Editorial Review

Donation after cardiac death: evaluation of revisiting an important donor source

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Introduction

To date, with a widening gap between organ supply and demand, many centres are revisiting donation after cardiac death (DCD) in order to enlarge the deceased donor pool. With increasing numbers of grafts that have suffered from prolonged warm ischaemia (WI), maintenance of organ viability has once again become an important factor to preserve current high standards for functional outcome and long-term survival after transplantation. The amount of injury differs for the various DCD donor categories (Table 1) [1]. Category III donors are most widely used, since the duration of WI is known and usually short. In addition, organ recovery can be planned in advance. Nevertheless, the time interval between withdrawal of treatment and cardiac arrest in the potential donor may account for additional WI injury due to low oxygenation and organ hypoperfusion. This period is usually not included in calculations of total WI time, but it is likely to be relevant to appreciate the real ischaemic insult that a particular organ has sustained. The length of this so-called agonal phase varies widely between individual donors, and many different upper limits for acceptable donation are in use, depending on which organs are to be procured. While, for example, in The Netherlands, a maximum period of 2 h is considered acceptable for kidney donation [2], US guidelines recommend no more than 60 min [3]. Since ischaemic injury accumulates as a continuum, influenced by a multitude of factors, setting an evidence-based cut-off value for the maximum length of the agonal phase remains difficult. Suntharalingam et al. have recently conducted a comprehensive multi-centre study to identify clinical parameters that independently predict the timing of death following treatment withdrawal. Their data show that younger age, higher FiO₂, and the mode of ventilation (no pressure support versus pressure support) are independently associated with a shorter agonal phase before cardiocirculatory death [4]. These are important findings, as they may allow better identification of patients suitable for DCD and facilitate timing of organ retrieval. Various guidelines are in use for the maximum acceptable duration of true WI (commonly defined as the interval between a mean arterial pressure below 60 mmHg and initiation of organ perfusion). Most up-to-date evidence shows that, for the liver, a WI time above 20–30 min and, for the kidney, a WI time longer than 45–60 min is associated with increased complications post-transplant [5]. In some countries, donation after withdrawal of treatment is illegal. As a result, transplant programmes have to rely solely on uncontrolled DCD in which the average WI time is considerably longer. However, uncontrolled DCD may have one advantage over category III donors: Serious brain injury is associated with a significant pro-inflammatory and pro-coagulatory response in the donor, which has a negative effect on organ quality and increases the risk of immunological complications post-transplant [6]. Most controlled DCD donors have sustained irreversible cerebral injury. As a result, their organs may suffer more from negative immunological and coagulatory effects than grafts derived from uncontrolled DCD donors whose primary medical condition is usually not neurologic. In renal transplantation, the detrimental effect of delayed graft function (DGF) on graft survival (GS) appears to be more pronounced in kidneys derived from brain-injured donors versus organs coming from uncontrolled DCD donors [7]. These data suggest that WI plus profound cerebral injury could account for a different, more detrimental form of DGF than observed in uncontrolled DCD kidneys that have sustained only WI.

Mechanism of warm ischaemic injury

Tissue ischaemia leads to a cascade of cellular injury and repair responses. Lowering organ temperature to 0–4°C will slow down such responses, although accumulation of injury will continue at a rate of ~10% from normal [8]. For this reason, hypothermic organ preservation cannot be extended beyond certain time constraints, since cold ischaemia will keep the graft in an acceptable condition for only a limited period.
The onset of ischaemia immediately impairs oxidative metabolism. This leads to the depletion of adenosine triphosphate (ATP), an increase in anaerobic glycolysis and the inhibition of Na⁺/K⁺ ATPase. Membrane transport mechanisms will slow down, causing intracellular accumulation of water and ions which results in cell oedema and disruption of the cytoskeleton. Impaired oxidative metabolism triggers the formation of reactive oxygen species (ROS) that have a direct detrimental effect on the cell. ROS will also facilitate the production of other free radicals such as nitric oxide (NO), further disrupting the cytoskeleton. Anaerobic glycolysis lowers the intracellular pH due to the synthesis of lactic acid, which negatively influences cellular homeostasis. In addition, hypoxia will inhibit cytoprotective mechanisms, such as upregulation of heme oxygenase-1 (HO-1) and heat shock protein-70. Impaired cytoprotection will render the graft more susceptible to further ischaemic injury [9]. At reperfusion, more injury ensues when damaged endothelial cells express intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, which attract host leukocytes. These leukocytes release more ROS and inflammatory mediators, aggravating cellular injury. Ischaemia–reperfusion injury also stimulates antigen-independent, innate immunity via complement activation and Toll-like receptor (TLR)-mediated pathways. Innate immune activation in turn triggers the adaptive immune response, in part through TLR-induced surface expression of CD80 and CD86 on dendritic cells. This will cause early T cell-regulated inflammatory damage to the graft. Adaptive immune activation will also increase the risk of acute rejection. Both innate and adaptive immune responses eventually contribute to the development of chronic allograft pathology [10]. Recent evidence suggests that ischaemia–reperfusion injury is a highly coordinated and specific process mediated by components of both innate and adaptive arms of immunity [11].

