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Expanding the Donor Kidney Pool: Utility of Renal Allografts Procured in a Setting of Uncontrolled Cardiac Death

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The chronic shortage of deceased kidney donors has led to increased utilization of donation after cardiac death (DCD) kidneys, the majority of which are procured in a controlled setting. The objective of this study is to evaluate transplantation outcomes from uncontrolled DCD (uDCD) donors and evaluate their utility as a source of donor kidneys.

From January 1995 to December 2004, 75 865 kidney-alone transplants from donation after brain death (DBD) donors and 2136 transplants from DCD donors were reported to the United Network for Organ Sharing. Among the DCD transplants, 1814 were from controlled and 216 from uncontrolled DCD donors. The log-rank test was used to compare survival curves.

The incidence of delayed graft function in controlled DCD (cDCD) was 42% and in uDCD kidneys was 51%, compared to only 24% in kidneys from DBD donors ($p < 0.001$). The overall graft and patient survival of DCD donors was similar to that of DBD donor kidneys ($p = 0.66$; $p = 0.88$). Despite longer donor warm and cold ischemic times, overall graft and patient survival of uDCD donors was comparable to that of cDCD donors ($p = 0.65$, $p = 0.99$).

Concerted efforts should be focused on procurement of uDCD donors, which can provide another source of quality deceased donor kidneys.

Key words: Cardiac death, kidney donor, kidney transplantation, uncontrolled outcomes

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Introduction

There is an increasing disparity between the number of patients waiting for kidney transplantation and the number of deceased organs available. Several strategies have been employed to reduce this ever-widening gap, which include living donor kidney transplantation, utilizing extended criteria donor kidneys, en-bloc kidneys from pediatric donors and hepatitis-positive donors (1–3). More recently, kidneys from donation after cardiac death (DCD) donors have been gaining acceptance. European centers, utilizing a greater percentage of DCD kidneys than the United States, have shown that these kidneys function with almost an equal efficacy as kidneys from donation after brain death (DBD) donors (4–11).

With this continuing interest in DCD kidneys, we examined the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database. The aim of this study was to compare the results of kidneys procured from DCD vs. DBD donors with focus on the subset of uncontrolled DCD donors. These uncontrolled donors encompass those who had an unplanned cardiopulmonary arrest and could not be resuscitated before brain death was determined. The variables that were chosen for the purposes of comparison were graft survival, patient survival, incidence of primary nonfunction, incidence of delayed graft function (DGF), donor age and the impact of donor warm and cold ischemic time (DWIT & CIT).

Materials and Methods

Database

The OPTN/UNOS database as of September 14, 2005, was queried from January 1995 through December 2004. A total of 78 001 deceased donor kidney transplants were documented, with 75 865 from DBD and 2136 from DCD donors. Of the DCD donors, 1814 (85%) were from controlled donors and 216 (10%) were from uncontrolled donors. There were an additional 106 DCD donors where the exact circumstances surrounding the death were unclear or improperly documented (mDCD). Multiple organs, en-bloc or dual kidney transplantations were excluded from this study.

Definitions

The definition of controlled DCD (cDCD) donors alludes to those donors that were hemodynamically stable and extubated in a controlled environment either in the operating room (OR) or in the intensive care unit (ICU).

The uncontrolled DCD (uDCD) donors refer to those donors who had an unplanned cardiopulmonary arrest and could not be resuscitated before brain death was determined. This usually occurs in the emergency room, ICU or on the way to the OR. The UNOS data classify DCD donors as controlled or uncontrolled but do not specify the exact setting in which death occurs. The DWIT is measured from the time of cardiac arrest to the time of perfusion of the organ with preservation solution. The CIT refers to the time from procurement to the time of implantation of the donor kidney.

Statistical analysis

Graft survival rates were estimated with the use of the Kaplan-Meier product limit method. The log-rank test was used to evaluate differences in survival curves for the two groups of grafts. The Kruskal-Wallis nonparametric test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. Variables that significantly influenced graft failure in univariate analysis were included in a multivariate Cox regression analysis. Less than 5% of values were missing for any covariate, except for the control setting of DCD donors where 5% of values were missing. Missing data for this analysis were replaced with modal values for categorical variables. Continuous variables such as age, waiting time, CIT, and the peak value for panel-reactive antibodies were categorized, since their effects on the hazard function were nonlinear. When HLA typing results for either the recipient or donor were missing, ABDR MM was replaced with the maximum number of HLA-A, B, DR antigen mismatch (6 ABDR MM) in univariate and multivariate analysis. Plots of log [−log (survival function)] against time were used to check the validity of the proportionality assumption in the Cox model. Since the curves were parallel, this assumption was judged to be appropriate. Relative risks and their 95% confidence intervals were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. All statistical tests were two-tailed.

