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Renal Transplantation from Non-Heart Beating Donors: A Promising Alternative to Enlarge the Donor Pool

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Abstract. The aim of this study was to compare the survival and midterm function of kidneys from non-heart beating donors (NHBD) with those of kidneys from heart beating donors (HBD). From 1989 to 1998, 144 kidneys were procured from NHBD at the Hospital Clínico San Carlos in Madrid, of which 95 were transplanted. The kidney grafts were maintained from the moment of the diagnosis of cardiac arrest until the time of procurement by cardiopulmonary bypass. There was no significant difference in renal function and the number of rejection episodes between the NHBD and HBD transplants. The NHBD kidneys showed a 5.73-fold increase in the incidence of delayed graft function (adjusted relative risk 95% confidence interval, 2.82 to 11.62). One- and five-year survival rates for NHBD grafts were 84.6 and 82.7%, respectively, compared with 87.5 and 83.9% for HBD ($P = 0.5767$). Cox analysis showed that the predictive factors for worse NHBD graft survival were type of NHBD donor and the occurrence of corticoresistant rejection. Ninety of the NHBD organs were procured from subjects suffering irreversible cardiac arrest on the street who were transferred to our center for the sole purpose of donation. Fifty-four of these kidneys were transplanted and all showed primary function. When a strict protocol is adhered to, the outcome of renal transplant from NHBD compares well with that from HBD. It is believed that the high number of organs obtained from subjects undergoing irreversible cardiac arrest on the street might encourage the adoption of new criteria for the management of this type of pathology with the ultimate goal of kidney donation.

The ever-increasing number of patients undergoing dialysis and the adoption of less restrictive transplant criteria have led to a shortage of cadaveric kidneys for transplant. Despite the fact that since 1991 there has been a progressive decrease in the number of patients waiting for a renal transplant in Spain, by the end of 1997, 4035 patients were waiting for kidneys from a total population approaching 39 million (1). Although there is a need to extend the use of brain-dead donors with heartbeats, there is still room for additional sources of organs, and this has prompted the use of non-heart beating donors (NHBD).

In 1989, a NHBD procurement and transplant program was started at the Hospital Clinico San Carlos, Madrid. After overcoming numerous hurdles, this hospital is presently the largest procurement center for this type of transplant in our country and supplied 46% of the NHBD kidneys transplanted in Spain in 1997 (1). Over the past year, NHBD kidneys were used in 32% of all transplants performed at this center and the current rate approaches 40%. Many of our donors are subjects who die suddenly on the street and, after unsuccessful cardiopulmonary resuscitation (CPR), are transferred to the hospital for the sole purpose of donation.

The use of NHBD has been the subject of numerous reports (2–21), and it is clear that this type of donation is on the rise. This article relates the experience gained at the Madrid center, which, to date, handles the largest number of procured and transplanted kidneys from NHBD of any single center in Western society. The aim of this study was to compare the survival and midterm function of kidneys from NHBD with those of kidneys from heart beating donors (HBD).

Materials and Methods

Study Population

In 1989, a program to procure kidneys from NHBD was started at the Hospital Clínico San Carlos in Madrid, Spain. The grafts were maintained from the moment cardiac arrest had been diagnosed until the time of procurement by cardiopulmonary bypass involving extracorporal circulation, external oxygenation, and intense hypothermia (22). In addition to the classical prerequisites for the brain-dead donor, our current acceptance criteria for NHBD kidneys are:

- Maximum time of oligoanuria before cardiac arrest: 60 min
- Maximum time of warm ischemia (from the start of cardiac arrest to the start of perfusion): 120 min
- Maximum pump perfusion time: 240 min
- Donor age <55 yr

A recent addition to the program is the procurement of organs from subjects who die suddenly on the street and are transported to the center for donation (23). To this end, a formal agreement has been

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established with municipal emergency facilities (SAMUR, phone 061), whereby after unsuccessful CPR patients are transferred to our hospital. To be accepted as possible donors, these subjects were also required to fulfill the following criteria:

- Known cause of death, ruling out violence
- Nonbleeding injuries to the thorax or abdomen
- External cardiac massage and mechanical ventilation performed within 15 min of the start of cardiac arrest
- Transfer of subjects to the hospital with external cardiac massage, mechanical ventilation, and intravenous liquid perfusion
- No external signs of possible intravenous drug addiction to control the risk of HIV or hepatitis C or B positivity

Family and legal consent was obtained for all 144 kidneys procured in this manner. Of these, 95 were transplanted. The organs obtained were classified according to Maastricht donor categories (24). To include all of our donor types, a fifth category was added to this classification scheme:

