Controlled donation after cardiac death: a European perspective

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Abstract

Terminally ill patients who do not meet brain death criteria and die of cardiac arrest after withdrawal of life support may be considered as potential organ donors: such donors are referred to as controlled donors after cardiac death (DCD). Controlled DCD donors are increasingly being used in Northern Europe and the United States in an effort to expand the donor pool. Ethical concerns regarding the diagnosis of death based on cardiopulmonary rather than neurological criteria have largely been resolved over the past decade. Follow-up studies of recipients by several transplant centers have shown that functioning controlled DCD kidneys are equivalent to kidneys from conventional brain-dead donors with respect to long-term prognosis. Concerns about long-term repercussions for the higher incidence of delayed graft function with DCD kidneys are not supported by the current evidence. The donor pool may be further expanded by transplanting selected kidneys from older DCD, in particular for the increasing population of older kidney transplant candidates. Successful transplantation of these delicate organs is possible when donors and recipients are carefully managed by well-trained, motivated, and effectively collaborating transplant personnel.

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1. Introduction

Kidney transplantation results in longer life expectancy and superior quality of life compared with dialysis treatment and therefore is the treatment of choice for many patients with end-stage renal disease [1,2]. However, the number of available donor kidneys currently is not sufficient to treat all candidates for transplantation despite increases in living donor kidney donation [3,4] and expansion of criteria for kidney donation after brain death (DBD) [5,6]. Procurement of kidneys from donors after cardiac death (DCD; also referred to as non–heart-beating donation) holds the potential to expand the donor pool 2.5 to 4 times [7], which theoretically should suffice to stabilize or even reduce the contemporary waiting lists for kidney transplantation [8].

In 1995, 4 types of DCD were recognized by the participants of the first international conference on non–heart-beating donation in Maastricht (Table 1) [9]. Maastricht category 1 constitutes patients who are declared dead outside the hospital and are subsequently transferred to the hospital with the purpose of organ donation. Maastricht category 2 donors are patients who die in hospital after unsuccessful resuscitation, mostly in accident and emergency departments. Both situations occur unexpectedly and therefore are referred to as uncontrolled DCD donations. Maastricht category 3 donors are patients in intensive care units (ICUs) who do not meet brain death criteria from whom supportive treatment is withdrawn because of medical futility. These patients in whom cardiac arrest is awaited are referred to as controlled DCD. Maastricht category 4 donors are brain-dead donors with cardiac arrest before organ procurement.

The practice of DCD donation differs throughout the world. Since the early 1980s, several transplant centers in Europe have expanded their donor pools with DCD [10-31]. Initially, most European centers predominantly relied on uncontrolled DCD. More recently, the contribution of controlled DCD has increased. In Japan, brain death legislation was not introduced until 1997, and so far, the concept of brain death is not readily accepted by the general public. Therefore, organ donation in Japan has relied almost exclusively on living donors and DCD (mostly controlled category 4 donors) [32-35]. In the United States, surgical
practice has been more conservative with respect to transplantation of DCD kidneys. However, since the late 1990s, the contribution of controlled DCD to the donor pool has been steadily increasing and currently constitutes approximately 5% of all deceased donors [36-46]. Uncontrolled DCD have only rarely been used in the United States [47].

In this article, we will review the experience with controlled kidney donation after cardiac death (ie, category 3 DCD) from a European perspective. The experience with uncontrolled DCD is reviewed by Sanchez-Fructuoso and colleagues in a separate article in this issue of Transplantation Reviews.

2. History of organ donation after cardiac death

After the initial success of kidney transplantation between identical twins in the 1950s [48], the first successful cadaveric kidney transplantation was reported in 1963 [49]. The donor died after cardiac arrest during open heart surgery, and the kidney was kept in a refrigerator at 4°C until transplantation 125 minutes later. After a period of delayed graft function (DGF), the kidney continued to function during the first year after transplantation. However, this successful case was a rare exception because 67 other contemporary attempts at DCD kidney transplantation had failed within the first year after grafting [50]. These poor results were generally attributed to “the damage which occurs to the kidney during the terminal phase of the donor’s life, or in the period between his death and the time when the transplantation is carried out” [51].

