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ORIGINAL ARTICLE

Impact of pulsatile perfusion on postoperative outcome of kidneys from controlled donors after cardiac death

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Summary

Pulsatile perfusion (PP) might be a cost-effective cold preservation technique to reduce the incidence of delayed graft function (DGF) in kidneys from deceased donors. With the aim to address whether PP can reduce the incidence of DGF in kidneys from controlled donors after cardiac death (cDCD), we compared the clinical outcome of 30 recipients of kidneys from cDCD preserved by static cold storage (cDCD-SCS) with 30 recipients of cDCD kidneys preserved by PP (cDCD-PP). The end-points were the incidence of primary nonfunction (PNF), DGF and acute rejection (AR), the length of hospitalization, 1, 3, 6 and 12-months graft function, graft survival and patient survival. Donor, recipient and preimplantation data were well matched. DGF was significantly lower (53.3% vs. 86.6% $P < 0.001$) and the length of hospitalization shorter (10 vs. 14 days $P < 0.033$) in the cDCD-PP group. Similarly, postoperative and short-term graft function (7 and 30 days and 6 and 12 months, respectively) was statistically better in the cDCD-PP than in the cDCD-SCS. In summary, in this cohort, clinical introduction of PP was associated with a significant reduction of DGF, shorter hospitalization and better graft function than SCS.

Introduction

Kidney transplantation is the most cost-effective treatment for patients with end-stage renal failure (ESRF) [1]. Unfortunately, the gap between transplants performed and the waiting list continues to widen. To counterbalance this trend, the use of kidneys from donors after cardiac death (DCD) has been proposed as one effective strategy to overcome this shortage crisis. Kidneys from DCD may increase the donor pool by 25–40% [2–5] and have shown similar long-term graft survival to kidneys from conventional deceased donors after brain death (DBD) [6–10]. However, the high incidence of delayed graft function (DGF) associated with these organs has limited or even precluded their routine use in many transplant units [11–12]. DGF complicates post-transplant management, increases the duration and costs of hospitalization, and has an adverse effect on long-term graft survival [13–17]. There is no specific treatment yet available and, undoubtedly, new strategies to reduce the incidence of DGF in DCD kidneys are required.

Kidneys from DCD are submitted to an unavoidable period of warm ischaemic insult followed by a variable period of cold ischaemic injury, but are not subjected to the physiological disturbances secondary to brain death [18,19] DGF is a frequent clinical manifestation of ischaemic acute tubular necrosis (iATN) [20,21]. DGF has been related to the length of warm and cold ischaemic times [18–21] and limiting these periods of injury during preservation, might reduce the incidence of DGF of kidneys from DCD. Although limiting pretransplantation warm ischaemia time (WIT) for kidneys from DCD is important [22], minimization of cold ischaemic time (CIT) is also a desirable goal [23–26]. However, it is still a matter

of debate as to whether simply reducing CIT is an adequate strategy to overcome the high incidence of DGF in DCD kidney transplantation or whether substantial improvements to the current preservation technique for these organs are needed. The intuitive thought that ischaemic kidneys from DCD should be subjected to shorter CIT to improve outcome is gathering support [9,22]. However, given the time required for HLA typing, cross-matching and admitting suitable recipients, reaching the proposed target of less than 12 h of CIT would be difficult to achieve – particularly when other organs (liver, pancreas, in which the issue of ischaemia is still more critical) are recovered from the same donor and may be transplanted in the same unit. Therefore, a different strategy is needed to reduce the incidence of DGF in kidneys from DCD.

There is still no definitive evidence as to whether the use of pulsatile perfusion (PP) is a cost-effective strategy to preserve kidneys from DCD, although, retrospective evidence suggests that PP does reduce the incidence of DGF of kidneys from deceased donors, particularly in those from extended criteria DBD and DCD [27–31]. This evidence comes mainly from the analysis of US databases, and it has not been confirmed by an appropriately powered randomized controlled trial [32]. Moreover, because there is little published information on the relative benefits of PP compared to shorter CIT, it is still uncertain whether PP itself diminishes the incidence of DGF in kidneys from controlled DCD (cDCD). With the aim of addressing these questions we analysed the impact of introduction of PP as preservation technique on the clinical outcome of recipients of kidneys from our cDCD kidney transplantation programme.

Methods

Patients and comparative analysis

The demographic data and clinical outcome of patients transplanted in the Oxford Transplant Centre between 1st March 2002 and the 31st December 2005 were collected prospectively in our transplant-database, retrospectively confirmed by review of the clinical files and analysed. To address whether PP can diminish the incidence of DGF in cDCD, we performed a comparative analysis between our first 30 recipients of kidneys from cDCD preserved by static cold storage (cDCD-SCS) and 30 sequential recipients of cDCD kidneys preserved by PP (cDCD-PP).

