ORIGINAL ARTICLE

Transplantation of kidneys from uncontrolled donation after circulatory determination of death: comparison with brain death donors with or without extended criteria and impact of normothermic regional perfusion

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SUMMARY

The aim of this study was to compare the outcomes of kidney transplants from uncontrolled DCD (uDCD) with kidney transplants from extended (ECD) and standard criteria donors (SCD). In this multicenter study, we included recipients from uDCD ($n = 50$), and from ECD ($n = 57$) and SCD ($n = 102$) who could be eligible for a uDCD program. We compared patient and graft survival, and kidney function between groups. To address the impact of preservation procedures in uDCD, we compared *in situ* cold perfusion (ICP) with normothermic regional perfusion (NRP). Patient and graft survival rates were similar between the uDCD and ECD groups, but were lower than the SCD group ($P < 0.01$). Although delayed graft function (DGF) was more frequent in the uDCD group (66%) than in the ECD (40%) and SCD (27%) groups ($P = 0.08$ and $P < 0.001$), graft function was comparable between the uDCD and ECD groups at 3 months onwards post-transplantation. The use of NRP in the uDCD group ($n = 19$) was associated with a lower risk of DGF, and with a better graft function at 2 years post-transplantation, compared to ICP-uDCD ($n = 31$) and ECD. In conclusion, the use of uDCD kidneys was associated with post-transplantation results comparable to those of ECD kidneys. NRP preservation may improve the results of uDCD transplantation.

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Introduction

The use of kidneys following donation after circulatory determination of death (DCD) has been developed as a response to the shortage of available kidneys following donation after brain death (DBD). Indeed, DCD kidney transplantation has increased in prevalence worldwide [1] and constitutes a growing percentage of overall deceased-donor kidney transplantation, ranging from 14.3% in the United States [2] to 29% in the UK [3]. Nevertheless, these kidneys are not widely accepted, because in addition to important ethical and logistical concerns, the initial series reported an increased risk of primary nonfunction (PNF), delayed graft function (DGF), poor early and long-term graft survival rates [4,5], and related to warm ischemia time (WIT) (no-flow and low-flow periods). WIT is accepted as a necessary consequence of the use of these donors [6]. Selection of the donor, type of preservation, and reduction of cold ischemia time are the modifiable factors that could contribute toward the improvement of the results.

Different categories of DCD, originally called non-heart-beating donors, were defined by the Maastricht classification according to the circumstances of the death [7]. Controlled DCD (cDCD, category III) is the main source of these donors across the world, in which cardiac arrest, associated with a withdrawal of care, is to be expected. Despite a higher rate of DGF, graft survival rates from cDCD have improved over the three last decades [8], and similar graft and patient survival rates at 3 years post-transplantation have been reported recently by the UK registry and by a meta-analysis [9,10]. The uncontrolled DCD (uDCD, category II) concerns the unsuccessful resuscitation of patients who have suffered a witnessed cardiac arrest outside the hospital accompanied by unsuccessful cardiopulmonary resuscitation [7]. In this situation, warm ischemia is longer than in controlled DCD and exposes to more severe ischemia reperfusion injuries. However, few recent series have indicated that if the protocol process is strictly adhered to, uDCD kidneys could be a valuable source of organs for transplantation [11–16]. The uDCD program was initiated in France in 2006, using a national framework protocol from the Agency of Biomedicine (Agence de la Biomédecine, ABM). Angers and Nantes University hospitals have been enrolled in the French uDCD program since 2008. In May 2011, normothermic regional extra-corporal perfusion (NRP) replaced *in situ* cold perfusion through Gillot's cannula (ICP) [17].

The aim of this study was to analyze and compare the results of kidney transplantation from uDCD with those of kidney transplantation from DBD donation with or without extended criteria. The second objective was to analyze the impact of NRP on uDCD kidney outcomes.

Materials and methods

Study design

Data were prospectively obtained from 50 recipients who received a graft from uDCD between May 2008 and July 2013. The uDCD inclusion criteria for the recipients were those of the French national program (i.e., aged between 18 and 60 years, first kidney transplantation, no HLA sensitization using single antigen Luminex HD® technology, ABO compatibility, and the patient's informed consent to receive a uDCD kidney graft). In Angers center, women were considered at higher immunological risk and were initially excluded as potential recipients of uDCD kidneys. These carefully selected patients were compared with two other groups of patients, using the same selection criteria (but without any past or current Panel Reactive Antibody according to Luminex screening test), who received transplantation in our centers during the same period of time but from either an ECD or SCD. Kidney recipients from living donors, or simultaneous kidney–pancreas transplantation were excluded. The composition of the three groups is detailed in the flow chart (Fig. S1). All the data were prospectively collected by systematically screening patients' medical records. A local independent ethics committee (n ° 2015-18) approved the protocol study.