- Type I: dead on arrival (irreversible cardiac arrest on the street)
- Type II: unsuccessful resuscitation (This includes patients brought into the emergency room while being resuscitated by the ambulance crew)
- Type III: imminent cardiac arrest in intensive care (ventilator switch-off)
- Type IV: cardiac arrest during or after the brain death diagnostic procedure
- Type V: unexpected cardiac arrest in intensive care

Data corresponding to the NHBD transplants ($n = 95$) were compared with those corresponding to adult cadaveric HBD transplants ($n = 354$) performed at this center during the same period. The transplant recipients were subjected to the same immunosuppressive treatment, *i.e.*, quadruple sequential therapy (anti-thymocyte globulin 7 d, azathioprine, prednisone from the time of transplant and the introduction of cyclosporine on day 5) or triple therapy (cyclosporine plus prednisone and azathioprine or mycophenolate). Data obtained from other types of transplants performed at this center (*en bloc* pediatric or living donors) were not included in the study. The median follow-up period was 38 mo (range, 15 to 66 mo).

Statistical Analyses

The *t* test or ANOVA was used to compare continuous variables (expressed as means ± SEM), while categorical variables were compared using the χ^2 test. Stratified logistic regression was performed according to the type of transplant to predict inadequate renal function (creatinine clearance <60 ml/min corresponding to the global distribution median) at 12 mo posttransplant using the Cockcroft-Gault equation (25). The following variables were recorded: cold and warm ischemia time, donor and recipient age, gender, HLA compatibility, months on dialysis, type of dialysis, type of treatment, number of transplant, peak preformed reactive antibodies, cause of death of donor (trauma or no trauma), corticoresistant and corticosensitive rejection, and weight of recipient. Variables shown to significantly influence renal function at 12 mo by univariate analysis were included in a multivariate logistic regression analysis. Adjusted relative risks (adjRR) and their 95% confidence intervals (95% CI) were calculated with the estimated regression coefficients and their SEM in the logistic regression analysis. Patient and graft survival rates were estimated using the Kaplan–Meier method. Loss of the graft was taken as the re-requirement for dialysis and rates include never-functioning kidneys. The Breslow exact test was used to evaluate differences in the survival curves. Adjusted risk ratios were calculated using the Cox regression model. The existence of interactions was evaluated. Variables showing a P value <0.15 in the univariate analysis were selected for the multivariate analyses. The null hypothesis was rejected in each statistical test when $P < 0.05$. Analysis was performed using Windows SPSS version 7.5 software.

Results

Renal Transplants from Non-Heart Beating Donors

The NHBD kidneys ($n = 144$) were grouped according to Maastricht donor categories (24), which were modified to include all of our donors (see Materials and Methods) as follows: 90 (62.5%) type I, 26 (18.1%) type II, 6 (4.2%) type III, 4 (2.8%) type IV, and 18 (12.5%) type V (Figure 1). Ninety-five of the 144 kidneys procured were transplanted. The remaining kidneys were rejected for use due to poor macroscopic appearance ($n = 7$), renal trauma ($n = 9$), biopsy showing considerable renal damage (thrombotic microangiopathy) ($n = 6$), prolonged cold ischemia ($n = 4$), technical problems ($n = 10$), hepatitis B or C or HIV positivity ($n = 10$), and other ($n = 3$). Of the 95 transplanted kidneys, 89 (93.7%) showed primary function and six never functioned (6.3%). The six never-functioning kidneys had been procured from type II and V donors. These results are shown in Figure 1. There was no difference in the warm ischemia time sustained by grafts showing primary function and those that never functioned (78.6 ± 7.5 *versus* 60.0 ± 19.1 min; $P = 0.304$). Six func-