Organ donation and surgical retrieval

All cDCD's were Maastrich category 3, under 65 years of age and had suffered irrecoverable brain injury but did not meet the criteria for diagnosis of brain-stem death. None had primary renal disease, diabetes mellitus, systemic sepsis or malignancy. However, 13% (8/60) had previous history of chronic hypertension. In both groups, donors were transported to the operating theatre immediately after 10 min of cardiac arrest. Both kidneys were perfused *in situ* with 1 l of 0.9% saline solution (Baxter, Medical, Houston, TX, USA) at room temperature containing 1.5 million IU of streptokinase (Streptase®; CSL Behring UK Ltd, West Sussex, UK) followed by 2 l of 4 °C Marshall's solution (Soltran Kidney Perfusion Solution®; Baxter, Medical, Houston, TX, USA) with 10 000 IU of heparin (Monoparin®; CP, Pharmaceuticals Ltd, Wrexham, UK). After donor nephrectomy, each kidney was perfused *ex vivo* with 1 l of cold Marshall's solution with 5000 IU of heparin and routine surgical back-table was performed. It was only after the back-table when the preservation techniques differed between both groups. Before packing and transport, the organs in the SCS group were surrounded by 250 ml of cold Marshall's solution, bagged and submerged in ice, whereas in the PP group, the kidney was put into the Life-port kidney perfusion device® (Organ Recovery Systems, Des Plaines, IL, USA) and continuously perfused with 1 l of 4 °C KPS-1® solution, (UW solution for machine perfusion; Organ Recovery Systems) to which 40 U of human insulin (Actrapid®, Novo Nordisck A/S, UK), 8 mg of dexamethazone (DBL®; Faulding Pharmaceuticals Plc, Warwickshire, UK) and 10 ml of 20% Mannitol (Polyfusor®; Fresenius Kabi Limited, Warrington, UK) had been added.

The initial perfusion pressure was set at 40 mmHg and was adjusted with the aim to maintain renal resistance (RR) below 0.40. Although, perfusion parameters (pressure, flow and RR) were not taken as viability test, the dynamics of these parameters were monitored and recorded (data not shown) and no kidney was discarded on the basis of these parameters.

Induction and maintenance immunosupressive regimes

All cDCD received perioperative induction therapy (IT) with polyclonal (Anti-Thymocyte Globulin, ATG®; Fresenius, Kabi Limited, Warrington, UK) or monoclonal antibodies: Basiliximab (Simulect®; Novartis Pharma, Numberg, Switzerland) or alemtuzimab (Campath-1H®, Berlex, Montville, NJ, USA) Maintenance therapy in both groups was based on tacrolimus (TAC), mycophenolate mofetil (MMF) and prednisolone (PDN). All patients treated with alemtuzimab remained steroid-free after transplantation. In this subgroup, TAC was switched to sirolimus (SIR) at 6 months post-transplant. In all cases of DGF, introduction of full-dose of calcineurin inhibitors (TAC) was delayed until graft function recovered or the diagnosis of acute rejection (AR) was established.

Table 1. Comparison of donor and recipient characteristics and pre-implantation data between controlled DCD preserved by SCS (cDCD-SCS) and PP (cDCD-PP).

	cDCD-SCS *n* = 30 (100%)	cDCD-PP *n* = 30 (100%)	*P*-value§
Donor data			
Age (years)*	40.3 ±2.6/17–60	41.6 ± 2.9/17–61	NS
Gender: Female:Male†	12:18 (40:60)	13:17 (43:57)	NS
Cerebrovascular disease†	12 (40)	11 (37)	NS
History of hypertension†	5 (16)	3 (10)	NS
Creatinine clearance (μmol/l)‡	103 (69–120)	95 (65–106)	NS
Recipient data			
Age (years)*	54.1± 2 /34–76	47.2 ± /20–69	<0.006
Gender: female : male†	11:19 (37:63)	10:20 (33:67)	NS
Days on waiting list†	410 [176–683]	493 [291–1220]	NS
First transplant†	29 (97)	25 (84)	NS
Pre-transplant antibodies†	10 (33)	16 (40)	NS
Highly sensitized (PRA* >85%)†	1 (3)	2 (7)	NS
Number of HLA mismatches†			
0	1 (3)	1 (3)	NS
1–2	14 (47)	8 (27)	NS
3–4	15 (50)	18 (60)	NS
5–6	0 (0)	1 (3)	NS
Preimplantation data			
Warm ischaemia time (min)‡	18.5 (15–23)	18 (13–30)	NS
Cold ischaemia time (min)‡	1076 (876–1320)	1115 (918–1363)	NS
<12 h	1 (3)	0 (0)	NS
<4 h	4 (12)	4 (12)	NS
14–18 h	8 (27)	9 (30)	NS
18–24 h	12 (40)	10 (33)	NS
>24 h	5 (17)	7 (23)	NS
Implantation time (min)‡	40 (32–60)	55 (43–63)	<0.003

PRA, panel reactive antibodies.
*Values are mean/range.
†Values are number (%).
‡Values are median (interquartile range).
§Significance $P < 0.05$. Two tailed *t*-test.

