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Single Graft Utilization From Donors With Severe Acute Kidney Injury After Circulatory Death

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Abstract: Chronic shortages of organs for transplantation have led to the use of marginal kidneys from donors after circulatory death with acute kidney injury (AKI), but the utilization of kidneys with severe AKI is not well established. We retrospectively analyzed eight kidney transplantation (KTx) cases from donation after circulatory death (DCD) with terminal creatinine (t-Cr) concentrations higher than 10.0 mg/dL and/or oliguria for more than 5 days (AKI network criteria: stage III). Although all patients showed delayed graft function, no cases of primary nonfunction (PNF) were found. Five patients maintained stable renal function for approximately 15.5, 10, 10, 5, and 0.5 years after KTx. Only 1 patient showed biopsy-proven acute rejection. Also, 2 patients developed graft failure: one attributable to chronic antibody mediated rejection at 11.3 years after KTx, and one attributable to recurrence of IgA nephropathy at 4.6 years after KTx. Kidneys with AKI stage III yielded great outcomes without the risk of primary nonfunction and rejection. Although the AKI kidneys were associated with delayed graft function, these results suggest that even the most severe kidneys with AKI stage III from DCD donors can be considered a valid alternative for recipients on a waiting list for KTx.

(*Transplantation Direct* 2018;3:e355; doi: 10.1097/TXD.0000000000000768. Published online 19 March, 2018.)

Recent efforts have been undertaken worldwide to expand donor pools, including the wider use of marginal kidneys from donation after circulatory death (DCD),¹⁻⁴ of dual kidney transplants,^{5,6} and of revised graft perfusion methods for preventing reperfusion injury.^{7,8} Nevertheless, marginal kidneys from DCD have been regarded as inappropriate for donor pool expansion. These grafts have developed a higher frequency of delayed graft function (DGF), acute rejection, and graft loss because of several factors related to poor graft outcome, such as donor age, a history of cerebrovascular

event (CVE) and hypertension, cold ischemic time (CIT), and acute kidney injury (AKI). By contrast, some earlier reports have described that 5-year graft and patient outcomes from DCD kidneys are compatible with those from donation after brain death kidneys.^{9,10} We also reported improved results for recipients of transplanted DCD kidneys.¹¹

An analysis presented in the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients Annual Report revealed that more than 20% of marginal kidneys have been declined for use in transplantation. Although AKI is frequently associated with multiple organ failure and death, most patients can fully recover renal function.¹²⁻¹⁶ Short-term follow-up showed that kidneys with AKI stage I and II are useful for strategies for discarded organs.^{17,18} Nevertheless, most kidneys included among these data were obtained from donation after brain death donors. Outcomes of DCD kidneys with AKI stage III remain controversial. This report describes cases of 8 patients who received kidneys from DCD donors with stage III AKI and presents analysis of the frequency of primary nonfunction (PNF) and DGF, pathological findings, and long-term graft outcomes.

CASE DESCRIPTION

The study was conducted in accordance with the principles of the Declaration of Helsinki. We retrospectively analyzed 8 kidney transplantations (KTx) of DCD kidneys with terminal creatinine (t-Cr) concentrations higher than 10.0 mg/dL and/or oliguria for more than 5 days (Table 1 and Figure 1). These

Received 26 October 2017. Revision requested 5 December 2017.

Accepted 29 December 2017.

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The authors declare no funding or conflicts of interest.

Y.T., K.I., I.N., and S.F. participated in research design. Y.T., K.I., and S.F. participated in the writing of the article. Y.T., K.I., Y.O., K.M., K.K., A.S., T.M., I.K., K.K., I.N., and S.F. participated in the performance of the research. Y.T. and K.I. contributed new reagents or analytic tools. Y.T. and K.I. participated in data analysis.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000768

