

## TRANSPLANTATION OF KIDNEYS FROM DONORS WHOSE HEARTS HAVE STOPPED BEATING

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**ABSTRACT**

**Background** Attempts have recently been made to expand the number of cadaveric kidneys available for transplantation by using kidneys from donors without heartbeats in addition to those from brain-dead donors with beating hearts. We studied the efficacy of transplanting kidneys from donors without heartbeats on the basis of aggregate results from the Kidney Transplant Registry of the United Network for Organ Sharing.

**Methods** We compared the early function and survival rates of 229 kidney grafts from donors without heartbeats with those of 8718 grafts from cadaveric donors with heartbeats. All transplantations were performed at 64 U.S. transplantation centers. Cox proportional-hazards analysis was used to evaluate 10 major risk factors for graft failure.

**Results** The survival rate at one year was 83 percent for kidney grafts from donors without heartbeats, as compared with 86 percent for grafts from donors with heartbeats ( $P=0.26$ ). Among the kidneys from donors without heartbeats, the survival rate at one year was 89 percent for grafts from donors who had died of trauma, as compared with 78 percent for grafts from donors who had died of other causes ( $P=0.04$ ). The survival rates were high for grafts from donors without heartbeats despite the poorer early function of these grafts; 48 percent of the recipients required dialysis within the first week after transplantation, as compared with 22 percent of the recipients of grafts from donors with heartbeats. The primary-failure rate for kidneys from donors without heartbeats was 4 percent, as compared with 1 percent for kidneys from donors with heartbeats.

**Conclusions** Transplantation of kidneys from donors whose hearts have stopped beating, especially those who have died of trauma, is often successful, and the use of kidneys from such donors could increase the overall supply of cadaveric kidney transplants. (N Engl J Med 1998;338:221-5.)

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**A**T the end of 1996, more than 34,000 patients undergoing dialysis were on the national waiting list for kidney transplants, but only about 8600 cadaveric kidneys were transplanted in that year.<sup>1</sup> The number of patients awaiting cadaveric kidneys has increased progressively in recent years, and by the year 2000, more than 42,000 patients will be on the waiting list. Aside from the social costs of an inadequate supply of kidney transplants, the inability to treat pa-

tients optimally is frustrating for both the patients and the physicians who perform transplantation.

Use of kidneys from donors whose hearts have stopped beating could increase the supply of kidney transplants by a factor of 2 to 4.5.<sup>2</sup> Currently, more than 99 percent of cadaveric kidneys available for transplantation come from donors whose hearts are beating but who are brain-dead and in the hospital. Most of the early kidney transplantations, performed during the 1960s, used kidneys from donors whose hearts had stopped beating.<sup>3,4</sup> Under some circumstances, such kidneys can withstand warm ischemia for up to one hour,<sup>5,6</sup> and kidneys removed from patients after their hearts have stopped beating can function well.<sup>7-22</sup> To determine the efficacy of transplanting kidneys from donors without heartbeats, we compared 229 transplants from such donors with 8718 transplants from cadaveric donors with beating hearts.

**METHODS****Study Population**

Since 1994, the United Network for Organ Sharing (UNOS) has collected information from organ-procurement organizations on cadaveric organs procured from donors without heartbeats in whom life support was withdrawn after family members had given consent for donation. Transplantation centers that accept kidneys from donors without heartbeats notify UNOS of their willingness to do so, and kidneys from such donors are allocated according to the same point system used to distribute kidneys from brain-dead donors with heartbeats.

From 1994 to 1996, a total of 229 kidneys from donors without heartbeats were collected by 30 of the 63 U.S. organ-procurement organizations (range, 1 to 38 kidneys per organization) and transplanted at the 64 U.S. transplantation centers (range, 1 to 31 kidney transplantations per center) that accepted kidneys from donors without heartbeats. A total of 8718 cadaveric kidneys from donors with heartbeats were transplanted by the same 64 centers during the same period. The graft-survival rates at the 64 centers did not differ significantly from those at the 186 centers that did not accept kidneys from donors without heartbeats. The analysis included follow-up information provided on UNOS survey forms at scheduled intervals after transplantation and received at the UNOS Kidney Transplant Registry through June 1997.

