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ORIGINAL ARTICLE

Follow-up after renal transplantation with organs from donors after cardiac death

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Summary

Kidneys obtained from donors after cardiac death (DCD) are known to have higher rates of primary nonfunction and delayed graft function (DGF) than heart beating cadaveric donor (CAD) kidneys, but little is known about long-term function of DCD grafts that survive to 1 year. To investigate the outcomes of renal transplant recipients whose DCD graft functioned for at least 1 year, this study analyzed data collected from 326 DCD graft recipients and 340 CAD-matched controls enrolled in a prospective, multinational, observational study – Neoral®-MOST (Multinational Observational Study in Transplantation) (Novartis, Basel, Switzerland). No differences were found in the demographics or immunosuppression between the two groups. All patients received a Neoral®-based immunosuppressive regimen. Donors after cardiac death graft recipients had a higher incidence of DGF (40% vs. 27% CAD; $P < 0.001$). One year glomerular filtration rate (GFR) and GFR-decline after 1 year were similar in DCD and CAD recipients (GFR 56 ml/min DCD vs. 59 ml/min CAD; GFR-decline −1.3 ml/min DCD vs. −1.4 ml/min CAD; $P =$ not significant). Multifactorial analyses confirmed that GFR at 1 year was significantly influenced by donor age and gender, DGF, and acute rejection; however, DCD status was not an independent risk factor in cyclosporine-treated patients with grafts that had functioned for at least 1 year.

Introduction

The escalating disparity between demand for and supply of kidneys for transplantation has necessitated expanding the range of donors through utilization of organs from nonheart beating donors, also called donors after cardiac death (DCD). Although DCD could increase the availability of donor kidneys by up to 30% [1], their use is limited by legal, ethical and logistical difficulties in organ retrieval, as well as concerns about poor long-term graft outcome.

Warm ischemia is an almost inevitable consequence of DCD kidney retrieval and is known to be associated with higher rates of primary nonfunction and delayed graft function (DGF). The link between DGF and reduced short-term graft survival [2,3] has generated concern about the long-term outcome of patients transplanted with DCD kidneys.

Prediction of long-term renal graft outcome from DCD comes mainly from single-center studies using small numbers of patients with limited follow-up [4,5]. The aim of the present study was to examine outcomes in a larger cohort of renal transplant recipients whose DCD graft functioned for at least 1 year post-transplantation, and to investigate the effect of demographic and transplant-related risk factors on graft function.

Materials and methods

Study design

Neoral®-MOST (Multinational Observational Study in Transplantation) is an international, prospective, observational study that was established to investigate the use and impact of different immunosuppressive regimens based on Neoral® (cyclosporine A microemulsion, Novartis Pharma AG, Basel, Switzerland) on clinical outcomes after solid organ transplantation. The renal section of the study involved 155 centers in 38 countries located in Europe, Asia-Pacific, Latin-America, Canada, and Australia. To qualify for enrolment, participants needed to have received a cyclosporine-based immunosuppressive regimen at transplantation (Neoral®) with no investigational drugs at enrolment and throughout follow-up. All participants gave informed consent. This study received appropriate Ethics Committee approval in accordance with the Declaration of Helsinki.

A range of prospective data were collected from *de novo* patients at routine clinic visits; there were up to four assessments within 12 months post-transplantation and then one or two assessments per year over a follow-up period lasting 2–5 years within the study. Data collected at each visit included details of any medical condition, vital signs, serum creatinine, and details of the patient's immunosuppressive regimen and post-transplant complications. For patients who were enrolled in their maintenance period, prospective data collection was complemented with retrospective key data at transplantation and at 1 year post-transplantation.

Controls

The selection of matched controls was based on the date of transplantation of each DCD kidney. The recipient of a heart beating cadaveric donor (CAD) kidney transplanted at the same center either immediately before or after the DCD transplant was used as a control.

Analysis

The analysis focused on long-term function of DCD kidneys once they had survived for 1 year and, thus, enrolled patients, with prospectively collected data, who had DCD renal grafts functioning for at least 1 year post-transplantation.

Statistical method

Glomerular filtration rate at 1 year post-transplantation was estimated using calculated creatinine clearance (via Cockcroft-Gault [6]) normalized to body surface area. Analysis of covariance (ANCOVA) was used to assess the relevance of different factors for GFR at 1 year. Multifactorial analyses included only patients for whom all parameters used in the model were available.

