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ORIGINAL ARTICLE

Urological complications and their impact on survival after kidney transplantation from deceased cardiac death donors

Meriem Khairoun,[1] Andrzej G Baranski,[1] Paul J M van der Boog,[2] Ada Haasnoot,[1] Marko J K Mallat[2] and Perla J Marang-van de Mheen[3]

1 Department of Transplantation Surgery, Leiden University Medical Centre, Leiden, The Netherlands
2 Department of Nephrology, Leiden University Medical Centre, Leiden, The Netherlands
3 Department of Medical Decision Making, Leiden University Medical Centre, Leiden, The Netherlands

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Correspondence
Dr Perla J. Marang-van de Mheen, Department of Medical Decision Making, J10-S, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31715264574; fax: +31715266838; e-mail: p.j.marang@lumc.nl

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Summary

Urological complications after kidney transplantation may result in significant morbidity and mortality. However, the incidence of such complications after deceased cardiac death (DCD) donor kidney transplantation and their effect on survival is unknown. Purpose of this study was to estimate the incidence of urological complications after DCD kidney transplantation, and to estimate their impact on survival. Patient records of all 76 DCD kidney transplantations in the period 1997–2004 were reviewed for (urological) complications during the initial hospitalization until 30 days after discharge, and graft survival until the last hospital visit. Urological complications occurred in 32 patients (42.1%), with leakage and/or obstruction occurring in seven patients (9.2%). The latter seems to be comparable with the incidence reported in the literature for deceased heart-beating (DHB) transplantations (range 2.5–10%). Overall graft survival was 92% at 1 year and 88% at 3 years, comparable to the rates reported in the literature for kidneys from DHB donors, and was not affected by urological complications ($\chi^2 = 0.27$, $P = 0.61$). Only a first warm-ischaemia time of 30 min or more reduced graft survival ($\chi^2 = 4.38$, $P < 0.05$). We conclude that urological complications occur frequently after DCD kidney transplantation, but do not influence graft survival. The only risk factor for reduced graft survival in DCD transplant recipients was the first warm-ischaemia time.

Introduction

Because of shortage of organs retrieved from deceased heart-beating (DHB) donors and the growing number of patients on the waiting list, some transplant centres together with national transplant organizations have decided to use the organs retrieved from deceased cardiac death (DCD) donors. The Netherlands Transplant Foundation was one of the first in the world to introduce this form of organ procurement, with the aim to increase the pool of organs and decrease the number of patients on the waiting list.

However, the acceptance of kidneys from DCD donors is not widespread; there are still centres that are reluctant to accept and transplant these kidneys. This reluctance is based on the clinical observations that transplanted kidneys from DCD donors have a higher rate of delayed graft function (DGF), primary nonfunction and acute rejection than kidneys from DHB donors, attributable to a longer warm-ischaemia time during procurement and transplantation [1–5]. On the other hand, many studies have shown that kidneys from DCD donors have comparable long-term graft survival as kidneys from DHB donors [1–4,6–8].

Although urological complications have historically contributed significantly to morbidity and mortality [9], they have become less frequent in recent years. For kidneys transplanted from DHB donors, the incidence of

urological complications (because of leakage and/or obstruction) is reported to vary between 2.5% and 10% [10–13]. However, long-term graft survival did not seem to be affected by surgically treated urological complications, but this may in part be because of the inclusion of living related kidney transplantations where urological complications were less frequent and who had better graft survival [14]. Another study found that urinary tract infections occurred in 41% of patients after kidney transplantation from DHB or living donors, and showed a tendency towards increased risk of graft loss for patients with urinary tract infection [15].

However, the incidence of urological complications after DCD donor kidney transplantations is not known, nor their effect on graft survival. Given that more patients require dialysis after DCD donor kidney transplantations (because of DGF) which may cause hypoxia and anaemia, in combination with immunosuppressive drugs and the fact that the kidney is not producing any urine, may result in slower recovery and higher risk of urological complications. The purpose of this study therefore was to assess the incidence of urological complications after DCD donor kidney transplantation, and to estimate their effect on patient and graft survival in a single centre.

Patients and methods

Between January 1997 and December 2004, 76 patients received a kidney transplant from a DCD donor at the Leiden University Medical Centre (LUMC), with the number of transplantations increasing from one per year in 1997 to 19 in 2004. The LUMC is one of the seven centres in the Netherlands where kidney transplantations are performed.

