts and provides viable source of additional organs (Iyer et al. 2013). The same group later compared continuous ex-vivo perfusion and Celsior solution to cold storage preservation (DCD pig model, $N = 8$) and found that the perfusion group was successfully weaned off CPB posttransplant (5/6) while none of cold storage (0/3) hearts were viable (Iyer et al. 2015). Desrois et al. based on pig model ($N = 10$) concluded that cold storage doesn't provide enough protection for DCD hearts (no function was returned at all) and alternative strategies need to be found (Desrois et al. 2014). Saez et al. using pig model ($N = 5$) also found DCD hearts can be successfully resuscitated using OCS (Garcia Saez et al. 2015).

Clinical Procurement Methods of DCD Hearts

Australian Experience

The Australian experience is based on direct organ procurement and use of OCS (Dhital et al. 2015). The process starts with the potential donor located in close proximity to the operating room where transplant teams are ready. Following withdrawal of life support, the patient can legally be pronounced dead 2 or 5 min after cessation of circulation (depending on the Australian States laws). Donor is then urgently transferred to the operating room and prepped for procurement. After sternotomy, 1.5 L of blood is collected for priming of the OCS device with separate administration of heparin. Heparin cannot be given to the DCD donor per Australian regulations prior to declaration of death. The aorta is crossed clamped, and 1 L of crystalloid St. Thomas cardioplegia solution supplemented with erythropoietin and glyceryl trinitrate is administered to aortic root at 150 mmHg of pressure. The heart is vented through the left atrial appendage and IVC incisions and explanted. It is then connected to the OCS device. The OCS circuits are primed with 1.5 L of donor blood and 500 ml of Transmedics priming solution (buffered electrolytes, vitamins, steroids, and mannitol). In addition, Transmedics maintenance solution (isotonic electrolytes, amino acids, dextrose-insulin, and low dose adenosine) is infused at a rate of 0–30 mL/h to maintain coronary perfusion within acceptable range of 650–900 mL/min. After connecting the heart to OCS, oxygenated and supplemented blood flows into the ascending aorta to provide antegrade coronary perfusion. Blood returns to the right side of the heart and is then directed through a cannula into pulmonary artery to the circuit reservoir. The superior and inferior vena cava are closed and a vent is placed into the left atrium for decompression. Additional adenosine and epinephrine infusions, and adjustments in pump flow are used to keep the following parameters within expected range: aortic pressure of 65–90 mmHg, coronary flow of 650–900 mL/min, and heart rate of 65–100 beats per minute.

Once the heart is started on the OCS, its function is determined by aortic pressure, coronary flow, and most of all by lactate concentrations in venous and arterial blood. Total lactate concentration less than 5 mmol/L and evidence of lactate extraction (venous lactate <arterial lactate) is considered criteria for myocardial viability.

UK Experience

The UK group has experience with direct procurement followed by OCS and procurement after establishing normothermic regional perfusion (NRP) followed by OCS (Messer et al. 2016; Tsui and Oniscu 2017). While direct procurement and OCS is similar to the Australian group, use of NRP utilizes a different approach to DCD heart procurement. Procedure setup is similar; after withdrawal of life support, cessation of circulation and 5 min of observation, the donor is taken to the operating room. Following complete sternotomy, 30,000 units of heparin is injected into the heart and aortic arch branches are clamped to prevent circulation to the brain. Extracorporeal oxygenator cannula and pump for NRP are placed into the ascending aorta and right atrium. NRP is started at a flow rate of 5 L/min with concomitant use of vasopressin and dopamine infusions to maintain mean arterial pressure of 50 mmHg and temperature of 35 °C or higher. At the same time, perfusion is restored to other transplantable organs (liver, pancreas, kidneys, lungs), while excluding perfusion to extremities and head. Once the heart function has recovered, NRP is weaned off. During NRP, arterial troponin and lactate are monitored, and following weaning off NRP, the focus is on cardiac index (CI) and pressures (CVP, PCWP) measured via PA catheter, and ventricular and valvular function assessed by TEE. Criteria for accepting the heart after NRP are CI $>$ 2.5 l/min/m2, CVP $<$12, PCWP $<$12, and EF $>$ 50% on TEE. If the heart is functionally and structurally sound, procurement occurs as routinely done and the explanted heart is connected to the OCS.

Clinical Results

What is evident from these DCD protocols is that as compared to simpler method of procuring DBD heart after cardioplegia and cooling, methods of procurement involving DCD hearts are elaborate and complex to allow resuscitation of the heart and final evaluation for transplant viability. Despite this complexity, the clinical data is very promising and both the Australian and UK groups have excellent outcomes. Both 30 day and 1 year survival in the Australian series ($N = 12$) (Dhital et al. 2017) are 100% while in the UK group for direct procurement and perfusion technique ($N = 18$) are 94.4% and for NRP technique ($N = 13$) 100%.