As kidney preservation by machine perfusion and cold storage improved, 1-year graft survival from deceased donors increased from 12% in the period 1962–1965 to 46% in the period 1969–1973 [52-56]. At the same time, in 1968, brain death was recognized as a clinical and legal entity by an ad hoc committee at Harvard Medical School [57]. This allowed procurement of organs without warm ischemic injury from deceased donors with intact circulation [58]. As a result, donation after cardiac death was abandoned in favor of DBD in the 1970s. The parallel introduction of the immunosuppressive drug cyclosporine led to a dramatic decrease in acute rejections and improvement in graft survival, contributing greatly to successful kidney, liver, and heart transplantation [59,60].

As clinical outcomes of kidney transplantation improved over the years, more and more patients with end-stage renal disease opted for transplantation to improve quality of life and life expectancy. As a consequence, waiting lists for kidney transplantation have increased in the United States and Europe since the 1980s [61,62]. With the gradual increase in waiting time, the transplant community took a renewed interest in the procurement of organs from DCD to expand the donor pool. Several transplant centers, including our group from Maastricht, have reported that long-term clinical outcomes of DCD kidney transplants are comparable to DBD grafts [10,13,16,20,23,37]. For further reading on the history of donation after cardiac death, we refer to the review by DeVita et al [63].

3. Ethical and legislative aspects of donation after cardiac death

There are some general ethical principles concerning deceased organ donation [64-66]. First and foremost, the donor must be dead before organ procurement can take place (dead donor rule). Diagnosis of death—which based on cardiopulmonary or neurological criteria—is based on both cessation of function and irreversibility of this condition. Cessation of function is demonstrated by absence of responsiveness, as well as pulse and respiratory effort. In a US national meeting on DCD donation, it was concluded that absence of circulation by monitoring of arterial pulse pressure is sufficient for diagnosis of death, and electrocardiographic silence is not required [67]. Thus, the absolute criterion for diagnosis of death is considered circulatory arrest and not cardiac or electrical arrest. The requirement of irreversibility in DCD donation is open for ethical discussion because of different definitions of irreversibility and time pressure to diagnose death while the organs suffer warm ischemic injury [64]. Occasionally, ethical commentaries have stated that controlled DCD donation violates the dead donor rule because circulatory arrest may be reversed if cardiopulmonary resuscitation is initiated [68]. In the context of withdrawal of life support, however, cardiopulmonary resuscitation is not intended, and consensus within the transplant community defines irreversibility as cessation of function without the capability of spontaneous recovery [67]. An observational period of 5 minutes after circulatory arrest is generally accepted to meet the requirement of irreversibility (no-touch period) [69].

Secondly, care of living patients must not be compromised in favor of potential organ recipients. In other words, patient treatment should prevail donor management. Nevertheless, end-of-life care of potential DCD seems to deviate substantially from published guidelines [68]. Several strategies that aim to minimize warm ischemic injury to donor organs, including withdrawal of treatment in the operating room and cannulation before death, potentially compromise end-of-life care. To provide continuity of care, it is common practice in the Netherlands and United Kingdom to withdraw treatment in the ICU and transport the donor to
the operating room after death. In clinical practice, this does not lead to inferior transplant outcomes [70]. Furthermore, we argue that invasive instrumentation of a potential donor before death is not ethically sound. In the Netherlands and the United Kingdom, organs from controlled DCD are therefore preserved either after rapid laparotomy and direct aortic cannulation or after rapid in situ preservation in the ICU after a 5-minute no-touch period after death. To prevent conflict of interests, the medical team providing care for dying patients and diagnosing death should be separate from the surgical team responsible for organ procurement. Of particular concern to controlled DCD donation, the decision to withdraw life-sustaining treatment should be made separately from the decision to donate organs [71]. Finally, protocols for donation after cardiac death should be discussed and approved by the medical ethical committee of each institution [72].

Legislation concerning DCD donation differs greatly throughout Europe. In the Netherlands, the United Kingdom, and Switzerland, DCD donation is encouraged by the government, and laws have been passed that allow invasive instrumentation of potential DCD to preserve organs before consent has been obtained from the relatives [73,74]. In Germany, however, the law prohibits procurement of organs from deceased donors that have not been formally declared brain dead, and this practically rules out DCD donation. In Spain and France, controlled DCD donation is impossible because legislation prohibits procurement of organs after withdrawal of life-supporting treatment in the ICU.