**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 the survival curves for the two groups of grafts. The death of a recipient was documented as a graft failure. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-square test was used to compare categorical vari-

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ables. Variables that significantly influenced graft failure in univariate analyses were included (along with the dichotomous variable for the presence or absence of a heartbeat in the donor) in a multivariate Cox regression analysis. Less than 5 percent of values were missing for any covariate. Missing data for this analysis were replaced with modal values for categorical variables and mean values for continuous variables. In addition, continuous variables such as age, weight, cold-ischemia time, and the peak value for panel-reactive antibodies were categorized, since their effects on the hazard function were nonlinear. Plots of  $\log[-\log(\text{survival function})]$  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 percent 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 characteristics of the recipients and the donors are shown in Table 1. The proportions of female and white patients were significantly higher in the group receiving grafts from donors without heartbeats than

in the group receiving grafts from donors with heartbeats. For donors without heartbeats, the average warm-ischemia time associated with the procurement surgery was 14 minutes, whereas for donors with heartbeats, there was no record of warm-ischemia time because it was close to 0 minutes. The second warm-ischemia time, or the time required to restore circulation in the recipient, was only three minutes longer for the recipients of kidneys from donors without heartbeats than for the recipients of kidneys from donors with heartbeats. Pump perfusion was used more frequently for kidneys from donors without heartbeats (50 percent vs. 20 percent).

The outcome of transplantation in the two groups of recipients is shown in Table 2. Anuria occurred on the first day in 11 percent of grafts from donors with heartbeats, as compared with 21 percent of grafts from donors without heartbeats ( $P < 0.001$ ). Twenty-two percent of the recipients of kidneys from do-

TABLE 1. CHARACTERISTICS OF RENAL-TRANSPLANT RECIPIENTS, DONORS, AND RENAL GRAFTS.\*

CHARACTERISTIC	DONORS WITHOUT HEARTBEATS (N = 229)		DONORS WITH HEARTBEATS (N = 8718)		P VALUE
	no.†	value	no.†	value	
<b>Recipients</b>					
Age (yr)	229	46±13	8718	44±13	0.07
Height (cm)	212	168±11	7903	170±11	0.02
Weight (kg)	225	72.4±17.1	8470	73.6±17.2	0.26
Peak panel-reactive antibody (%‡)	221	15.4±25.6	8458	15.1±25.3	0.93
Male sex (%)	121	53	5321	61	0.01
Race (%)					0.49
White	145	63	5186	59	
Black	58	25	2391	27	
Other	26	11	1141	13	
Regraft (%)	25	11	1087	12	0.48
No. of hospital days	229	17±14	8718	15±14	<0.001
<b>Donors</b>					
Age (yr)	229	35±17	8681	33±18	0.08
Height (cm)	203	170±16	8556	167±21	0.01
Weight (kg)	215	73.4±24.2	8664	69.8±23.0	0.07
Serum creatinine (mg/dl)§	218	1.3±2.9	8680	1.3±1.9	0.28
Male sex (%)	150	66	5478	63	0.24
Race (%)					<0.001
White	197	86	6709	77	
Black	12	5	1089	12	
Other	20	9	920	11	
<b>Grafts¶</b>					
Pump perfusion (%)	114	50	1782	20	<0.001
First warm-ischemia time (min)	220	14±14	NA	NA	
Cold-ischemia time (hr)	224	25±10	8481	22±9	<0.001
Second warm-ischemia time (min)	208	23±20	7840	20±19	0.02
No. of HLA-B, DR mismatches	229	2.1±1.1	8718	2.0±1.2	0.36

\*Plus-minus values are means ±SD. NA denotes not applicable.