Technical aspects

All kidneys were procured from controlled donors (category III from the Maastricht criteria) [16]. Organs were procured using either of the two surgical techniques, depending on the centre performing the organ explantation. Using the first technique, in-situ cooling was achieved by inserting a double balloon triple lumen (DBTL) catheter via the femoral artery into the abdominal aorta and inserting a drain via one of the femoral veins into the inferior vena cava as the decompression system. The second technique consisted of open laparotomy, where a perfusion cannula was inserted into one of the iliac arteries followed by a thorax drain into the inferior vena cava as the decompression system. Regardless of the technique, either University of Wisconsin or histidine tryptophan ketoglutarate was used as preservation solution [5,17,18]. A 'no-touch period' of 10 min (in the early years) and 5 min in recent years, was kept between the determination of patient's death and insertion of the DBTL catheter or the first incision. The change in 'no-touch period' was undertaken in the Netherlands in an effort to reduce the first warm-ischaemia time, thereby improving the outcomes of organs procured from DCD donors [2]. The first warm-ischaemia time, defined as the time between patient's death and start of in-situ cold perfusion, varied between 9 and 40 min (median 19 min, average 20 min) in our group of patients.

All kidneys were transplanted in the following way: the iliac vessels were reached through the pararectal incision, and the donor's renal vessels were connected to the common or external iliac vessels of the recipient, using end-to-side anastomoses. The internal iliac artery has not been used for the arterial anastomosis during DCD donor kidney transplantation in our hospital. The ureter was anastomosed to the urinary bladder using the Lich–Gregoir technique [19,20]. Double-J stenting for vesico-ureteric anastomosis is used in most patients [12].

Perioperative management

Prophylactic intravenous antibiotics are given for 24 h perioperatively, consisting of Cefazoline 1000 mg three times per day. The induction and maintenance immunosuppression regimen consisted of tacrolimus or cyclosporine with prednisone and mycophenolate mofetil. All patients with clinical symptoms of rejection underwent a biopsy. Treatment for the first rejection period (R1) consisted of Solumedrol, and the second (R2) was treated with antithymocyte globulin (ATG).

Definitions and methods

Patient records were reviewed retrospectively to assess graft survival and the occurrence of urological and other complications. Follow up of patient and graft survival was based on the last visit of the patient to the hospital or the outpatient clinic (or date of death in case of deceased patients). Median duration of follow up was 4 years for patient survival and 3.7 years for kidney graft survival. Complications were included when they occurred within the initial hospitalization period up to 30 days after discharge. Urological complications were defined as ureter obstruction or leakage and/or urinary leakage from the bladder (determined by creatinine measurement in the drain fluid, ultrasound, CT-scan or pyelography) and/or urinary tract infections (determined by cultures or positive urine sediment). Delayed graft function was defined as the need for dialysis within the first week after transplantation [21]. Acute rejection was diagnosed based on clinical criteria and confirmed by histological findings of

transplant biopsies. Graft loss was defined as removal of the graft or return to dialysis. Patient death with a functioning graft was considered as graft loss, to be able to compare our outcomes with the data from the Eurotransplant International Foundation (who use this definition). Within these Eurotransplant data, 88% of the transplants from DCD donors in 2004 are from the Netherlands [22].

We estimated the occurrence of urological (and other) complications, and described the causes for their occurrence and treatment. Patients with and without urological complications were compared on possible differences in other variables. Differences between groups were tested using the chi-squared test for categorical variables and the *t*-test for continuous variables. In case of cells with expected count less than 5, the Fisher's exact test was used. The 1-year and 3-year survival rates for patient and graft survival were estimated using the Kaplan–Meier method. To test for differences in survival, the survival rates of patients with and without urological complications were compared using the log-rank test. In all statistical analyses, a *P*-value of less than 0.05 was considered statistically significant.

Table 1. Complications after 76 deceased cardiac death donor kidney transplantations (Leiden University Medical Centre, 1997–2004).