Demographics and clinical study endpoints

Demographic and clinical variables studied are shown in Table 1. End-points were the incidence of primary nonfunction (PNF), immediate graft function (IGF), and DGF, AR, length of hospitalization, 1-, 6-month and 1-year serum creatinine, graft and patient survival rates. PNF was defined as a graft that never achieved enough function to maintain the patient without regular dialysis from the time of transplantation. The indications for postoperative dialysis were hyperkalaemia (>6.6 mmol/l or <6.5 with ECG changes), fluid overload and uncontrollable acidosis. DGF was defined as the need for dialysis during the first week after transplantation, excluding those episodes of dialysis secondary to fluid overload or hyperkalaemia during the first 24 h post-transplant. Acute rejection was retrospectively assessed using histological confirmation reports (Banff-97 criteria [33]) Implantation data are shown in Table 1. WIT was defined as the interval between cardiac arrest and the beginning of *in situ* cold perfusion and CIT as the time from *in situ* cold perfusion to reperfusion of the graft with arterial blood in the recipient. Implantation time was measured as the interval from when the kidney was out of ice to the time in which the arterial clamp was 'off'. Renal transplant survival and patient survival were defined respectively as time from transplantation to the date when a patient returned to regular dialysis or died. In the survival analysis, death with a functioning transplant was censored at the date of the patient's death.

Statistical analysis was performed using the SPSS.14 statistical package (SPSS inc, Chicago, IL, USA). Graft survival rates were calculated using the Kaplan–Meier product limit method. *t*-test and Fisher's exact test were used to compare continuous or categorical variables as appropriate. Two-tailed *P*-values <0.05 were considered to indicate statistical significance.

Results

From March 2002 to December 2005, 246 kidney transplants were performed at the Oxford Transplant Centre with grafts from deceased donors. One hundred and eighty-six (75%) were performed with grafts from DBD and 60 (25%) with kidneys from Maastrich category 3 DCD (cDCD). The Oxford cDCD kidney transplantation programme started on March 1st, 2002. During the first 2 years all kidneys from cDCD were preserved by SCS whereas from March 1st, 2004 to December 31st, 2005, all kidneys from cDCD were preserved by pulsatile perfusion.

Demographics and peri-implantation data

Donor and recipient data of cDCD-SCS and cDCD-PP groups are shown in Table 1. Patients in both groups were well matched in terms of donor and recipient characteristics. There were no differences in donors' age, gender, cause of death and final creatinine clearance. Equally, there was no difference on recipient gender, primary disease, days on waiting list, number of transplant, level of pre-transplant antibodies and HLA mismatch between both groups. The only difference between both groups was recipient age. In the cDCD-PP group recipients were younger than in the cDCD-SCS (47 years/20–69 vs. 54 years/34–76 $P < 0.006$). Donor organ recovery and preservation protocols were similar in both groups with no significant difference in the length of WIT and CIT (Table 1). Only nine (15%) kidneys of our cDCD cohort had less than 14 h of CIT. From the remainder group, 17 (28%) were preserved between 14 and 18 h, 22 (37%) between 18 and 24 h and 12 (20%) more than 24 h. There was no difference in the distribution of these kidneys between cDCD-SCS and cDCD-PP groups. Although the median CIT in both groups was 18 h in both groups, kidneys in the cDCD-PP group were more likely to have longer CIT than those in the cDCD-SCS group (Table 1). Implantation time was significantly longer in the cDCD-PP than in the cDCD-SCS (55 vs. 40 min $P < 0.003$), essentially because all kidneys in the cDCD-PP group were weighed and the arterial patch trimmed before surgical implantation (Table 1).

Induction therapy (IT) in the cDCD-SCS group was mainly based on polyclonal antibodies (94%) whereas in the cDCD-PP group the majority of patients were treated with monoclonal antibodies (93%) (Table 2) In the

Table 2. Comparison of immunosuppressive regime and clinical outcome between controlled DCD preserved by SCS (cDCD-SCS) and PP (cDCD-PP).

	cDCD-SCS *n* = 30 (100%)	cDCD-PP *n* = 30 (100%)	*P*-value‡
Induction therapy*			
Anti-thymocite Globuline (ATG§)	28 (94)	2 (7)	<0.000
Basiliximab	1 (3)	13 (43)	<0.002
Alemtuzimab	1 (3)	15 (50)	<0.006
Maintenance therapy*			
TAC/Sir + MMF	30 (100)	30 (100)	NS
Prednisolone	30 (100)	15 (50)	<0.000§
Postoperative outcome			
Primary nonfunction*	0 (0)	0 (0)	NS
Delayed graft function*	25 (86.6)	16 (53.3)	<0.000
First fifteen transplants	14 (93)	8 (53)	NS
Second fifteen transplants	12 (80)	8 (53)	NS
Hospitalization (days)†	14 (9–22)	10 (6–12)	<0.033
Acute rejection	1 (3.5)	1 (3.2)	NS
Graft lost	1 (3.5)	1 (3.5)	NS
Patient lost	1 (3.5)	1 (3.5)	NS
Medium-term outcome			
Clinical follow-up†	1021 (840–1180)	420 (367–516)	<0.000
Acute rejection*	1 (3.5)	3 (10)	NS
1 year graft survival*	28 (93)	30 (100)	NS
2 years graft survival*	27 (87)	29 (93)	NS
1 years patient survival*	28 (93)	30 (100)	NS
2 years patient survival*	27 (87)	29 (93)	NS