TABLE 1.**Donor characteristics**

Kidney	1	2	3	4 and 5	6 and 7	8
Age	61	56	53	26	67	39
Sex	Male	Male	Male	Male	Male	Female
Cause of death	Cerebrovascular disease	Cerebrovascular disease	Cerebrovascular disease	Anoxic encephalopathy	Cranio-cerebral trauma	Anoxic encephalopathy
AKI stage	III	III	III	III	III	III
t-Cr, mg/dL	11	9.15	11.98	14.96	10.61	15.48
t-Uo, mL/d	200	150	30	570	40	0
Oliguria interval, d	4	5	3	7	3	7
Cr on admission, mg/dL	0.9	1.12	1.23	1.15	0.81	0.69
Cannulation	–	+	+	+	+	+
Machine perfusion	–	–	–	–	–	–
Heparin	+	+	+	+	+	+
Admission interval in ICU (day)	10	33	11	9	6	22
Withdrawal of life support	–	–	–	–	–	–
Hypertension	–	–	+	–	–	–
Diabetes	–	–	–	–	–	–
Drug use						
NSAIDs	–	–	–	–	–	–
VCM	–	–	–	–	–	–
Amnoglycosides	–	–	–	–	–	–
Other antibiotics	CEZ	CEZ	Unasyn	CEZ	Zosyn	MEPM
Sepsis	–	–	–	–	–	–
Hypoalbuminemia (<3.0 mg/dL)	+	+	+	+	+	+

t-Uo, terminal urine output; NSAIDs, nonsteroidal anti-inflammatories; VCM, vancomycin; CEZ, cefazolin sodium; MEPM, meropenem hydrate.

were the worst 8 kidneys at our center in terms of t-Cr concentration.

The mean donor age was 49.38 years (Table 1). All donors were classified as AKI stage III based on AKI network criteria.^{19,20} The averages of t-Cr and terminal urine output in donors were 12.34 mg/dL and 200 mL/d, respectively. Of the 6 donors, 2 had CVEs and 1 had CVEs and a history of HT. The average interval in the intensive care unit (ICU) after admission was 15.2 days. All donors had hypoalbuminemia. The mean recipient age was 55.63 years (Table 2). Recipients 4 and 5 were transplanted with a single graft from a donor. Recipients 6 and 7 were also transplanted with a single graft from another donor. The average interval of dialysis

before KTx was 17.88 years. The mean warm ischemic time (WIT) was 3.25 minutes. The mean total ischemic time (TIT) was 8.56 hours. We used cyclosporine or tacrolimus, mycophenolate mofetil, and methylprednisolone as the basic immunosuppressive regimen. Basiliximab (20 mg/d, twice) or antithymocyte globulin (1.5 mg/kg per day, 4-5 times) was administered as an induction therapy. Where possible, methylprednisolone was tapered off on postoperative day 14 (14POD). The average of follow-up periods for recipients was 8.0 years.

All recipients developed DGF (Table 3). However, all transplanted kidneys functioned sufficiently without maintenance dialysis within 1 month after KTx (the average interval and times of dialysis after KTx were 13.25 days and 6.25 times). The

