TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

# Recommendations for donation after circulatory death kidney transplantation in Europe

L. W. Ernest van Heurn,[1] David Talbot,[2] Michael L. Nicholson,[3] Mohammed Z. Akhtar,[4] Ana I. Sanchez-Fructuoso,[5] Laurent Weekers[6] and Benoit Barrou[7]

1 Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands
2 Department of Liver/Renal Transplant, Freeman Hospital, Newcastle Upon Tyne, UK
3 Department of Surgery, NIHR Cambridge Biomedical Research Centre, Cambridge, UK
4 Oxford Transplant Centre, University of Oxford, Oxford, UK
5 Department of Nephrology, Hospital Clínico Universitario San Carlos, Madrid, Spain
6 Department of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium
7 Department of Urology - Transplantation, GHzu Pitié Salpêtriere, Paris, France

**Keywords**
donation after cardiac death, donation after circulatory death, guidelines, kidney, nonheart beating donation, review.

**Correspondence**
L. W. Ernest van Heurn, Department of Surgery, Academic Medical Centre , Amsterdam, The Netherlands P.O. Box 22660 1100 DD Amsterdam
Tel.: +31 20 5665693;
fax: +31 20 5669287;
e-mail: e.vanheurn@amc.nl

**Conflicts of interest**
The authors declare no conflict of interest.

Received: 13 May 2015
Revision requested: 19 June 2015
Accepted: 26 August 2015

doi:10.1111/tri.12682

## Summary

Donation after circulatory death (DCD) donors provides an invaluable source for kidneys for transplantation. Over the last decade, we have observed a substantial increase in the number of DCD kidneys, particularly within Europe. We provide an overview of risk factors associated with DCD kidney function and survival and formulate recommendations from the sixth international conference on organ donation in Paris, for best-practice guidelines. A systematic review of the literature was performed using Ovid Medline, Embase and Cochrane databases. Topics are discussed, including donor selection, organ procurement, organ preservation, recipient selection and transplant management.

## Introduction

Donation after circulatory death (DCD) has shown to provide a valuable expansion of the number of donor organs available for transplantation. In some countries such as the Netherlands and the United Kingdom, DCD transplantation has almost doubled the number of deceased organ donors (NHSBT data 2014). However, DCD organs sustain an inevitable period of warm ischemia after circulatory arrest, which may have serious implications for early and late graft function after transplantation. There are many comparative studies between DCD kidney transplantation and transplantation of kidneys from donors after brain death (DBD) with, depending on the number of included patients and the selection of DCD donors, variable results [1–3]. The general opinion is that DCD transplantation is associated with a higher risk of primary nonfunction (PNF) and delayed graft function (DGF). The higher incidence of DGF after DCD transplantation, however, is not associated with graft survival as in DBD grafts [4,5].

Despite the higher incidence of PNF and DGF after DCD transplantation, little is known about the specific risk factors for kidney function after transplantation and selection of DCD grafts. Very strict organ selection may reduce the

risk of poor initial function after transplantation, but it also carries the risk that viable organs are discarded, which may result in the death of patients on the waiting list who otherwise could have been transplanted [6].

To extend the number of DCD kidneys, more knowledge about risk factors associated with poor kidney function and graft survival is required. Most risk factors for the outcome of kidney transplantation have been identified in DBD only, or in cohorts, which include both DBD and DCD grafts [7,8] It is inappropriate to extrapolate the results of DBD kidney viability studies to DCD kidneys because of the influence of the prior warm ischemia. Therefore, we looked for specific risk factors for DCD kidney function and graft survival after transplantation, graded the level of evidence of the available literature and formulated recommendations of best-practice guidelines, when possible.

The guidelines are divided into sections including on donor selection, ischemia times, kidney procurement, kidney preservation and recipient selection. A number of issues surrounding the management of patients, including paediatric kidney transplantation, are discussed. A recommendation table is provided as a summary at the end with the corresponding level of evidence.