4. Donor selection

4.1. Transmittable diseases

Selection of potential DCD starts with exclusion of transmittable diseases. Patients with malignancies, active systemic infections, or serological evidence of human immunodeficiency virus or hepatitis virus infection should not become organ donors. Exceptions can be made for recipients already infected with human immunodeficiency virus or hepatitis virus or when the benefit of transplantation outweighs the risk of transmission of a particular malignancy [75]. Such donors should be evaluated on a case-by-case basis.

4.2. Chronic degenerative changes

If there is no risk of disease transmission to the recipient, the functional capacity of the organs is assessed. European practice generally is more liberal with respect to transplantation of marginal kidneys than in the United States. A general upper age limit for kidney donation is not reasonable because renal function and structure vary widely between older individuals. Although creatinine clearance declines with age in most individuals, up to 35% of subjects have stable kidney function over time [76]. Similarly, in a cross-sectional study of autopsy cases without renal disease, the percentage of sclerosed glomeruli was increased in subjects older than 50 years but ranged from 1% to 36% in this age category [77]. Besides age, cardiovascular risk factors such as hypertension, diabetes mellitus, and smoking are associated with chronic kidney disease in the general population [78]. However, only 15% of healthy subjects with essential hypertension developed chronic kidney disease over a follow-up period of 13 years [79]. With such individual variation, the acceptance of kidneys from expanded criteria donors for transplantation should be based on absence of functional and structural abnormalities rather than on an arbitrary age limit or combination of risk factors.

The functional capacity of the kidney is determined by estimation of the glomerular filtration rate (GFR) and measurement of proteinuria [80-82]. Structural abnormalities of the kidney may be diagnosed by histological assessment of preimplantation biopsies [83,84]. This has been shown to be a useful tool for selection of kidneys from DCD with advanced age that are suitable for transplantation [11]. At our institution, kidney transplants from DCD older than 65 years (n = 24) were associated with inferior kidney function (GFR of 28 ± 15 vs 43 ± 15 mL/min after 1 year; P = .01) and graft survival (52% vs 68% after 5 years; P = .19) compared with younger DCD kidneys (n = 176). Importantly, exclusion of grafts with severe vascular and glomerular pathology in preimplantation kidney biopsies resulted in similar graft survival of older and younger DCD. There is currently no consensus about the limits of functional and structural abnormalities that allow maximal expansion of the donor pool with acceptable clinical outcomes [84-86].

4.3. Acute kidney injury

If renal functional capacity of the potential donor is considered sufficient for transplantation and permission for organ donation is obtained, supportive treatment is subsequently withdrawn. The period from withdrawal of support until circulatory arrest may sometimes be protracted, especially with potential donors who do not receive ventilatory support. From a practical point of view, many US transplant centers consider a maximal waiting time of 1 to 2 hours for controlled DCD kidney donation [87]. However, as long as blood pressure, oxygen saturation, and urine output remain normal, there is no reason why the kidneys would not be suitable for transplantation [88]. Although warm ischemic injury is of more concern with uncontrolled DCD kidneys, prolonged periods of hypotension before death or failure to start timely perfusion after circulatory arrest may lead to acute ischemic injury in controlled DCD kidneys as well. Warm ischemia time (WIT) should be kept to a minimum with logistic and surgical techniques appropriate in the setting of optimal end-of-life care for potential donors and their families. Kidney transplantation from DBD and DCD with acute renal failure in the ICU has been done successfully and is associated with similar long-term outcomes as with conventional kidney donors [89-91].
5. Management of the potential donor

Until withdrawal of treatment, careful monitoring and supportive treatment of potential DCD is in the best interest of both the potential donor and the recipients. Care of potential brain-dead organ donors has recently been reviewed by Wood et al [92]. Management of the potential DCD is less demanding because hormonal deficiencies, cardiac arrhythmias, and hypothermia associated with brain death do not occur regularly. Therefore, patient management focuses on cardiovascular status with the goals to achieve normovolemia, maintain blood pressure, and optimize cardiac output using the lowest concentration of vasoactive drug support possible. Mean arterial pressure should be maintained at 60 mm Hg or greater with central venous pressure of 6 to 8 mm Hg and urine output of 1 mL kg\(^{-1}\) h\(^{-1}\) or greater. Vasoactive drug support is necessary when hemodynamic instability persists despite adequate volume resuscitation. More than 90% of donors can be successfully managed with volume resuscitation and low doses of vasopressors (≤10 \(\mu\)g kg\(^{-1}\) min\(^{-1}\) of dopamine or dobutamine) [93]. Graft function may be further optimized by avoidance of hydroxyethylstarch and correction of electrolyte disorders, in particular hypernatremia [94].