After reperfusion, energy levels in the graft are rapidly restored. This fuels cytoprotective processes, such as the formation of HO-1 and vascular endothelial growth factor expression, which protect cells from the host immune attack [12]. A sequence of events follows, initiating the repair of endothelial, epithelial and parenchymal cells. Although mechanisms and rates differ between various cell types, cell differentiation, migration and proliferation directed by growth factors and molecular signalling pathways play an important role in the repair response [13].

**Novel approaches**

DCD grafts are exposed to significantly more ischaemia–reperfusion injury than organs derived from donation after brain death (DBD). In general, the most obvious and economic approach to minimize injury would be to keep WI time as short as possible and to limit cold ischaemic time. Reducing ischaemic times by just a few percent is likely to have a much larger impact on outcome than the application of novel technical or pharmacological interventions [14]. Normothermic recirculation and normothermic machine perfusion are sophisticated novel organ preservation techniques, which aim at providing oxygen and nutrients to the graft during organ preservation to better maintain viability and perhaps fuel cellular repair mechanisms [15,16]. In the Hospital Clinic in Barcelona, Spain, a protocol for normothermic recirculation of uncontrolled DCD donors is in use: Before cold storage (CS) is initiated, the donor is rewarmed and re-circulated for a brief period with normothermic extracorporeal membrane oxygenation via the femoral vessels. The group reports resuscitation of otherwise non-transplantable liver grafts [17]. Donor pre-treatment with anti-inflammatory, anti-coagulatory and other agents as well as addition of thrombolytic agents to the systemic flush solution could mitigate the initial ischaemic insult [18]. However, treatment of a donor-to-be before the legal determination of death is associated with serious ethical concerns. For the near future, finding agents that are beneficial for both the critically ill intensive care unit (ICU) patient and his or her potential donor organs may be the most pragmatic approach.

### Controversial issues

Apart from ethical concerns about donor pre-treatment, one of the largest other controversies in DCD to date surrounds the issue of donor type substitution. A most striking example is the recent situation in The Netherlands (Figure 1): In a short time period, controlled DCD has become very popular, with exceptional rates approaching 50% of all deceased donor procedures. Surprisingly, this did not result in enlargement of the donor pool. The absolute number of kidney donations and transplants remained approximately the same, whereas the number of procured thoracic organs decreased (source: Eurotransplant Annual Report 2008). It is very difficult and politically sensitive to pinpoint a single cause for this alarming phenomenon, but it seems plausible that some form of substitution could be involved [19]. A possible mechanism might be that donor families are given a choice between a controlled DCD and a DBD procedure. For the family, the timely withdrawal of treatment followed by cardiocirculatory arrest may be perceived as a more emotionally acceptable way to cope with the loss of a beloved one, even if the patient meets legal brain death criteria or progression to brain stem death is imminent. In addition, current high pressure on ICU beds may add to an eagerness to initiate donation procedures as soon as possible, rather than to wait up to a few days for brain stem death. Also, a lower threshold to perform early decompressive neurosurgical interventions in patients with cerebral injury could have resulted in an absolute decrease in the number of ICU patients who eventually progressed to brain stem death. All these factors together could lead to relatively more DCD procedures, and hence, fewer available hearts, livers and pancreata.

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**Table 1. Maastricht classification of donors after cardiac death**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Organ recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Dead on arrival</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>II</td>
<td>Unsuccessful resuscitation</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>III</td>
<td>Awaiting cardiac arrest</td>
<td>Controlled</td>
</tr>
<tr>
<td>IV</td>
<td>Cardiac arrest while brain dead</td>
<td>Uncontrolled</td>
</tr>
</tbody>
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Another persistent concern in DCD is the question when exactly a patient may be declared dead from a cardiocirculatory point of view. In order to maintain societal support for DCD, it is essential to have transparent policies for the indication to initiate withdrawal of treatment and a well-defined no-touch period afterwards. Common consensus requires that the physicians who are involved in the cessation of life support and the declaration of death are always strictly separated from the organ procurement team. In addition, the most up-to-date evidence suggests that the declaration of cardiocirculatory death should be no earlier than 2 min after asystole, since auto-resuscitation has never been reported after this period [20]. Most protocols to date dictate a no-touch period of 3–5 min, although some centres use a 10-min interval [5,21].