## Methods

Potentially relevant studies were identified with a structured computerised search of the English literature of Ovid Medline, Embase and Cochrane databases. Keywords included 'donation after cardiac death', 'donation after circulatory death', 'nonheart beating donor', 'kidney transplantation' 'viability', 'extracorporeal membrane oxygenation', 'cold storage', 'hypothermic machine perfusion (HMP)', 'hypertension', 'diabetes', 'obesity', 'organ preservation', 'tissue and organ procurement' 'transplantation', 'warm ischemia time' and 'outcome' combined with free text searching. The level of scientific evidence of the relevant studies was assessed, and accordingly, recommendations were made and graded by an expert panel. These recommendations were presented at 6th International Conference on Organ Donation after Circulatory Death in Paris of the European Society of Organ Transplantation, where the concept recommendations were presented, discussed with the various expert panels and congress participants.

## Donor selection

### Age

In comparative studies including data from national and large centre databases with multivariate risk analyses for DCD kidney transplantation, donor age is an independent risk factor for PNF, DGF, creatinine clearance 1 year after transplantation and graft survival [9,10–18]. The hazard ratio for graft failure is higher and may be more than doubled for DCD kidney transplantation from donors aged 60 or older compared with donors aged 40 years or younger [10,12,14,19].

Paediatric DCD kidney transplantation is rarely done [20]. In general, paediatric donor kidneys are at increased risk for graft thrombosis due to low flow and relatively small vessels [21,22]. This risk is aggravated by warm ischemic damage with an inflammatory response and oedema of the kidney [23]. In a relatively large comparative study of paediatric DBD and DCD kidneys, DCD kidneys had a higher risk of both PNF (OR: 5.3) and DGF and were associated with a higher risk of graft failure with a hazard ratio of 2.5. In the same group, also kidneys from donors younger than 10 years of age had an increased risk of graft failure [24].

### Donor BMI, hypertension, diabetes, serum creatinine, and cause of death

High donor BMI as a risk factor for DGF and graft failure was found to have a hazard ratio of up to 1.84 for DCD kidneys from donors with BMI > 45 kg/m² [12,16,25,26].

Hypertension, diabetes, high donor creatinine and donor cause of death are DCD donor variables which affect transplant outcome in large retrospective cohort studies. Donor hypertension, diabetes, high donor creatinine and death from cerebro-vascular accident may increase the risk of DGF and graft loss [12,16,26,27]. These findings are largely influenced by the large UNOS database and are generally consistent with the findings in other, smaller, cohorts of DCD transplants, which fail to reach statistical significance. The reported additional risk of graft loss is usually relatively limited. However, data may be biased by donor selection prior to transplantation and exact measurements are usually not present.

### Pre-implantation renal biopsy

In kidneys from DBD donors, pre-implantation histology is a predictor of outcome and can improve transplant outcome if those kidneys are not transplanted that are identified as probable failures [28–30]. In DCD kidneys, two groups showed that baseline donor kidney disease assessed with histology scores influenced graft survival and that pre-implantation histology assessment might improve the selection of old donors after cardiac death [31,32]. Histological assessment of pretransplant kidneys with small needle biopsies is reproducible and representative [33].

## Ischaemia time

### Agonal time

Agonal time, defined as the period of time between withdrawal of life support and circulatory arrest, is in most

 

protocols limited to 2 h to maximize the period of relatively poor tissue oxygenation due to respiratory failure and decreasing tissue perfusion after life support has been withdrawn. It has been shown to be possible to extend this period to longer than 4 h without adverse effects with an equivalent renal function of DCD kidneys procured after a prolonged agonal time and kidneys with a shorter agonal time [34,35].

### Warm ischaemia time

A period of warm ischemia, the time between circulatory arrest to the start of organ perfusion, had, in a series of 2562 DCD kidneys in the UNOS database, no detrimental effect on transplant outcome other than a higher incidence of DGF, if this period was limited to 30 min [16]. This finding was confirmed by an analysis of 845 Maastricht III DCD kidneys transplanted in the UK. A subgroup of 173 kidneys with a primary warm ischaemia time greater than 20 min had no increased graft failure rates in comparison with kidneys with shorter ischaemia times.

Others showed that a warm ischaemia period of greater than 40 min was an independent risk factor for kidney failure and was particularly significant if present with another risk factor such as cold ischemic time above 18 h or donor age greater than 55 years [36].