When the relatives of the potential donor are present and bid their loved one farewell, and when the organ procurement team is ready, supportive treatment is withdrawn, preferably according to a standardized protocol [71,95]. However, European practice with respect to withdrawal of life-sustaining treatment differs greatly according to the preferences of individual physicians [96]. Nevertheless, Ozark and DeVita [71] make a suggestion toward a uniform protocol for withdrawal of supportive treatment in potential DCD. After administration of opioids and sedatives to prevent pain and recall, all nonventilatory supportive measures are withdrawn. Subsequently, ventilator support is stopped, and the patient is extubated, providing additional sedation if the patient is stressed as may be demonstrated by increased respiratory rate or retention of secretions. If legally allowed, heparin may be administered to improve graft quality close to the time of death (eg, when the systolic blood pressure falls less than 60 mm Hg) [71]. A standardized checklist for withdrawal of life support that may improve quality of end-of-life care in the ICU is available [97].

6. Organ preservation

6.1. In situ perfusion technique

As discussed previously, DCD organs are inevitably subjected to a period of warm ischemia. During this period, cell death pathways are activated, which set the stage for graft injury at reperfusion [98]. Indeed, prolonged WIT is associated with reduced graft survival [99,100]. Therefore, several techniques have been developed to reduce warm ischemic injury of DCD organs before procurement, either by applying topical or intravascular cooling or by reestablishing blood flow by mechanical resuscitation or extracorporeal circulation [19,41,42,46,101-107].

Over the past 2 decades, we have generally used in situ perfusion with double-balloon triple-lumen catheters for procurement of DCD kidneys [108]. This catheter is introduced via the femoral artery into the aorta, and subsequent inflation of the 2 balloons allows selective perfusion of the abdominal aorta, flushing and cooling the kidneys. This technique is minimally invasive, can be performed in the accidents and emergency department as well as in the ICU, and should allow fast and effective use by surgeons with limited experience in donation procedures. In situ perfusion provides additional time to make necessary arrangements for legal, logistical, and medical requirements for organ procurement from uncontrolled DCD. For controlled DCD, however, logistical requirements for rapid laparotomy and direct aortic cannulation can be arranged before withdrawal of supportive treatment. If this approach is possible, it may be favored over in situ perfusion because it is associated with reduced WIT, lower discard rate, and superior graft survival [109]. Moreover, organs other than kidney’s may be procured through this technique [42].

Histidine tryptophan ketoglutarate solution is used for kidney perfusion because its low viscosity facilitates flush-out at high flow rates. Addition of heparin and streptokinase to the perfusion solution results in thrombolysis and improves graft quality [110,111]. Administration of a vasodilator such as phentolamine may prevent renal vasospasm and increase perfusion efficacy [101,112,113].

6.2. Machine pulsatile perfusion

After organ procurement, kidneys may be preserved through machine pulsatile perfusion or by cold static storage until the time of transplantation [114]. There has been considerable debate about the relative merits of either technology. Randomized clinical trials comparing the 2 preservation modalities have often been underpowered to detect clinically important differences in graft outcome. A meta-analysis of these trials showed that a 20% reduction in the risk of DGF of both DBD and DCD can be achieved by using machine perfusion over cold storage [115]. This conclusion was confirmed by a registry analysis of 907 paired kidneys transplanted in the United States, with DGF in 26% of cold-stored kidneys vs 19% of machine-perfused kidneys procured from the same donors [116]. No difference in long-term graft survival was observed in this study. In contrast, recent analysis from the Collaborative Transplant Study suggests that machine perfusion is associated with inferior long-term outcome [117]. This may be explained by the tendency of transplant centers to pump only marginal kidneys, which may be hard to account for in multivariate analyses of graft outcome. The ongoing European Machine Preservation Trial, in which 600 kidneys (including DCD kidneys) are preserved by machine perfusion or cold storage with pairwise
randomization, may provide additional information on the advantages of either preservation method.

