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REVIEW

Kidney donation after cardiac death

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Abstract

There is continuing disparity between demand for and supply of kidneys for transplantation. This review describes the current state of kidney donation after cardiac death (DCD) and provides recommendations for a way forward. The conversion rate for potential DCD donors varies from 40%-80%. Compared to controlled DCD, uncontrolled DCD is more labour intensive, has a lower conversion rate and a higher discard rate. The super-rapid laparotomy technique involving direct aortic cannulation is preferred over *in situ* perfusion in controlled DCD donation and is associated with lower kidney discard rates, shorter warm ischaemia times and higher graft survival rates. DCD kidneys showed a 5.73-fold increase in the incidence of delayed graft function (DGF) and a higher primary non function rate compared to donation after brain death kidneys, but the long term graft function is equivalent between the two. The cold ischaemia time is a controllable factor that significantly influences the outcome of allografts, for example, limiting it to < 12 h markedly reduces DGF. DCD kidneys from donors < 50 function like standard criteria kidneys and should be viewed as such. As the majority of DCD kidneys are from controlled donation, incorporation of uncontrolled donation will expand the donor pool. Efforts to maximise the supply of kidneys from DCD include: implementing organ recovery from emergency department setting; improving family consent rate; utilising technological developments to optimise organs either prior to recovery from donors or during storage; improving organ allocation to ensure best utility; and improving viability testing to reduce primary non function.

Key words: Donation after cardiac death; Donation after brain death; Extended criteria donor; Viability assessment; Renal transplantation; Delayed graft function; Graft survival; Agonal phase; Kidney preservation

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INTRODUCTION

There is continuing disparity between demand and supply of kidneys for transplantation. Efforts to reduce demand by health education, control of blood pressure and improved management of diabetes mellitus are either inadequate or are non existent in some parts of the world. More kidney transplants would result in shorter waiting times and limit the morbidity and mortality associated with long-term dialysis therapy[1]. To improve supply, exclusion criteria have been relaxed to include use of "marginal" or extended criteria donors (ECD). ECD is defined as any brain-dead donor aged > 60 years or a donor aged > 50 years with 2 of the following conditions: history of hypertension, terminal serum creatinine level ⩾ 1.5 mg/dL (133 μmol/L), or death resulting from a cerebrovascular accident[2]. Evans[3] noted that the number of potential donors of 43-55 per million of population (pmp) was insufficient to meet the demand and called for

donation after cardiac death (DCD) in addition to both living-related and living-unrelated kidney donation.

DCD refers to kidney donation from patients with irremediable brain injuries who do not meet the criteria for brain death testing and who experience cardiopulmonary arrest after withdrawal of ventilatory support[4]. Other categories of DCD are shown in Table 1. Category V was a later addition[5]. Maastricht categories Ⅲ and Ⅳ are referred to as controlled whereas categories Ⅰ, Ⅱ, and V are regarded as uncontrolled. DCD represents a growing source of kidneys for transplantation in the United States, although not to the same extent as in Europe[6]. Review of United Network for Organ Sharing data showed a yearly trend of increasing DCD (controlled more than uncontrolled) donors between 1995 and 2004[7]. Similarly, the number of organs recovered from DCD grew from 64 in 1995 to 391 in 2004[8].

Despite early post transplant complications, DCD kidneys show comparable function and survival after the immediate postoperative period and have been demonstrated to provide a survival benefit to recipients over waiting for donation after brain death (DBD) kidneys[6]. The aims of this review are to describe the current state of kidney DCD and identify possible risk factors affecting the frequency and outcome of DCD kidney transplantation and provide recommendations for a way forward.

HISTORICAL PERSPECTIVES

Initial efforts at using deceased donors for renal transplantation were from cardiac death donors probably due to lack of an enabling law and an unclear definition of brain death. At the time (1960s) there was less effective use of kidney preservation and immunosuppressive drugs[9,10]. As a result, outcomes of such transplantation were poor and it was not surprising that with the establishment of brain stem legislation, DCD programmes were abandoned. Things have improved since those early days and due to a continuing lack of organs, many transplant centres in the developed world have returned to DCD[11,12].

The first kidney transplant in the world from DBD was performed in Belgium in June 1963. But it was only in 1987 that the Belgian law on organ donation and transplantation was published, with its opting-out principle but with no emphasis placed on recovering organs after cardiac death. The development of DCD kidney transplantation hinged on: (1) an enabling law; (2) the first International Congress on non heart beating donation (now referred to as DCD) in 1995, where the four categories of Maastricht were defined[13]; (3) ethical approval; and (4) the desire for viability testing assessment (looking for some indicative measure of the likelihood of kidney function post transplantation) of the DCD organ prior to implantation, and hence the introduction of machine perfusion technology[14].

SPREAD OF PRACTICE

A report covering the first 25 years (1981 to 2005) of DCD kidney transplantation in Maastricht showed DCD activity resulted in a 44% increase in organ donation[15]. There has been a steady increase in DCD activity in the United Kingdom from 5.6% (42/745) of deceased donation activity in 2001/02 to 36.93% (373/1010) in 2010/11. The United Kingdom witnessed an 87% increase in DCD activity between 2007 and 2010[16]. For Belgium, DCD activity represented 11.38% of all donors in 2006[17]. Since its implementation four and a half years ago, DCD has accounted for 10.9% of deceased donor activity in Ontario, Canada[18]. The majority of DCD kidneys are from controlled donors meaning that the number of organs can be further increased by utilising uncontrolled donors[3,4,12,19-30] although the associated workload is considerably more and the yield rate poorer. Reports from some centres show that DCD from deaths outside the hospital may be a good source of donor kidneys and may provide a way to successfully increase the donor pool for organ transplantation[31]. While there is increasing acceptance of DCD grafts in adults, transplant centres appear reluctant to use these grafts in the paediatric population[22].