### Cold ischaemia time

Cold ischaemia has a negative impact on transplant outcome. Evidence from animal experiments suggests that organs derived from DCDs are more sensitive to cold ischaemia than those from DBDs [37,38]. Large clinical series show that a long period of cold ischaemia in DCD kidneys is associated with a higher incidence of PNF, DGF and poor graft survival [10,16,39]. Individual centres reviewing paired kidneys found that the second of a pair of DCD kidneys with longer cold ischaemia had a higher incidence of DGF [40]. The limits of acceptable cold ischaemia time are not known, but the negative influence of cold ischaemia on transplant outcome is likely to be additional to the other donor risk factors, for example donor age or prolonged warm ischaemia.

## Procurement of DCD kidneys

Warm ischemic damage in DCD can be reduced by lowering the temperature as quickly as possible or by perfusing the organs at body temperature to partly correct warm ischaemic injury, before the organs are cooled down [41–43].

Three perfusion techniques are commonly used to preserve kidneys before procurement including rapid laparotomy with direct aorta cannulation, *in situ* perfusion (ISP), and extracorporeal regional perfusion (RP).

Rapid laparotomy and direct aorta cannulation can only be performed in Maastricht category III donors, if consent for donation is obtained before withdrawal of life support. It allows introduction of large cannulas enabling high flow cold perfusion [44]. As a laparotomy is done, topical cooling (TC) of the organs can be performed.

*In situ* perfusion with insertion of the cannulas into the femoral vessels can be used in both Maastricht category I or II (uncontrolled) donors and in controlled donors, often before consent for donation has been obtained [44]. The cannula with a double balloon and a triple lumen has a relatively small diameter providing a lower flow than cannulas used for direct aorta cannulation [45].

Regional perfusion uses extracorporeal machine oxygenation circuit to selectively perfuse the abdominal organs after cannulation of the femoral vessels. This technique has been originally used to cool organs down in DBD donors and later in uncontrolled DCD donors [hypothermic regional perfusion (HRP)] [46–48]. In a second phase, it has been used to reperfuse the organs at body temperature (normothermic RP, NRP). The concept relies on experimental studies, mostly performed in liver or kidney transplantation models in pigs [41–43,49].

The choice for which method is preferable depends on the Maastricht category (controlled versus uncontrolled) and the environment.

### Kidney procurement in Maastricht category I and II donors

In uncontrolled donors, both ISP and NR can be used to procure kidneys. There is some evidence that NRP may beneficial to restore energy status; however, the number of clinical studies is small [41,47,49]. Small retrospective clinical studies show excellent results of HRP and NRP to procure uncontrolled DCD kidneys [50–54,55]. NRP in eight kidneys has a lower incidence of PNF and DGF than kidneys preserved with ISP (44 kidneys) or total body cooling by extracorporeal support at 4 °C (eight kidneys) [50]. In another comparative study in 53 patients, kidneys after NRP had earlier diuresis and better creatinine clearance 1 month after transplantation [54].

### Kidney procurement in Maastricht category III donors

In a single centre retrospective study of Maastricht category III donors, direct aortic cannulation resulted in a shorter warm ischemia time and a lower discard rate than ISP [44]. The findings were confirmed after adding a second cohort from another centre: direct aorta cannulation in 63 donors was associated with a lower discard rate (4.8 vs. 28.2%),

 

shorter warm (22 vs. 27 min) and cold (19 vs. 24 h) ischaemia time and improved graft survival (86.2% vs. 76.8% at 1 year) compared with ISP (102 donors) [56]. Others reported PNF in three grafts after technical difficulties inserting the cannulas using ISP [57].

Hypothermic regional perfusion and NRP are also used in controlled donors with good results [58–65]. In a comparative study, HRP at 22 °C (19 kidneys) was associated with less DGF (21% vs. 55%) and a lower estimated glomerular filtration rate (e-GFR) at 1 month than direct aorta cannulation; however, after 1 year, the eGFR was equivalent [59,60]. NRP in 24 kidneys showed comparable results as a historical group of 100 DBD kidneys [64,65]. The costs and complexity of NRP are relatively high. As there is no high level evidence that NRP in controlled DCD is superior to direct aorta cannulation, it is questionable whether the potential benefits outweigh the costs and risks. In addition, NRP done badly (eg blocked lines) produces irreversible damage to the organ.