Definition of the donor categories

uDCD group

uDCD donor inclusion criteria, according to the French national protocol, were as follows: aged between 18 and 55, a witnessed cardiac arrest (all donors included were from Maastricht's category II [7]), at least 30 min of optimal care without cardiopulmonary resuscitation after an initial no-flow period of less than 30 min, absence of known renal disease, medical his-

tory of cancer, diabetes or hypertension, and traumatic cardiac arrest. The warm ischemia time (WIT), defined as the time between cardiac arrest and the beginning of organ preservation, had to be less than 150 min. All kidneys were machine perfused (Lifeport®; Organ Recovery System, Brussels, Belgium) over at least 2 h, perfusion pressure was monitored, and kidneys with vascular resistances above 0.3 mmHg/ml/min were discarded. To achieve transplantation, the kidney had to meet all the criteria described above and the morphologic aspect of the kidney graft, assessed by a surgeon, had to be normal and cold ischemia time had to be less than 18 h. If these criteria were not met, the kidneys were discarded.

ECD and SCD groups

The ECD group was defined according to the UNOS criteria: donor age $\geq$ 60 years, or age $\geq$ 50 years old if associated with at least two risk factors from among arterial hypertension history, serum creatinine > 130 μmol/l, or death caused by a cerebrovascular event [18]. Brain death donors who did not meet the criteria for ECD were classified in the SCD group [19].

Immunosuppression

As recommended by the French national protocol, all transplanted patients from uDCD donation received induction therapy with rabbit antithymocyte globulin (ATG, Thymoglobulin®, Genzyme, Sanofi-Aventis, Gentilly, France) at a dose of 1.25 mg/kg/day for 7–10 days. For ECD and SCD recipients, the induction therapy was ATG or anti-IL2R (Basiliximab, Simulect®, Novartis, Rueil Malmaison, France) and this was left at the discretion of the transplantation team.

Maintenance immunosuppression consisted of a triple regimen of calcineurin inhibitors (CNI), mycophenolate mofetil, and steroids. Some patients of the ECD and SCD groups were included in clinical trials with steroid free immunosuppressive regimens [20]. CNI were introduced as of the first day of transplantation, except for patients receiving ATG induction (introduction delayed from 5 to 7).

Kidney preservation strategies

Two perfusion techniques were used to preserve uDCD kidneys: "*In situ* Cold Perfusion," and Normothermic Regional Perfusion. The first was achieved using cold preservation solution (IGL-1®; Institut Georges Lopez, France) through a catheter placed in the femoral artery (Gillot's catheter) [17]. Preservation solution administration was achieved using a nonpulsatile perfusion pump, and the range of the volume of solution perfused varied from 14 to 20 l. NRP was obtained by cannulation of both the femoral artery and vein, connected to a blood oxygenator, a heat exchanger, and a nonpulsatile roller pump. Balloon aortic occlusion is performed at the same time to prevent brain and coronary perfusion. The NRP system was prepared systematically by the Extra-Corporeal System team [21]. NRP was supported for 60 min with a progressively increasing flow (2–3.7 l/min), the temperature exchange was set at 36 °C, and blood oxygenator was set to a Fi02 of 40%. The maximum time allowed for normothermic circulation was 4 h and cooling through the extracorporeal circulation was run just before organ retrieval.

Graft function and histological assessment

Graft function was assessed using the estimated glomerular filtration rate (GFR) which was calculated using the abbreviated modification of diet in renal disease formula (MDRD) [22]. PNF was defined as the absence of renal function recovery after kidney transplantation. DGF was defined as the need for at least one dialysis session during the first week post-transplantation, with subsequent recovery of renal function.

Patients transplanted in Nantes University Hospital received systematic graft histological assessments. Kidney transplant biopsies were performed before transplantation and at three and twelve months post-transplantation. Kidney graft lesions were classified by a pathologist according to the Banff 2007 classification [23]. All the recorded acute rejections were biopsy proven.