†The number is the number of recipients or donors for whom data were available.

‡The data shown are the highest panel-reactive antibody values in all tested serum samples.

§To convert the values for creatinine to micromoles per liter, multiply by 88.4.

¶The first warm-ischemia time was the time from the cessation of warm-blood perfusion to the start of preservation of the organ. The cold-ischemia time was the time from the start of preservation of the organ to its removal from cold storage. The second warm-ischemia time was the time from the removal of the organ from cold storage to perfusion with warm blood, whether venous or arterial.



nors with heartbeats required dialysis during the first week after transplantation, as compared with 48 percent of the recipients of kidneys from donors without heartbeats. The less-than-optimal state of the kidneys from donors without heartbeats was reflected in the proportion of recipients with high serum creatinine concentrations at the time of discharge. Primary graft failure (defined as a graft that never functioned) was reported in 4 percent of the recipients of kidneys from donors without heartbeats, as compared with 1 percent of the recipients of kidneys from donors with heartbeats.

The graft-survival rate at one year for kidneys from donors without heartbeats was 83 percent, as compared with 86 percent for kidneys from donors with heartbeats ( $P=0.26$ ) (Fig. 1). The difference of three percentage points occurred within the first month, suggesting that it was due to a difference in ischemic damage. There were no longer-term consequences of ischemia; the loss rate between one month and one year was the same for the two groups of kidneys. Five recipients of kidneys from donors without heartbeats (2 percent) and 312 recipients of kidneys from donors with heartbeats (4 percent) died with functioning grafts during the study period. Less than 1 percent of patients were lost to follow-up during the study period (1 who received a kidney from a donor without a heartbeat and 72 who received kidneys from donors with heartbeats). One year after transplantation, the mean ( $\pm$ SD) serum creatinine concentration in the patients with functioning grafts was  $1.9 \pm 0.9$  mg per deciliter ( $170 \pm 80$   $\mu$ mol per liter) in the 91 recipients of kidneys from donors without heartbeats and  $1.8 \pm 0.8$  mg per deciliter ( $160 \pm 70$   $\mu$ mol per liter) in the 3598 recipients of kidneys from donors with heartbeats.

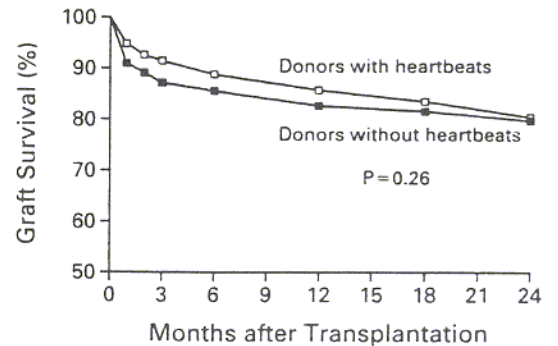
The graft-survival rate at one year for kidneys from donors without heartbeats who had died of trauma was 89 percent, as compared with 78 percent for kidneys from donors without heartbeats who had died of other causes ( $P=0.04$ ) (Fig. 2). We considered the possibility that this effect might be the result of the younger age of donors who had died of trauma, but when the analysis was stratified according to the donor's age, the cause of death was still correlated with the graft-survival rate. The survival of grafts from donors without heartbeats who had died of trauma was similar to that of grafts from donors with heartbeats. Survival was significantly poorer for kidneys from donors without heartbeats who had died of other causes ( $P=0.02$ ). However, the survival of grafts from donors without heartbeats who had died of nontraumatic causes did not differ significantly from the survival of grafts from donors with heartbeats who had died of similar causes ( $P=0.23$ , data not shown).

Multivariate regression analysis of 10 potential risk factors showed that all factors except the presence

TABLE 2. EARLY FUNCTION OF KIDNEY GRAFTS FROM DONORS WITHOUT HEARTBEATS AND DONORS WITH HEARTBEATS.