Table 1 Maastricht classification of donation after cardiac death

Maastricht category	Description
Ⅰ	Dead on arrival at hospital
Ⅱ	Unsuccessful resuscitation
Ⅲ	Awaiting death by cardiovascular arrest
Ⅳ	Death by cardiovascular arrest during or after brain death diagnostic procedure
Ⅴ	Unexpected cardiac arrest in a critically ill patient

Now even more extended criteria kidneys

The increasing demand for renal transplantation has prompted many centres to consider donors exhibiting signs of acute renal failure (ARF) prior to cardiac arrest. The major concern with such donors is about the expected poor quality of graft function. Sohrabi *et al*[32] reviewed 49 single renal transplant recipients from category Ⅲ donors after cardiac death between 1998 and 2005, at Newcastle, United Kingdom. According to the RIFLE criteria (risk, injury, failure, loss and end stage renal disease)[33], nine of these recipients had kidneys from donors with "low severity pre-arrest ARF". There was no statistically significant difference in delayed graft function (DGF) and rejection rates between the two groups. Sohrabi *et al*[32] concluded that low severity ARF in kidneys from controlled DCD can be a reversible condition after transplantation. It is noteworthy that all but one of those kidneys had hypothermic machine perfusion and viability testing prior to transplantation.

TECHNICAL CONSIDERATIONS

Soon after circulatory death and prior to recovery of organs, effective *in situ* preservation is required to allow do-

nation to occur particularly from uncontrolled asystolic donors. Kidney storage/preservation has an important effect on outcome. Several technical advances in the area of kidney recovery and preservation have occurred. Utilisation of available technology could result in a significant increase in the number of kidneys available for transplantation[34].

In situ perfusion vs super rapid laparotomy

Insertion of a double-balloon triple-lumen catheter allows selective perfusion of the abdominal aorta to preserve the kidneys *in situ*. This is particularly useful in uncontrolled DCD as it can be started prior to obtaining full consent from relatives. In a series of 133 *in situ* perfusion procedures initiated in one centre, only 56 (42%) led to transplantation. In the remaining 77 cases (58%), the donation procedure was abandoned or both kidneys were discarded because of complications (31), poor graft quality (23), lack of consent (13) and medical contraindications (8) or unknown cause (2). Snoeijs and co-workers[35] found that increasing donor age [odds ratio (OR) = 1.06 per year, $P < 0.001$] and uncontrolled DCD donation (OR = 5.4, $P < 0.001$) independently correlated with *in situ* perfusion complications.

There is evidence to support the super-rapid laparotomy technique as the preferred method of kidney recovery from Maastricht category Ⅲ DCD donors. In a retrospective cohort study of 165 controlled DCD procedures in two regions in the Netherlands between 2000 and 2006, two methods were used to preserve kidneys from controlled DCD donors were compared: *in situ* preservation using a double-balloon triple-lumen catheter inserted *via* the femoral artery (102 donors) and direct cannulation of the aorta after rapid laparotomy (63 donors)[36]. The super-rapid laparotomy group was associated with a lower kidney discard rate (4.8% *vs* 28.2%), a shorter warm ischaemia time (22 min *vs* 27 min) and a higher 1-year graft survival rate (86.2% *vs* 76.8%)[36]. Snoeijs *et al*[35] reported superior graft survival for kidneys from controlled DCD donors managed by super rapid laparotomy. The association between increasing catheter insertion time and inferior graft outcome emphasizes the need for fast and effective surgery-rapid laparotomy with direct aortic cannulation is preferred over *in situ* perfusion in controlled DCD donation.

Extracorporeal support

Extracorporeal membrane support to maintain circulation before cooling and organ retrieval has been used to improve the condition of DCD kidneys, with lower rates of DGF compared with standard retrieval conditions. Experimentally, normothermic perfusion has been used in conjunction with hypothermic techniques as a resuscitation technique to improve graft outcome. An *ex-vivo* porcine kidney model showed that energy levels could be replenished to improve tissue perfusion during reperfusion. This technique was translated into a porcine transplant model demonstrating that it was a feasible and safe method of preservation. Normothermic preservation techniques have the potential to be adapted into an improved method of retaining tissue viability or assessing the condition of the kidney compared with hypothermic techniques[37].

After donor asystole is confirmed by the electrocardiogram strip recording, the extracorporeal membrane oxygenator (ECMO) support is set up through the right femoral veno-arterial route, an occlusion balloon catheter is inserted through the left femoral artery to occlude the thoracic aorta, and bilateral femoral arteries are ligated or occluded by Forgarty balloon catheters. Usually, the ECMO is set up to begin within 10 min after asystole. The ECMO, combined with a cooler, provides cold oxygenated blood to the abdominal visceral organs, and prevents warm ischaemic injuries. Ko and co-workers[38] reported on eight renal grafts procured from four DCD donors using ECMO support (range: 45-70 min) stating that with the exception of the first two renal grafts with delayed function, all others had immediate function postoperatively. Even though Maglioccа *et al*[23] used a short agonal period of 60 min as cut off, their normothermic ECMO supported DCD program increased the potential donor pool by 33% (61 *vs* 81 patients) and the number of kidneys transplanted by 24% (100 *vs* 124).

Reznik *et al*[39] developed an *in situ* kidney preservation protocol with application of the extracorporal *normothermic* abdominal perfusion for organ resuscitation in uncontrolled DCD. They examined leucocytes from modified donor oxygenated blood circulating in the device and reported on 10 uncontrolled donors with warm ischaemia time from 45 to 92 min. A normothermic extracorporal perfusion device was applied to all 20 kidneys after ischemic damage. Following transplantation, there was immediate graft function in six and all kidneys functioned eventually with a mean ± SE creatinine of 118.5 ± 19.9 mm at 3 mo. Treatment of ischemically damaged kidney by normothermic extracorporal perfusion with leukocyte depletion before procurement seems to be a challenging protocol for expanding donor pool and demands further study.

