Keynote Lecture Series

Heart transplantation from donation after circulatory determined death

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Fifty years since the first successful human heart transplant from a non-heart beating donor, this concept of heart transplantation from donation after circulatory determined death (DCD) promises to be one of the most exciting developments in heart transplantation. Heart transplantation has established itself as the best therapeutic option for patients with end-stage heart failure, with the opportunity to provide these patients with a near-normal quality of life. However, this treatment is severely limited by the availability of suitable donor hearts. In recent times, heart transplantation has been limited to using donor hearts from donors following brain stem death. The use of donor hearts from DCD had been thought to be associated with high risk and poor outcomes until recent developments in organ perfusion and retrieval techniques have shown that this valuable resource may provide an answer to the global shortage of suitable donor hearts. With established DCD heart transplant programmes reporting encouraging results, this technique has been shown to be comparable to the current gold standard of donation after brain death (DBD) heart transplantation.

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Introduction

Heart transplantation worldwide has been accepted as the best treatment for patients with medically refractory end stage heart failure. Recent data from the International Society for Heart and Lung Transplantation from 1982 to 2014 including data on more than 100,000 heart transplants show continuously improving median survival with patients from 2002–2008 benefitting from a median survival of 11.9 years (1). Despite being such an effective therapy, its utilization is limited by the short supply of suitable donor hearts. In the United Kingdom (UK), only 27% of hearts from donors following brain stem death [donation after brain death (DBD)] that are offered are eventually accepted for transplantation. Unfortunately, this translates to 43% of patients on the heart transplant waiting list either dying or becoming too sick to be suitable for a heart transplant (1).

To address the increasing demand for heart transplantation, the heart transplant community were forced not only to extend the acceptability criteria for DBD hearts but also to re-explore heart transplantation using hearts from donation after circulatory determined death (DCD). Until recently, anxieties concerning the unquantifiable warm ischemic injury to the myocardium following cardiac arrest coupled with the inability to assess function of the asystolic heart have been major hurdles preventing further attempts at transplanting DCD hearts. However, with advances in technology, research and the desperate need for suitable donor hearts, successful DCD heart transplant programmes have been established with very encouraging results to date.

The potential for DCD heart donation

Donor shortage is not limited to cardiac transplantation alone. Despite early transplantation being largely from DCD, the mainstay of transplantation has been from DBD. It has only been since the end of the century following the

definition of the categories of DCD by the International Congress on Non-Heart Beating Donation that transplant programmes have seriously considered DCD organs to expand the donor pool (2,3).

Renal transplantation has led the way with the use of DCD transplantation in the modern era with early experiences in the 1990s suggesting a 20% increase in kidney transplantation as a result of the use of DCD organs (4). In the UK, DCD kidney transplantation has expanded from around 100 DCD kidney transplants per annum in 2003/04 to over 800 in 2013/14 accounting for an overall 40% of deceased donor renal transplantation (5). In the UK, DCD organ donation from Maastricht category III donors contributed to 32% of all organs transplanted from deceased donors in 2016–2017 (6).

A retrospective review of the UK transplant registry data held by NHS Blood and Transplant over a 3-year period from 2011 to 2013, revealed that of 3,073 DCD donors referred, 149 (5%) would be potential DCD heart donors (7). In this analysis, DCD donors referred were considered unsuitable for heart donation based on lack of appropriate consent, age over 50 years, cardiac arrest in the donor, a cardiac cause of death, cardiac risk factors, cardiovascular disease, the use of any inotropes in the donor and a functional warm ischemic time (FWIT) of greater than 30 minutes. FWIT is defined as the time from when the systolic blood pressure of the donor reaches 50 mmHg following withdrawal of life supporting therapy (WLST) till mechanical asystole. The time limit of 30 minutes for FWIT is adopted from that used by abdominal transplant surgeons. However, there has been well established small and large animal models to suggest that heart would be tolerant to 30 minutes of warm ischemia (8). Although the application of this criteria is more stringent than the current protocols applied to DCD heart transplantation in the UK, this conservative projection would have translated to at least a 30% increase in heart transplant activity over the same period.

Animal models of DCD heart donation

There have been a number of animal models of DCD heart transplantation that have been explored.

The Japanese group experimented on a canine model using exsanguination as a mode of death, antemortem conditioning followed by *in situ* machine perfusion and cooling to 20 ℃ prior to heart retrieval and cold storage (9). They were able to wean the hearts of cardiopulmonary bypass in a recipient model in this series. However, there are a number of issues in translating this into practice in the UK. First antemortem interventions are not allowed in the UK and such pre-conditioning of the donor heart prior to death would not be possible. Secondly, this method does not allow for functional assessment of the donor organ on its own. However, this method showed that cold storage of DCD hearts with evidence of myocardial viability post-transplantation might be a potential strategy.