VARIABLE	DONORS WITHOUT HEARTBEATS (N=229)	DONORS WITH HEARTBEATS (N=8718)	P VALUE
	no. (%)		
No urinary output in first 24 hours	47 (21)	954 (11)	<0.001
Dialysis in the first week	109 (48)	1912 (22)	<0.001
Antirejection treatment	43 (19)	1209 (14)	0.04
Serum creatinine at discharge*			<0.001
<2.1 mg/dl	85 (38)	4703 (55)	
2.1-4.0 mg/dl	56 (25)	2301 (27)	
>4.0 mg/dl	84 (37)	1562 (18)	
Primary failure	9 (4)	99 (1)	<0.001

\*Data were not available for 4 patients with grafts from donors without heartbeats and 152 with grafts from donors with heartbeats. To convert the values for creatinine to micromoles per liter, multiply by 88.4.



NO. OF GRAFTS	8718	7136	6368	3983	2308	1169
Donors with heartbeats						
Donors without heartbeats	229	178	153	97	61	40

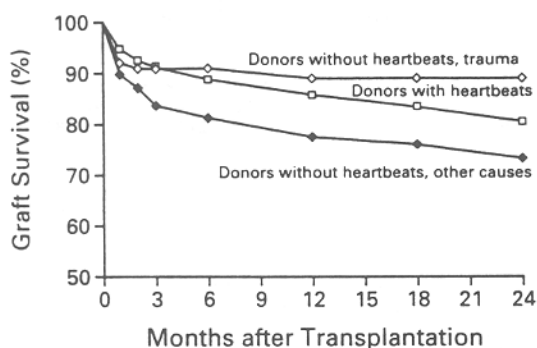
Figure 1. Graft-Survival Rates for Kidney Transplants from Donors with Heartbeats and Donors without Heartbeats.

Data are from the United Network for Organ Sharing for the period from 1994 to 1996.

or absence of a heartbeat in the donor were significantly associated with the risk of graft failure, after adjustment for the remaining factors (Table 3). In view of the effect of all the listed factors on graft survival, the difference between kidneys from donors without heartbeats and those from donors with heartbeats was small.

DISCUSSION

Although the initial experience in transplanting kidneys from donors without heartbeats was in the United States,<sup>3,4</sup> much of the recent experience has been in



NO. OF GRAFTS FROM DONORS WITHOUT HEARTBEATS

Death from trauma	106	82	74	41	24	18
Death from other causes	123	96	79	56	37	22

**Figure 2.** Graft-Survival Rates for Kidney Transplants from Donors with Heartbeats and Donors without Heartbeats, According to the Cause of Death in the Donors without Heartbeats.

P=0.02 for the comparison between donors with heartbeats and those without heartbeats who died from causes other than trauma. P=0.04 for the comparison between donors without heartbeats who died from trauma and those without heartbeats who died from other causes.

**TABLE 3.** RISK FACTORS FOR GRAFT FAILURE ACCORDING TO THE REGRESSION ANALYSIS.

FACTOR	NO. OF RECIPIENTS	RELATIVE RISK (95% CI)*	P VALUE
Previous transplant			
No	7835	1.0	
Yes	1112	1.3 (1.13-1.56)	<0.001
Age of recipient			
14-50 yr	5976	1.0	
51-60 yr	1888	1.2 (1.03-1.35)	0.02
>60 yr	1083	1.3 (1.14-1.56)	<0.001
Weight of recipient			
≤80 kg	6263	1.0	
>80 kg	2684	1.2 (1.08-1.37)	0.001
Peak panel-reactive antibody			
0-20%	7163	1.0	
>20%	1784	1.3 (1.17-1.53)	<0.001
No. of HLA-B, DR mismatches			
0	1277	1.0	
1 or 2	3750	1.5 (1.20-1.77)	<0.001
3 or 4	3920	1.7 (1.37-2.05)	<0.001
Cold-ischemia time			
0-30 hr	7423	1.0	
>30 hr	1524	1.3 (1.09-1.42)	0.001
Cause of death in donor			
Trauma	4629	1.0	
Other	4318	1.2 (1.06-1.36)	0.005
Race of donor			
Nonblack	7846	1.0	
Black	1101	1.3 (1.21-1.53)	<0.001
Age of donor			
0-10 yr	677	1.5 (1.24-1.85)	<0.001
11-40 yr	5023	1.0	
41-50 yr	1502	1.2 (1.01-1.40)	0.04
51-60 yr	1120	1.5 (1.09-1.83)	<0.001
>60 yr	625	2.0 (1.69-2.49)	<0.001
Heartbeat in donor			
Present	8718	1.0	
Absent	229	1.1 (0.83-1.57)	0.41