Definition of infectious episodes and malignancies

For all patients, we identified, by systematically screening patients' folders, infectious events and malignancies. Recorded infectious events were severe infections, defined as the need for a hospital stay. The diagnosis of cytomegalovirus (CMV) was considered if clinical manifestations were associated with polymerase chain reaction (PCR) positivity. BK-virus infections were recorded if the PCR for BK virus was positive in both blood and urine samples. All solid organ cancer, skin cancer, and post-transplantation lymphoma disorders (PTLD) were recorded.

Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables as an absolute value and percentage. Groups were compared using standard tests (χ^2 test for categorical variables; Mann–Whitney *U*-test or Kruskal–Wallis test for continuous variables). The Kaplan–Meyer method was used to analyze patient and graft survivals. A log-rank test was used to compare the survival curves. Univariate and multivariate logistic regression were used to analyze the factors associated with the presence of DGF and month 12 post-transplantation eGFR > 40 ml/min/1.73 m^2 in the uDCD group. The cutoff value of the eGFR (40 ml/min/1.73 m^2) was determined as the median value of the eGFR in the uDCD group at month 12 post-transplant. Associations between DGF or the eGFR and studied factors are given as odds ratios [11] with 95% confidence intervals. All *P* values were two-sided. A *P* value lower than 0.05 was considered statistically significant. Statistical analysis was performed using Graphpad Prism® (GraphPad, La Jolla, CA, USA) and SPSS software® 22.0 (IBM, Bois Colombes, France).

Results

Study population

A total of 209 patients were included in the study. A total of 50 (37 in Nantes, 13 in Angers), 57 (46 in Nantes, 11 in Angers), and 102 (63 in Nantes, 39 in Angers) transplant recipients were included in the uDCD, ECD, and SCD groups, respectively. The mean follow-up of the uDCD, ECD, and SCD groups was 26.8 ± 16.9 [0.3–61.7], 31.8 ± 17.7 [0.1–63.0], and 38.8 ± 18.0 [5.8–78.0] months, respectively. As expected, the mean ages of donors and recipients differed significantly between groups: patients and donors were significantly older in the ECD group compared to the uDCD and SCD groups. Donor serum creatinine was significantly higher in the uDCD group than other groups. Table 1 details donor-related characteristics. No difference was observed between groups with regard to dialysis duration before transplantation and distribution of original nephropathy. The uDCD group had more HLA mismatches and a shorter mean cold ischemia time than the ECD and SCD groups. Table 2 details the characteristics of the recipients and transplantations according to the three groups.

Patient and graft survival

Patient survival rate was 97.9%, 96.5%, and 100% at 12 months and 93.5%, 93.6%, and 100% at 36 months for the uDCD, ECD, and SCD groups, respectively (Fig. 1a). Patient survival within the SCD group was significantly greater than survival within the uDCD group ($P = 0.020$) and the ECD group ($P = 0.016$), and no significant difference was observed between the uDCD and ECD groups ($P = 0.884$).

Death-censored graft survival rates were 93.9%, 98.1%, 99.0% at 12 months and 86.5%, 92.4%, and 96.6% at 36 months within the uDCD, ECD, and SCD groups, respectively (Fig. 1b). The graft survival rate was significantly lower within the uDCD group when compared to the SCD group ($P < 0.03$), but not to the ECD ($P = 0.187$) group. In the uDCD group, six grafts were lost during follow-up: 3 due to PNF, 2 due to patient noncompliance, and 1 secondary due to immunosuppression arrest following the occurrence of Kaposi sarcoma. No PNF was observed within the ECD and SCD groups.

Table 1. Donor characteristics according to donation type.

	uDCD (*n* = 50)	ECD (*n* = 57)	SCD (*n* = 102)	*P* value uDCD vs. ECD	*P* value uDCD vs. SCD
Age (years)	45.5 ± 6.6	60.4 ± 6.9	39.5 ± 11.8	<0.001	0.001
Sex (men/women)	47/3	32/25	68/34	<0.0001	<0.001
Cause of death (%)					
Cardiac arrest	100	–	–	–	–
Stroke	–	82.5	35.3	–	–
Cardiorespiratory causes	–	3.5	15.7	–	–
Suicide	–	–	8.8	–	–
Polytraumatism	–	14.0	38.2	–	–
Others	–	–	2.0	–	–
Donor serum creatinine (μmol/l)	137.8 ± 23.6	102.4 ± 71.1	86.1 ± 42.5	0.001	<0.001

Table 2. Recipient and transplant characteristics according to donation type.