Warm Ischemia and Reperfusion

Even with successful clinical application of some of the methods mentioned herein, search for the composition and properties of the most cardioprotective initial reperfusion solution continues. As discussed previously, the two important factors that are most harmful to the tissue in DCD organs are warm ischemia and reperfusion injury. Harmful effects of warm ischemia are prevented by minimizing its duration while preventing or minimizing reperfusion injury is a subject of ongoing debates. Degree of reperfusion injury is highly influenced by the characteristics of the initial reperfusion solution, and ideal composition of this solution is a subject of ongoing research. Using a principle that intracellular calcium and sodium overload has a central role in the pathogenesis of reperfusion injury, White et al. found that hypocalcemic and moderately acidic (pH = 6.9) initial reperfusion solution minimizes edema and optimizes functional recovery of the heart, thus reducing myocardial stunning in a DCD pig model (White et al. 2017). This is in concordance with multiple studies on the optimal choice of cardioplegia electrolyte composition during cardiac surgery induced ischemia, although the concentrations of calcium differ between the studies, which is likely related to differences in concentration of magnesium. Another study by White et al. found that profoundly hypothermic initial reperfusion had negative effect on myocardial recovery in a pig DCD model (White et al. 2016). Normothermic (35 °C) initial reperfusion solution showed increased coronary flow, less myocardial injury, greater

preservation of endothelial integrity, and myocardial recovery. This is contrary to standard DBD practice where hypothermic cardioplegia is used. While DBD organs are transported in a cold storage after procurement, DCD hearts are placed on normothermic ex-vivo perfusion (OCS) which may be a reason why a few minutes of hypothermia is questionable. On the other side, Farine et al. determined that mild hypothermia (30 °C for 10 min followed by rapid rewarming to 37 °C) mechanical postconditioning (intermittent periods of ischemia, two cycles of reperfusion followed by 30 sec of ischemia), and hypoxia (<10% oxygen for 2 min) during reperfusion improve recovery of hemodynamic function and reduce LDH levels (marker of cell death) in DCD Wister rats models (Farine et al. 2016). The theory of modifying the physical conditions of initial reperfusion lies in slowing down production of free oxygen radicals while restoring electrolyte and acid-base balance. As compared to White et al., Farine found no difference in hemodynamic recovery when using mildly acidic reperfusion (6.8 to 7.4 pH).

Other potential methods for resuscitation of donor hearts include pharmacologic postconditioning to reduce the ischemia reperfusion injury, which is achieved by scavenging free radicals, reducing inflammatory response, activating reperfusion injury salvage kinases associated with reduced apoptosis, and inhibiting cell sodium-hydrogen exchange transporters. For example, Watson et al. showed cardioprotective properties of erythropoietin and reduction of ischemia-reperfusion injury, likely by activating SAFE – kinase cytoprotective signaling pathway on a rat model (Watson et al. 2013). Hing et al. on the other hand showed cytoprotective properties of a combination of cariporide and glyceryl trinitrate by inhibition of sodium–hydrogen exchange transporter and reduction of ischemia-reperfusion injury (Hing et al. 2009). Many other pharmacologic substances (steroids, adenosine, insulin, and others) showed some potential benefit in reduction of ischemia-reperfusion injury via above mentioned mechanisms.

Conclusion

DCD heart transplant is currently in its infancy. The success of initial experiences in Europe and Australia has demonstrated that it can be done, and increasing lack of organs available for transplant implies that it has to be done. Since the DCD heart transplant represents significant distancing in methodology from the DBD transplant, the next step before widespread adoption is to confirm reproducibility of the above mentioned methodologies and results. Continued research on different aspects of DCD procurement and implantation procedure is necessary including determination of optimal physiologic and pharmacologic characteristics of reperfusion and continuous perfusion solutions, superiority between cold low flow ex-vivo perfusion and normothermic higher flow ex-vivo perfusion, improved methods for organ evaluation, and discovery of new biomarkers or other methods for evaluating physical recovery.

Unfortunately, application of these technologies in the USA is far from clinical reality and most efforts have been investigational and concentrated in the laboratories. For true clinical utility, major changes in legislature and policy need to be implemented before this significant and potentially promising process can be developed in the USA. Given the significant organ shortage and the life-saving opportunity that a heart transplant offers, it is imperative that the USA make the necessary changes in this area, which will likely come to fruition in the next 5 years.

Cross-References

- ▶ Donor Operation and Organ Preservation
- ▶ Ex Vivo Perfusion
- ▶ History of Heart Transplant
- ▶ Regulatory Agencies
- ▶ Surgical Complications

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