TAC, tacrolimus; MMF, mycophenolate of mofetil.
*Values are number (%).
†Values are median (interquartile range).
‡Significance $P < 0.05$. Two tailed *t*-test.
§Significance $P < 0.05$. Fisher's exact test.

cDCD-SCS 28 patients (94%) received anti-thymocyte globulin (ATG), one patient (3%) received basiliximab and one (3%) received alemtuzimab. In contrast, in the cDCD-PP only two patients (7%) were induced with ATG, 13 (43%) were treated with basiliximab and 15 (50%) received alemtuzimab. Maintenance was based on TAC, MMF and PDN. However, 15 (50%) in the cDCD-PP were steroid-free after transplantation and received SIR instead of TAC after the 6th month post-transplant.

Clinical outcome

The median follow-up was 1021 days in the cDCD-SCS and 420 days in the cDCC-PP and 27 (87%) and 28 (93%) recipients reached 2-years follow up respectively. Clinical introduction of PP in our cDCD programme did reduce the incidence of DGF in our cohort of cDCD. The rate of DGF diminished from 86.6% in the cDCD-SCS group to 53.3% in the cDCD-PP group ($P \leq 0.000$) (Table 2). The benefit in terms of DGF was reflected on the length of hospitalization (LH) and graft function. Patients in the cDCD-PP had shorter hospitalization (10 days vs. 14 days, $P < 0.033$) and lower creatinine levels at 7 and 30 days [259 ± 27 (145) vs. 461 ± 33 (179) μmol/l, $P = <0.000$ and 199 ± 20 (111) vs. 282 ± 33 (175), $P = 0.031$]. Similarly, graft function at 6 months, [163 ± 10 (52) vs. 201 ± 21 (111) μmol/l, $P = 0.05$] and 1-year [154 ± 9 (46) vs. 193 ± 25 (110) μmol/l, $P = 0.05$] was better in the cDCD-PP group than in the cDCD-SCS group (Fig. 1). Postoperative and 1-year actuarial uncensored graft survival was better in the cDCD-PP group than in the cDCD-SCS but this difference did not reach significance (100% vs. 93%, $P = 0.64$) (Fig. 2).

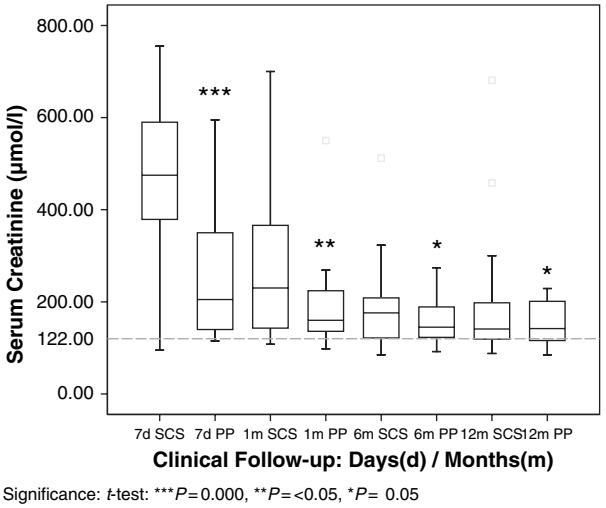

Figure 1 Postoperative and 1-year graft function of kidneys from cDCD-SCS and cDCD-PP. Clinical follow-up is shown in days (d) and months (m) (*x*-axis) and levels of serum creatinine in μmol/l (*y*-axis). Series: preservation technique. SCS, static cold storage; PP, pulsatile perfusion.

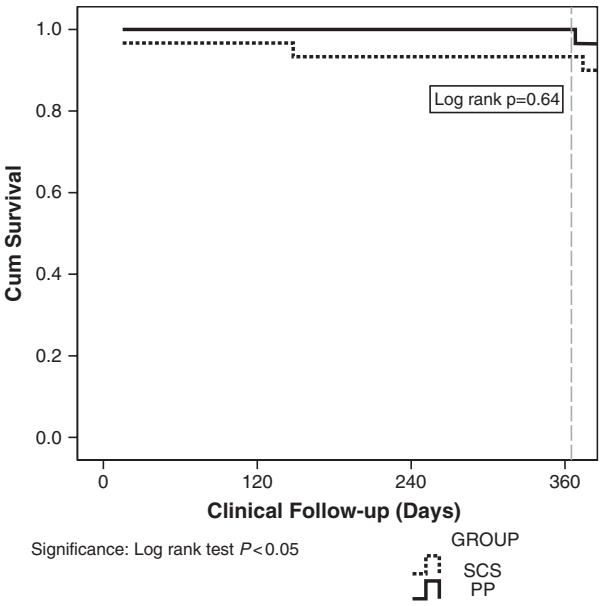

Figure 2 Postoperative and 1-year graft survival of kidneys from cDCD-SCS and cDCD-PP. Clinical follow-up is shown in days (*x*-axis) and graft survival as Cum survival (*y*-axis). Series: Preservation technique. SCS, static cold storage; PP, pulsatile perfusion.