Results

A total of 666 patients were enrolled into the study, 326 recipients of DCD grafts and 340 matched CAD controls. Of these, 377 patients (184 DCD and 193 CAD) provided sufficient data for analysis. Patient demographic and background details were comparable between the two groups – see Table 1. Regarding causes of donor death, there was a difference in causes classified as 'other' or 'unknown'; however, no further detailed information was available from the data collected in MOST. Recipients of DCD grafts were of a similar age to their CAD counterparts, DCD graft donors were slightly younger (median of 36 years vs. 38 years for CAD donors; $P =$ not significant), and both recipient groups received similar immunosuppressive therapy, both initially and at 1 year. The only significant difference was the expected higher incidence of DGF experienced in the DCD graft recipients (40% vs. 27% for CAD group; $P < 0.001$).

Graft survival at 1 year was, by definition 100%, with approximately 3% graft loss in each group by 5 years. There was no statistically significant difference between the GFR values in the two groups at 1 year (56 ml/min for DCD recipients vs. 59 ml/min for CAD recipients). Furthermore, both groups showed a similar decline in renal function after 1 year (−1.3 ml/min for DCD recipients vs. −1.4 ml/min CAD recipients; $P =$ not significant) (Fig. 1).

Multifactorial analyses on DCD and matched CAD controls confirmed that DCD (i.e. nonheart beating donor) graft status had no independent effect on GFR at 1 year; however, donor gender, DGF and acute rejection were significant predictors of 1 year GFR (Table 2). Donor age was also a significant predictor of GFR at year 1 ($P < 0.001$). Amongst DCD graft recipients, the key factors influencing calculated GFR were donor age ($P < 0.001$), and DGF (Table 3). Post-transplantation GFR is affected by a multitude of factors, not all of which can be captured in this setting; so, the limited model fit obtained was not unexpected.

Table 1. Study participants: demographic and background details ($n = 666$).

	Median (interquartile range) or %		
	DCD-graft recipients ($n = 326$)	CAD-graft recipients ($n = 340$)	*P*-value
Recipient age (range), years	44 (33–51)	44 (34–54)	NS
Donor age (range), years	36 (22–46)	38 (23–51)	NS
Donor gender			
Female	29%	33%	NS
Male	71%	67%	
Cause of donor death			
Head trauma	28%	45%	NS
Stroke/cerebrovascualr accident	12%	25%	NS
Cerebral anoxia	6%	4%	0.002
Other	32%	9%	
Unknown	22%	17%	
Warm ischemia time (range), hours	30 (0–77)	20 (0–90)	
Cold ischemia time (range), hours	18 (11–23)	19 (15–24)	NS
Period of transplantation			
≤1995	86 (26%)	87 (25%)	
1996–1999	137 (42%)	142 (42%)	
≤2000	103 (32%)	111 (33%)	
Delayed graft function (DGF)	40%	27%	<0.001
Acute rejection within year 1	31%	26%	NS
Immunosuppressive regimen at year 1			
Dual therapy	23%	23%	
Triple therapy (MMF)	34%	32%	
Triple therapy (Aza)	35%	38%	
Other	8%	7%	

CAD, cadaveric (heart-beating) donor; DCD, donors after cardiac death (nonheart beating); NS, not statistically significant; MMF, mycophenolate mofetil (Hoffman La Roche; Basel, Switzerland).

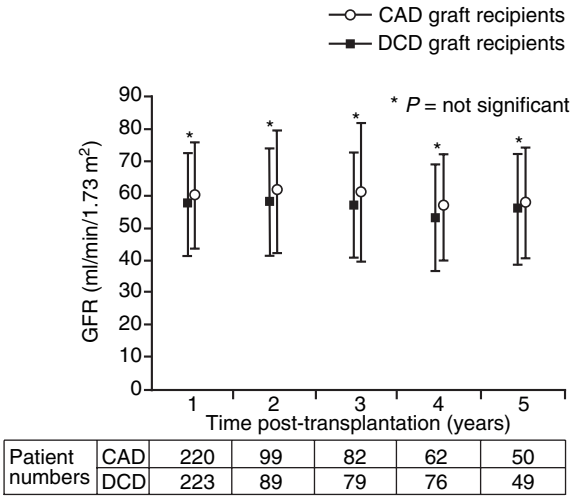

Figure 1 Renal function (GFR) in recipients of grafts from donors after cardiac death (DCD) versus cadaveric donors (CAD) at 1 year post-transplantation. Recipients of grafts from DCD and the heart beating CAD control group showed a similar decline in GFR after 1 year (−1.3 ml/min for DCD group versus −1.4 ml/min CAD group; P = not significant [NS]).