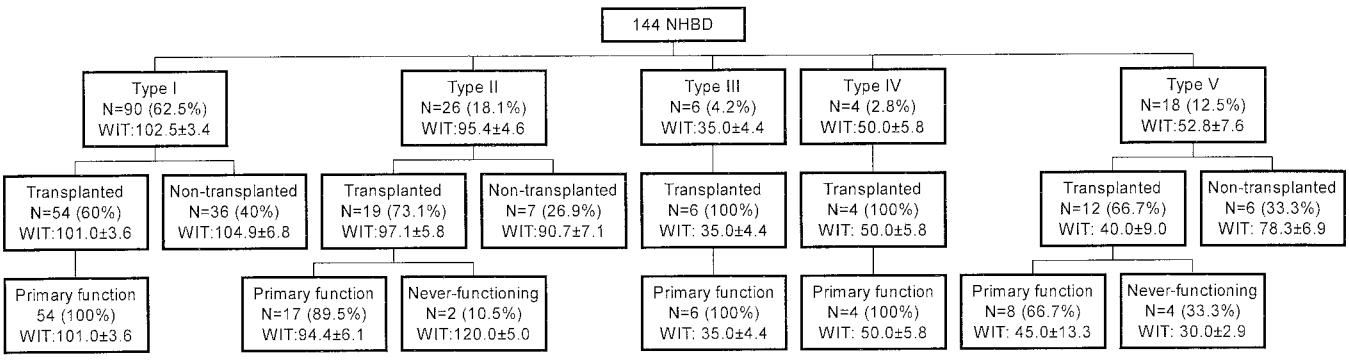

Figure 1. Procured, transplanted, and never-functioning kidneys according to the modified Maastricht donor classification. A total of 144 kidneys was procured from non-heart-beating donors (NHBD) at the Hospital Clinico San Carlos (Madrid, Spain) during the period 1989–1998.

Table 1. General characteristics of NHBD and HBD transplants performed at the Hospital Clinico San Carlos (Madrid, Spain) from 1989 to 1998[a]

Characteristic	NHBD					HBD		
	Modified Maastricht Donor Category							
	Type I	Type II	Type III	Type IV	Type V	P^1		P^2
Donor age (yr)	35.0 ± 1.6	32.7 ± 2.6	21.0 ± 0.4	33.0 ± 5.2	32.3 ± 4.5	0.102	40.5 ± 0.9	0.000
Male recipients (%)	64.0	82.4	50.0	100.0	41.7%	0.095	63.6	0.439
Dialysis time (mo)	40.9 ± 8.2	41.5 ± 8.5	36.5 ± 12.7	9.9 ± 0.9	72.0 ± 18.9	0.264	47.8 ± 2.6	0.471
Recipient age (yr)	47.4 ± 1.9	47.8 ± 2.5	43.6 ± 5.8	50.4 ± 3.1	43.0 ± 3.7	0.327	47.9 ± 0.7	0.792
Male donors (%)	94.0	94.1	100.0	50.0	83.3	0.034	62.1	0.000
HLA match (mean number)	1.86 ± 0.15	2.18 ± 0.20	2.00 ± 0.36	0.50 ± 0.29	1.33 ± 0.28	0.014	2.07 ± 0.06	0.035
Peak PRA (%)	13.2 ± 2.9	16.9 ± 5.5	3.0 ± 1.5	0.7 ± 0.75	32.8 ± 8.9	0.021	15.4 ± 2.4	0.476
Current PRA (%)	3.1 ± 1.4	4.0 ± 2.4	2.0 ± 1.0	0 ± 0	19.6 ± 9.4	0.010	7.4 ± 1.0	0.238
Regraft (%)	10.0	17.6	16.7	0	16.7	0.815	12.7	0.546
Warm ischemia time (min)	100.6 ± 3.9	93.8 ± 6.0	35.0 ± 4.4	50.0 ± 5.8	40.0 ± 9.0	0.000	0	0.000
Cold ischemia time (h)	19.5 ± 0.5	18.7 ± 1.1	21.8 ± 0.9	16.0 ± 1.9	19.2 ± 0.9	0.178	18.3 ± 0.3	0.038

[a] NHBD, non-heart beating donor; HBD, heart beating donor; PRA, panel-reactive antibody; P^1, ANOVA of the different NHBD types; P^2, *t* test for independent samples used to compare NHBD and HBD data.

tioning kidneys that had been transplanted at other centers were lost to follow-up.

Table 1 describes the characteristics of the grafts according to the modified Maastricht donor classification. Stratification according to donor type showed no differences in renal function estimated as serum creatinine 1 yr after transplant (type I, 1.63 ± 0.10; type II, 1.39 ± 0.09; type III, 1.42 ± 0.09; type IV 1.85 ± 0.5; and type V, 2.17 ± 0.87 mg/dl; $P = 0.453$). However, differences were shown in graft survival ($P = 0.002$) (Figure 2), with relative risks using the type I donors as the reference category of 0.88 (95% CI, 0.09 to 8.51) for type II, 2.39 (95% CI, 0.25 to 22.99) for type III, 3.79 (95% CI, 0.39 to 36.43) for type IV, and 9.48 (95% CI, 2.37 to 37.99) for type V. It should be noted that 54 of the 90 kidneys procured from subjects who died on the street showed primary function. Worst survival rates were shown by kidneys obtained from donors suffering unexpected cardiac arrest in intensive care (type V); 33% of these grafts never functioned. Because the ischemia time sustained by these kidneys had been short, this prompted us to review the medical history of the corresponding donors. The review disclosed that before irreversible cardiac arrest, these donors had suffered several other cardiac arrests accompanied by hypotension that was difficult to manage and the requirement for vasoconstrictive agents. There were also cases of cardiopulmonary dysfunction. The donors had been chosen during the initial stages of the NHBD program and, in view of the poor results, more restrictive acceptance criteria for kidneys from this type of donor were adopted, including a maximum time of oligoanuria before cardiac arrest of 60 min. Patient survival was similar when the transplants were stratified according to NHBD type ($P = 0.438$).