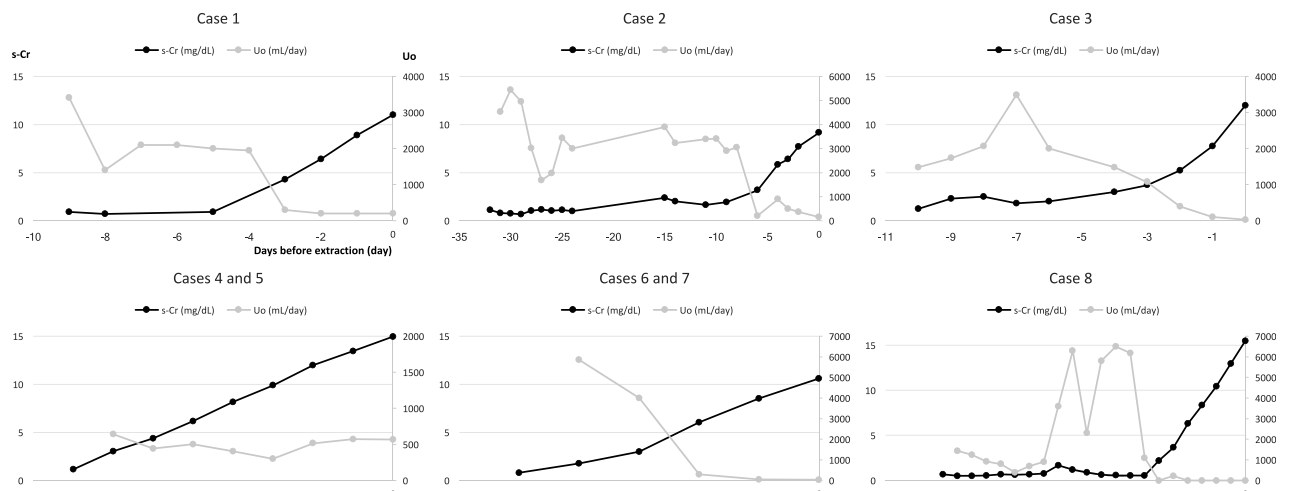


FIGURE 1. Trends of serum Cr concentrations (mg/dL) and urine outputs (mL/day) in donors until donation. Patients 4/5 and patients 6/7 were transplanted grafts from the same donors.

TABLE 2.
Recipient characteristics

Recipient	1	2	3	4	5	6	7	8
Age	46	44	50	65	67	64	63	46
Sex	Female	Male	Male	Female	Male	Male	Female	Male
Cause of ESRD	Purpura nephritis	Unknown	IgA nephropathy	Chronic glomerulonephritis	Unknown	IgA nephropathy	Unknown	Alport syndrome
Pre-KTx dialysis interval, y	25	7	15	25	16	16	17	23
Time of Tx	1	1	1	1	1	1	1	1
HLA-AB MM	1	2	0	2	2	2	3	2
HLA-DR MM	0	0	0	1	1	0	0	0
HLA-MM	1	2	0	3	3	2	3	2
WIT, min	14	1	1	2	2	2	2	2
TIT, h	12.6	6.1	6.7	7.71	7.93	4.3	14.5	8.63
Induction of immunosuppression	CYA + MMF + steroid	CYA + MMF + steroid	BXM + CYA + MMF + steroid	BXM + CYA + MMF + steroid ^a	BXM + CYA + MMF + steroid ^a	BXM + FK + MMF + steroid	ATG + CYA + MMF + steroid	ATG + FK + MMF + steroid ^a

^a Steroid tapered off (on 14 days after KTx).

ESRD, end-stage renal disease; MM, mismatch; IgAN, IgA nephropathy; CYA, cyclosporine; FK, tacrolimus (FK506); MMF, mycophenolate mofetil; BXM, basiliximab; ATG, antithymocyte globulin.

serum Cr at 1 week after KTx remained high (the average was 9.21 mg/dL). However, that of 1 and 6 months after KTx decreased over time (respective averages were 3.03 and 1.62 mg/dL). Moreover, the lowest serum Cr and the highest estimated glomerular filtration rate (respective averages were 1.14 mg/dL and 52.85 mL/min per 1.73 m²) showed excellent outcomes.

Except for patient 1, who suffered biopsy-proven acute antibody-mediated rejection (AMR) on 12POD, all severe AKI kidneys recovered spontaneously from acute tubular necrosis (ATN) within 1 month and exhibited no evidence of rejection with decreasing serum Cr concentration (less than 3.5 mg/dL) (Table 3). During 6 months to 2 years of follow-up, all grafts were functional of stable serum Cr concentrations (less than 2.0 mg/dL) with the longest graft survival of more than 15 years (patient 2) (Table 3 and Figure 2). Patient 1 was treated with 500 mg supplementary methylprednisolone for 2 days and tapered by 4 mg/d. After treatment for acute AMR, the kidney graft function was well maintained for 10 years. However, she developed chronic AMR at 11 years after KTx and returned to hemodialysis. Patient 3 exhibited stable renal function until 2 years after KTx. At that point, he was found to have microhematuria. Graft biopsy confirmed the lack of rejection. Nevertheless, the subsequent recurrence of his original disease was noted: IgA nephropathy. Despite maintaining basic immunosuppression with low-dose methylprednisolone (4 mg/d), he lost his kidney graft at 2.6 years after diagnosis by recurrence of IgA nephropathy. Patient 6 maintained excellent renal function for 2 years with a standard immunosuppression protocol. After suffering from unexpected diaphyseal fracture on his left femur, he was diagnosed as having cancer on his right kidney with multiple lung and bone metastases. This fracture was attributable to bone metastasis. He died of respiratory insufficiency with a functioning kidney graft at 1 month after diagnosis. Patients 2, 4, 5, 7, and 8 have exhibited normal renal function, respectively, for approximately 15.5, 10, 10, 5, and 0.5 years after KTx.