To minimize ischemic injury, Farney *et al*[40] utilised extracorporeal interval support for organ retrieval after cardiac arrest and reported an overall actuarial kidney graft survival rates of 89%, 76% and 76% at 1, 3 and 5 years, respectively. The use of extracorporeal interval support in locally recovered kidneys reduced the incidence of DGF from 55% to 21% ($P = 0.016$)[40].

Chest compression

Mateos-Rodríguez *et al*[41] conducted a retrospective observational study involving a historical comparison between standard manual chest compressions (2008) and mechanical chest compression (2009) on the failure rate of transplanted kidney grafts in recipients of organs from DCD donors who had mechanical chest compressions to maintain a circulation before organ retrieval. There were 2/39 (5.1%) failures in the transplanted kidneys from do-

nors receiving mechanical chest compressions and 3/33 (9.1%) in the manual chest compressions group. The difference between the two groups was not significant but worryingly, three patients achieved successful return of spontaneous circulation in the mechanical chest compression group after initiation of the DCD donor protocol.

ETHICAL AND LEGAL IMPLICATIONS

The introduction of DCD programmes generated a lot of ethical dilemmas: the determination and timing of death; timing of interventions to maintain organ viability for the benefit of the recipient; and conflicts of interests, for example, separation of responsibilities of the medical teams in the different phases of the procedure (patient treatment, withdrawal of life sustaining treatment and actual donation). There are further issues regarding how consent is obtained and whether sufficient respect and care is given to the patient and his family[42,43]. It is important to develop an ethical framework for DCD that enjoys community-wide support.

No religion formally forbids donation or receipt of organs or is against transplantation from living or deceased donors. Addressing the participants of the First International Congress of the Society for Organ Sharing in 1991, Pope John Paul Ⅱ supported organ donation but called for serious consideration of the questions posed by it. For the noble act of organ donation after death, the real death of the donor must be fully ascertained[44].

Although end-of-life care should routinely include the opportunity to donate organs and tissues, the duty of care toward dying patients and their families remains the dominant priority of health care teams. The complexity and profound implications of death are recognised and should be respected, along with differing personal, ethnic, cultural and religious perspectives on death and donation. Decisions around withdrawal of life-sustaining therapies, management of the dying process and the determination of death by cardio-circulatory criteria should be separate from and independent of donation and transplant processes[14]. Ongoing controversies relate to whether the DCD donor is dead after 5 min of absent circulation[42]. Three of 39 potential donors achieved successful cardiac resuscitation when mechanical chest compression was applied[41]. This supports the position that in many circumstances with DCD, the declaration of death might not be as a result of "irreversible cessation of respiratory and circulatory activity". Joffe and co-workers[45] conducted a survey of 147 paediatricians affiliated with a university teaching children's hospital. The survey had four paediatric patient scenarios in which a decision was made to donate organs after 5 min of absent circulation. The study's background information described the organ shortage, and the debate about the term "irreversibility" applied to death in DCD. The response rate was 54% (80 of 147) with most respondents stating they were not confident that the donor was dead. However, it must be bourne in mind that where there has been a deliberate decision to withdraw life sustaining treatment, there would be a "do not resuscitate policy" in operation. Patients treated in accordance with many DCD protocols (based on medical guidelines for the determination of death) have death pronounced when their condition might well be reversed by intervention that was intentionally withheld. It is felt that the inclusion of "irreversible" in the legal definition makes that definition excessively demanding and out of step with the ordinary concept of death[46]. The use of ECMO or mechanical chest compression requires careful explanation to donor families of possible scenarios.

Ko *et al*[38] developed an innovative approach to overcoming unhelpful legislation. Both family consent and legal consent were required for DCD organ/tissues in Taiwan. A district attorney had to come to the bedside to confirm asystole in the donor, confirm the family consent, and complete some legal documents before legal consent was issued for organ donation. The resultant warm ischaemia time from such a practice would be unpredictably long precluding DCD organ donation in Taiwan. They developed a method of using ECMO to maintain a donor for a longer time and prevent warm ischaemic injury of the donor abdominal organs leading to better immediate postoperative function than those reported by other methods.

The first successful renal transplantation in the Arab world took place in Jordan in 1972 from a DCD donor. Religion has an important part in personal life and government legislation in the Arab world; thus, organ recovery and transplantation had to wait for religious edicts (*fatwas*) to be passed about the permissibility of organ donation and brain death diagnosis before starting transplantation activities[47].

SERVICE DEVELOPMENT

In the development of DCD programmes, local support is essential. DCD programmes place additional demand on emergency theatres and may sometimes lead to cancellation of elective theatre sessions. Given the number of ethical issues discussed above, it is important to secure the understanding and support of colleagues, hospital managers and the community. The rapid uptake of DCD in Ontario, Canada can be attributed to strong proponents in the critical care and transplantation communities[18].

In developing a paediatric DCD program, an evidence-based, consensus-building approach to setting institutional policy about DCD can address the controversies openly. A multidisciplinary task force commissioned to engage in fact finding and deliberations about clinical and ethical issues in paediatric DCD, examined issues including values and attitudes of staff, families, and the public; number of possible candidates for DCD at the hospital; risks and benefits for child donors and their families; and research needs. Following this, consensus was reached on a set of foundational ethical principles for paediatric DCD. With assistance from the local organ

procurement organisation, the task force developed a protocol for paediatric kidney DCD which most members believed could meet all the requirements of the foundational ethical principles. The hospital implemented the protocol on a limited basis and established a process for considering proposals to expand the eligible donor population and include other organs[48].

The Canadian example highlights the importance of local leadership and advance planning that includes education and engagement of stakeholders, mechanisms to assure safety and quality and public information[49]. A national forum was held in 2005 to discuss and develop recommendations on the principles, procedures and practice related to DCD, including ethical and legal considerations. The forum also recognized the need to formulate and emphasize core values to guide the development of programs and protocols based on the medical, ethical and legal framework established at this meeting. Following this, a strong majority of participants supported proceeding with DCD programs in Canada with very successful results. Structured implementation in the author's centre resulted in a successful controlled DCD programme providing 61 successful renal transplants from 35 donors in 3 years-contributing to approximately 50% of the total number of cadaveric renal transplants during the period[12].