### Peritoneal cooling

Topical cooling is used to obtain a faster and deeper cooling of the organs before and during procurement. It has been used in donors with ISP before laparotomy using two catheters to flush and drain the peritoneal cavity [66]. In an animal study, the renal temperature was significantly lower with TC in addition to normal cold intravascular flush [67]. Immersing the cooling coil in subzero fluids gave a faster decrease in the intraperitoneal temperature with reduction in DGF [68]. The disadvantage is that it adds more technical procedures to be done in ICU, and it is more difficult to present to the patient's family.

### Streptokinase in kidney procurement

In rats, the addition of streptokinase to a warm preflush was associated with an improvement of functional capillary density of the kidney and reduced early manifestation of tubular necrosis [69]. In pigs, the addition of streptokinase (1.5 MIU/l) gave better cooling, machine perfusion characteristics and histology scores [70]. In a randomized controlled study in humans, machine preserved DCD kidneys from streptokinase-treated donors showed superior machine preservation characteristics with lower perfusate biomarker concentrations as indicators for kidney injury [71].

## Preservation of DCD kidneys

### HMP versus cold storage

The two different approaches currently in use for the preservation of transplant kidneys are static cold storage (CS) and HMP. In CS, the kidneys are stored in melting ice; in HMP, the kidneys are preserved recirculating cold preservation solution.

Level 1 evidence comparing HMP with CS includes one meta-analysis of published articles between 1971 and 2001, including both DBD and DCD kidneys [72]. The meta-analysis suggested that HMP was associated with a relative risk of DGF of 0.804 [0.672–0.961] and that the reduction in DGF associated with HMP predicted a modest improvement in 10-year graft survival of 3%. However, the quality of the analysed studies was generally poor.

In DCD transplantation, four randomized controlled trials (RCTs) containing a total of 351 kidneys compared CS and HMP [18,73–75]. Although the majority of the available evidence is in favour of HMP, reducing the incidence of DGF, the recent RCT evidence failed to reach uniform conclusions. The best evidence from two recent RCTs is contradictory [18,75]. In a European trial which perfused kidneys immediately after explantation, HMP reduced the incidence of DGF; in a randomized study in the United Kingdom, kidneys were machine perfused at a later stage, and in this study, there was no difference between CS and HMP. Therefore, the question of whether or not HMP reduces the incidence of DGF should be considered unanswered.

### Machine preservation intrarenal resistance

Machine preservation characteristics are commonly used for graft selection of DBD and DCD kidneys; however, the level of evidence of the benefits of this selection is usually poor. Results are often biased, as kidneys with high intrarenal resistance are not transplanted [76–81]. Two studies, in which kidneys were transplanted irrespective of intrarenal resistance, one including both DBD and DCD kidneys and the other DCD kidneys only, showed that intrarenal resistance was an independent risk factor for PNF, DGF and 1-year graft survival [82,83]. The predictive value of intrarenal resistance was poor to moderate, so that it cannot be used as a stand-alone quality tool to predict outcome with sufficient precision.

### Machine perfusate biomarker concentration

The value of machine perfusate biomarker concentration as predictor for kidney allograft outcome has been studied extensively [84,85]. Most studies are of relatively poor quality or include only DBD kidneys [86–88]. The number of acceptable or good-quality studies including DCD kidneys is limited [85–92]. From these studies, it can be concluded that the predictive value of the currently used perfusate biomarker concentrations is too low to justify to discard otherwise good donor kidneys.

## Recipient selection for DCD kidneys

A meta-analysis in 2005 shows that DCD kidney transplantation carries a 3.6 fold increase in the risk of DGF compared with DBD kidneys, which is confirmed by more recent comparative studies [10,16,39,93–99]. There have been no specific recipients characteristics identified that are associated with DGF in DCD transplantation although there was a trend for more DGF in male recipients and patients with prolonged dialysis [39]. The effect of recipient age on graft function and graft survival remains unclear [16,18,59].