DISCUSSION

The average waiting time for dialysis patients to receive kidney grafts in Japan is 13 years, as opposed to the 4 to 6 years prevailing in most countries.^{21,22} The number of recipients on a waiting list for KTx has been increasing. Therefore, DCD donors have become an accepted organ resource to alleviate the chronic shortage of kidney grafts. Based on the criteria used at our center,¹¹ we have frequently used marginal kidneys from DCD donors.

Several investigators have reported excellent graft outcomes using DCD kidneys with AKI.^{1,3,23,24} By contrast, grafts with AKI stage III before extraction have been regarded as high risk and as inappropriate for KTx: approximately 35% kidneys were discarded because of increased t-Cr and/or oliguria.¹⁷ In a healthy person, AKI can usually be attributed to exacerbation of renal function because of hypoxia, ischemia, or nephrotoxicity. However, AKI is regarded as a reversible condition, which can recover spontaneously with tubule regeneration.¹²⁻¹⁵ By graft biopsy, ATN before KTx revealed no significant relation with 1-year kidney graft survival.²⁵ Although AKI kidneys are well associated with a higher frequency of DGF, some recent large cohort studies

TABLE 3.
Outcomes of post-KTx

Recipient	1	2	3	4	5	6	7	8
PNF	–	–	–	–	–	–	–	–
DGF	+	+	+	+	+	+	+	+
Post-KTx dialysis interval, day/times	13/6	8/4	13/4	14/7	17/7	14/7	24/11	8/4
Cr 1 wk, mg/dL	11	10.33	12.11	8.78	7.95	10.2	7.69	5.6
Cr 1 mo, mg/dL	5	2.82	3.5	1.79	3.07	3.18	3.23	1.66
Cr 6 mo, mg/dL	2	1.5	1.5	1.16	1.76	1.4	1.51	1.11
Lowest Cr, mg/dL	1.42	1.25	1.29	0.64	1.07	1.07	1.32	1.01
highest eGFR, mL/min per 1.73	ND	44.7	ND	69.9	52.6	54.1	32.2	63.6
AR (POD)	12	–	–	–	–	–	–	–
Pathology findings	Mild AMR, moderate ATN	Mild ATN	WNL	ND	WNL	ND	Moderate interstitial fibrosis	Mild arteriosclerosis
Graft survival, y	11.3	15.4	4.6	9.8	9.8	2 ^a	4.8	0.5
Latest Cr, mg/dL	Hemodialysis	1.5	Hemodialysis	1.45	1.22		2.41	1.11
Latest eGFR, mL/min per 1.73 m ²	Hemodialysis	38.6	Hemodialysis	27.8	44.9		16.4	57.3
Cause of graft loss	cAMR		IgAN recurrence					
Cause of death						RCC, lung/bone meta		

^a Death with functioning graft.

Cr, creatinine; eGFR, estimated glomerular filtration rate; AR, acute rejection; WNL, within normal level; ND, not done; IgAN, IgA nephropathy; RCC, renal cell carcinoma.

have demonstrated that renal function with AKI stage III at 6 months after KTx is comparable to those of kidneys with no AKI or with AKI stage I or II.^{17,18} As expected, grafts of AKI stage III from DCD donor involved a higher frequency of DGF. Nevertheless, no cases of PNF were reported: these severe AKI kidneys functioned sufficiently within 1 month after KTx. Thereafter, they maintained excellent graft function not only during short-term but also at long-term follow-up for over 15 years. Ugarte et al²⁶ reported that the PNF of AKI kidneys was not a higher percentage than that of no-AKI kidneys, which is consistent with our observations.