Results

The yearly trend of DCD donors shows an increase in the use of DCD kidneys, with a disproportionate increase in the number of controlled donors over uncontrolled donors (Figure 1).

Figure 2 compares DBD and DCD donors, demonstrating statistically similar graft ($p = 0.66$) and patient ($p = 0.88$) survival curves. The DCD group was then dissected into cDCD, uDCD and mDCD groups. There was no difference in the incidence of primary graft nonfunction between DBD and cDCD or uDCD donors (Figure 3). The incidence of DGF, however, was statistically significant among DCD subgroups when compared to DBD donors. The incidence of DGF was 42% in cDCD, 51% in uDCD and only 24% in DBD donors (Figure 3). However, graft and patient survival curves were statistically no different between DBD, cDCD and uDCD donors (Figure 4).

The question this posed was why were these kidneys from uDCD donors doing as well as the kidneys from DBD donors? The characteristics of recipients and DBD, cDCD, uDCD and mDCD donors are shown in Table 1. Many characteristics have a statistically significant difference among groups because of the large patient population, but very little clinical difference. Larger clinical differences are seen in donor age, DWIT, CIT and the use of machine perfusion. The donor age between the DBD and the cDCD kidneys were comparable (36.3 vs. 36.7 years), but uDCD donors were composed of a younger group of donors with a mean age of 28.6 years. Machine perfusion was utilized in 54.2% of uDCD donor kidneys, 42.1% of cDCD donors and only 10.5% of DBD donors. The DWIT is logically higher in DCD donor subgroups (DBD 0 min, uDCD 23.7 min, cDCD 17.0 min; $p < 0.001$). Similarly, the CIT is also significantly longer in uDCD and cDCD donors compared to DBD donors (DBD 19.8 h, uDCD 24.6 h, cDCD 20.0 h; $p < 0.001$). Thus, despite increased DGF and longer DWIT and CIT, the graft and patient survival was similar between DBD donors and both cDCD and uDCD donor kidneys (Figure 4).

Univariate and multivariate analyses were performed in order to adjust for potential confounders (Table 2).

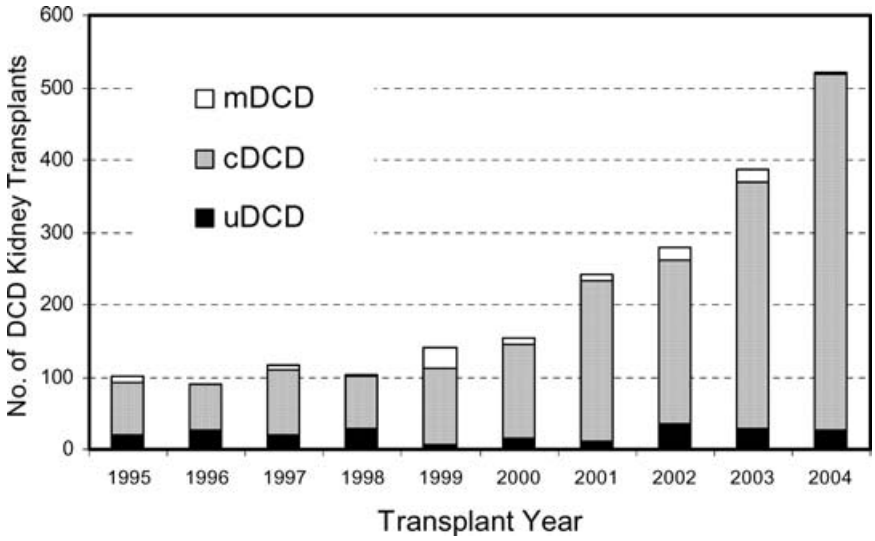

Figure 1: Yearly trend of kidney transplantation from DCD donors (1995–2004). cDCD = controlled DCD, uDCD = uncontrolled DCD, mDCD = DCD, circumstances unknown.