Delayed graft function is generally considered to impact long-term graft survival, but almost every study evaluating the consequences of DGF in DCD shows that DGF has not the same adverse affect on graft survival as in DBD. An exception is a study of U.S. Renal Data System database including 708 DCD kidneys where DGF was an independent predictor of graft loss in a multivariate analysis [16].

The incidence of PNF is also higher in DCD kidneys than in DBD kidneys [6,16,96]. There have been no recipient characteristics identified affecting this outcome.

Death censored graft survival of DCD kidneys depends on the selection of DCD kidneys and is in most studies slightly higher to equivalent to DBD kidneys. Particularly in children and in re-transplantation, DCD kidneys were at higher risk for graft failure [10,16,99].

### Paediatric recipients

Theoretically, DCD kidneys need a higher arterial blood pressure to get an adequate perfusion pressure, as DCD kidney transplantation is associated with an inflammatory reaction and oedema. There is evidence that DCD kidney transplantation in children is associated with a higher rate of DGF and reduced graft survival rate than paediatric DBD kidneys with a more than doubled hazard ratio [99]. When allocating a DCD kidney to a child, it is necessary to weigh the slightly higher risk of graft failure by accepting a DCD kidney against the risks associated with staying on the waiting list for a longer period.

### Retransplantation

Repeated transplantation is a known risk factor for worse outcome after kidney transplantation. Two studies tested the consequence of repeated transplantation for PNF with inconsistent results. The Maastricht team reported no effect of retransplantation on the incidence of PNF in a selected group, in which DCD kidneys were preferably not allocated for retransplantation, and the UK database shows that the incidence of PNF was more than doubled after DCD retransplantation (3% vs. 7% in first and second graft recipients, respectively [10,98]). This and the U.S. Renal Data System show a lower graft survival after DCD retransplantation with a hazard ratios of 2.74 [1.96–3.82] and 4.59 [2.19–9.64] for second and third transplants, respectively, in the latter study [10,16]. It is unknown whether retransplantation with DCD kidneys provides survival advantage as compared to remaining longer on the waiting list for a DBD kidney.

## DCD kidney transplant management

The incidence of PNF and DGF is increased in DCD kidney transplantation. Few studies discuss protocols for improving the outcome of DCD transplant procedures [100–104].

### Fluid management

Fluid depletion in kidney transplantation is associated with decreased initial graft function [105,106]. In DBD kidneys, pre-operative and operative fluid loading reduced the DGF rate [107–110]. In a retrospective study in recipients of DCD kidneys, low intra-operative central venous pressure and low blood pressure in recipients from DCD increased the risk of PNF [103]. It may be beneficial to keep the recipient well hydrated, avoid immediate post-transplant dialysis with a negative balance and monitor venous pressure during and immediately after the surgical procedure.

### Post-transplant monitoring

Patients with a nonfunctioning graft should be monitored regularly with echo Doppler, renography or both to rule out other causes than acute tubular necrosis for, usually temporary, inadequate function of the transplanted kidney. Moreover, it is difficult to diagnose rejection in patients with a nonfunctioning graft. Therefore, biopsies should be taken frequently. Many centres take weekly biopsies until kidney function improves.

### Immunosuppressive therapy protocol

Donation after circulatory death kidneys are susceptible to calcineurin inhibitor (CNI)-mediated vasoconstriction and nephrotoxicity. Prompt use of CNI may exacerbate ischemic injury, delay recovery from DGF and impair long-term graft function. It is possible to avoid or postpone the use of CNI's or use low doses. Polyclonal antibodies or imTOR inhibitors may be used to postpone or avoid the use of CNI's in DCD kidney recipients. In addition, antithymocyte globulins (ATG) seem to protect against the damage caused by ischemia–reperfusion [111].