	uDCD (n = 50)	ECD (n = 57)	SCD (n = 102)	P value uDCD vs. ECD	P value uDCD vs. SCD
Recipient related					
Age	42.8 ± 10.2	53.3 ± 6.5	41.4 ± 10.3	<0.001	0.405
Sex (M/F)	46/6	42/15	90/12	0.051	0.967
Pretransplant RRT, n (%)	42 (84)	46 (80.7)	81 (79.4)	0.656	0.498
Duration of RRT (months)	24.9 ± 27.6	29.4 ± 20.5	31.4 ± 33	0.383	0.279
Time on the waiting list (months)	15.4 ± 12.8	17.5 ± 15.5	15.0 ± 14.5	0.460	0.842
Original nephropathy, n (%)					
ADPKD	13 (26)	16 (28.1)	19 (18.7)	0.810	0.294
IgA nephropathy	8 (16)	2 (3.5)	15 (14.7)	0.129	0.834
Other GN	5 (10)	7 (12.3)	25 (24.5)	0.139	0.035
TIN/urologic	8 (16)	6 (10.5)	13 (12.7)	0.402	0.584
Vascular nephropathy	3 (6)	9 (15.8)	8 (7.8)	0.109	0.669
Undetermined nephropathy	10 (20)	17 (29.8)	18 (17.7)	0.243	0.123
Others	3 (6)	0	4 (3.9)	0.098	0.684
Transplantation related					
HLA mismatches	4.4 ± 1.2	3.7 ± 1.0	3.5 ± 1.2	0.001	<0.001
No-flow duration (min)	7.1 ± 6.2	/	/	/	/
Low-flow duration (min)	135.8 ± 11.3 11.311.3	/	/	/	/
Cold ischemia time (min)	724.6 ± 199	1310 ± 394	1073.7 ± 450	<0.001	<0.001
Induction therapy, n (%)					
Thymoglobulin	50 (100)	7 (12.3)	15 (14.7)	<0.001	<0.001
Basiliximab	0	47 (87.7)	86 (85.3)	<0.001	<0.001
Maintenance therapy					
CNI, n (%)	47 (94)	55 (96)	101 (99)	0.662	0.104
FK, n (%)	44 (93)	48 (87)	89 (88)	0.781	0.896
Cyclosporine, n (%)	3 (7)	7 (13)	12 (12)	0.265	0.262
Delay for CNI introduction (days)	8.3 ± 5.1	0.79 ± 2.2	0.65 ± 1.8	<0.001	<0.001
Steroid use, n (%)	49 (98)	35 (64)	77 (76)	<0.001	<0.001
Steroid withdrawal at month 6, n (%)	29 (59)	16 (46)	49 (64)	0.222	0.615
Switch for mTOR at month 12, n (%)	13 (26)	7 (12)	9 (9)	0.069	0.004

RRT, Renal Replacement Therapy; APKD, Autosomal Polycystic Kidney Disease; GN, Glomerulonephritis; TIN, Tubulointerstitial Nephritis; CNI, Calcineurin Inhibitors.

Evolution of post-transplant kidney function

Incidence of DGF was significantly higher in the uDCD group in comparison with other groups. The delay in achieving a serum creatinine value below 250 μmol/l was significantly longer in the uDCD group when compared with the SCD group but not when compared with the ECD group. These data are summarized in Table 3. As illustrated in Figure 2, at month 3 and beyond, the estimated GFR (eGFR) did not differ significantly between the uDCD and ECD groups. The SCD group had a higher eGFR at 12 months post-transplantation than the other groups. At 36 months post-transplantation, the eGFR within the uDCD group was not statistically different to that of the SCD or ECD groups, but the ECD eGFR was statistically lower than the SCD eGFR ($P < 0.01$). Proteinuria at 12 months post-transplantation was comparable within the uDCD and SCD groups, while the ECD group had significantly higher proteinuria than the SCD group ($P < 0.01$, data not shown). Results of histological assessment are given in supplemental data.

Rejection episodes (AR), infectious, and carcinologic events

Incidence of cellular AR was significantly lower within the uDCD group compared to the ECD and SCD groups, and the mean number of AR per patient was significantly lower within the uDCD group compared to