The use of extracorporeal membrane oxygenator support after cardiac arrest, as practiced by some centres, may raise paradoxical ethical concerns. If the heart is reperfused with oxygenated blood, it will likely resume a normal rhythm, thus potentially affecting the ‘state of death’ that had been declared a few minutes earlier based on the cardiocirculatory criteria. Hence, physicians often choose to inflate a thoracic aortic balloon or administer lidocaine to prevent the heart from resuming activity. Nevertheless, it may be argued that irreversible brain injury has already taken place when cardiac reanimation occurs, provided that a reasonable 2–5 min no-touch period was observed after cardiac arrest [22].

**Clinical evidence**

**The kidney**

For kidney recipients, dialysis is always available as a backup in the case of insufficient immediate graft function. Therefore, kidneys were the first organs to be transplanted from DCD donors. Renal grafts comprise by far the largest group of DCD organs actually used for transplantation (Figure 2a). To date, DCD kidneys of all Maastricht categories are used worldwide, but categories III and II are predominant. Many centres use rapid *in situ* cooling techniques for category II kidney-only donor management. After unsuccessful resuscitation, both kidneys are perfused with cold preservation solution following insertion of a double-balloon triple-lumen (DBTL) catheter via the femoral artery. Various protocols are in use for category III donor management. Although DBTL catheter *in situ* cooling can also be utilized when extra-renal organs are to be procured, rapid laparotomy with aortic cannulation and systemic cold perfusion is nowadays the most widely used technique for the DCD multi-organ donation scenario. Some centres do use DBTL catheter cooling for category
DCD kidney transplants

- UNOS
- Eurotransplant

DCD versus total deceased donor kidneys transplanted

Year of transplantation:
- 1996: 9535, 122
- 1997: 118, 0
- 1998: 68, 17
- 1999: 44, 23
- 2000: 84, 39
- 2001: 245, 69
- 2002: 291, 79
- 2003: 110, 22
- 2004: 130, 13
- 2005: 392, 11
- 2006: 754, 22
- 2007: 207, 26
- 2008: 1256, 47

DCD liver transplants

- UNOS
- Eurotransplant

DCD versus total deceased donor livers transplanted

Year of transplantation:
- 1996: 12, 0
- 1997: 17, 1
- 1998: 24, 0
- 1999: 23, 1
- 2000: 39, 2
- 2001: 69, 6
- 2002: 79, 22
- 2003: 111, 13
- 2004: 185, 26
- 2005: 271, 32
- 2006: 290, 36
- 2007: 287, 47
- 2008: 276, 32
III kidney-only donors, however, evidence suggests that rapid laparotomy with aortic cannulation leads to comparable results and fewer technical complications [23]. Category I donors are used to some extent by a few centres, e.g. by the Madrid group in Spain. This centre employs strict emergency service protocols to minimize WI time and has a high organ discard rate (57%) due to stringent donor selection criteria. In a country where category III DCD is illegal, this pragmatic approach provides an alternative source of donors to bridge the gap between organ supply and demand. The group reports 68% DGF, 6% primary non-function (PNF) and a similar 5-year GS as achieved with DBD kidneys (~75%) [24]. However, when interpreting these numbers, it should be kept in mind that kidneys have been subjected to an exceptionally strict selection process with a considerable discard rate: The group uses only those donors with a known time between cardiac arrest and initiation of adequate cardiopulmonary resuscitation under 15 min, no violence as cause of death, no thoracic or abdominal bleeding injuries, no more than 120 min between start of resuscitation and initiation of organ preservation and the availability of a next of kin within 4 h. DCD category IV donors including sudden cardiac death after the declaration of brain death are a very rare group for which hardly any isolated data are available.