Discussion

The survival benefit [1] and better quality of life [34,35] of patients that receive kidney transplants over those remaining on the waiting list has been recognized. Unfortunately, the gap between the number of transplants performed and the waiting list continues to increase. In the United Kingdom the number of patients on the national kidney active waiting list grows by 10–15% per year, whereas the number of transplants from conventional DBD is, if anything, moving in the opposite direction. Moreover, despite the rise in the number of transplants performed with kidneys from living donors (LD) from 463 in 2004 to more than 600 at the end of 2006, the imbalance between organ demand and supply continues. To counterbalance this trend, UK Transplant has recommended the use of kidneys from DCD as an effective strategy to increase transplant rates [36,37]. Currently, fourteen transplants units in the UK have a DCD kidney transplantation programme and an increase of 20–40% in the kidney donor pool has been reported by some of these units [38]. In line with these encouraging results, during 2002–2005, our own DCD programme grew from five transplants in 2002 to 24 in 2005, constituting 22%

of our kidney-alone transplant activity during 2005 (data not shown) and confirming the potential benefits of the introduction of kidney transplantation from DCD.

Recent reports underscore the benefit of minimizing of CIT on DGF and graft survival of kidneys from DCD and suggest that the outcome of kidney transplants from these donors may be superior when CIT is kept under 14 h. Sudhindran *et al.*, reported that when kidneys from cDCD were transplanted within 13 h of CIT, the incidence of DGF decreased by 20% and 5-year graft survival was similar to that obtained from kidneys from conventional DBD transplanted contemporaneously [22] Similarly, Doshi *et al.*, showed that kidney grafts from DCD with less than 14 h of CIT achieved similar 1 and 5-year graft survival to conventional DBD [7] More recently, Locke *et al.*, showed that when CIT was limited to less than 12 h the incidence of DGF in DCD kidneys was reduced by 15% and approached that of DBD [9] These results suggest that kidney transplantation from DCD would significantly benefit from CIT less than 14 h and that it would be desirable and cost-effective to keep CIT below 12 h. However, even if these findings are confirmed in randomized studies and appropriate alterations are made to allocation policies to minimize CIT, this strategy should overcome some intrinsic logistic difficulties. To achieve CIT lower than 14 h might exclude the possibility of transplanting more than one organ from a single DCD donor by the same surgical team – for example, in our transplant unit when pancreas and kidneys are both retrieved from a DCD, kidneys are transplanted after the pancreas has been implanted. In the data presented here, we have only achieved the proposed target of <14 h of CIT in nine (15%) of our cDCD kidneys – this illustrates the logistic challenge posed by such a strategy. On the contrary, clinical introduction of PP has also been associated with a significant improvement in graft function and survival of all marginal donor kidneys including those from extended criteria DBD, DCD or those kidneys submitted to longer CIT [27,30]. Although our study is not a controlled randomized trial and two relatively small consecutive cohorts of patients have been compared, our results show that introduction of cold preservation by PP does significantly reduce both incidence of DGF and length of hospitalization as well as allowing better graft function in a homogenous cohort of cDCD subjected to more than 14 h of CIT. These encouraging results are in line with those coming from retrospective analysis of large DCD kidney registries [7,9,10]. However, these results should be confirmed by well-powered prospective randomized controlled trials. Two large randomized clinical trials of PP versus SCS are currently ongoing in Europe. The Eurotransplant multicenter clinical trial is comparing PP and SCS in kidneys from DCD and DBD. Whereas, the PPART study in the UK is comparing both techniques only in kidneys from DCD. Unfortunately, early results from these trials are conflicting and inconclusive. Recently, Moers C *et al.* reported the results of the Eurotransplant trial during the last ESOT annual conference in Prague, concluding that there was no difference in the incidence of DGF between PP and SCS (Cyril Moers, personal communication). In contrast, early clinical outcome of recipients of kidneys from cDCD included in the PPART study in our unit show lower incidence of DGF in the PP group (data not shown), suggesting that kidneys from cDCD preserved by PP might have better early post-transplant graft function than those preserved by SCS.