The NHBD program shows two clearly distinguishable periods. The first, from 1989 to 1992 in which 17 transplants were performed (five type II and 12 type V), may be considered the starting period, or stage I. For several reasons mainly

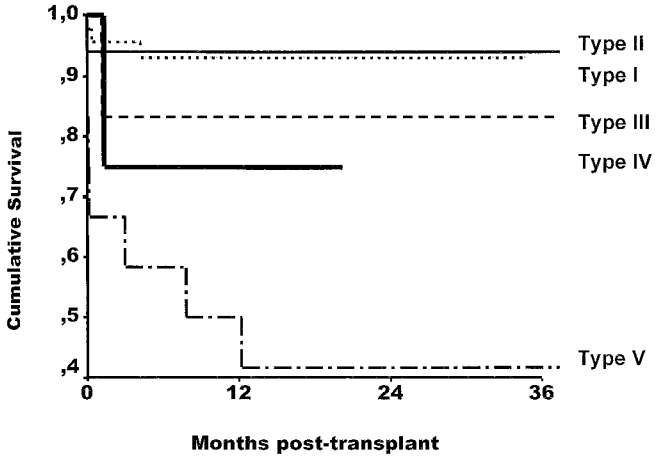

Figure 2. Actuarial graft survival in NHBD transplants according to modified Maastricht categories. Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989–1998.

concerning hospital infrastructure, no further transplant was performed until 1995 when the second stage of the program was initiated. This period, including 78 transplants (54 type I, 14 type II, six type III, four type IV, and zero type V), extends to October 1998. It may be observed that NHBD represent an increasing proportion of the donor pool (from 11% in 1995 to the current 37.7%).

A comparison of the two program stages showed that the proportion of never-functioning kidneys was higher during stage I (29.4% *versus* 2.6%; $P = 0.002$). Similarly, graft survival was worse during stage I (52.9% *versus* 91.3% at 3 yr, respectively; $P = 0.0001$) (Figure 3). No differences in HBD graft survival rates were observed between the two stages ($P = 0.3610$) (Figure 4).

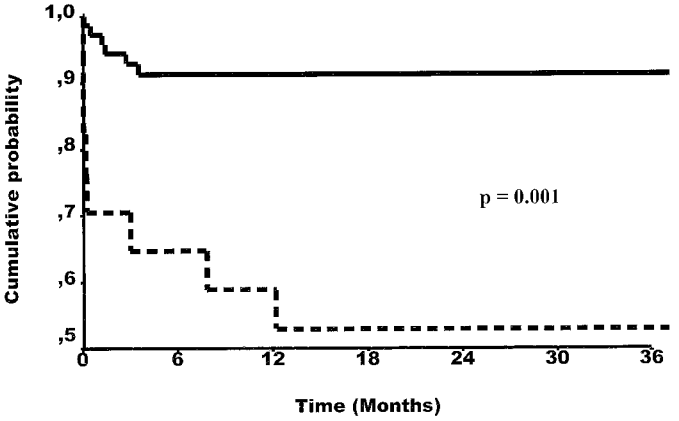

Figure 3. Actuarial graft survival in NHBD transplants according to the time period. Stage I: 1989 to 1992 (broken line). Stage II: 1995 to 1998 (solid line). Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989–1998.

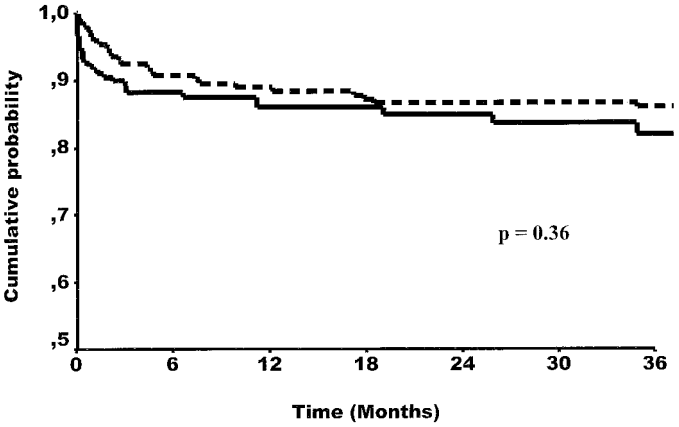

Figure 4. Actuarial graft survival in heart beating donor (HBD) transplants according to the time period. Stage I: 1989 to 1992 (broken line). Stage II: 1995 to 1998 (solid line). Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989–1998.