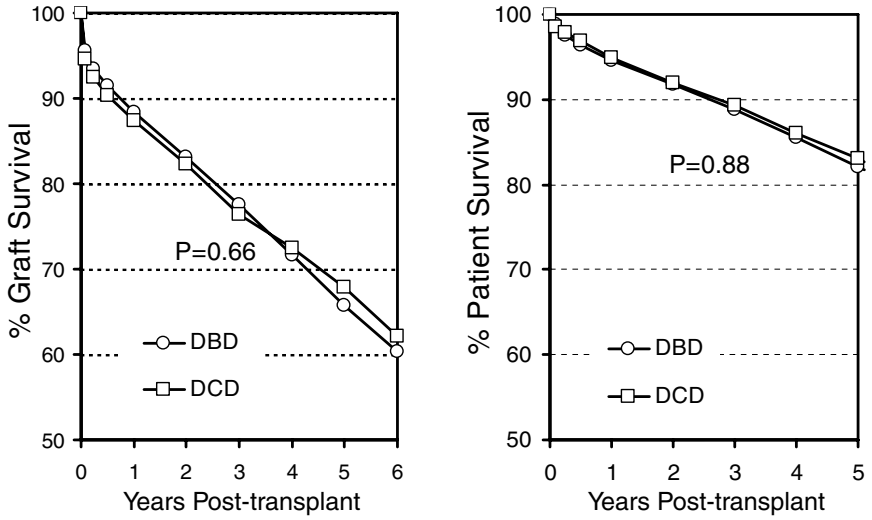

Figure 2: Graft and patient survival in DBD vs. DCD donor kidneys.

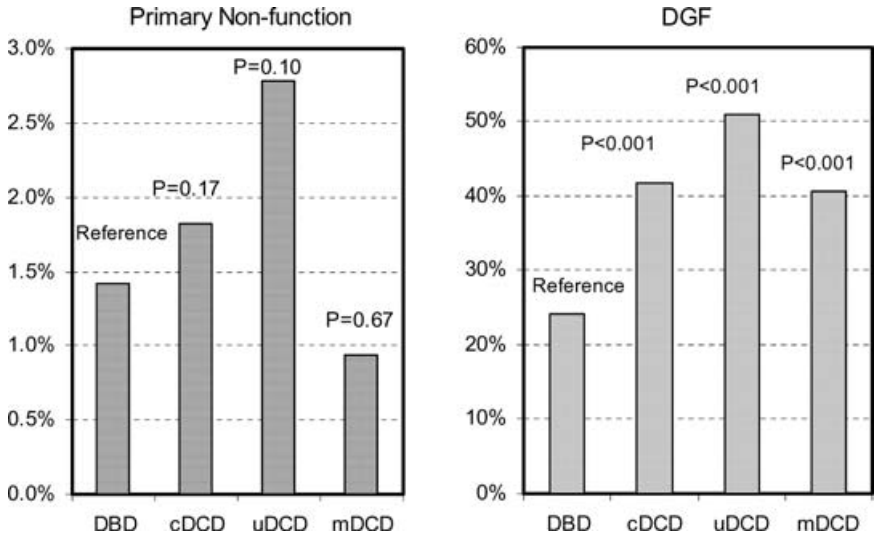

Figure 3: Incidence of primary nonfunction and DGF in DBD, cDCD, uDCD and mDCD donor kidneys. cDCD = controlled DCD, uDCD = uncontrolled DCD, mDCD = DCD, circumstances unknown.

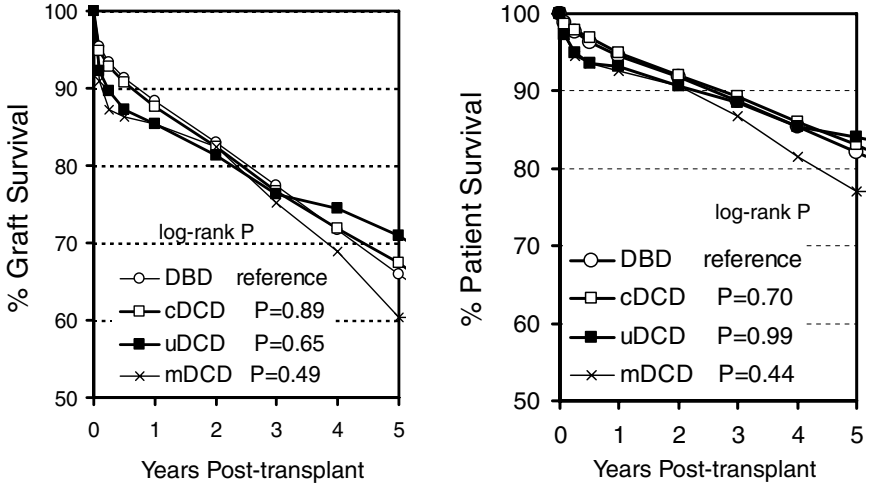

Figure 4: Graft and patient survival in DBD vs. cDCD, uDCD and mDCD donor kidneys. cDCD = controlled DCD, uDCD = uncontrolled DCD, mDCD = DCD where circumstances unknown.