In our study, the significant differences between the cDCD-SCS and cDCD-PP groups were recipient age, preservation solution and the immunosuppressive regimes used. cDCD-PP recipients were younger than those in the cDCD-SCS. Some multivariate analyses have associated recipient age over 45 years with inferior graft survival of kidneys from DBD [39–41]. However, in contrast to graft survival, no significant association between recipient age and the incidence of DGF in DBD has been found and little is known about the effect of recipient age on the incidence of DGF in cDCD [42]. Therefore, although we cannot exclude an age-related effect, our results suggest that the lower incidence of DGF in the cDCD-PP group is more likely to be related to the different modes of preservation.

Clinical organ preservation has improved little since the breakthrough introduction of University of Wisconsin solution (UW) by Belzer and Southard in the late 1980s [43]. UW remains the gold standard solution for organ preservation, despite evidence to suggest that some additives in UW may not be required [44] and indeed do more harm than good [45] and that the potential benefit of UW only emerges in those cases with CIT longer than 24 h [46]. We believe that a comparison between SCS and PP in which both groups are preserved with the same solution (UW-CSS and UW-MP, respectively) would be valuable, but the retrospective nature of our analysis excluded this possibility. Although we cannot rule out the effect of UW-MP on the lower incidence of DGF and better graft function in our cDCD-PP group, the fact that in both groups, around 80% of the kidneys were cold preserved for less than 24 h enables us to believe that any impact of the UW-MP in the cDCD, is not the main cause of the better early allograft function in the PP group. Moreover, a recent analysis of 9389 kidney transplants performed by the UK transplant [47] showed no difference in 1-year graft survival between kidneys preserved by UW and Marshall's solution (Hazard ratio UW versus Marshall: 1.00 vs. 1.03, $P = 0.8$). Similarly, we use

a cocktail of substances as additives to the UM-MPS (Dexametasone, Insuline and Mannitol) because some of these substances have been associated with better graft function after transplantation in some studies [48–51] although none of them has been confirmed by prospective randomized trials.

Induction therapy with polyclonal antibodies (anti-thymocyte globulin) or monoclonal antibodies (basiliximab, daclizumab or alemtuzimab) is associated with lower rates of AR and DGF than placebo in kidney transplantation. In addition, there is an increasing body of evidence suggesting the benefit of induction therapy with antibodies, possibly related to a protective effect against allo-antigen independent immune responses associated with ischaemia-reperfusion injury [52]. Randomized trials suggest that ATG is superior to basiliximab in reducing the incidence of AR, but fail to show any significant difference in the incidence of DGF [53–55]. Therefore, we do not believe that the particular drug used for induction played a major role in the lower incidence of DGF observed in the cDCD-PP group. Furthermore, there was no statistical difference in the incidence of DGF, AR, graft function and survival between those recipients of basiliximab or alentuzumab in the cDCD-PP group (data not shown). However, it is clear that the issue of induction therapy in DCD kidney transplantation needs to be addressed in randomized controlled trials of polyclonal versus monoclonal antibodies.

Undoubtedly, in a sequential study such as this, the issue of the learning curve should be considered – this is a well-recognized phenomenon in both cancer surgery and transplantation [56]. Although a larger number of cases is needed to dilute out this possible effect on the higher incidence of DGF in the cDCD-SCS, the similar results obtained from the comparison of the first fifteen patients with the second fifteen in both groups suggest that both, the higher incidence of DGF in the cDCD-SCS and the lower incidence of DGF in the cDCD-PP group are more likely to be related to the preservation technique than to a learning process. Finally, the potential benefit of PP on long-term survival of kidneys from DCD is still a matter of debate and will require long-term follow-up of randomized studies or careful analysis of registry data.

Conclusions

In our unit, the introduction of cold preservation by pulsatile perfusion of kidneys from controlled nonheart-beating donors was associated with significantly reduced the rate of DGF, the length of hospitalization superior graft function compared to static cold storage. The results of our analysis highlight the potential of pulsatile perfusion as one effective strategy to diminish the incidence of DGF and improve graft function in kidneys from controlled DCD. However, the analysis of the results from controlled randomized trials with larger number of DCD is still needed despite our encouraging results. Whether these benefits extend to kidneys from optimal cDCD transplanted with less than 14 h of cold ischaemia time and the cost-benefit of machine perfusion remain questions that deserve further analysis.

Authorship

JJP-M, SVF, PJF: designed and performed the analysis of the data and wrote the paper. JJP-M, HHC: collected the data. AM, IQ, SS, AV, CD, PJF: performed the surgical procedures and contributed to the analysis and review of the manuscript.