Renal Transplants from Non-Heart Beating Donors versus *Heart Beating Donors*

No significant difference in renal function (estimated by serum creatinine and creatinine clearance) was observed between NHBD and HBD transplants, except during the first month of follow-up (Table 2). Logistic regression analysis showed no effect in terms of worse renal function for NHBD *versus* HBD transplants (RR 1.27; 95% CI, 0.68 to 2.38; $P = 0.46$). Proteinuria was also similar in the transplant groups (243 ± 74 mg/d in NHBD transplants *versus* 328 ± 55 in HBD, $P = 0.511$ at 3 yr, and 287 ± 107 mg/d in NHBD transplants *versus* 307 ± 68 in HBD, $P = 0.779$ at 5 yr). Table 1 lists the general characteristics of the two study groups. No differences between groups were detected in the number or type of rejection episodes. The number of rejection episodes for patients receiving NHBD and HBD kidneys, respectively, was as follows: no episodes, 56.8% *versus* 57.4%; one episode, 42.0% *versus* 34.3%; two or more episodes, 1.2% *versus* 8% (P = NS). NHBD kidneys showed longer periods of delayed graft function (DGF) than those procured from HBD (10.5 ± 1.0 *versus* 2.84 ± 0.37 d; $P = 0.000$). NHBD kidneys showed a 5.73-fold increase in the incidence of DGF (adjRR CI 95%, 2.82 to 11.62). The factors associated with worse renal function in the HBD transplants were: DGF greater than 14 d (adjRR 1.20; 95% CI, 1.16 to 1.23) and from 1 to 14 d (adjRR 1.17; 95% CI, 1.14 to 1.20), donor age >55 yr (adjRR 2.08; 95% CI, 1.93 to 2.30), recipient age >55 yr (adjRR 1.28; 95% CI, 1.24 to 1.34), corticoresistant rejection (adjRR 1.18; 95% CI, 1.16 to 1.21), and recipient weight >80 kg (adjRR 1.21; 95% CI, 1.19 to 1.27). No statistically significant prognostic factors for worse renal function were recorded for the NHBD transplants.

One- and five-year survival rates for all of the NHBD grafts were 84.6 and 82.7%, respectively, compared to 87.5 and 83.9% for grafts from HBD ($P = 0.5767$) (Figure 5). Taking into account the second stage of the program only (1995 onward), the NHBD kidneys showed a higher survival rate (90.9% at 4 yr) than HBD kidneys (81.9% at 4 yr), although the difference was not significant ($P = 0.255$). The causes for the loss of NHBD grafts were: acute rejection ($n = 3$; 21.4%), chronic rejection ($n = 2$; 14.3%), surgical complications ($n = 2$; 14.3%), thrombotic microangiopathy due to cyclosporine toxicity ($n = 1$; 7.1%), and primary graft failure ($n = 6$; 42.9%). HBD graft losses were attributed to: acute rejection ($n = 21$; 36.8%), chronic rejection ($n = 17$; 29.8%), surgical complications ($n = 8$; 14.0%), primary graft failure ($n = 1$; 1.8%), and other ($n = 10$; 17.5%).

Table 3 shows the results of the univariate analysis of the variables under study stratified according to transplant type in relation to graft loss. In the HBD transplants, the variables related to worse graft survival were peritoneal dialysis, donor age ≥55 yr, and the occurrence of rejection (corticosensitive and corticoresistant) (Table 4). The negative predictive factors for NHBD graft survival were: donor types III, IV, and V and one or more episodes of corticoresistant rejection (Table 4). Patient survival was similar in the NHBD and HBD transplant groups ($P = 0.2666$).

Discussion

Thanks to the work of García-Rinaldi published in 1975 (26), the *in situ* preservation of cadaveric kidneys by cold perfusion using a catheter introduced into the aorta via the femoral artery has permitted a reduction in the warm ischemia time sustained by the kidneys of NHBD. This technique fell into disuse throughout the 1980s when the issue of cold perfusion was scarcely addressed (2,4–6). However, the ever-increasing shortage of kidneys has led to the reconsideration of the NHBD, which over the past few years has been estimated to permit a 7 to 40% increase in the number of transplants performed (3,7–9,15,16,18,19). In the present center, the NHBD program has increased the number of available kidneys by 32% over the past year and is predicted to exceed this figure in 1998.