In addition to improving graft function after transplantation, machine perfusion may be used to test the viability of DCD kidneys to reduce the incidence of primary nonfunction [118]. Perfusion characteristics are recorded and may be used to select DCD kidneys at risk for primary nonfunction [119]. The increase in kidney weight during machine perfusion does not predict postoperative graft function [120]. Measurement of α-glutathion S-transferase or fatty acid binding proteins in the preservation solution indicates injury to proximal tubular epithelial cells and may be useful in selection of viable DCD kidneys for transplantation [15,121,122]. We have recently found that DCD kidneys release redox-active iron into the preservation solution during machine perfusion, which may catalyze the generation of reactive oxygen species. The level of perfusate iron is an independent predictor of primary nonfunction that adds predictive value to current donor and graft characteristics [123]. Furthermore, normothermic perfusion has shown great promise in preclinical animal studies but has yet to be applied to clinical kidney transplantation [124,125].

6.3. Reducing cold ischemia time

The adverse effects of prolonged cold ischemia on graft outcome have been well documented and include higher incidences of DGF and acute rejection and reduction of long-term graft survival [117,126-130]. Although the association between cold ischemia time and DGF varies across publications, a recent analysis of almost 100,000 kidney transplants in the Collaborative Transplant Study indicates that the relative risk of graft failure increases by 10% to 15% after 18 hours of cold ischemia time [117]. Kidneys from DBD and DCD are affected by prolonged cold ischemia to similar degrees. These findings strongly suggest that efforts should be made to transplant all kidneys within 18 hours of procurement. In the Netherlands, it is not allowed to start human leukocyte antigen typing of the potential DCD before circulatory arrest, causing potential delay in transplantation that may be further prolonged by allocation and transport within the Eurotransplant region. Therefore, local allocation of DCD kidneys may reduce cold ischemia time considerably [70]. Furthermore, it is essential that all transplant personnel involved are motivated to maximize efficiency and cooperation. Indeed, a French transplant center has recently reported an impressive reduction of mean cold ischemia time from 23 to 13 hours after the introduction of a simple quality assurance program [131].

7. Management of the recipient

7.1. Recipient selection

Since 2001, DCD kidneys have been allocated according to the same rules as DBD kidneys in the Netherlands, and all Dutch transplant candidates are therefore potential DCD kidney recipients [132]. This policy is supported by the similar long-term outcomes for recipients of DCD and DBD kidneys and the general principle of equal access to care as outlined in the Dutch Organ Donation Act. When placed on the waiting list, potential recipients are informed of the different donor types. Nowadays, however, not all grafts confer the same prognosis for their recipients, as donor criteria have been extended in an effort to expand the pool of kidneys for transplantation. For example, kidneys from DBD donors older than 60 years are associated with more than 1.7 times the risk of graft failure compared to ideal deceased donor kidneys [5]. Despite this reduced graft survival, most patients receiving kidneys from expanded criteria donors live longer than patients who refuse such kidneys and instead wait until kidneys from standard criteria donors are offered [6]. Currently, transplant physicians make decisions that weigh survival and quality of life on dialysis for a particular patient against the shorter waiting times for kidneys with worse prognosis. We advocate a change in practice toward shared decision making, which encourages patients to make an informed, autonomous decision about which types of donor kidneys they are willing to receive [133]. It has been demonstrated that most patients are capable of making such complex decisions when adequately informed [134].

7.2. Hemodynamic management during transplant surgery

Postoperative renal function is not only determined by pretransplant donor and graft characteristics but also by the hemodynamic status of the recipient during kidney transplantation. Early graft function requires adequate perfusion of the kidney, which can be achieved by expansion of the intravascular volume of the recipient. Indeed, fluid loading before or during surgery reduces the DGF rate in DBD kidney transplantation, whereas preoperative hemodialysis is associated with an increased incidence of DGF [135-139]. Studies on recipient hemodynamics during transplant surgery have mostly focused on traditional donor sources that have a low risk of primary nonfunction (PNF). In a multivariate analysis of DCD kidney transplants, we have recently demonstrated that recipient hemodynamic status is a major and independent predictor for PNF, which may be more important than donor and graft characteristics of the transplanted kidneys [140]. In a subgroup of recipients of paired kidneys, 29% of the recipients with lower central venous pressure of the pair experienced PNF compared with 11% of their counterparts, although the kidneys were retrieved from the same donors. Therefore, extra attention to recipient hemodynamic management by expansion of the intravascular volume may improve the outcome of DCD kidney transplantation.