Table 1: Characteristics of recipients, grafts and donors according to DBD, cDCD, uDCD and mDCD kidney transplantation

	DBD (ref) (n = 75 865)	cDCD (n = 1814)	uDCD (n = 216)	mDCD (n = 106)	p values
Recipient					
Age (year) mean ± SD	46.6 ± 14.6	48.6 ± 13.4	47.0 ± 13.3	47.0 ± 12.6	<0.001
Peak PRA (%)	15.5 ± 27.8	13.7 ± 25.4	14.9 ± 27.6	15.5 ± 28.2	0.002
African American (%)	28.1	31.2	32.9	36.8	0.003
Regraft (%)	10.1	9.7	7.9	3.8	0.11
Diabetes mellitus (%)	20.8	20.5	19.4	17.0	0.75
Waiting time (days)	666 ± 621	739 ± 610	626 ± 569	732 ± 549	<0.001
Donor					
Age (year) mean ± SD	36.3 ± 16.7	36.7 ± 15.9	28.6 ± 15.2	36.1 ± 15.9	<0.001
Race (%)					<0.001
White	74.8	86.9	73.6	83.0	
African American	10.8	7.0	15.3	10.4	
Hispanic	11.1	4.0	8.8	5.7	
Others	3.3	2.1	2.3	0.9	
Cause of death (%)					<0.001
CVA/stroke	40.3	21.4	13.4	16.0	
Head trauma	46.8	46.5	66.2	39.6	
Others	12.9	32.1	20.4	44.4	
ECD (%)	14.6	10.2	5.1	13.2	<0.001
Female (%)	41.1	34.7	23.6	36.8	<0.001
Graft					
DWIT (min)	0	17.0 ± 12.9	23.7 ± 18.6	15.5 ± 16.4	<0.001
CIT (h)	19.8 ± 8.4	20.0 ± 8.3	24.6 ± 9.5	26.4 ± 9.8	<0.001
ABDR MM	3.3 ± 1.8	3.7 ± 1.7	3.4 ± 1.7	3.6 ± 1.7	<0.001
Machine perfusion (%)	10.5	42.1	54.2	20.8	<0.001

Transplanting kidneys from cDCD, uDCD or mDCD donors are not significant risk factors compared to DCD donors after adjusting for all potential confounders such as recipient age, panel reactive antibodies, race, regraft, diabetes, waiting time, donor age, cause of death, CIT and HLA matching.

We also substratified the graft and patient survival as a function of DGF in the three groups and noticed that DCD kidneys with DGF fared statistically much better than DBD donor kidneys with DGF (Figure 5).

Discussion

The number of patients waiting for deceased kidney transplantation has been increasing exponentially. Patients waiting for kidney transplantation numbered 27 000 in 1994 and increased to 57 000 in 2003. The number of available organs from deceased donors in 1994 was 9500 and increased to only 11 000 in 2003 (12). Despite the increase in living donor kidney transplantations and introduction of extended criteria donor kidneys, this gap continues to widen with no real solution in sight.

The initial experience of using kidneys from DCD donors comes from the United States before the advent of brain death legislation in the 1970s. Since that time, the majority of donor kidneys have been procured from DBD donors. Support for the use of DCD kidneys has been thin, with ethical and logistic difficulties and the presumption that prolonged DWIT would lead to increases in DGF and ultimately poorer long-term graft and patient survival. The ethical issues surrounding DCD donor transplantation include the need to separate decisions regarding treatment and care of the dying patient and decisions about organ donation. There correspondingly needs to be separate teams of caregivers for a patient who will potentially be a DCD donor. Prompt response is also necessary for the procurement of DCD donor organs, and requires a transplant team to be available 24 h a day. Additionally, the current legislation of individual countries plays a major role in the utilization of DCD donors. Some European countries allow cannulation and *in situ* perfusion of organs before families can be approached about donation. This decreases DWIT and preserves the option to donate for the families. The majority of DCD donor use has thus been from European centers, with studies coming out of The Netherlands, Switzerland, Spain and the United Kingdom (4–11,13–15). Japan, accepting brain death concepts in 1999, has also been an experienced source of DCD donor kidneys (16,17). The encouraging results from these studies were an impetus for looking at the United States' UNOS database. This article focuses on the use of uncontrolled DCD kidneys, a large untapped resource here in the United States.