The viability of the kidney from the NHBD, which is invariably subjected to a period of warm ischemia, is the most

Table 2. Serum creatinine in NHBD and HBD transplants performed at the Hospital Clinico San Carlos (Madrid, Spain) from 1989 to 1998[a]

Time Period	Serum Creatinine (mg/dl)		*P* Value
	HBD	NHBD	
1st month	2.16 ± 0.11 (*n*=326)	2.94 ± 0.26 (*n*=76)	0.006
3rd month	1.59 ± 0.04 (*n*=311)	1.59 ± 0.09 (*n*=68)	0.914
6th month	1.63 ± 0.05 (*n*=295)	1.59 ± 0.07 (*n*=66)	0.187
1st year	1.59 ± 0.04 (*n*=259)	1.63 ± 0.12 (*n*=46)	0.706
2nd year	1.65 ± 0.04 (*n*=217)	1.43 ± 0.09 (*n*=24)	0.225
3rd year	1.63 ± 0.05 (*n*=186)	1.43 ± 0.08 (*n*=17)	0.233
4th year	1.62 ± 0.04 (*n*=142)	1.63 ± 0.20 (*n*= 9)	0.950
5th year	1.69 ± 0.06 (*n*=110)	1.62 ± 0.13 (*n*= 9)	0.777

[a] To convert the values for creatinine to micromoles per liter, multiply by 88. Abbreviations as in Table 1.

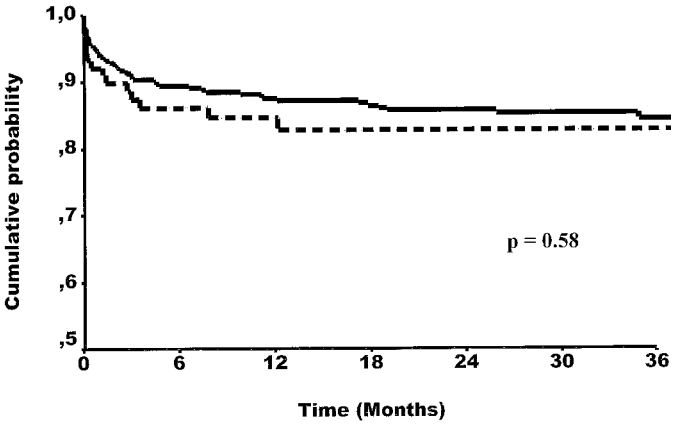

Figure 5. Graft survival curves for NHBD and HBD transplants. HBD transplants (solid line), NHBD transplants (broken line). Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989–1998.

crucial factor for transplant outcome. In practice, it is common to find that a large proportion of these grafts never function (10,14). In our study, warm ischemia time did not seem to be a crucial factor for primary function, although it is difficult to compare findings because the concept of warm ischemia is often poorly defined. Here, warm ischemia time was defined as the time from the start of cardiac arrest (including the time taken to perform resuscitation measures) to the start of cold perfusion. Some authors quantify this factor in a different way, while others provide no information with regard to its measurement.

The present observation that never-functioning kidneys had not been subjected to longer periods of warm ischemia than functioning kidneys is paradoxical and contradictory to the findings of others (12). This reflects the role of factors that may not be easily evaluated, such as the hemodynamic characteristics of the subject before cardiac arrest or the efficacy of resuscitation and maintenance measures. Most of the never-functioning kidneys in this study had been procured from subjects who had suffered uncontrolled, irreversible cardiac arrest in the intensive care unit or, in other words, heart failure had not been provoked by a consensus to switch off the ventilator. For this group of donors, we included a new category in the Maastricht classification scheme due to our reluctance to assign such donors to either the type II or III Maastricht categories (since the former mainly refers to patients transferred to the hospital emergency room while being resuscitated by the ambulance crew in whom CPR measures are unsuccessful and the latter includes patients who die in intensive care as the result of ventilator switch-off). The kidneys procured from type V donors suffered shorter periods of effective warm ischemia than those harvested from types I or II. However, when the medical records of this type of donor were reviewed, it was found that they had undergone several hours of maintained hemodynamic instability and even several previous cardiac arrests resulting in a much longer period of real or effective ischemic insult to the kidney. This prompted us to adopt the criterion that the donor should maintain adequate diuresis for at least 1 h before cardiac arrest.

Our experience clearly reflects the difficulty involved in quantifying warm ischemic damage. Several diagnostic methods have been developed to this end and include proton magnetic resonance spectroscopy (27) and the tetrazolium test, which estimates the activity of mitochondrial enzymes (28), both used in animal kidneys, and the analysis of purine metabolism (29) and glutathione *S*-transferase (30) in humans. However, until such techniques become more widely adopted, the careful selection of donors is of utmost importance. This is reflected in the present NHBD program by the change from an initial stage, showing a not insignificant proportion of never-functioning kidneys, to a second stage, in which values were comparable to those recorded using HBD.