Gundry *et al.*, used a hypoxic lamb model with ante-mortem pre-conditioning prior to DCD heart retrieval (10). Implantation was performed with the recipient cooled to 20 ℃. In his initial experiments, the time from withdrawal to donation was limited to less than 21 minutes with cold storage time less than 2 hours. Here again, no functional assessment was possible, and success might be attributed to the short warm and cold ischemic times.

Gundry then proceeded to extend the period of warm ischemia to 30 minutes using a combination of pharmacological pre- and post-conditioning agents and replicated this success in a primate model, limiting cold static storage to 60 minutes (11).

The use of normothermic regional perfusion, originating from Barnard's clinical work, was explored by Ali *et al.* using a porcine model of hypoxic induced DCD (12). Following death, cardio-pulmonary bypass was established and after allowing for a period of less than hour with the heart off-loaded and allowed to recover, bypass was weaned and the heart functionally assessed using load independent contractility. This suggested that the DCD heart maintains viability and recovers function similar to that of the BSD heart and may be suitable for clinical transplantation. This was also confirmed in the human setting where a DCD heart was able to be successfully weaned off normo-thrmic regional perfusion (NRP) and support the circulation suggesting that DCD hearts were indeed functionally suitable for transplantation (13).

The history of human DCD heart donation

The first adult heart transplant in the world that was performed by Barnard at the Groote Schuur Hospital in 1967 was from a DCD donor (14). The donor had been involved in a road traffic collision and sustained severe traumatic brain injury. Brain stem testing was not legally recognised at the time and so DCD was the only available option. Following WLST, the donor arrested and death was declared 5 minutes after electrical asystole. The donor was then systemically heparinized and initially placed on cardio-

pulmonary bypass. Following this, perfusion was limited to the heart while it was cooled. In this setting, the recipient was co-located and the heart retrieved without cardioplegia followed by continuous antegrade coronary blood perfusion.

However, following the publication of the accepted definition of brain death, heart transplantation shifted towards DBD donors (15). It was only in 2004 that attention was drawn to the potential for DCD for cardiac transplantation in the pediatric population in a bid to reduce the unacceptably high waiting list mortality (16). The work by Gundry *et al.* (11) formed the basis of the techniques used by the team in Denver, Colorado when embarking on their clinical programme of paediatric DCD heart transplantation (17). Here they utilized a system of ante-mortem heparinization and cannulation, together with co-location of the donor and recipient. Additionally, they limited the time from mechanical asystole to confirmation of death to 75 seconds whereas in the UK it is a mandatory 5 minutes. These strategies were employed to decrease the cold ischemic time and are considered to attribute to the success of this strategy.

However, the success of these techniques relied on antemortem interventions and a short cold ischemic time which could only be achieved by collocating the donor and recipient. Furthermore, this did not allow for functional assessment of the heart following the hypoxic insult of circulatory death till after implantation in the recipient

However, wider acceptance of DCD heart donation was reported in 2015 following the transplantation of three adult DCD hearts in Sydney using direct procurement and perfusion (DPP) (18). This technique involves removing the asystolic heart and reanimating the organ upon an *ex-situ* perfusion platform [TransMedics Organ Care System (OCS), Andover, MA, USA)] (19). Unfortunately, heart function could not be assessed using this technique. It was therefore thought by many that without a functional assessment prior to transplantation this would place the recipient at unacceptably high risk of primary graft failure as post-operative extracorporeal membrane oxygenation (ECMO) support was reported at 30%. This limited the team to donors less than 40 years old and a donation withdrawal ischemic time to less than 30 minutes.

In 2015, Papworth Hospital performed the world's first DCD heart transplant using functional assessment of the donor heart through the technique of normothermic regional perfusion. This technique allowed re-perfusion of the heart and abdominal viscera within the donor with the exclusion of the cerebral circulation. This permitted functional assessment of the donor heart *in situ* allowing the team to extend donor age up to 50 years and the donation withdrawal ischemic time to 247 minutes.

Techniques of DCD heart retrieval

There are three techniques for procurement of DCD cardiac allografts that are practiced in the UK: (I) normothermic regional perfusion followed by *ex-situ* machine perfusion (NRP); (II) DPP; (III) normothermic regional perfusion followed by cold storage.

Following the planned withdrawal of life-supporting therapy which is carried out by the local anesthetic or intensive care independent of the retrieval in the adjoining anesthetic room or closely situated intensive care unit, the donor is monitored by the local team. Following the identification of mechanical asystole, a hands-off period of 5 minutes is allowed prior to the declaration of death in keeping with the guidance in the UK as published by the Academy of Medical Royal Colleges (20). Once death is confirmed the donor is promptly transferred to the operating room where the retrieval teams are scrubbed in preparation for organ retrieval.