Marks *et al*[8] discussed the implementation and effect of the federally initiated Organ Donation Breakthrough Collaborative and reviewed living and deceased donation data, from 1995 to 2004. Prior to 1995 the annual growth in deceased donation was 2%-4% but after initiation of the collaborative, deceased donation increased 11%. Identification and dissemination of best practices for organ donation have emphasized new strategies for improved consent, including revised approaches to minority participation, timing of requests and team design.

The experience of Geraci *et al*[50] demonstrates the importance of national regulatory laws on organ donation. When compared to European countries and the United States, the Italian DCD program, which started in 2007, took longer to get established. A combination of lack of awareness, ethical issues and a restrictive law requiring for confirmation of death only after a 20-min flat electrocardiogram is obtained after cardiac arrest made DCD a non-starter. However, recent data showing that up to 40-min warm ischaemia time is compatible with preservation of organ viability has encouraged Pavia's group to establish the DCD "Programma Alba"[50].

Potential donor audit

Potential donor audits are necessary in studying the feasibility of DCD programmes. The viability of a DCD program can be determined by conducting a potential donor audit[12,51,52]. Such an audit should take into consideration medical suitability, logistic availability, family refusal to consent, and the likelihood of the donation to proceed to successful organ recovery as well as the risk of technical failures. Daemen *et al*[51] determined from a potential donor audit that 24.0-49.6 kidneys were realistically available annually meaning the potential DCD kidney donors were large and the impact on organ shortage would be considerable. They used this data to persuade support for the establishment of a DCD program in The Netherlands.

OUTCOME OF DCD

Conversion rate

Of 100 patients referred to transplant co-ordinators in one series, 71 were identified as potential DCD donors and of these 29 went on to become actual donors (conversion rate of 40.8%). Fifty-six kidneys were retrieved and 53 successfully transplanted giving a discard rate of 5.7% (3/53)[21]. The series from the author's centre reported a conversion rate of 44% and discard rate of 12.9% (9/70)[12] whereas 77% (67/87) were converted in Ontario Canada[18]. The series from Madrid exhibited a high discard rate (34%) despite the use of cardiopulmonary bypass.

Family refusal continues to be an important block to increasing the donation rate particularly in the United Kingdom. In a study to explore why family members declined organ donation from a deceased relative, protecting the body (keeping the body whole and intact) was the most frequently recurring theme[53]. More concerted efforts at supporting bereaved families in understanding the donation process and in balancing the emotions of giving the "gift of life" with the perceived "sacrifice" of organ donation may increase the number of families assenting to donation.

DGF and primary non function

When compared with kidneys recovered from DBD, DCD kidneys have increased rates of DGF and primary non function (PNF)[15,27,30]-mainly due to increased warm ischaemia time during recovery but also due to cold ischaemia. Based on a porcine model of DCD, Jani *et al*[54] hypothesised that DCD kidneys have increased caspase-1 due to warm ischemia and increased caspase-3 and apoptosis due to cold ischaemia. The DCD kidneys showed a 5.73-fold increase in the incidence of DGF[55]. Primary (donor) warm ischaemia time > 20 min was also found to correlate with increased DGF[20].

Ischaemic injury to the renal allograft prior to implantation is considered as the major cause of PNF and DGF. Van den Eijnden *et al*[56] studied acute kidney injury and renal function of DBD and DCD kidneys using isolated perfused rat kidneys. Using living rats served as controls, Fisher F344 rats were either maintained brain dead for 4 h (DBD) or subjected to cardiac arrest for 45 min (DCD). To eliminate additional effects of cold ischaemia, kidneys were immediately re-perfused and assessed. Renal dysfunction and injury (measured by urine production, anaerobic glucose metabolism resulting in lactate formation, and significant higher luminal release of intracellular and lysosomal enzymes) were most pronounced in DCD kidneys. By comparison DBD kidneys showed increased

Table 2 Comparison of the outcome of renal transplantation from controlled and uncontrolled donation after cardiac death

Series	Type/number	Patient survival (%)	Graft survival (%)	DGF (%)	PNF (%)	Comments
Gagandeep *et al*[7]	UC 216	93 (1-yr) 84 (5-yr)	85 (1-yr) 72 (5-yr)	51	2.8	UNOS data
2006 (1995-2004)	C 1814	95 (1-yr) 83 (5-yr)	88 (1-yr) 67 (5-yr)	42	1.8	Comparable survival between groups
Hoogland *et al*[19]	UC 128	61 (10-yr)	50 (10-yr)	61	22	Pioneering centre for DCD
2011 (1981-2008)	C 208	60 (10-yr)	46 (10-yr)	56	21	
Dominguez-Gil *et al*[61]	UC 649		88.9 (1-yr)	75.7	6.4	Higher DGF for UC
2011 (2000-2008)	C 2343		85.9 (1-yr)	50.2	5	

DCD: Donation after cardiac death; DGF: Delayed graft function; PNF: Primary non function; UC: Uncontrolled DCD; C: Controlled DCD.

urine production and abnormal K+ reabsorption probably as a result of depletion of adenosine triphosphate levels[56].

Reperfusion injury is also important in the causation of DGF and PNF in DCD compared with DBD organs. It is thought that the importance of nitric oxide in the generation of reperfusion injury is pivotal to the outcome. The Leicester group used an *ex vivo* porcine model of kidney transplantation to compare the effects of reperfusion with and without nitric oxide supplementation on initial renal blood flow and function. Nitric oxide supplementation during initial reperfusion of DCD kidneys improves renal blood flow but should be considered with caution due to potential deleterious effects of accumulated nitrogenous free radicals which may impair renal blood flow[57].