Discussion

This multicenter, matched-pair analysis of 377 renal transplants found that DCD status did not affect long-term renal outcome in functioning grafts, and DCD grafts that survived to 1 year post-transplantation (on a cyclosporine microemulsion-based regimen) maintained similar renal function to that of CAD control grafts. This is consistent with data from other studies [5,7,8] and lends further support to the routine transplantation of kidneys from DCD [9,10].

The rate of DGF was significantly higher among DCD graft recipients, concurring with previous reports [9, 11]; however, donor status did not independently affect graft function at 1 year in the surviving grafts. Although the detrimental effect of DGF on renal allograft survival has often been cited as the basis of clinical reluctance to use DCD kidneys, studies have yielded conflicting results and the issue remains controversial. A report by Shoskes [12] concluded DGF was an important independent predictor of poor graft survival in cadaveric renal transplantation: in the absence of early rejection, DGF reduced extrapolated

Table 2. Multifactorial analysis of factors influencing normalized glomerular filtration rate (GFR) at year 1 in recipients of renal grafts from DCD and matched heart beating CAD controls with donor age as a covariate (only patients with complete information are included; $n = 377$).

Risk factor	*P*-value
(a)	
DCD renal graft	0.113
DGF	0.002
Cytomegalovirus infection within year 1	0.719
Acute rejection within year 1	<0.001
Donor gender	0.051
$R^2 = 0.198$ (moderate fit)	

Significant risk factors	Adjusted mean (95% CIs)	*P*-value
(b)		
DGF		
Present	52.6 (49.8–55.4)	0.002
Absent	57.7 (55.0–60.4)	
Acute rejection within year 1		
Present	52.3 (49.2–55.3)	0.001
Absent	58.0 (55.7–60.4)	
Donor gender		
Male	56.8 (54.5–59.0)	0.051
Female	53.5 (50.5–56.6)	

CI, confidence intervals.

Table 3. Multifactorial analysis of factors influencing normalized GFR at year 1 in recipients of renal grafts from DCD with donor age a covariate (only patients with complete information are included; $n = 184$).

Risk factor	*P*-value	Adjusted mean (95% CIs) [for significant risk factors only]
DGF	0.008	Present 52.3 (48.7–55.9) Absent 58.4 (54.5, 62.3)
CMV infection within year 1	0.966	–
Acute rejection within year 1	0.589	–
Donor gender	0.385	–
$R^2 = 0.133$ (moderate fit)		

CI, confidence intervals.

graft half-life from 12.9 to 8.0 years and decreased 1 year graft survival from 91% to 75%. Conversely, a recent study by Brook *et al.* [8] found that high rates of DGF associated with DCD renal allografts did not lead to poor graft survival when compared with grafts with DGF from heart beating donors (graft survival at 3 years: 84% DCD vs. 73% heart beating donors; $P < 0.05$).

Kidneys injured by prolonged ischemia and DGF, such as those from DCD, experience higher rates of graft loss and acute rejection [13]. Although the rate of acute rejection recorded in this study was higher in DCD graft recipients (31% DCD vs. 26% CAD), the difference was not statistically significant.

Donor age was a significant predictor of GFR at 1 year. Previous studies have shown that increased donor age adversely influences renal allograft function [14,15]. Kidneys from CADs aged >50 years [14] and from DCD donors aged >55 years [15] have significantly reduced long-term graft survival. This is presumed to be due to a decrease in the number of functional nephrons secondary to glomerulosclerosis, resulting in impaired functional reserve.

The influence of immunosuppressive therapy on outcome in DCD kidney grafts has also been investigated. Delayed introduction and/or dose reduction of nephrotoxic immunosuppression in the early postoperative period have been used to decrease additional injury to DCD renal grafts that may already be damaged from prolonged warm ischemia time [5,8].

In summary, the findings from this Neoral®-MOST study corroborate and enhance data from previous studies supporting the use of DCD kidney transplants despite the acknowledged worse short-term outcomes. DCD graft status had no independent effect on GFR at 1 year post-transplantation in surviving grafts. Renal function in DCD grafts that survived to 1 year post-transplant was comparable with that from CAD grafts over the next 4 years, implying that long-term graft survival will also be comparable.

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