Normothermic regional perfusion

Following the declaration of death, the patient is brought into the operating room and draped for thoraco-abdominal organ retrieval. A median sternotomy is performed first with prompt administration of heparin into the right atrium and pulmonary artery. Tracheal re-intubation is carried out simultaneously. The aortic arch vessels are clamped to exclude cerebral circulation as per the guidelines of organ retrieval in the UK (20). The aorta and right atrium are cannulated respectively to allow for NRP. Absence of cerebral perfusion is cross-checked with carotid Doppler. Once flow via the NRP circuit is established, a laparotomy is performed. After a period of up to 45 minutes, during which the heart is supported by NRP and is allowed to recondition, NRP is weaned. Functional assessment is then performed by means of trans-oesophageal echocardiography and thermodilution cardiac output studies by via a pulmonary artery flotation catheter.

For the instrumentation of the allograft on the TransMedics OCS, 1.5 L of donor blood are collected via the NRP circuit to prime the OCS in addition to the manufacturer provided priming solution. The heart is then arrested with 500 mL of cold crystalloid cardioplegia (St

Thomas' no two solutions) to which is added supplementary erythropoietin and glyceryl trinitrate. The heart is then cannulated for instrumentation on the OCS.

DPP

In this method, a sternotomy and laparotomy are performed simultaneously. Following the opening of the pericardium, 1.5 L of donor blood is collected in a heparinised blood collection bag via a cannula inserted into the right atrium to prime the OCS. Myocardial protection during procurement is achieved by the delivery of 500 mL of supplemented cold crystalloid cardioplegia as described for NRP. The heart is then instrumented on to the OCS in a similar fashion.

Perfusion on the TransMedics OCS

In addition to the manufacturer supplied prime solution, the collected donor blood is passed through a leucocyte filter to make up the priming volume of the OCS as per the manufacturer's guidelines. Attention was paid to ensure that donor blood collection was performed prior to the delivery of cardioplegia. An additional variable infusion of TransMedics maintenance solution containing dextrose-insulin and adenosine is added to the circuit along with a variable infusion of adrenaline.

The aorta of the donor heart is cannulated to allow retrograde perfusion of the heart via the coronaries in the setting of a competent aortic valve. The heart is drained via cannulation of the pulmonary artery and a superior pulmonary vein vent is also placed to prevent any distension of the left ventricle.

Aortic flow is maintained between 800–1,000 mL/min and the adenosine containing maintenance solution adjusted accordingly to maintain and aortic pressure of 65–90 mmHg. The donor heart is paced epicardially to a rate between 70–90 beats per minute as required. If on reperfusion, the heart donor heart was noted to be in ventricular fibrillation, direct current cardioversion was performed to restore sinus rhythm. In addition to coronary flow and electrocardiographic monitoring, arterio-venous samples were taken to assess lactate metabolism as a surrogate for cardiac function.

Transplantation of the DCD heart

Irrespective of the method of DCD heart procurement utilised, the beating heart on the OCS was arrested with 1 L of cold St Thomas' cardioplegia and transplanted. Most transplant teams use a system of either antegrade or retrograde cardioplegia during implantation to further limit the burden of myocardial ischemia.

Early results

In the modern era it was the paediatric transplant community that spear-headed the revival of DCD heart transplantation with the first reported case series of three paediatric DCD heart transplants. Since then this team have reported further success and a recent review in the International Society for Heart and Lung Transplantation Registry revealed a total of 21 paediatric DCD heart transplants had been performed between 2005 and 2014 (21). Reported, was a similar overall survival between infant DCD and DBD recipients.

There are currently four centres worldwide that have established clinical DCD adult heart transplant programmes. Three of these centres are based in the UK—Papworth Hospital, Harefield Hospital and Wythenshawe Hospital. St Vincent's Hospital in Australia remains the only adult centre outside the UK performing DCD heart transplantation.

To date April 2017, Dhital *et al.* reported 12 DCD heart transplants all performed using the DPP technique in Sydney, Australia. At the time of writing, all recipients remain alive although as reported through personal communication, 30% required ECMO support postoperatively. Donors are limited to 40 years old and the donation withdrawal ischemic time limited to 30 minutes.

Papworth Hospital practises NRP, DPP and NRP/Cold storage. The decision for which technique to use remains limited by the governing body for transplantation in the UK, NHS Blood and Transplant who have deemed it such that NRP is performed only in three donor referral hospitals. With 39 DCD heart transplants to date, Papworth Hospital has the largest DCD heart transplant programme in the world with very encouraging early results. In their programme, recipient's survival to discharge following DCD heart transplantation is 93%, with only 13% requiring ECMO support in the post-operative period. Recipients required a median stay of 5 days in intensive care with a median stay of 20 days in hospital.