Sola *et al*[58] studied the incidence of DGF in a group of 3365 renal transplant recipient patients from various Spanish centres noting that the incidence of DGF remained constant in the 3 years studied (30.4%, 30.8% and 29.2%, respectively). The main factors leading to DGF included donor age, DCD, time of vascular anastomosis (secondary warm ischaemia) and cold ischaemia time (CIT). The presence of DGF was significantly associated with acute rejection, cytomegalovirus infection, worse renal function and arterial hypertension at 3 mo post-transplantation. Pine *et al*[59] assessed the impact of CIT among a DCD cohort of renal transplants performed between 2002 and 2009 in Leeds demonstrating an increased incidence of DGF among the extended CIT group, but the long term outcomes were comparable. A large series of 6057 DCD kidney transplants reported to the Organ Procurement and Transplantation Network database, with complete endpoints for DGF and graft survival revealed that donor age (> 50 years) and CIT (> 30 h) were the strongest predictors of DGF[20]. Fifty-five percent of patients needed at least one session of hemodialysis (DGF) postoperatively[60].

Use of DCD whether controlled or uncontrolled is associated with high PNF and DGF but the long term outcome is satisfactory (Table 2)[7,19,61]. However, some reports showed no significant difference between DCD and DBD. In a retrospective series of 446 deceased donor kidney transplant recipients between 1995 and 2009, 24 (5.4%) patients who received DCD kidney grafts had a longer hospital stay after transplantation, but there was no statistically significant difference in DGF and PNF[62].

Given the high incidence of DGF associated with DCD renal transplantation, the development of a model for predicting DGF after renal transplantation[63] may prove useful. This involves a multivariable logistic regression analysis of 24 337 deceased donor renal transplant recipients (2003-2006), a nomogram, depicting relative contribution of risk factors, and a novel web-based calculator (http://www.transplantcalculator.com/DGF) as an easily accessible tool for predicting DGF. The most significant factors associated with DGF were CIT, donor creatinine, body mass index, DCD and donor age. Another use of the model is in predicting the risk of graft failure. A 25%-50% probability of DGF was associated with a 50% increased risk of graft failure relative to a DGF risk < 25%, whereas a > 50% DGF risk was associated with a 2-fold increased risk of graft failure[63]. Whether this model is it practicable or not is controversial.

Graft survival

Table 3[7,12,55,64-70] shows that in most series the graft survival of DCD and DBD kidney transplants are comparable at various time points post transplantation. Based on a death censored 5-year graft survival [standard criteria donors (SCD): 79.5%; DCD: 77.9%; ECD: 66.7%], not all DCD kidneys should be considered as marginal[67]. In a large series comprising 83 kidney transplants from DCD and 3177 adult DBD transplants performed over the same period in Spain, Sánchez-Fructuoso *et al*[65] showed that both graft function and graft survival of DCD kidney transplants were at least similar to those from DBD transplants. Pine and co-workers[68] found DCD graft function was worse than the DBD equivalent at 1- and 3-year, but noted that the medium-term recipient and graft outcomes were comparable. There were no statistically significant differences in serum creatinine levels or in the graft survival rates between groups at 12 mo[62]. Akoh *et al*[12] in a smaller series of 61 transplants found equivalence between DBD and DCD in kidney graft function at 12 mo. Data from the United Kingdom transplant registry for transplantations performed between 2000 and 2007 show that kidneys from controlled DCD provide good graft survival and function up to 5 years in first-time recipients, and are equivalent to kidneys from brain-death donors[69].

The use of DCD donors in the paediatric population is very limited; however graft survival is comparable to DBD grafts. Abt and co-workers[22] reviewed the United

Table 3 Comparison of the outcome of renal transplantation from donation after cardiac and brain dead donors

Series	Type number	Patient survival (%)	Graft survival (%)	DGF (%)	PNF (%)	AR (%)	Comments
Gagandeep *et al*[7]	DCD 2136	95 (1-yr) 83 (5-yr)	87 (1-yr) 68 (5-yr)	40.8	1.8		UNOS data
2006 (1995-2004)	DBD 75865	95 (1-yr) 84 (5-yr)	88 (1-yr) 66 (5-yr)	24	1.4		No difference in long term survival
Akoh *et al*[12]	DCD 57	93	88	44	0	15.8	Conversion rate of 44%.
2009 (2005-2008)	DBD 58	96	93	14	11.7	27.6	Outcome of DCD equivalent with DBD
Sanchez-Fructuoso *et al*[55]	DCD 95	Equivalent	84 (1-yr) 82.7 (5-yr)	5.73 ×			90 donors were out of hospital arrests. Of these, 54 transplants had primary function
2000 (1989-1998)	DBD 354		87.5 (1-yr) 83.9 (5-yr)	1 ×			
Farney *et al*[64]	DCD 53	94	87	57		19	Incidence of DGF was 57% (60% without *vs* 20% with extracorporeal support, P = 0.036)
2008 (2003-2007)	DBD 316	Similar	Similar	19		10	
Sanchez-Fructuoso *et al*[65]	DCD 83		97 (2-yr) 84 (6-yr)	58.8			Cr at 3 and 12 mo better for DCD. DGF is a risk factor for worse graft outcome in DBD but not DCD
2004 (1990-1998)	DBD 3177		97 (2-yr) 84 (6-yr)	28.9			
Wijnem *et al*[66] 1995	DCD 57	75(5-yr)	54 (5-yr)	60	14		No difference in graft or patient survival at 5 yr
	DBD 114	77 (5-yr)	55 (5-yr)	35	8		
Locke *et al*[67]	DCD 2562		79.9(5-yr)	38.7	1.6		DCD < 50 yr function like SCD. Limiting CIT to < 12 h reduces DGF by 15%
2007 (1993-2005)	DBD 62800		77.9 (5-yr)	19.5	0.7		
Pine *et al*[68]	DCD 103	98 (1-yr) 95 (3-yr)	97 (1-yr) 92 (3-yr)	58	4	12	DCD has poorer early graft function but equivalent long term function
2010 (2002-2007)	DBD 183	97 (1-yr) 96 (3-yr)	96 (1-yr) 95 (3-yr)	22	1	16	
Summers *et al*[69]	DCD 748	86.4 (5-yr)	85.1 (5-yr)	46.7	2.7	16	DGF is not predictive of poorer graft outcome. Large UK registry data
2010 (2000-2008)	DBD 6882	88.0 (5-yr)	83.2 (3-yr)	21.4	2.6	24	
Cooper *et al*[70]	DCD 382	Equivalent	65 (5-yr) 45 (10-yr)	27.5	1.05		No difference in PNF
2004 (1984-2000)	DBD 1089		71 (5-yr) 48 (10-yr)	21.3	0.83		

DCD: Donation after cardiac death; DBD: Donation after brain death; DGF: Delayed graft function; PNF: Primary non function; AR: Acute rejection DCD; Cr: Creatinine.