\*CI denotes confidence interval.

Europe,<sup>6,7,9-11,15,16,18,20,21</sup> led by the Netherlands<sup>15</sup> and Japan,<sup>8,12,19,22</sup> where kidneys from cadaveric donors with heartbeats have been difficult to obtain. Interest in the use of grafts from donors without heartbeats has increased in the United States recently, with several encouraging studies.<sup>13,14,16,17</sup> Our study of the results of 229 transplantations performed at 64 centers in the United States largely confirms the previous reports from single centers.

The most important finding of our study was that the survival of kidney grafts from donors without heartbeats was similar to that of grafts from donors with heartbeats. One year after transplantation, the kidneys from donors without heartbeats functioned well (as indicated by the mean serum creatinine concentration), suggesting that long-term survival rates for these kidneys will be similar to those for kidneys from donors with heartbeats, despite the poorer early function of the grafts from donors without heartbeats. Kidneys from donors without heartbeats who had died of trauma survived as well as those from donors with heartbeats. We do not know whether the small difference in survival associated with the cause of death in the donors without heartbeats reflects differences in their care before their hearts stopped beating.

In the early period after transplantation, kidneys from donors without heartbeats did not function as well as those from donors with heartbeats, a finding reported in several previous studies.<sup>2,6,8,9,12,14,15</sup> Nearly half the recipients of kidneys from donors without heartbeats required dialysis during the first week after transplantation, and 4 percent of the kidneys in this group never functioned. The survival curves show that the difference between the survival of kidneys from donors without heartbeats and the survival of those from donors with heartbeats was entirely due to graft failure in the first month after transplantation. This means that the disadvantage of using kidneys from donors without heartbeats could be reduced considerably or eliminated if a kidney-viability test were available to exclude poor kidneys, particularly those that will never function. Several such tests have been developed: the tetrazolium test, which measures the metabolic activity of tubules either by visual timing of the color change<sup>23</sup> or by spectrometric measurement,<sup>24</sup> proton magnetic resonance spectroscopy,<sup>25</sup> and measurement of alpha glutathione S-transferase activity.<sup>26</sup> However, none of those tests have yet been validated for the purpose of documenting the viability of human kidneys.

The number of patients waiting for cadaveric kidney transplants has increased by about 2400 per year since 1988. If 2400 more kidneys from 1200 donors without heartbeats could have been procured each year, the waiting list would not have increased. Even today, the waiting list would not increase if each of the 63 organ-procurement agencies in the United

States obtained kidneys from two donors without heartbeats each month. A program for procuring kidneys from donors without heartbeats has been reported to result in a 40 percent increase in the overall supply of cadaveric kidneys,<sup>2</sup> and there may be twice as many donors without heartbeats as donors with heartbeats. A 40 percent increase in the supply of cadaveric kidneys in the United States would mean that there would be 3440 more kidneys available for transplantation than in 1995, an increase that (if maintained) might begin to reduce the number of patients on the waiting list for cadaveric kidney transplants each year.

In conclusion, the early results from 64 U.S. centers suggest that graft survival at one year is not adversely affected by transplanting kidneys from donors whose hearts have stopped beating. The supply of cadaveric grafts could be increased by using kidneys from these donors.

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