Wijnen et al. from The Netherlands looked at 57 DCD donors and matched DBD donor controls (11). They found the incidence of DGF in DCD kidneys to be 60%, compared to 35% in DBD kidneys. However, there was no difference in graft or patient survival after 5 years. Similar to the study

Table 2: Estimated relative risks of graft failure using univariate and multivariate Cox regression analysis

		Univariate		Multivariate	
Factors	Levels	Unadjusted RR (95% CI)	p values	Adjusted RR (95% CI)	p values
Recipient age (year)	≤20	1.21 (1.14–1.28)	<0.001	1.40 (1.28–1.44)	<0.001
	21–50	1.0		1.0	
	51–60	1.12 (1.09–1.16)	<0.001	1.08 (1.05–1.12)	<0.001
	>60	1.46 (1.41–1.51)	<0.001	1.40 (1.35–1.45)	<0.001
Peak PRA (%)	0–10	1.0		1.0	
	11–50	1.09 (1.05–1.13)	<0.001	1.08 (1.04–1.12)	<0.001
	51–100	1.31 (1.26–1.36)	<0.001	1.34 (1.29–1.40)	<0.001
Recipient race	Black	1.44 (1.41–1.49)	<0.001	1.43 (1.38–1.47)	<0.001
	Others	1.0		1.0	
Previous Tx	No	1.0		1.0	
	Yes	1.20 (1.15–1.25)	<0.001	1.28 (1.23–1.34)	<0.001
Recipient DM	Yes	1.24 (1.20–1.27)	<0.001	1.26 (1.22–1.30)	<0.001
	No	1.0		1.0	
Waiting time	≤3 years	1.0		1.0	
	>3 years	1.14 (1.11–1.18)	<0.001	1.02 (0.98–1.05)	0.35
Donor age (year)	1–15	1.13 (1.08–1.19)	<0.001	1.12 (1.07–1.18)	<0.001
	16–35	1.0		1.0	
	36–50	1.33 (1.29–1.37)	<0.001	1.25 (1.20–1.30)	<0.001
	51–60	1.67 (1.61–1.73)	<0.001	1.45 (1.38–1.52)	<0.001
	>60	2.28 (2.17–2.39)	<0.001	1.69 (1.57–1.82)	<0.001
Donor COD	Trauma	0.72 (0.70–0.74)	<0.001	0.90 (0.87–0.93)	<0.001
	Others	1.0		1.0	
ECD	Yes	1.76 (1.70–1.81)	<0.001	1.17 (1.11–1.24)	<0.001
	No	1.0		1.0	
Donor sex	Male	1.0		1.0	
	Female	1.17 (1.14–1.20)	<0.001	1.05 (1.02–1.08)	0.001
CIT (h)	0–24	1.0		1.0	
	25–36	1.05 (1.01–1.08)	0.006	1.06 (1.02–1.09)	0.001
	>36	1.14 (1.10–1.18)	<0.001	1.14 (1.10–1.19)	<0.001
ABDRMM	0–6	1.07 (1.06–1.08)	<0.001	1.05 (1.05–1.06)	<0.001
Donor type	DBD	1.0		1.0	
	cDCD	1.01 (0.91–1.11)	0.90	1.02 (0.92–1.13)	0.73
	uDCD	1.06 (0.83–1.35)	0.66	1.13 (0.88–1.44)	0.33
	mDCD	1.13 (0.80–1.60)	0.49	1.05 (0.74–1.49)	0.77