Complications	Total $n = 76$	Men $n = 51$	Women $n = 25$
Urological complications	32 (42.1)	18 (35.3)	14 (56.0)
Urinary leakage	1 (1.3)	0	1
Ureter obstruction	2 (2.6)	2	0
Bladder obstruction	4 (5.2)	4	0
Urinary tract infection	31 (40.8)	17	14
Bleeding	12 (15.8)	7 (13.7)	5 (20.0)
Graft bleeding	7 (9.2)	5	2
Wound haematoma	5 (6.6)	2	3
Function disorders	37 (48.7)	27 (52.9)	10 (40.0)
Delayed graft function	36 (47.4)	26	10
Primary nonfunction	1 (1.3)	1	0
Rejection	4 (5.2)	2 (3.9)	2 (8.0)
One rejection episode	3 (3.9)	1	2
Two rejection episodes	1 (1.3)	1	0
Other complications	8 (10.5)	6 (11.8)	2 (8.0)
Nephrocalcinosis	3 (3.9)	3	0
Thrombosis	3 (3.9)	2	1
Lymphocele	1 (1.3)	0	1
Abdominal wall abscess	1 (1.3)	1	0

Values in parentheses are percentages.

Results

A total of 76 patients with end-stage renal failure received kidneys from DCD donors. Of these patients 51 were men and 25 women.

Complications

Urological complications occurred in 32 patients (42.1%, Table 1) with a tendency to occur more in women than in men (56% vs. 35%, $\chi^2 = 2.95$, $P = 0.09$). Urinary leakage and/or obstruction of ureter or bladder occurred in seven patients (9.2%), six male patients and one female patient (Table 1), comparable to the incidences reported in the literature for patients receiving kidneys from DHB donors (range 2.5–10%) [10–13]. Bladder obstruction occurred in four male patients (5.2%), because of prostate hypertrophy (three patients), which was successfully treated by insertion of a bladder catheter, or to ureter stenosis (one patient). Ureter obstruction occurred in two male patients: in one patient the obstruction occurred in the transplant ureter after removal of the double J stent and in the other patient (without a double J stent) the distal ureter was obstructed because of a thrombus. Treatment consisted of insertion of a pyelostomy catheter in both cases. Urinary leakage occurred in one female patient because of necrosis of the ureter, which was managed by surgical intervention (insertion of a double J stent and re-implantation of the ureter into the urinary bladder).

Urinary tract infection occurred in 31 patients (40.8%, Table 1) with a tendency to occur more in women than in men (56% vs. 33%, $\chi^2 = 3.60$ $P = 0.06$). The most common pathogens were *Enterococcus faecalis*, *Pseudomonas aeruginosa* and *Escherichia coli*. In three of these patients, the urinary tract infection resulted in pyelonephritis. Treatment consisted of culture-guided antibiotic therapy. Patients with urinary retention (five patients) were also treated with insertion of a bladder catheter. In seven patients removal of the double J stent was necessary, on average 17.7 days (SD 3.4) after insertion, to prevent recurrent urinary infection. No difference in the occurrence of urinary tract infection was found between patients with and without a double J catheter (44% vs. 32%, $\chi^2 = 0.89$, $P = 0.35$).

Other complications included bleeding, occurring in 12 patients (Table 1): five patients had a (subcutaneous) wound haematoma and seven patients had haematoma localized around the transplanted kidney. These complications required additional surgery in three patients. DGF occurred in 36 patients (47.4%) and was treated with (intermittent) dialysis. Renal vascular thrombosis occurred in three patients (two arterial and one venous, Table 1) who all lost their graft during the initial hospital stay. Four patients (5.3%) developed acute rejection, all confirmed by biopsy: three patients had one rejection episode and one patient had two episodes. Treatment consisted of Solumedrol and the patient with a second rejection episode received ATG to treat the second

Table 2. Characteristics of patients with and without urological complications after DCD donor kidney transplantation (Leiden University Medical Centre, 1997–2004).