The question of how to best preserve DCD kidneys has remained unresolved until recently. Many centres embarked on static CS, whereas others strongly advocate hypothermic machine perfusion (MP), especially for category II grafts. Retrospective studies suggest a short-term and long-term outcome benefit of MP versus CS [25]. A prospective study conducted in the United Kingdom on MP versus CS for DCD kidneys was terminated early as the investigators expected that it would not show any difference in outcome after transplantation [26]. However, the recent large European prospective randomized controlled trial comparing MP with CS preservation showed that MP indeed reduced the risk of DGF with an adjusted odds ratio (OR) of 0.57 for all common types of deceased donor kidneys, regardless of whether the graft came from a DCD, DBD or expanded criteria donor. In addition, MP reduced the risk of graft failure in the first year post-transplant with an adjusted hazard ratio of 0.52 versus CS [27]. Hence, with this level of evidence and since the incidence of DGF is particularly high in DCD kidneys, MP appears to be the best choice to preserve a DCD kidney graft. Two very recent analyses derived from the same prospective study showed that MP characteristics such as perfusate flow, intravascular resistance and the biomarkers glutathione S-transferase and heart-type fatty acid-binding protein do have some predictive potential for DGF. However, none had any relevant prognostic value for serious complications such as PNF and graft failure. Therefore, MP dynamics and perfusate biomarker measurements may help to fine-tune postop-
Kokkinos et al. conducted a comprehensive meta-analysis of currently available clinical data on DCD kidney transplant outcomes. Their study showed that, for all categories pooled, the incidence of DGF has an OR of 3.64 when compared to DBD kidneys. PNF also occurs more frequently (OR 2.43). DCD kidney recipients tend to stay more days in-hospital after transplantation (OR 4.56). GS of DCD kidneys is generally somewhat inferior to DBD grafts, with ORs of 0.70 at 3 months and 0.89 at 10 years post-transplant, although this last OR tested non-significant. Acute rejection rates and patient survival post-transplant do not differ from DBD kidney recipients [30]. Snoeijis et al. showed that the use of elderly DCD donors was associated with unacceptable clinical outcomes. They concluded that transplantation of 65+ DCD renal grafts cannot be justified without further refinement in their selection, for example, by histological assessment of pre-transplant biopsies [31]. In summary, DCD kidneys show an inferior short-term function, but seem to have only a mild GS disadvantage in the long run, as long as donor age is under 65. Although these data will convince many transplant professionals that the introduction of a DCD programme can be a safe addition to the deceased donor pool, some consideration should be observed when interpreting long-term results. Today, follow-up data of more than 5 years post-transplant are only available for a relatively small number of DCD kidney recipients. These were the patients who received a kidney transplant when DCD was cautiously re-introduced by some centres. Therefore, their grafts may have gone through a much stricter selection process than the average DCD kidney undergoes nowadays. This could bias the long-term DCD outcome we are currently looking at, towards a better GS than DCD kidneys transplanted today will show after the same time interval. Ongoing monitoring of long-term outcome, therefore, remains important to keep results in line with current clinical standards.

The liver

In contrast to the kidney, DCD liver transplantation is introduced into programmes around the world with much more hesitation. Between 1996 and 2008, 1683 DCD livers were transplanted in the USA and 186 in Eurotransplant (Figure 2b). Due to the lack of life-sustaining replacement therapy, most extra-renal organs undergo a more stringent selection process in order to prevent PNF, which implies re-transplantation or death within 7 days post-transplant. Many studies have shown that the liver, especially its sinusoidal cells and the biliary system, is less tolerant to ischaemic injury than a renal graft [32]. The burden of increased ischaemic type biliary complications in DCD livers may account for additional post-transplant morbidity that is not necessarily outlined by basic survival analyses.

To date, all livers are preserved by static CS. Although evidence coming from kidney preservation studies may be extrapolated to the liver as well, MP preservation of liver grafts has not reached the clinic yet. Clinical MP for livers is often considered less feasible due to the more complex system needed to perfuse both the hepatic artery and portal vein, rendering a potential device less transportable [33]. However, if these technical concerns are overcome, MP could be a promising method to enlarge the potential DCD liver pool. In addition, MP may offer the option of in vitro viability testing as a tool to aid decisions on organ quality. The question remains whether MP will help reduce ischaemic type biliary lesions.

In a retrospective analysis by Freeman et al., overall post-transplant outcome of DCD liver transplants in the USA between 2000 and 2006 (n = 1007 in their study) was inferior compared to DBD livers: 4-year adjusted GS was almost 20% lower [34]. Both Mateo et al. and Lee et al. have published detailed analyses of DCD liver transplant outcome. Much effort was directed at identifying selection criteria for the acceptance of a DCD liver. From the evidence currently available, it is clear that non-steatotic liver grafts from relatively young DCD donors (<45 years) with short WI time (≤15 min) kept on CS preservation for ≤10 h are safe candidates for transplantation. Interestingly, recipient characteristics had no relevant predictive value for GS, as long as the aforementioned criteria were met. GS for this group (84.9% at 1 year; 69.4% at 5 years) was comparable to that of DBD livers [35,36]. To summarize, data currently available suggest that, with careful selection of suitable donors, DCD liver transplantation is within reach of everyday transplantation practice and could reduce the number of patients on the waiting list.