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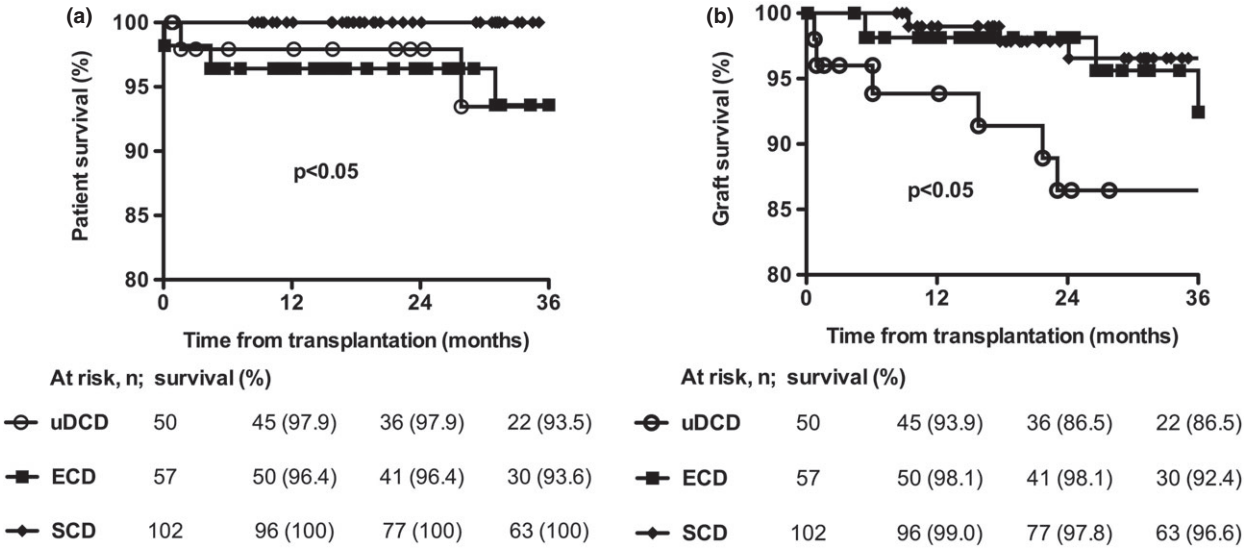

Figure 1 Patient (a) and death-censored graft (b) survivals in uDCD, ECD, and SCD groups. Comparison was made using log-rank test.

Table 3. Early post-transplant function.

	uDCD (n = 50)	ECD (n = 57)	SCD (n = 102)	P value uDCD vs. ECD	P value uDCD vs. SCD
PNF (n)	3	0	0	/	/
DGF, n (%)	33 (66)	23 (40)	28 (27)	0.008	<0.001
Mean HD sessions (n)	6.2 ± 3.6	4.0 ± 3.3	2.2 ± 2.1	0.022	<0.001
Delay to creatinine <250 μmol/l (days)	35.9 ± 25.4	22.9 ± 41.4	10.8 ± 17.5	0.071	<0.001

PNF, Primary Nonfunction; DGF, Delayed Graft Function; HD, Hemodialysis.

the ECD group, but not the SCD group. There was no significant difference between groups with respect to the delay time to AR and in the occurrence (% and delay) of donor-specific antibodies. Table 4 summarizes these results.

At year 3 post-transplantation, uDCD patients experienced a significantly lower number of infectious events compared to ECD patients, but no difference was observed between the uDCD and SCD groups. No difference was observed for incidences of viral infections. There was no difference in the prevalence of cancers between groups. Table 5 details these results.

Impact of the use of NRP

NRP has been the preservation modality in uDCD since May 2011, replacing ICP. We individualized the NRP-uDCD group and analyzed post-transplantation outcomes when compared to the ICP-uDCD group and ECD group. Among the 50 uDCD recipients, 31 had received kidneys which had been subject to ICP preservation and 19 had received kidneys which had been subject to NRP preservation. Donor-, recipient-, and transplantation-related characteristics were not different between NRP-uDCD and ICP-uDCD groups (Table 6). Firstly, patient and graft survival rates did not differ between the NRP-, ICP-uDCD, and ECD groups (Fig. S2). The eGFR was comparable between the NRP-uDCD, ICP-uDCD, and ECD groups until month 12 post-transplant. At month 24 post-transplantation, the eGFR was significantly higher within the NRP-uDCD group compared to other groups irrespective of whether graft loss was, or was not, taken into account (Fig. 3). Finally, we analyzed the impact of NRP use on DGF and the MDRD-eGFR at month 12. We observed that, following adjustment in consideration of the other factors analyzed, the use of NRP was associated with a decreased risk of DGF and a better graft function at month 12 post-transplantation within the uDCD group (Table 7).