Prolonged CIT exhibited a negative effect on the frequency of DGF and long-term graft survival in DCD kidneys.²⁷ According to the DCD protocol in single institutions, limited WIT and TIT are within 45 to 60 minutes and 24 hours. The American Society of Transplant Surgeons recommends minimization of WIT and TIT.²⁸ Family consent was provided for prearrest cannulation. Therefore, 5 donors were subjected quickly to regional in situ cold perfusion after the declaration of death. Our analysis showed that the mean WIT (3.25 minutes) and TIT (8.56 hours) were much shorter,

suggesting that CIT minimization can facilitate quick recovery from DGF because of AKI.

Generally, for marginal kidneys, a donor older than 60 years adversely affects graft survival from DCD kidney.^{3,29} Some earlier reports have described that AKI in older patients develops to end-stage renal disease much more easily than in younger patients.^{30–32} Kane-Gill et al³³ reported that a history of HT, drugs, and mechanical ventilation play a crucially important role in the development to AKI for elderly patients. In addition, the length of stay in the ICU and hypoalbuminemia (<3.0–3.5 mg/dL) were found to have a significant effect on the progress to AKI.^{34,35} Results suggest that the comorbidity of severe AKI in aged donors, such as patients 1, 6, and 7 in this study, represent an important risk factor affecting long-term graft survival.

In conclusion, kidneys with AKI stage III, which were the worst 8 cases in terms of t-Cr concentrations before extraction, yielded excellent outcomes with no increase in the risk of PNF and rejection. This report describes that a single DCD kidney with t-Cr concentrations greater than 10.0 mg/dL and oliguria can be considered a valid alternative for recipients on a waiting list for KTx.

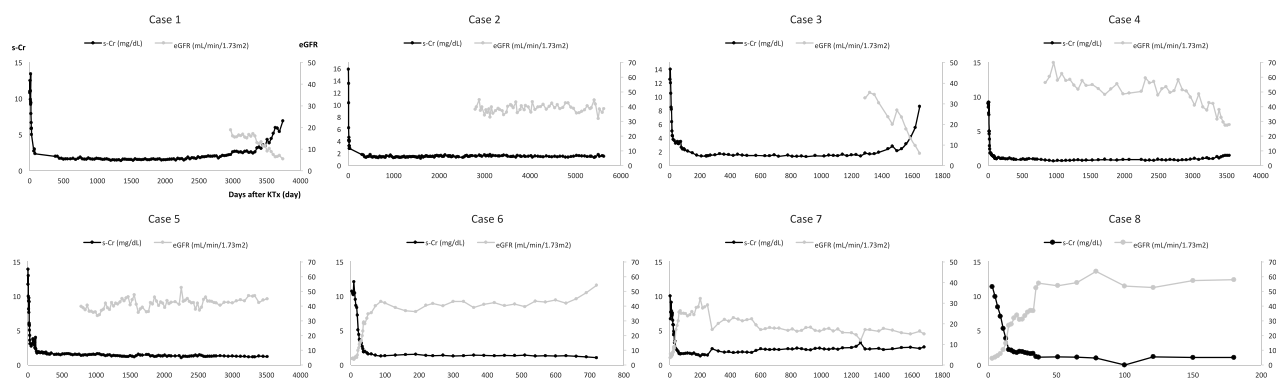


FIGURE 2. Trends of serum Cr concentrations (mg/dL) and eGFR (mL/min per 1.73 m²) in recipients after KTx. Patients 4/5 and patients 6/7 were transplanted grafts from the same donors.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Tamotsu Tojimbara for helpful advice. Additionally, the authors thank Dr. Takeshi Hachisuka, Dr. Sayaka Morita, and Dr. Akira Kondo for their daily suggestions and contributions to this study.

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