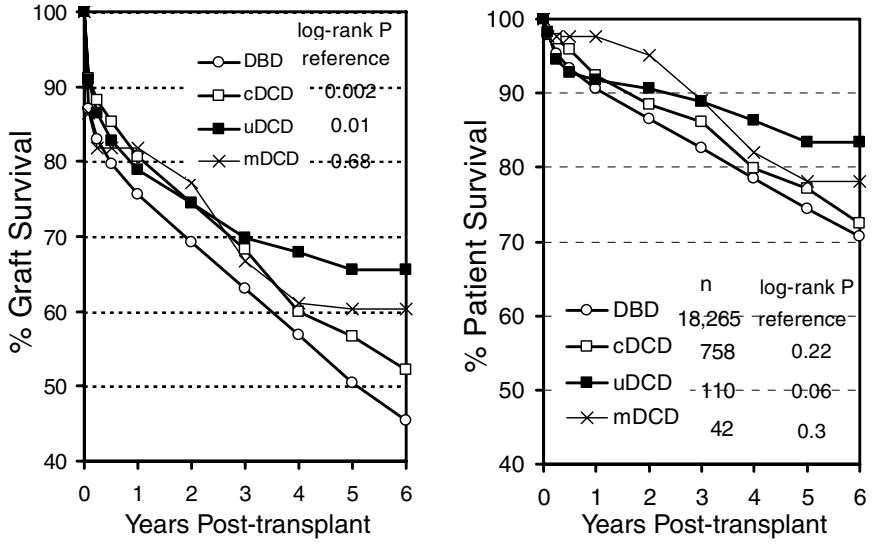

Figure 5: Graft and patient survival as a function of DGF in DBD vs. cDCD, uDCD and mDCD donor kidneys. cDCD = controlled DCD, uDCD = uncontrolled DCD, mDCD = DCD where circumstances unknown.

from The Netherlands, as well as multiple other studies (4–10,14,18–20), DCD kidneys in our study showed a statistically higher incidence of DGF. Despite this higher incidence of delayed function, there was no difference in 5-year graft or patient survival between DCD and DBD donor kidneys in our study.

It is now well known that kidney recipients from cDCD donors fare well after transplant. The uDCD donors, who are much higher in number, are rarely procured in the United States. Reluctance to procure these organs stems from concerns about logistic difficulties, ethical concerns and the resulting increased DWIT. However, Casavilla et al. reported similar outcomes between controlled and uncontrolled DCD donors (21). Shiroki et al. from Japan compared kidney donors who suffered cardiac arrest before brain death and those who were cannulated immediately after cardiac arrest (17). Despite a longer DWIT in uncontrolled donors, both groups showed similar incidences of DGF and primary nonfunction. Additionally, Weber et al. from Switzerland looked at 122 DCD donors in a matched pairs analysis with DBD donors and found that graft survival was not affected by dividing DCD donors into controlled and uncontrolled subgroups (10). In our analysis, we found that despite an increased incidence of DGF and longer DWIT, uDCD donor kidneys had the same long-term outcome as cDCD and DBD donor kidneys (Figure 4). Our results are based on data from the OPTN/UNOS database, and a potential source of bias may exist secondary to the under-reporting of graft loss in more proximal eras. However, our study spans 10 years and consistent results are obtained even when analyzing earlier years. Our study of the OPTN/UNOS database thus confirms the results of these other studies and should negate concerns surrounding the use of kidneys from uncontrolled DCD donors.

An interesting finding was noted when we looked at graft and patient survival as a function of DGF. We found that DCD kidneys did statistically better than DBD kidneys. Other studies have noted similar findings, concluding that DGF affects graft survival in DBD kidneys but not DCD kidneys (5,10,14). One hypothesis by Brook et al. suggests that brainstem death causes cytokine release and inflammatory effects not seen in DCD donor kidneys, and may account for the discrepancy in outcome (14).

The use of DCD donors has been reported to increase the available donor pool by 16–40% (8,15,22,23). An audit out of a Washington, DC, hospital found 5–6 times as many potential DCD donors as potential DBD donors (24), and a Canadian study estimated a potential increase of 30–87% with the incorporation of DCD donor kidneys (25). In 2003, The Netherlands reported the use of 87 DCD donors, which was 39% of all kidneys transplanted in that country. The United States utilized 264 DCD donors, which comprised only 4% of all kidneys transplanted (26). If the United States increased their utilization of DCD donor kidneys to equal that of The Netherlands, it would translate into a total of 2574 donors, potentially increasing the donor pool by approximately 50%. DCD donor kidneys, both controlled and uncontrolled, can provide much needed kidneys for transplantation, with the same long-term outcome as DBD donor kidneys.

In conclusion, our analysis of the UNOS data suggests that despite a statistically increased incidence of DGF and longer DWIT and CIT there is no difference in the graft survival and patient survival between DCD and DBD donor kidney groups. Additionally, despite less favorable pretransplant conditions, graft and patient survival between the uDCD donor kidneys and the cDCD donor kidneys was also comparable. Concerted efforts therefore should be focused not only at procuring kidneys from controlled DCD donors but also uncontrolled DCD donors, which would significantly increase the current donor pool.

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