Network for Organ Sharing database from 1995-2005 to determine the national experience with paediatric recipients of DCD organs. Among 4026 renal transplants performed in children 18 years and younger, 26 (0.6%) received a renal allograft from a DCD donor. The 1- and 5-year graft survival rates were 82.5% and 74.3% for kidneys from DCD donors compared to 89.6% and 64.8% from DBD.

Allocation

Both kidneys retrieved by a transplant team are usually implanted at a single unit, often sequentially. Goldsmith *et al*[71] analysed the impact of a prolonged CIT on the second transplanted kidney and the effects on short-term and long-term outcomes in DCD renal implants from 2002 to 2009. The CIT was significantly longer with the second kidney (P = 0.04) as was DGF. Five-year patient survival was comparable between groups, but 5-year graft survival was higher in the second transplanted group. The results confirm that, provided recipient centres were willing to accept higher initial rates of DGF, it was acceptable to transplant DCD grafts sequentially without jeopardizing long-term graft or recipient outcome.

Although DCD kidneys have a high incidence of DGF and have been considered marginal, neither a tool for stratifying the risk of graft loss nor a specific policy governing their allocation exists. Locke *et al*[67] compared outcomes of 2562 DCD, 62 800 SCD and 12 812 ECD transplants reported between 1993 and 2005, and evaluated factors associated with risk of graft loss and DGF in DCD kidneys. Donor age was the only criterion used in the definition of ECD kidneys that independently predicted graft loss among DCD kidneys. Kidneys from DCD donors < 50 had similar long-term graft survival to those from SCD. While DGF was higher among DCD compared to SCD and ECD, limiting CIT to < 12 h decreased the rate of DGF 15% among DCD < 50 kidneys. Allocation policy for kidneys from cardiac-death donors should reduce cold ischaemic time, avoid large age mismatches between donors and recipients, and restrict use of kidneys poorly matched for human leucocyte antigen in young recipients[69].

Effect on DBD

Dominguez-Gil *et al*[61] conducted a survey of 27 European countries to determine the level of DCD activity. Only 10 confirmed any DCD activity, the highest rates being described in Belgium, the Netherlands and the United Kingdom (mainly controlled); and France and Spain (mainly uncontrolled). During 2000-2009, as DCD

increased, DBD decreased by 20% in the three countries with a predominant controlled DCD activity, while DBD had increased in the majority of European countries. However, recent United Kingdom statistics showed that the number of DBD donors increased by 5% between 2007 and 2010, reversing the 13% decrease between 2001 and 2007[16].

Despite these concerns, the increasing number of DCD donors does not appear to be directly responsible for decreased numbers of DBD donors[6]. The risk that efforts in DCD programs endanger regular DBD programs because of limited organisational resources is not supported by published data. Koffman[72] showed that DCD consistently increased the number of available kidneys without any effect on DBD donations. Ledinh *et al*[26] evaluated the organ procurement and transplantation activity from DCD in their unit (Belgium) over an 8-year period to determine its effect on transplantation programs, or DBD activity. They concluded that the establishment of a DCD program enlarged the donor pool and did not compromise the development of DBD program.

Cost implications

Pascual and co-workers[1] concluded that patients younger than 40 years or scheduled for kidney retransplantation should not receive an ECD kidney. ECD kidneys confer a survival benefit for ERF patients compared to remaining on dialysis or on the waiting list[2]. However, the financial impact and the long-term benefits of these kidneys have been questioned. Saidi *et al*[73] analysed the cost implications of 271 deceased donor kidney transplants in adult recipients classified into four categories-163 (60.1%) SCDs, 44 (16.2%) ECDs, 53 (19.6%) DCDs and 11 (4.1%) ECD-DCDs. The hospital charge was higher for ECD, ECD-DCD and DCD kidneys compared to SCDs, primarily due to the longer length of stay and increased requirement for dialysis (70 030 dollars, 72 438 dollars, 72 789 dollars and 47 462 dollars, respectively, $P < 0.001$). They observed that after a mean follow-up of 50 mo, graft survival was significantly less in the ECD group compared to other groups.

Factors affecting outcome of DCD

Several factors influence the outcome of DCD and associated renal transplantation.

Multiorgan retrieval

Questions have been asked as to whether multiorgan retrieval diminish the quality of DCD kidneys due to increased length of time of explantation of the kidney from the donor and the associated risks of re-warming. To address this, Goldsmith *et al*[74] performed a retrospective study of 201 DCD donors from 2002 to 2009 at a single unit to compare the immediate and short-term outcomes between kidney-only *vs* multiorgan retrievals. Their results showed that immediate graft function, rates of acute rejection and graft/recipient survival were comparable. This might however, be due to the highly selective use of uncompromised donors for multiorgan DCD donation[74].

Age

Allografts from older donors are associated with inferior function, suboptimal graft survival[75] and a higher discard rate[12]. Pine and co-workers[76] examined the impact of age matching on the outcomes among a cohort of DCD renal transplant recipients. They divided the cohort into two groups based upon the donor/recipient age ratio: age-matched (between 25th and 75th percentiles, n = 99) and non-age-matched (< 25th percentile and > 75th centile, n = 100). They failed to demonstrate any significant difference between the two groups in terms of early complications or long-term outcome or function. Age matching did not appear to affect graft outcomes, particularly for young donors, but may have a role in older donors[76].