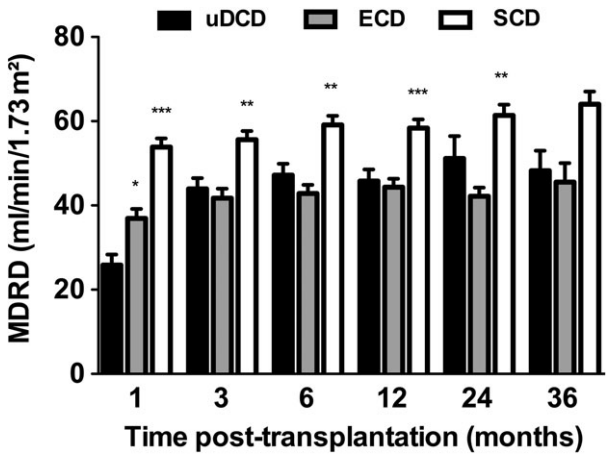

Figure 2 Post-transplant kidney function according to donation type (uDCD, ECD, and SCD). MDRD-eGFR (ml/min/1.73 m^2) between month 1 and month 36 post-transplantation. Kruskal–Wallis test as used to compare uDCD group to ECD and SCD groups. Comparison between uDCD and ECD or SCD group is indicated at each time analysis by an asterix (*<0.05, **<0.01, ***<0.001).

Discussion

The results of our study suggest that transplantation with uDCD kidneys provides similar results when compared with transplantation with kidneys from ECD. We found that patient and graft survival rates from uDCD were comparable to ECD but remained inferior when compared with the SCD group. Moreover, our results suggest that the use of NRP might improve early and long-term outcomes of uDCD transplantation.

Previous studies have demonstrated that kidneys from DCD, mainly cDCD, were a valuable source of kidneys and provided comparable results to those from DBD in terms of patient and graft survival, despite a higher rate of DGF [10,14,24]. It has become accepted in some countries that kidneys from DCD might provide a solution to the disparity between organ supply and demand. However, this procedure remains a marginal source of organ procurement given the importance of logistical difficulties and consequences of WIT. Most of the available studies focused on kidneys from cDCD [9,13,25,26], and many studies do not differentiate between controlled and uncontrolled DCD [10,24]. In two studies, transplantation results were similar between uDCD and cDCD [27,28] and encouraging data provided by monocentric studies have prompted some countries to develop a uDCD program [15,29]. In a meta-analysis, Kokkinos and al [10] showed that long-term survival and kidney function from DCD (controlled and uncontrolled) transplantation was similar to DBD transplantation.

PNF, occurring in 0% [16,26] to 26% of cases [4,15,27,28], has been the main limitation when it comes to worldwide use of uDCD. In our study, three cases of PNF were observed within the uDCD group (6%): two cases following ICP preservation, in which early scintigraphic examination and renal graft biopsy highlighted the absence of renal perfusion and suggested cortical necrosis. The latest case was observed within the context of pre-emptive transplantation and the patient started hemodialysis at month 6 post-transplantation. Even if debatable, PNF was deemed to apply in this patient's case, so as to not underestimate the PNF rate. For these three cases, contralateral kidneys were not later transplanted by other transplantation teams for reasons of poor morphological graft conditions in two cases and a high level of renovascular resistance index in the latter. Risk factors known to be associated with PNF are prolonged WIT, CIT, and donor age, but there is actually no clear threshold for the discarding of kidneys as the predictive value of each isolated parameter remains poor [27,30].

Table 4. Cumulative rejection episodes in uDCD, ECD, and SCD groups during follow-up.

	uDCD (n = 50)	ECD (n = 57)	SCD (n = 102)	P value uDCD vs. ECD	P value uDCD vs. SCD
Biopsy-proven AR, n	5	16	21	0.019	0.105
Acute cellular rejection, n (%)	3 (6)	16 (28.1)	21 (20.6)	0.004	0.031
Mean occurrence (months)	4.7 ± 1.5	8.7 ± 10.4	11.0 ± 15.7	0.866	0.930
1-year incidence, n (%)	3 (6)	12 (21.1)	16 (15.7)	0.028	0.118
Acute humoral rejection, n (%)	2 (4)	1 (1.8)	2 (1.9)	0.597	0.598
1-year incidence, n (%)	2 (4)	0 (0)	1 (1.0)	0.216	0.251
Donor-specific antigen occurrence, n	3	10	12	0.068	0.262
Mean occurrence (months)	14.0 ± 11.9	31.8 ± 5.3	31.3 ± 6.0	0.160	0.220

AR, Acute Rejection.