7.3. Delayed graft function and acute rejection

Most recipients of DCD kidneys will undergo a period of DGF in which they continue to depend on dialysis treatment. During this period, clinical diagnosis of acute rejection is difficult because of continued renal failure. A solution to this problem may be provided by taking
ultrasound-guided biopsies from the graft to exclude rejection as a cause of renal dysfunction every week until resolution of DGF, as currently performed at our institution [141,142]. If rejection is diagnosed, treatment should be initiated promptly. To further complicate recipient management, potent immunosuppression by calcineurin inhibitors to prevent acute rejection is nephrotoxic and reduces renal blood flow, which may prolong recovery from DGF (in particular with the use of cyclosporine) [143-145]. However, avoidance of calcineurin inhibitors and corticosteroids is associated with an unacceptably high incidence of acute rejection [141,142]. If rejection is diagnosed, treatment should be initiated promptly. To further complicate recipient management, potent immunosuppression by calcineurin inhibitors to prevent acute rejection is nephrotoxic and reduces renal blood flow, which may prolong recovery from DGF (in particular with the use of cyclosporine) [143-145].

Over the past decades, the Maastricht group has gathered extensive experience in procurement and transplantation of DCD kidneys from both controlled and uncontrolled donors. In a multicenter study of 57 DCD kidneys retrieved in our organ procurement area from 1980 to 1992, long-term graft survival of DCD kidneys is similar to matched DBD kidneys [20,23]. A small randomized controlled trial by the centers in Leicester and Newcastle (United Kingdom) failed to show benefit of induction therapy with daclizumab (monoclonal antibody against interleukin-2 receptor) and delayed introduction of the calcineurin inhibitor tacrolimus (monoclonal antibody against interleukin-2 receptor) and delayed introduction of the calcineurin inhibitor tacrolimus over early administration of tacrolimus without induction therapy for DCD kidneys, except for a small subgroup of kidneys that underwent machine perfusion [147]. Different immunosuppressive regimens for DCD kidneys that evolved over time were retrospectively compared by Sanchez-Fructuoso et al [148]. They conclude that induction therapy with daclizumab and triple therapy with low-dose tacrolimus, mycophenolate mofetil, and steroids was superior to 3 other regimens evaluated. Adequately powered clinical trials of immunosuppressive regimens that are specifically tailored to recipients of DCD kidneys are necessary, as the use of DCD kidneys is expanding.

Because of the high incidence of DGF, the costs of controlled DCD kidney transplantation are higher than with conventional DBD grafts. Compared with dialysis treatment, however, transplantation of extended criteria donor kidneys is still cost-effective [149]. Finally, interventions to prevent renal injury due to ischemia and reperfusion are needed to reduce the incidence of DGF and to allow expansion of the donor pool with organs that have suffered prolonged warm ischemic injury.

8. Clinical outcome of controlled DCD kidney transplantation

Clinical outcome of DCD kidney transplantation has been compared to outcome of conventional DBD kidney transplantation in several studies [10,12-14,16-18,20,21,23,24,26-28,37-39,44,132,150,151]. In general, DCD kidneys are more often associated with DGF and PNF, although in most studies, the higher incidence of PNF does not reach statistical significance. This may be explained by the small sample size of most single-center studies on DCD kidney transplantation. Despite the inferior short-term graft function of DCD kidneys, most studies show that long-term graft survival of DCD kidneys is similar to matched DBD kidneys. Moreover, the higher rate of initial graft dysfunction does not increase the incidence of acute rejection, interstitial fibrosis, or reduced GFR [152]. Finally, the deleterious effect of DGF on long-term graft survival of DCD kidneys is not observed in DCD kidneys [20,23,153,154], strongly suggesting a different pathophysiology of DGF associated with brain death and warm ischemia. For this review, we will focus more closely on studies by European transplant centers that include controlled DCD (Table 2).

Over the past decades, the Maastricht group has gathered extensive experience in procurement and transplantation of DCD kidneys from both controlled and uncontrolled donors. In a multicenter study of 57 DCD kidneys retrieved in our organ procurement area from 1980 to 1992, long-term graft