In accordance with the findings of others (10,13,17,18), HBD and NHBD graft survival was similar, although reduced NHBD graft survival rates have been reported previously by other authors (15,19,21). However, it is difficult to make comparisons because donor characteristics vary tremendously. In 1995, a team of experts established a classification system in

Table 3. Univariate risk ratios for graft failure according to Cox regression analysis[a]

Variable	Type of Transplant			
	HBD		NHBD	
	36 mo Cumulative Probability (%)	RR (95%CI)	36 mo Cumulative Probability (%)	RR (95%CI)
Cause of death of donor				
trauma	88.24	1	90.10	1
no trauma	81.57	1.41 (0.80 to 2.46)	84.04	1.37 (0.37 to 5.12)
No. of transplant				
first	85.59	1	90.97	1
successive	76.48	1.85 (0.93 to 3.69)	61.63	3.44 (0.86 to 13.80)
Recipient age (yr)				
≥55	84.75	0.80 (0.45 to 1.41)	90.30	0.78 (0.20 to 3.14)
<55	84.20	1	86.12	1
Weight (kg)				
≥81	91.78	1.22 (0.28 to 5.38)	100	
<81	95.30	1	91.16	
Peak PRA (%)				
≥50	78.69	1.89 (0.99 to 3.62)	31.11	6.58 (1.74 to 24.92)
<50	85.79	1	92.98	1
DR compatibility				
≥1	79.05	1	87.84	1
0	85.80	0.60 (0.30 to 1.19)	87.52	0.90 (0.19 to 4.34)
Donor age (yr)				
≥55	71.85	2.17 (1.22 to 3.87)		
<55	88.47	1	87.64	
Cold ischemia time (h)				
≥18	84.71	0.87 (0.50 to 1.49)	87.56	0.84 (0.21 to 3.37)
<18	83.71	1	87.76	1
Gender				
male	85.45	1	89.17	1
female	82.66	1.35 (0.78 to 2.32)	84.12	1.54 (0.41 to 5.72)
Treatment				
thymoglobuline	84.77	1	75.00	1
no thymoglobuline	83.89	1.00 (0.56 to 1.81)	94.74	0.23 (0.06 to 0.91)
Type of dialysis				
hemodialysis	85.75	1	86.81	
peritoneal dialysis	72.02	2.55 (1.14 to 5.69)	100	
Corticoresistant rejection				
yes	68.74	4.93 (2.66 to 9.17)	63.37	6.44 (1.44 to 28.91)
no	93.41	1	95.30	1
Corticosensitive rejection				
yes	89.67	0.96 (0.47 to 1.96)	94.74	0.55 (0.07 to 4.56)
no	86.20	1	88.79	1
Delayed graft function				
absence	92.36	1	93.75	1
1 to 14 d	86.43	1.65 (0.73 to 3.72)	96.77	0.64 (0.04 to 10.32)
15 to 21 d	70.34	3.04 (1.04 to 8.89)	87.91	1.62 (0.15 to 17.90)
>21 d	80.00	4.59 (1.36 to 15.50)	50	13.75 (1.41 to 133.7)
Time on dialysis (mo)				
<36	84.93	0.96 (0.56 to 1.66)	79.68	0.86 (0.64 to 8.85)
≥36	68.74	1	92.05	1

[a] Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989 to 1998. RR, relative risk; CI, confidence interval. Other abbreviations as in Table 1.

Table 4. Adjusted risk ratios for graft failure according to Cox regression analysis[a]

Variable	Type of Transplant	
	HBD	NHBD
	AdjRR (95%CI)	AdjRR (95%CI)
Type of dialysis		
peritoneal dialysis	4.61 (1.28 to 16.57)	
hemodialysis	1	
Donor age (yr)		
≥55	3.23 (1.15 to 9.03)	
<55	1	
Corticoresistant rejection		
yes	5.12 (1.87 to 13.96)	7.00 (1.07 to 45.85)
no	1	1
Corticosensitive rejection		
yes	3.29 (1.22 to 8.91)	
no	1	
Maastricht categories		
type I and II		1
type III and IV		10.04 (1.21 to 83.41)
"type V"		5.22 (0.80 to 34.16)

[a] Data were obtained from the Hospital Clinico San Carlos (Madrid, Spain) over the period 1989 to 1998. The "type V" category was added such that all of our donor types were specified. AdjRR, adjusted risk ratio. Other abbreviations as in Tables 1 and 3.