**Table 1.** Recommendation table Donation after circulatory death (DCD) kidney.

| Recommendations | Grade | References |
|---|---|---|
| Donor selection | | |
| Transplantation of old aged donor kidneys to recipients with a long life expectancy (e.g. young recipients) should be avoided | B | [10,12,14,19] |
| DCD kidneys from young children should be used with caution | C | [24] |
| Donor BMI, hypertension, diabetes and death from cerebro-vascular accident should be considered in allocation DCD kidneys | C | [12,16,25–27] |
| Pretransplant renal biopsy is helpful for selection and thereby improves graft survival of DCD kidneys from donors aged 60 years or older | D | [28,30–33] |
| Ischemia times | | |
| An agonal time of 2 h or longer is not an absolute contra-indication for kidney donation | B | [34,35] |
| The warm ischaemia time in DCD donors should be maintained as short as possible. In category III donors, a limited period of warm ischemia (up to 20–30 min) increases the DGF rate but has no or only minimal detrimental effect on graft survival, and is not a contra-indication for transplantation. DCD kidneys with a longer warm ischemia time than 40 min should be used with caution, particularly if there are more risk factors for primary nonfunction | C | [16,36] |
| Every effort should be made to minimize cold ischaemia time and to transplant DCD kidneys as soon as possible after explantation | B | [10,16,37–40] |
| Procurement | | |
| The best method to perfuse uncontrolled DCD kidneys is normothermic (or subnormothermic) extracorporeal support with oxygenation. However, if done badly, normothermic perfusion is very destructive and cold perfusion scenario is more forgiving | C | [41,47,49–52, 54,55] |
| A skin incision and dissection of the femoral vessels may facilitate the installation of femoral catheters if the donor receives cardiac massage | D | [44] |
| Rapid laparotomy and direct cannulation of the aorta is the preferred technique in Maastricht category III donors if logistically feasible. In situ preservation with a double balloon triple lumen catheter can be used safely to preserve kidneys in Maastricht category III donors, if direct cannulation of the aorta cannot be performed | C | [44,56,57] |
| In donors with *in situ* preservation (ISP), intraperitoneal cooling may allow a better cooling of the organs than ISP alone | D | [66–68] |
| It is recommended to use streptokinase (1.5 MIU/L) in the initial flush out during organ procurement | C | [69-71 ] |
| Preservation | | |
| Hypothermic machine perfusion is feasible and safe. In DCD kidneys, HMP has not shown an effect on graft survival | B | [18,72–75] |
| If HMP is used to preserve DCD kidneys, it may be preferable to use it immediately after kidney explantation | D | [18] |
| Discard of DCD kidneys on the basis of machine perfusion characteristics or machine perfusate biomarkers alone is not recommended | C | [82–88] |
| Recipient selection | | |
| The risk of DGF should not be considered as a criterion to discard a DCD kidney for transplantation | B | [10,16,39,93–99] |
| Children should preferably not receive a DCD kidney | C | [99] |
| DCD kidneys are not the first choice for patients with a retransplantation | C | [10,16,98] |
| Recipient management | | |
| DCD kidney transplantation should be avoided in patients with known cardiac failure or low blood pressure | D | |
| Optimal pre-operative, operative and direct postoperative fluid management is essential to optimize graft survival of DCD kidneys | C | [103,105,106] |
| In DCD kidney recipients with DGF, regular monitoring with echo Doppler, renography, or both is recommended, as well as frequent biopsies, in order to rule out acute rejection | D | |
| Delayed implementation or use of low-dose CNI could help to reduce the incidence of DGF | D | [104] |

There are few published clinical data on immunosuppression in DCD kidney recipients. In the 1990s, treatment with ATG and initiation of cyclosporine 2 days before the withdrawal of ATG was associated with a low incidence of rejection, but increased risk of opportunistic infections, which decreased patient and graft survival [102]. Results were improved by the use of anti-IL-2R antibodies combined with low doses of tacrolimus and mycophenolate mofetil [101]. In a randomized trial, induction with daclizumab and delayed introduction of tacrolimus reduced the incidence of DGF in DCD kidney recipients [104].

## Conclusion

Donation after circulatory death kidney transplantation has occurred as consequence of the need to address the organ deficit. These guidelines provide recommendations on donor selection, organ and recipient management. The paucity of high-quality evidence (grade A or above) highlights the need for ongoing research into how to optimize and risk stratify DCD kidneys for transplantation. The development of new techniques for organ procurement, *ex-situ* preservation and recipient management will result in improvements in outcomes. A summary of recommendations for clinical guidelines are provided in Table 1.

## Funding

The authors have declared no funding.

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