Table 2

<table>
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<tr>
<th>Publication</th>
<th>Donor type</th>
<th>Sample size*</th>
<th>Donor age (y) *</th>
<th>WIT (min) †</th>
<th>DGF (%)</th>
<th>PNF (%)</th>
<th>Acute rejection (%)</th>
<th>Creatinine 1 y †</th>
<th>Graft survival 1 y (%)</th>
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<td>141 ± 62</td>
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* Numbers in parentheses indicate the number of controlled DCD donors.
† Data are reported as median (range) or as mean ± standard deviation.
survival and function were similar to matched DBD kidneys [10]. In a recent analysis of 200 DCD kidney transplants from our institution in the period 1994–2005 (124 of which were from controlled donors), PNF was observed in 21% and delayed function in 58% of grafts [11]. Kidneys from DCD aged 65 years or older were associated with inferior long-term outcome. In a nationwide analysis of kidney transplants in the Netherlands, 100 controlled DCD transplants performed in the period 2001–2002 were compared with 176 DBD kidney transplants [132]. Transplantation of DCD kidneys was associated with a higher incidence of DGF and PNF, resulting in greater graft loss during the first 3 months after transplantation than DBD kidneys. The only risk factor for PNF of DCD kidneys was warm ischemia time longer than 30 minutes. It has to emphasized, however, that all other studies comparing DCD and DBD kidney transplants found similar long-term outcomes. Moreover, no attempts were made to reduce bias by matching the control group of DBD kidneys to the DCD kidneys in this study.

The DCD kidney transplant experience from the United Kingdom from 1988 to 2001 was summarized by Brook et al [155] and included 285 patients from the transplant centers at South Thames, Newcastle, Leicester, and Cambridge. Sixty-six kidneys were procured from controlled DCD (24%) and had significantly lower incidence of DGF and PNF compared with kidneys from uncontrolled DCD, resulting in superior long-term graft survival. The transplant team in Newcastle specifically compared the outcome of DCD grafts according to donor category and found that the rate of PNF tended to be lower with controlled DCD [156]. The transplant team in Zürich in Switzerland performed 122 kidney transplantations from controlled and uncontrolled DCD from 1985 to 2000 and compared these transplants with matched DBD controls [23]. Despite a significantly higher incidence of DGF for DCD kidneys, PNF and long-term graft survival were similar to DBD kidneys. In contrast to the results from the United Kingdom, graft survival was not influenced by DCD category.

9. Future prospects

Terminally ill patients who do not meet brain death criteria and die of circulatory arrest after withdrawal of life support because of medical futility should be considered as potential organ donors. The use of these controlled DCD (Maastricht category 3) is increasing in the United States and Northern Europe in an effort to expand the donor pool. Ethical concerns regarding the diagnosis of death based on cardiopulmonary rather than neurological criteria have largely been resolved over the past decade. Still, careful attention should be paid to provide high-quality end-of-life care to potential DCD and their families on the one hand without jeopardizing the viability of their organs on the other. Further research in this area is warranted and may lead to strategies to increase the consent rate for organ donation.

Currently, almost half of deceased donors in the Netherlands are DCD. This has not led to an increase in the deceased donor pool, however, because widespread introduction of DCD donation was preceded by a decrease in the availability of DBD donors. This may be explained by the declining number of motor vehicle accidents in Europe and by more aggressive neurosurgical approaches to relieve high intracranial pressures that result in brain death [157-159]. Moreover, end-of-life practice in ICUs has changed over the past decades [160]. Decisions to forego life-sustaining treatments in the absence of clinical improvement are now recommended by European and American intensive care medicine societies and may be requested by families. Currently, 33% of deaths in ICUs throughout Europe occur after withdrawal of supportive treatment as compared to 8% from clinically diagnosed brain death and 20% after unsuccessful cardiopulmonary resuscitation, with wide differences in practice throughout Europe [161]. These developments may contribute to the rise of controlled DCD donation and may explain the fall in DBD donation.

Further expansion of the donor pool may be provided by transplantation of selected kidneys from older DCD, in particular for the increasing population of older kidney transplant candidates. Moreover, transplantation of organs other than kidneys from controlled DCD has been done successfully in the United States, the United Kingdom, and the Netherlands [162-164]. Follow-up studies of recipients of controlled DCD kidneys by several transplant centers have shown that functioning kidneys are equivalent to DBD kidneys with respect to long-term prognosis. Concerns about long-term repercussions for the higher incidence of DGF with DCD kidneys are not supported by the existing evidence. The major challenge now is to decrease the incidence of PNF. Unpublished analyses from our research group show that failure of both kidneys from a single donor does not occur more frequently than expected from chance alone. This finding strongly suggests that PNF is not inherent to donor or graft characteristics, but rather that the margin of safety with such organs is reduced, implying that all transplant personnel must be motivated to cooperate effectively in order to successfully transplant these delicate organs.

References


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