Maastricht (24) that will undoubtedly serve to standardize protocols and aid the worldwide comparison of data. It should be noted that the majority of the present donors were "uncontrolled" (*i.e.*, the future donor was not subjected to medical control before suffering heart failure and consequently the transplant team was not alerted) and would, therefore, be expected lead to poor graft outcomes. Despite this limitation, our results are encouraging and comparable to those recorded for the HBD transplants. It should not be overlooked that before the sudden cardiac arrest, most of these subjects had a normal lifestyle and consequently were in excellent hemodynamic condition. Thus, the Maastricht category I ("dead on arrival") may represent a valuable source of donors. Indeed, in Madrid, subjects who die on the street before the arrival of emergency personnel and in whom CPR measures prove to be ineffective are transferred to our hospital for the sole purpose of donation. Despite the need for the rapid action of a procurement team, this new donor source has led to a substantial increase in the number of NHBD. The present series is the largest reported in the literature for type I donors. However, it is difficult to compare our series with others since most reports refer to type III/IV donors, or "controlled" donors (where the transplant team *is* alerted, which reduces warm ischemia time considerably with mean values substantially lower than ours). Thus, González Segura *et al.* (21) recently reported worse NHBD graft survival with respect to that of HBD in a series including 74% type IV donors ("cardiac arrest in a brain dead-donor"). Indeed, the largest multicenter series reported to date (20) fails to mention donor category, although judging from the short period of warm ischemia most were probably type III or IV donors. The present single-center investigation has an advantage in that it avoids differences in management criteria between the different centers, which could interfere with results. The good results obtained here using type I donors suggests that we should consider changing our approach to irreversible cardiac arrest occurring outside the hospital. We suggest the maintenance of CPR until the patient reaches the hospital for possible donation.

The different findings recorded during the two stages of our procurement program (1989–1992 and 1995–1998) permit us to reflect on two issues: first, the need to practice extreme caution when selecting a NHBD, especially a type V donor, and second, the recognition that a program of this type entails a training period in which disappointing results are likely to occur, but should not be a reason for discontinuing the program.

It should be noted that in the present study, renal function estimated by serum creatinine clearance was similar in patients receiving kidneys from NHBD and HBD. Various authors (10,13,18) report similar observations, although authors such as Nicholson (19) describe slightly less satisfactory outcomes for NHBD kidneys compared with HBD kidneys and relates this to frequent delayed function, which might have a detrimental effect on outcome. However, we were unable to find clear correlation between the time of delayed function and midterm renal function or graft survival in this type of transplant.

As would be expected, patients receiving NHBD kidneys underwent longer periods of oligoanuria and required longer periods of hemodialysis in accordance with data published by

other authors (9,11,17,18,20,21). Given the longer period of tubular necrosis, clinical signs of rejection may be scarce. Consequently, it is common practice in our center to perform a biopsy at 1 wk posttransplant when acute tubular necrosis persists, to check for subclinical acute rejection. In agreement with other authors (10,18,19,21), we did not detect a higher incidence of rejection in the NHBD transplants, although this has also been described previously (20).

Given that graft survival and midterm renal function were similar in the HBD and NHBD transplants, it seems that there were no longer-term consequences of warm ischemia in this type of transplant. This is in accordance with the findings of the largest published series (20). The time of warm ischemia is frequently quoted as one of the nonimmunologic factors that lead to the chronic destruction of the graft, although few controlled prospective studies have been designed to evaluate the influence of this factor (31). Yilmaz and Häyry (32) experimentally showed the deleterious influence of lengthy ischemia on vascular and glomerular lesions observed during chronic rejection. The NHBD transplant is an *in vivo* model that permits assessment of the effects of warm ischemia in transplants. Although we did not perform a complete histologic study, we can state that the survival and function of the NHBD grafts were similar to those of the HBD grafts, with no increase in proteinuria. Furthermore, the logistic regression analysis showed no effect of donor type on graft function. This may suggest that warm ischemia is not highly detrimental for midterm graft function.

It is concluded that NHBD represent a viable source of kidneys for transplant that has not yet been fully exploited. When a strict protocol is adhered to, the outcome of renal transplant from NHBD compare well in terms of survival and midterm renal function with that of transplants from HBD. Although the use of brain-dead donors with beating hearts could be extended, there is still a great need for additional sources. We feel that every effort should be made to encourage transplant centers that have not yet considered the use of NHBD to do so. The use of donors who die on the street as a result of cardiac arrest encourages a change in first-aid management criteria aimed at providing donors and may permit a substantial reduction in the number of patients waiting for transplant.

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