	With urological complications (n = 32)	Without urological complications (n = 44)	Test of difference
Age (years)	56.6 ± 12.5	47.0 ± 12.9	t = −3.24, $P < 0.01$
% men	56.3%	75.0%	χ^2 = 2.95, P = 0.09
% pretransplantation haemodialysis	59.4%	65.9%	χ^2 = 0.34, P = 0.56
Body mass index (kg/m^2)	23.8 ± 4.6	24.8 ± 2.8	t = 0.98, P = 0.33
Kidney 2nd warm-ischaemia time (min)	33.0 ± 8.0	33.7 ± 12.8	t = −0.20, P = 0.84
Kidney cold-ischaemia time (h)	21.2 ± 3.8	20.5 ± 5.3	t = −0.58, P = 0.56
% double J stenting	81.3%	70.5%	χ^2 = 1.16, P = 0.28
% with delayed graft function	40.6%	52.3%	χ^2 = 1.01, P = 0.32
Donor characteristics			
% male donor	56.3%	43.2%	χ^2 = 1.27, P = 0.26
Donor age	45.4 ± 17.6	39.7 ± 18.2	t = −1.36, P = 0.18
% donor hypotension	35.5%	25.0%	χ^2 = 0.96, P = 0.33
Duration donor hypotension (min)	15.0 ± 39.8	6.4 ± 16.3	t = −1.11, P = 0.28
Donor last serum creatinine before donation (μmol/l)	71.5 ± 32.5	67.2 ± 19.4	t = −0.66, P = 0.51
Donor 1st warm-ischaemia time (min)	20.8 ± 7.1	19.5 ± 6.3	t = −0.84, P = 0.41
Donor body mass index (kg/m^2)	24.2 ± 4.1	24.3 ± 4.8	t = 0.07, P = 0.95
% with HTK as preservation solution	86.7%	84.1%	χ^2 = 0.09, P = 1.00

Values are mean ± SD.
DCD, deceased cardiac death; HTK, histidine tryptophan ketoglutarate.

rejection. This percentage is much lower than reported in previous studies after kidney transplantation from DCD donors [23,24], which is probably because of the inclusion of kidney transplantations from uncontrolled DCD donors in these studies for whom higher rejection rates are reported [25], the inclusion of rejection episodes over a longer period of time (while rejections were only included in this study when they occurred during the initial hospitalization) and the fact that 88% of the transplantations in this study were first transplantations so that these patients were probably less immunized and therefore had lower risk of rejection.

Patients with urological complications on average were 10 years older than patients without urological complications, but did not differ in any of the other characteristics (Table 2).

Graft survival

Overall patient survival rates at 1 and 3 years were 99% and 96%, graft survival rates at 1 and 3 years of follow up were 92% and 88% respectively. These rates seem higher than the survival rates as estimated from the survival graphs from the Eurotransplant International Foundation for the cohort transplanted between 1997 and 2004, which are 94% and 89% respectively for 1-year and 3-year patient survival (with 93% and 86% completeness of data respectively, dated 16 April 2008), and 80% and 74% respectively for 1-year and 3-year graft survival (with 96% and 91% completeness of data respectively, dated 16 April 2008).

Overall, 14 recipients (18.4%) lost their grafts at some point after transplantation. The main reason for graft loss was death of the patient with a functioning graft (seven cases). Other causes were vascular thrombosis (three cases), rejection (two cases), primary nonfunction (one case) and persistent obstruction in the pyelum (one case).

The occurrence of urological complications did not influence patient or graft survival (Table 3). Adjustment for the difference in age between patients with and without urological complications did not change the results (hazards ratio 1.22 [0.40–3.71]). When exploring the data for possible other risk factors for graft survival as found in other studies [2,23], we found that only a first warm-ischaemia time of 30 min or more significantly influenced

Table 3. Influence of urological complications on patient and graft survival after deceased cardiac death donor kidney transplantation (Leiden University Medical Centre, 1997–2004).

	With urological complications	Without urological complications	Log rank test
Patient			
1-year survival	96.8%	100%	χ^2 = 1.04, d.f. = 1
3-year survival	93.4%	97.5%	P = 0.31
Kidney graft			
1-year survival	90.4%	93.2%	χ^2 = 0.27, d.f. = 1
3-year survival	87.1%	87.9%	P = 0.61

graft survival ($\chi^2 = 4.38$, $P < 0.05$) as was also shown by Keizer *et al.* [2]. One-year graft survival was 96% in those with a first warm-ischaemia time less than 30 min, compared with 63% in those with 30 min or more. However, this variable did not influence the occurrence of urological complications (respectively 41% vs. 50%, $\chi^2 = 0.23$ $P = 0.71$), so is probably influencing graft survival in another way.