Akoh and Rana[77] demonstrated that kidneys from donors over 60 years (a quarter of whom were hypertensive) are more likely to exhibit significant atherosclerosis and consequently a higher degree of graft dysfunction. They also showed that considering biopsy proven acute rejection, DGF and estimated glomerular filtration rate at 12 mo, donor and recipient age matching would produce best results in young to young; good in old to old; less good in young to old; and fair results in old donors to young recipients. The European senior program[78] showed that patient survival was better when younger donor organs were implanted into older recipients. Hariharan *et al*[79] reported that older kidneys have a better graft survival when transplanted into older recipients. Older to younger transplants were associated with the poorest graft survival outcomes in another study[80]. In using DCD kidneys from older donors there is a need to balance the likelihood of senescence, loss of nephron mass, reduced graft survival, increased risk of interstitial fibrosis, tubular atrophy, poor immediate function, progressive graft dysfunction and the higher impact of acute rejection on graft function with the benefits of the recipient being removed from dialysis. Given the worsening trend in organ supply, the ever increasing elderly population on transplant waiting lists with a shorter life expectancy, the higher death rate in the elderly while waiting for a transplant, using DCD kidneys from over 60 years old donors for the elderly would seem a pragmatic step[77].

Out of hospital arrests

The difficulty posed by potential donors arresting out of hospital is determining the severity of ischaemia. When considering the use of donors who suffer out of hospital arrests/death, the potential organ donors should be less than 50 years old, with less than 15 min of asystole without cardiac massage, with a known aetiology of death, and without general contraindications for donating[31]. Alvarez *et al*[31] used a cardiopulmonary bypass to preserve the organs while the legal aspects of donation were sorted out. Of 111 potential cadaver DCD donors; 53

donated. The average time before arrival to the hospital was 68 ± 2.64 min, and the average interval between cardiac arrest and the beginning of cardiopulmonary bypass was 111.33 ± 7.09 min. One hundred and five kidneys were recovered and 72 kidneys were transplanted, with a probability of survival of 83% at 36 mo.

Agonal phase

DCD is an increasingly important source of kidneys for transplantation, but because of concerns of ischaemic injury during the agonal phase, many centres abandon donation if cardiorespiratory arrest has not occurred within 1 h of controlled withdrawal of life-supporting treatment. The reasons for deciding on a short agonal period in most programmes include: prolongation of this period can expose the kidneys to irreversible ischaemic injury; the resource implications of closing a theatre to elective or emergency activity for more than 2 h during working hours in a busy hospital; and logistical difficulties associated with transplant retrieval teams waiting on stand-by for prolonged periods[12]. As viability requirements for other organs such as liver, heart and lung are more stringent, shorter agonal periods are allowed. The differing requirements may pose logistical problems for the process of organ recovery depending on how retrieval teams are organised.

In a retrospective chart review of all cases of DCD from 1995 to 2005, Naim *et al*[81] showed that the time of extubation to time of death ranged from four minutes to 30 min, with a mean of 14.5 min. Death was declared based on cardiac asystole confirmed by auscultation and transthoracic impedance, with organ procurement initiated five minutes later. Though utilising a cut off period of 2 h, the median agonal period of 35 DCD donors was 15 min[12]. Goldsmith and co-workers[82] in Leeds analysed all 201 DCD donations (2002 to 2009) and compared short *vs* long durations to asystole around the median time (20 min) and concluded that a long agonal phase may have an immediate effect on graft survival, but had no overall detrimental effect on longer-term outcomes. However, by extending the stand-by time beyond 2 h it may be possible to increase the number of actual donations. Sohrabi *et al*[83] reported that even after a 5-h agonal period, kidneys retrieved might still be transplantable provided they passed the viability assessment using machine perfusion. They successfully transplanted 16 kidneys retrieved from donors with an agonal period in excess of 2 h, but the discard rate was high-13% if less than 2 h; 33% if more than 2 h and 45% if more than 5 h.

Reid *et al*[84] reported the impact on donor numbers and transplant function using a minimum "cut-off" time of 4 h. The agonal phase of 173 potential DCD donors was characterised according to the presence or absence of: acidaemia; lactic acidosis; prolonged (> 30 min) hypotension, hypoxia or oliguria, and the impact of these characteristics on 3- and 12-mo transplant outcome evaluated by multivariable regression analysis. Of the 117 referrals who became donors, 27 (23.1%) arrested more than 1 h after withdrawal of life supporting treatment. Longer agonal phase times were associated with greater donor instability, but neither agonal-phase instability nor its duration influenced renal transplant outcome. In contrast, 3- and 12-mo estimated glomerular filtration rate in the 190 transplanted kidneys was influenced independently by donor age, and 3-mo estimated glomerular filtration rate by cold ischemic time. DCD kidney numbers were increased by 30%, without compromising transplant outcome, by lengthening the minimum waiting time after withdrawal of life supporting therapy from one to 4 h[84]. In another series of 17 potential controlled DCD donors, the mean time from treatment withdrawal to cardiac arrest was 2.3 h. Thirteen of 17 patients died within 1 h, and all but one died within 6 h[4]. The drive for a shorter agonal period has come mainly from liver transplantation. However, Ho *et al*[85] demonstrated that postextubation parameters, including duration and severity of hemodynamic instability or hypoxia might be a better predictor of subsequent graft function than just the agonal period.

CIT

Cold ischaemic injury is associated with reduced renal graft function and survival[67]. CIT is one of the controllable factors affecting graft function. In a report of kidney preservation involving 91 674 transplants in 195 centres spread over three continents, Opelz and Dohler[86] showed that graft survival in deceased donor transplants remained stable for up to 18 h of cold ischaemia and worsened further with time, particularly after 36 h. However, there is little evidence on the benefits of reducing cold ischaemic injury within a 24 h period in DCD kidney transplantation. Hosgood *et al*[87] demonstrated the progressive effects of cold ischaemic injury in DCD porcine kidneys over a 24 h hypothermic storage period. This highlights the need to minimise the cold storage period in order to improve graft function in DCD kidney transplantation.