References

1. Wolfe RA, Ashby VB, Milford EL, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
2. Daemen JHC, Oomen APA, Kelders WPA, *et al.* The potential pool of non-heart-beating kidney donors. *Clin Transplant* 1997; **11**: 149.
3. Sanchez-Fructuoso AI, Prats D, Torrente J, *et al.* Renal transplantation from non-heart-beating donors: a promising alternative to enlarge the donor pool. *J Am Soc Nephrol* 2000; **11**: 350.
4. Lacroix JD, Mahoney JE, Knoll GA. Renal transplantation using non-heart-beating donors: a potential solution to the organ donor shortage in Canada. *Can J Surg* 2004; **47**: 10.
5. Gagandeep S, Matsouka L, Mateo R, *et al.* Expanding the donor kidney pool: utility of renal allografts procured in a setting of uncontrolled cardiac death. *Am J Transplant* 2006; **6**: 1682.
6. Doshi MD, Hunsicker LG. Short and long-term outcomes with the use of kidneys and livers donated after cardiac death. *Am J Transplant* 2007; **7**: 122.
7. Kokkinos C, Antcliffe D, Nanidis T, Darzi AW, Tekkis P, Papalois V. Outcome of kidney transplantation from non-heart-beating versus heart-beating cadaveric donors. *Transplantation* 2007; **83**: 1193.
8. Tojimbara T, Fuchinoue S, Iwadoh K, *et al.* Improved outcomes of renal transplantation from cardiac death donors: a 30 years single center experience. *Am J Transplant* 2007; **7**: 1.
9. Locke JE, Segev DL, Warren DS, *et al.* Outcomes of kidneys from donors after cardiac death: implications for allocation and preservation. *Am J Transplant* 2007; **7**: 1797.
10. Chapman J, Bock A, Dussol B, *et al.* Follow-up after renal transplantation with organs from donors after cardiac death. *Transpl Int* 2006; **19**: 715.

11. Butterworth PC, Taub N, Doughman TM, *et al.* Are kidneys from non-heart-beating donors second class organs? *Transplant Proc* 1997; **29**: 3567.
12. Vanrenterghem Y. Cautious approach to use of non-heart-beating donors. *Lancet* 2000; **356**: 528.
13. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RL. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997; **63**: 968.
14. McLaren AJ, Jassem W, Gray DW, Fuggle SV, Welsh KI, Morris PJ. Delayed graft function: risk factors and the relative effects of early function and acute rejection on long-term survival in cadaveric renal transplantation. *Clin Transplant* 1999; **13**: 266.
15. Quiroga I, McShane P, Koo DD, *et al.* Major effects of delayed graft function and cold ischaemia time on renal allograft survival. *Nephrol Dial Transplant* 2006; **21**: 1689.
16. Matas AJ, Gillingham KJ, Elick BA, *et al.* Risk factors for prolonged hospitalization after kidney transplants. *Clin Transplant* 1997; **11**: 259.
17. Hagenmeyer EG, Häussler B, Hempel E, *et al.* Resource use and treatment costs after kidney transplantation: impact of demographic factors, comorbidities, and complications. *Transplantation* 2004; **77**: 1545.
18. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893.
19. Koostra G, Kievit J, Nederstigt A. Organ donors: heart-beating and non-heart-beating. *World J Surg* 2002; **26**: 181.
20. Rohr MS. Renal allograft acute tubular necrosis. A light and electron microscopic study of biopsies taken at procurement and after revascularization. *Ann Surg* 1983; **197**: 663.
21. Olsen S, Burdick JF, Keown P, Wallace AC, Racusen L, Solez K. Primary acute renal failure (acute tubular necrosis) in the transplanted kidney: morphology and pathogenesis. *Medicine* 1989; **68**: 173.
22. Sudhindran S, Pettigrew GJ, Drain A, *et al.* Outcomes of transplantation using kidneys from controlled (Masstrich category 3) non-heart-beating donors. *Clin Transplant* 2003; **17**: 93.
23. Lange H, Kulhman U. Organ procurement policy: should we reduce cold ischemia times? *Transplant Proc*, 1998; **30**: 4297.
24. Offermann G. What is a reasonably short cold ischemia time in kidney transplantation. *Transplant Proc* 1998; **30**: 4291.
25. Hauet T, Goujon JM, Vandewalle A. To what extend can limiting cold ischaemia/reperfusion injury prevent delayed graft function? *Nephrol Dial Transplant* 2001; **16**: 1982.
26. Carter JT, Chan S, Roberts JP, Sandy F. Expanded criteria donor kidney allocation: marked decrease in cold ischaemia and delayed graft function at a single center. *Am J Transplant* 2005; **5**: 2745.
27. Stratta RJ, Moore PS, Farney AC, *et al.* Influence of pulsatile perfusion on outcomes in kidney transplantation from expanded criteria donors . *J Am Coll Surg* 2007; **204**: 873.
28. Moustafellos P, Hadjianastassiou V, Roy D, *et al.* The influence of pulsatile preservation in kidney transplantation from Non-heart-beating donors. *Transplant Proc* 2007; **39**: 1323.
29. Matsuoka L, Shah T, Aswad S, *et al.* Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. *Am J Transplant* 2006; **6**: 1473.
30. Schold JD, Kaplan B, Howard RJ, Reed AI, Foley DP, Meier-Kriesche HU. Are we frozen in time? Analysis of the utilization and efficacy of pulsatile perfusion in renal transplantation . *Am J Transplant* 2005; **5**: 1681.
31. Nyberg S, Baskin-Bey ES, Kremers W, Prieto M, Henry ML, Stegall MD. Improving the prediction fo donor kidney quality: deceased donor score and resistive indices. *Transplantation* 2005; **80**: 925.
32. Wight J, Chilcott J, Holmes M, Brewer N. The clinical and cost effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. *Health Technol Assess* 2003; **7**: 1.
33. Racusen LC, Solez K, Colvin RB, *et al.* The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999; **55**: 713.
34. Russell JD, Beecroft ML, Ludwin D. Churchill DN: the quality of life in renal transplantation: a prospective study. *Transplantation* 1992; **54**: 656.
35. Laupacis A, Keown P, Pus N, *et al.* A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996; **50**: 235.
36. Transplant Activity in the UK. UK Transplant website, http://www.uktransplant.org.uk/ukt/statistics/transplant_activity_report/current_activity_reports/ukt/transplant_activity_uk_2005-2006_v2.pdf (accessed 8 August 2007).
37. Department of Health. *Organs for transplants: a report from the organ donation task force 2008*. Available at: http://www.dh.gov.uk (accessed 1 April 2008).
38. Brook NR, Waller JR, Nicholson ML. Non-heart-beating kidney donation. Current practice and future developments. *Kidney Int* 2003; **63**: 1516.
39. Pessione F, Cohen S, Durand D, *et al.* Multivariate analysis of donor risk factor for graft survival in kidney transplantation.*Transplantation* 2003; **75**: 361.
40. Siddiqi N, McBride MA, Hariran S. Similar risk profiles of post-transplant renal dysfunction and long-term graf failure: UNOS/OPTN database analysis. *Kidney Int* 2004; **65**: 1906.
41. He X, Johnston A. Risk factors for allograft failure in United Kingdom renal transplant recipients treated with cyclosporine A. *Transplantation* 2005; **79**: 953.
42. Asher J, Wilson OC, Gupta A, *et al.* A simple cardiovascular risk score can predict poor outcome in NHBD renal transplantation. *Transplant Proc* 2005; **37**: 3292.
43. Jamieson NV, Sundberg R, Lindell S, *et al.* Preservation of the canine liver for 24–48 h using simple cold storage with UW solution. *Transplantation* 1988; **46**: 517.