The lung

Clinical DCD lung transplantation is a slowly emerging field (Figure 2c). Approximately one decade ago, a few centres started small DCD lung transplant programmes. Data derived from animal studies had pointed out that lungs do not rely on arterial perfusion to deliver oxygen for cellular respiration. Since parenchymal cell oxygenation occurs through air spaces, merely ventilating non-perfused lungs will provide sufficient oxygen to prevent serious ischaemic tissue injury [37]. Therefore, pulmonary grafts derived from DCD donors will suffer less from WI compared to other organs, especially when procurement can be planned in advance. In category III DCD, the donor can be rapidly reintubated and ventilated after the legal 5-min no-touch period following cardiac arrest. In an uncontrolled donation setting, lung viability may also be preserved as long as adequate artificial ventilation is started immediately after cardiac arrest.

With only scarce evidence available, DCD lung preservation seems to rely on rapid organ cooling, as soon as ventilation is discontinued. For uncontrolled donors, Steen et al. have advocated intra-pleural cooling within the intact body, followed by warm ex vivo functional evaluation [38]. However, in a controlled DCD donor, systemic cold flush after rapid aortic cannulation may be sufficient to preserve organ viability.

Although various groups have reported cases or small numbers of successful DCD lung transplants at conferences, only a handful of such series has been published so far. One of the largest studies appeared in 2007, presenting the post-transplant outcome of 17 uncontrolled (categories I and II)
DCD pulmonary grafts. The authors report that, even with an organ discard of around 87%, the rate of primary graft dysfunction in the recipient (53%) was much higher than in DBD lungs (10–20%). Three-year patient survival was 58% [39]. Early results of another series in Australia were recently reported by Snell et al. Out of 11 donation attempts, eight Maastricht category III lungs were retrieved and successfully transplanted. At the moment of their report, all eight recipients survived for a mean of 311 days with an acceptable early clinical course [40]. In an Organ Procurement and Transplantation Network (OPTN) database analysis, Mason et al. compared the outcomes of 36 DCD lung transplants in the USA to average outcomes of DBD lungs. They concluded that DCD resulted in survival up to 2 years which was at least equivalent to that after DBD [41]. In the University Medical Center Groningen, The Netherlands, a significant DCD lung transplant programme exists since 2005. So far, 24 pulmonary grafts retrieved from DCD category III donors were successfully transplanted, with an early postoperative course comparable to DBD lungs. (M.E. Erasmus, personal communication, 1 May 2009). In conclusion, DCD has had a minimal impact on lung transplantation so far. However, interest in this new practice is increasing and larger studies presenting outcomes after transplantation are awaited with anticipation.

Other organs

The University of Wisconsin group from Madison, WI has published outcomes of a large consecutive series of DCD simultaneous pancreas and kidney transplants (n = 37). The authors report that 5-year patient, pancreas, and kidney survival was similar to that of DBD transplants [42]. DCD pancreas-only transplants are hardly ever reported, with some rare exceptions coming from Japan. Currently, most DCD pancreatic grafts are used to obtain islets for transplantation [43].

Transplantation of cardiac grafts derived from DCD donors has remained in a predominantly pre-clinical phase so far. Myocardial vulnerability to ischaemic injury would make donor management in the DCD setting challenging [37]. Although the potential donor pool expansion could be interesting [44], no centres have transplanted DCD hearts on a relevant scale. Clinical cases using a normothermic resuscitation and preservation device have been reported at meetings, but no reliable outcome data have ever been published [16].

For DCD intestinal transplantation, only scarce data are available. The number of suitable DBD grafts outnumbers the relatively small group of serious candidates for an intestinal allograft. Moreover, small bowel tissue is highly susceptible to WI injury. Therefore, no rationale seems to exist for transplanting intestines recovered from DCD donors [45].

Conclusion

DCD is rapidly earning its place in everyday clinical transplantation practice. Prolonged WI leads to organ injury at various levels, which should be minimized to preserve organ viability. This poses considerable challenges to DCD donor management. In contrast to the widespread scepticism only a few years ago, many centres today have adapted their protocols to incorporate the option of DCD. For the kidney, large series of long-term follow-up are now becoming available, with encouraging results. Transplantation of extra-renal organs is gaining acceptance, with livers and lungs as the most serious candidates. Also, there is increasing evidence that DCD pancreata are likely to perform equally well compared to those recovered from DBD donors. However, long-term clinical outcome data are very scarce, and more evidence has to become available before these organs can be considered to safely reduce the number of patients on the waiting list.

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References


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