Discussion

This study has shown that urological complications occurred in 42.1% of the patients after receiving a kidney from DCD donors. Urinary leakage and/or obstruction occurred in 9.2% of the patients, comparable with the incidence reported in the literature after transplantations using DHB donors (range 2.5–10%) [10–13]. Overall graft survival was 92% at 1 year and 88% at 3 years, comparable to the rates reported in the literature for kidneys from DHB donors [1,2,4]. Urological complications did not influence graft survival, but a first warm-ischaemia time of 30 min or more significantly reduced graft survival.

Even though all DCD donor kidney transplantations performed during the period 1997–2004 in our centre were included in this study, thereby including all eligible patients, our results might have been influenced by patient selection. In our patient population, only controlled (category III according to the Maastricht classification) donors were used. These are donors without resuscitation and a shorter first warm-ischaemia time period than the uncontrolled categories I and II [1,5,18]. In the Eurotransplant data, 81% of the DCD donors in 2004 is category III [22]. Therefore, the selection of category III donors in our centre is likely to have had a positive influence on the overall outcomes of transplantation, and may therefore be one of the reasons for the higher graft survival rates in our study than reported for the Eurotransplant region. The main reason for the sole use of this category of kidneys for transplantation in our centre is that it simplifies the logistics of organ procurement and cold storage because there is no requirement for machine perfusion and viability testing, and surgical intervention is confined to the operating room. However, there seems to be no reason why this selection of donors would have influenced the occurrence of urological complications, given that patients with and without urological complications did not differ on any of the donor characteristics. Similarly, it does not seem likely that this selection has biased the effect of these urological complications on graft survival. As a result, we think that our results can be generalized to other patients receiving a kidney from controlled DCD donors.

Both with respect to the incidence of urological complications and the impact on graft survival, our results are similar to the results found after kidney transplantation from DHB donors. The incidence of urinary leakage and/or obstruction was 9.2%, which is within the range of 2.5–10% reported in the literature for DHB donors [10–13]. Furthermore, urinary tract infections were found in 41% of the patients, similar to the incidence found in a previous study after kidney transplantation from DHB and living donors [15]. No impact of urological complications on graft survival was found in this study after kidney transplantation from DCD donors, as found in previous studies after receiving a kidney from DHB donors [14,15]. Therefore, it seems that apprehensions of urological complications and their impact on graft survival are not issues when accepting kidneys from controlled DCD donors for transplantation.

However, accepting kidneys from uncontrolled DCD donors for transplantation – not included in this study – may warrant further investigation. A previous study in patients receiving kidneys from uncontrolled DCD donors, found several risk factors that influenced graft survival (donor age above 55, acute early rejection, cardiovascular cause of donor death, warm-ischaemia time of 30 min or more and cold ischaemia time of 24 h or more) [23]. In contrast with these results, we found only the first warm-ischaemia time to be a risk factor for graft survival after kidney transplantation from controlled DCD donors, consistent with results from a previous study [2]. This suggests that a prolonged first warm-ischaemia time is a risk factor for early graft loss, both when using controlled and uncontrolled DCD donors in kidney transplantation [2,23]. One can only speculate on the reason why so many risk factors for survival were found for uncontrolled DCD donors and only one risk factor for controlled donors. Further research is required to assess which factors are responsible for differences in graft survival when using controlled or uncontrolled DCD donors in kidney transplantation.

Although many centres are still reluctant in using kidneys from DCD donors, our study suggests that good outcomes can be achieved when kidneys from category III donors are used. Both the occurrence of urological complications and graft survival seem comparable to that of kidneys transplanted from DHB donors. The main reason for this favourable survival outcome probably is that the first warm-ischaemia time is short enough in this category of DCD donors. The average first warm-ischaemia time in our series was 20 min, comparable to warm-ischaemia times reported in other studies with patients from controlled DCD donors [1]. However, it is clearly lower than reported in studies with patients from uncontrolled DCD donors [26,27], which may explain the favourable outcomes in this study. This makes kidney transplantation from controlled DCD donors a valuable source of kidneys

that could be used to meet the increasing demand for organs.

Authorship

MK: collected the data, performed the analyses and wrote the first draft of the manuscript. AB: designed the study, contributed to the data collection and writing of the manuscript. PB: contributed to the interpretation of the data, and writing the manuscript. AH: contributed to the collection of the data. MM: contributed to the collection of the data, and interpretation of the data. PM-M: designed the study, performed the analyses and contributed to the interpretation of the data and writing of the manuscript.

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