44. Jamieson NV, Lindell S, Sundberg R, Southard JH, Belzer FO. An analysis of the components in UW solution using the isolated perfused rabbit liver. *Transplantation* 1988; **46**: 512.
45. Contractor HH, Johnson PR, Chadwick DR, Robertson GS, London NJ. The effect of UW solution and its components on the collagenase digestion of human and porcine pancreas. *Cell Transplant* 1995; **4**: 615.
46. Muhlbacher F, Langer F, Mittermayer C. Preservation solutions for transplantation. *Transplant Proc* 1999; **31**: 2069.
47. British Transplantation Society. *BTS Submission for the National Institute for Health and Clinical Excellence Health Technology (NICE) Appraisal of Kidney Preservation*, 2008. http://www.uktransplant.org.uk (accessed on 1 March 2008).
48. Ambiru S, Uryuhara K, Talpe S, *et al.* Improved survival of orthotopic liver allograft in swine by addition of trophic factors to University of Wisconsin solution. *Transplantation* 2004; **77**: 302.
49. McAnulty JF, Reid TW, Waller KR, Murphy CJ. Successful six-day kidney preservation using trophic factor supplemented media and simple cold storage. *Am J Transplant* 2002; **2**: 712.
50. Koike N, Takeyoshi I, Ohki S, Tokumine M, Matsumoto K, Morishita Y. Effects of adding P38 mitogen-activated protein-kinase inhibitor to celsior solution in canine heart transplantation from non-heart-beating donors. *Transplantation* 2004; **77**: 286.
51. Yoshinari D, Takeyoshi I, Kobayashi M, *et al.* Effects of a p38 mitogen-activated protein kinase inhibitor as an additive to university of wisconsin solution on reperfusion injury in liver transplantation. *Transplantation* 2001; **72**: 22.
52. Tan HP, Smaldone MC, Shapiro R. Immunosupressive preconditioning or induction regimens. Evidence to date.. *Drugs* 2006; **66**: 1535.
53. Brennan D, Daller JA, Lake KD, *et al.* Rabbit antithymocite globuline versus basiliximab in renal transplantation. *N Engl J Med* 2006; **355**: 19.
54. Mourad G, Rostaing L, Legendre C, *et al.* Sequential protocols using basiliximab versus antithymocyte globulins in renal transplant patients receiving mycophenolate mofetil and steroids. *Transplantation* 2004; **78**: 584.
55. Shapiro R, Basu A, Tan H, *et al.* Kidney transplantation under minimal immunosuppression after pre-transplant lymphoid depletion with thymoglobulin or campath. *J Am Coll Surg* 2005; **200**: 505.
56. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM. Association of center volume with outcome after liver and kidney transplantation. *Am J Transplant* 2004; **4**: 920.