There is debate as to which technique of procurement is superior. The Sydney group, based on their experimental work (22), limit the time allowed from WLST to declaration of death to be eligible for DCD heart donation to 30 minutes.

The use of NRP allowing for a comprehensive functional assessment of cardiac function with data obtained from the pulmonary floatation catheter (PAFC) and trans-oesophageal echocardiography has allowed for this relatively short interval to be extended without compromising transplant outcomes (19). Additionally, the confidence provided by functional assessment has allowed for the inclusion of older donors, thus further expanding the potential donor pool. An early review describing the international experience of DCD heart transplantation to-date, highlighted that there was no significant difference in mortality between the two techniques (21). However, from a health-economics perspective, it did highlight that the percentage conversion of hearts perfused on the OCS that proceeded to transplantation was higher in those who had been assessed on NRP, allowing for a significant cost-saving. More recently, a timely study published by Messer *et al.* coinciding with the 50th anniversary of heart transplantation further confirms these findings (23). More importantly, they address the question of transplant outcomes of DCD hearts in comparison to the current gold-standard of DBD heart transplants. In a matched comparison, they found no significant difference in survival with a reported 92% 90-day survival in the DCD group (n=26) with no differences in intensive care duration, length of hospital stay or the need for mechanical support. Interestingly, they did report better early cardiac function of the DCD allografts compared with the matched DBD cohort.

Ethical considerations

The use of NRP is not possible in certain countries due to the many varying legal definitions of death that exist globally. In the UK, current practice is based on the code of practice guidelines published by the Academy of Medical Royal Colleges (20). These guidelines allow for the use of NRP and for perfusion of the heart to be restarted within the donor provided that cerebral circulation is not restored. There are other legislative differences that exist in the process of declaration of death internationally. In the UK, a period of 5 minutes after mechanical asystole has to be allowed prior to the declaration of death, whereas in Australia this time period varies between 3 to 5 minutes and in the paediatric cohort in Colorado was reduced to 75 seconds. Furthermore, the use of ante-mortem interventions such as ante-mortem heparin, while routinely practiced for DCD retrievals in some countries is unacceptable in the UK.

Co-location of the donor and recipient, while an exceptionally rare occurrence, has been intentionally employed to facilitate paediatric DCD transplantation (17). However, this is not a strategy that is routinely acceptable in many other countries on ethical and logistic grounds despite the proposed clinical benefits.

Future work

Although DCD heart transplantation has been shown to be a viable source of good quality donor hearts, there remains a lot of work that needs to be done to optimise this resource and allow patients to fully benefit from this procedure. Significant work has already been done in using post-conditioning agents on an *ex-situ* platform of perfusion to allow for better post-transplant outcome using pharmacological agents which has already translated into clinical practice (24). However, apart from using NRP, there remains significant doubt on the reliability of organ assessment on the OCS which is currently based on the use of lactate as a surrogate for organ quality together with flow parameters (25,26). Additionally, as with DBD transplantation, primary graft dysfunction (PGD) remains an issue and the platform of *ex-situ* perfusion allows for an opportunity to investigate potential bio-markers that may be used to predict PGD and indeed advise on organ quality.

Although DCD heart transplantation has relied heavily on *ex-situ* organ perfusion where normothermia was the preferred strategy (27), there are a number of heart perfusion devices currently being developed which may offer an alternative strategy to preservation of the DCD heart (28).

Conclusions

The results of the established DCD heart transplant programmes provide a strong case for DCD heart transplantation to be incorporated into existing heart transplant programmes worldwide. As experience grows, it will be important to follow the long-term outcomes of these pioneering programmes and promote wider adoption of this valuable resource for donor hearts for the ever-increasing number of patients with heart failure. However, we can say with increasing confidence that the current experience with DCD hearts has thus far proven to provide heart failure patients with at least equivalent outcomes to DBD heart transplantation. Additionally, the conservative estimates for the potential for DCD heart transplantation to increase

transplant activity have been exceeded (28,29). Despite it being 50 years since the first DCD heart transplant, the use of DCD hearts with distant procurement and isolated heart perfusion is in its infancy, and further research is required into defining the limits of this technique as well as mechanisms for optimising DCD hearts. With further developments in attenuating ischemic insults using pre- and post-conditioning strategies we may be able to extend the time limits and even allow for organ repair. The platform for isolated heart perfusion provides us with a unique opportunity to investigate heart assessment, donor-recipient matching and organ preservation. This future for heart transplantation and organ donation may not only be limited geographical boundaries but a global service to our patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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