Kidney preservation and machine perfusion

The procedure of flushing and keeping the kidney cool during retrieval and storage either on ice or in a pulsatile perfusion machine while awaiting implantation reduces cellular metabolism to the barest minimum and stabilises cell membrane to keep the internal milieu in the absence of the Na^+/K^+ pump. Machine perfusion has been shown to be beneficial for ECD kidneys[88], but the results from a United Kingdom based trial comparing machine perfusion with cold storage were equivocal[89]. The effect of machine perfusion on DCD kidneys may decrease DGF by up to 38% but has no effect on long-term function[6,90]. The use of pulsatile machine perfusion decreased the incidence of DGF only when donor age was > 60 years and improved long-term graft survival when donor age was > 50 years. The data suggest that the use of pulsatile machine perfusion in DCD kidneys < 50 years old provides little clinical benefit and may increase CIT[20]. Machine perfusion resulted in a 3.8% reduction in the incidence of DGF in a series of 78 174

DCD transplants[67]. Machine preservation allows viability testing, with the Dutch group using glutathione S-transferase, a measure of tubular damage, as guide whether to transplant or not[22]. Asher *et al*[91] reported experience with their own design machine perfusion device, and recommended that because results obtained from different perfusion systems are not comparable, local criteria of kidney viability should be established in each centre.

Intraarterial cooling of DCD kidneys requires a cheap, low-viscosity solution. Histidine-tryptophan-ketoglutarate (HTK) contains a high hydrogen ion buffer level that theoretically should reduce the observable acidosis associated with ongoing anaerobic metabolism. Wilson and co-workers[92] performed a retrospective comparison of the effect of two preservation solutions (HTK or Marshall's hypertonic citrate) on the viability of DCD kidneys on the Organ Recovery Systems LifePort machine perfusion circuit. Forty-two DCD kidneys (19 HTK and 23 Marshall's hypertonic citrate) were machine perfused between 2004 and 2005. There was evidence of greater buffering capacity in HTK, since the lactate:hydrogen ion ratios were consistently lower during the first 2 perfusion hours (1 h $P = 0.03$, 2 h $P = 0.02$). A linear regression analysis confirmed that this was related to the intra-arterial cooling solution ($P < 0.001$). Eighty three percent (10/12) of the uncontrolled donor kidneys preserved with HTK passed the viability test and were transplanted compared with only 20% (1/5) of the Marshall's hypertonic citrate-treated comparators. The advantages of improved pH buffering with HTK appear to have clinical relevance[92].

Kidneys from marginal and DCD donors are particularly susceptible to injury during hypothermic preservation and may benefit from alternative methods of preservation. Normothermic preservation can be adapted to improve the quality of kidneys for transplantation by a variety of techniques[37]. Jani *et al*[54] demonstrated in a porcine model of that in DCD kidneys, warm ischaemia preferentially activates caspase-1, whereas cold ischaemia activates caspase-3 and causes apoptosis. Perfusion storage may protect DCD kidneys through activation of antiapoptotic pathways involving B-cell lymphoma-extra large and hypoxia-inducible transcription factor-1α.

Kidney preservation using an extracellular-type cold storage solution from Institut Georges Lopez, a preservation solution with an extracellular sodium/potassium ratio and polyethylene glycol as a colloid, or the University of Wisconsin solution were comparable in preserving vasomotor functions in an isolated perfused kidney model. Vasomotor functions are negatively influenced by the combination of warm and cold ischemia. Maathuis *et al*[93] evaluated the influence of warm and cold ischemia in a rat Lewis-Lewis transplant model and showed that static cold storage preservation of ischemically damaged rat kidneys in either Institut Georges Lopez or University of Wisconsin-cold storage solution rendered equal results after transplantation.

RECOMMENDATIONS

The benefits of DCD kidney transplantation outweigh the increased risks of early graft loss. Expansion of the supply of DCD kidneys is likely to improve the treatment of wait-listed dialysis patients.

Prolonged, severe hypotension in the post-extubation period appears to be a better predictor of subsequent organ function than time from extubation to asystole. Time between profound instability and cold perfusion is a better predictor of outcome than time from extubation to asystole. Consideration needs to be given to extending the agonal period beyond 1 h. Such an action might increase the conversion rate.

There is need for comprehensive collection and reporting of outcome data for all-aged recipients of paediatric donation-after-cardiac-death organs to help facilitate the generation of evidence-based best-practice guidelines for paediatric DCD.

Compared to controlled DCD, uncontrolled DCD is associated with more work, lower conversion rate and a higher discard rate. However, the outcome of kidney transplantation from uncontrolled and controlled donors after cardiac death are equivalent. Expansion of the donor pool with uncontrolled donors to reduce the still growing waiting list for renal transplantation should be pursued.

CIT is a controllable factor that significantly influences the outcome of allografts, limiting CIT to < 12 h markedly reduces DGF.

Current data suggest that the results may be further improved by better patient selection and retrieval team organisation. Donor age correlates with outcome and organ allocation should reflect it. DCD < 50 kidneys function like SCD kidneys and should not be viewed as marginal or ECD.

For logistical reasons, new DCD programs should begin with Maastricht category Ⅲ donors within the adult population.

Most reports cover DCD from the intensive therapy setting. Extending DCD to the emergency department is likely to increase the yield even more.

CONCLUSION

DCD kidneys provide a valuable and increasingly important source of kidneys for transplantation. Every effort must be made to maximise the supply of kidneys from DCD including: (1) Implementing organ recovery from emergency department setting or at least starting the process there; (2) Improving family consent/assent rates to about 85%; (3) Utilising technological developments to optimise organs either prior to recovery from donors or during storage; (4) Improving organ allocation to ensure best utility; and (5) Improved viability testing to reduce PNF.

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