Table 5. Cumulative infectious and carcinologic events in uDCD, ECD, and SCD groups during follow-up.

	uDCD (n = 50)	ECD (n = 57)	SCD (n = 102)	P value uDCD vs. ECD	P value uDCD vs. SCD
Infectious events					
All type infection, n (%)	24 (48)	39 (68.4)	56 (54.9)	0.048	0.423
Bacterial infections					
Bacterial infection, n (%)	18 (36)	34 (59.6)	41 (40.2)	0.002	0.617
Number of bacterial events, n	40	72	67	0.005	0.693
1-year incidence	12 (24)	10 (17.5)	14 (13.7)	0.476	0.114
Viral infections, n (%)					
CMV disease	5 (10)	6 (10.5)	11 (10.8)	0.705	0.786
BKv disease	4 (8)	2 (3.5)	5 (4.9)	0.414	0.477
Cancers					
All types, n (%)	3 (6)	8 (14)	14 (13.7)	0.213	0.182
Nonmelanoma skin cancers	1	2	6	/	/
Solid cancer	0	5	5	/	/
PTLD	2	1	3	/	/

PTLD, Post-Transplantation Lymphoma Disorders.

Table 6. Donor, recipient, and transplant characteristics according to preservation strategy in uDCD group.

	NRP (n = 19)	ICP (n = 31)	P value
Donor related			
Age (years)	45.7 ± 5.7	45.3 ± 7.2	0.866
Sex (Men/Women)	19/0	28/3	0.278
Serum creatinine (μmol/l)	138.8 ± 21.3	137.1 ± 25.4	0.808
Recipient related			
Age	41.4 ± 10.1	43.8 ± 10.2	0.425
Sex (Men/Women)	16/3	28/3	0.661
Transplantation related			
HLA mismatches	4.2 ± 1.3	4.4 ± 1.1	0.480
No-flow duration (min)	6.4 ± 6.8	7.5 ± 5.8	0.560
Low-flow duration (min)	135.9 ± 11.5	135.7 ± 11.4	0.948
Cold ischemia time (min)	672.4 ± 214.2	756.5 ± 186.1	0.149
Early graft outcomes			
PNF (n)	1	2	/
DGF, n (%)	10 (53)	25 (81)	0.036
Mean HD sessions (n)	3.3 ± 3.7	5.4 ± 4.2	0.088
Delay to creatinine <250 μmol/l (days)	26.0 ± 3.7	42.4 ± 4.2	0.018

PNF, Primary Nonfunction; DGF, Delayed Graft Function; HD, Hemodialysis.

As expected, DGF was observed more frequently within the uDCD group than in other groups. The higher rate of DGF with kidneys from DCD is well known [11,28,31], but the impact of DGF on graft survival and renal function remains controversial [32]. It has been reported that graft survival was significantly better in recipients who developed DGF with kidneys from DCD compared to DBD recipients [33]. In addition, reduction of DGF by machine perfusion use in DCD does not provide the same beneficial effect on the rate of graft survival at 1 and 3 years as observed in DBD, suggesting different mechanisms for DGF [34].

Despite longer DGF, long-term graft function was similar between the uDCD and ECD groups, but remained significantly inferior to SCD at any time after transplantation. Previous results suggest that graft function obtained with kidneys from DCD was satisfactory, but few studies compared uDCD to DBD (SCD or ECD) in terms of graft function. Hanf *et al.* [16] have shown that graft function of kidneys from uDCD and

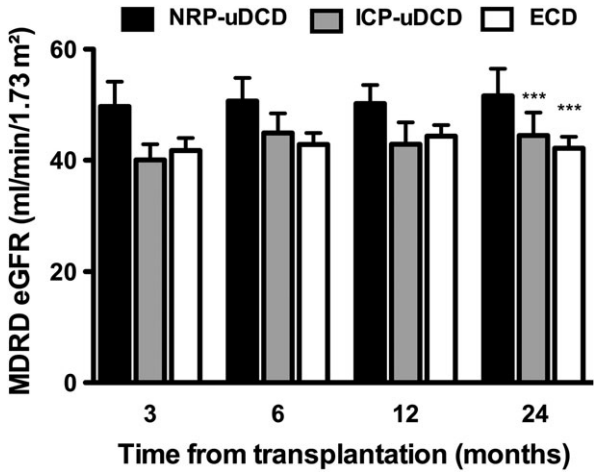

Figure 3 Post-transplant kidney function in NRP-uDCD, ICP-uDCD, and ECD groups. MDRD-eGFR between month 3 and month 24 post-transplantation according to donation types. Kruskal–Wallis test was used to compare NRP-uDCD group to ICP-uDCD and ECD groups. Comparison between NRP-uDCD and ICP-uDCD or ECD groups is indicated at each time analysis by an asterix (*<0.05, **<0.01, ***<0.001).

ECD is similar at one and 3 years after transplantation (according to UNOS criteria) but significantly lower than in a number of simultaneous pancreas and kidney transplantation recipients (regarded as the SCD group). Our results support similar conclusions, but we thought that the SCD as defined in our study were closest to the population of patients that could be candidates for transplantation using uDCD.

Some data have suggested that the extracorporeal support provided by NRP has the potential to improve organ quality, reducing both incidences of PNF and DGF [21,35,36]. Interestingly, we observed a decreased rate of DGF (OR 3.68 [1.06–12.8]) and similar 1-year post-transplantation graft function within both the NRP-uDCD and SCD groups. These results support the supposition that NRP can improve the early graft outcome, but this still needs to be confirmed by examination of a larger group of patients.

We observed a lower rate of BPAR within the uDCD group that may be explained by the systematic use of ATG as induction therapy for this group.

In contrast to other reports, there was no difference between groups with respect to infectious events [37]. Also, we did not observe any difference in interstitial fibrosis or borderline changes during histological analysis, as reported in previous studies [16,38].

Admittedly, our study has several limitations. Firstly, patients who were eligible for a uDCD procedure are carefully selected, which explains the small size of our study group. Secondly, we observed several baseline differences between the three groups, such as the patients' ages, immunosuppression regimens (induction and maintenance therapy), mean HLA mismatches, and cold ischemia times that could explain the lower rates of events like BPAR. These differences are directly linked to uDCD or ECD protocols. In France, ECD kidneys are preferentially given to old patients. Moreover, the uDCD protocol in France, issued by the ABM, requires ATG induction, and cold ischemia time of less than 18 h for transplantation to be permitted. These differences may represent a bias that could explain the

Table 7. Factors associated with DGF and eGFR>40 ml/min/1.73 m^2 in the uDCD group.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Factors associated with DGF						
Donor age (years)*	1.04	0.94–1.14	0.449	–	–	–
No-flow duration (min)*	0.92	0.88–1.10	0.880	–	–	–
Low-flow duration (min)*	0.91	0.83–0.98	0.022	0.92	0.84–0.99	0.035
Preservation duration (min)*	0.99	0.97–1.01	0.350	–	–	–
Cold ischemia duration (min)*	1.00	0.99–1.00	0.847	–	–	–
Use of NRP (yes)	0.22	0.05–0.89	0.034	0.17	0.03–0.87	0.034
Factors associated with eGFR > 40 ml/min/1.73 m^2 at year 1 post-transplant						
Donor serum creatinine*	0.93	0.97–1.02	0.561	–	–	–
Donor age (years)*	0.98	0.90–1.09	0.790	–	–	–
Acute rejection (yes)	0.18	0.02–1.69	0.134	–	–	–
Recipient age (years)*	0.98	0.92–1.04	0.527	–	–	–
Use of NRP (yes)	4.12	1.20–14.2	0.025	3.68	1.06–12.8	0.04

DGF, Delayed Graft Function; eGFR, Estimated Glomerular Filtration rate; NRP, Normothermic Regional Preservation.
*Each unit incrementation.

disparity between groups regardless of preservation strategy.

Conclusion

In summary, our work supports that view that kidneys from uDCD provide comparable post-transplant results when compared with kidneys from ECD. We suggest that uDCD kidneys should be considered for candidates awaiting ECD kidneys. The French protocol was in fact amended in 2013 and means that uDCD donation can now be accessed by recipients older than 60 years. Optimal preservation and careful selection of the kidneys may reduce the risk of PNF. These preliminary results suggest that NRP may improve the short- and long-term outcome of uDCD transplantation.

Authorship

JD: participated in conducting the study, collecting the data for the study and in the writing of the manuscript. JA: participated in the writing of the manuscript and in the statistical analysis. MV: participated in revising the manuscript. EL: participated in revising the manuscript. LD: participated in revising the manuscript. FT: participated in revising the manuscript. KR: participated in revising the manuscript. JS: participated in revising the manuscript. GK: participated in revising the manuscript. GB: participated in revising the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flowchart of the study.

Figure S2. Patient (a) and graft (b) survival rates of NRP uDCD, ICP uDCD and ECD groups.

Data S1. Histological assessment.

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