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Ricard Valero
Catiana Cabrer
Frederic Oppenheimer
Esteve Trias
Jacinto Sánchez-Ibáñez
Francisco M. De Cabo
Aurora Navarro
David Paredes
Antonio Alcaraz
Rafael Gutiérrez
Martí Manyalich

Normothermic recirculation reduces primary graft dysfunction of kidneys obtained from non-heart-beating donors

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R. Valero (✉)
Department of Anaesthesiology,
Hospital Clínic de Barcelona,
Villarroel 170, 08036 Barcelona, Spain
e-mail: rvalero@ medicina.ub.es
Fax: + 34-93-227-5409
Tel.: + 34-93-227-5500

C. Cabrer · E. Trias · J. Sánchez-Ibáñez
F. M. De Cabo · A. Navarro · D. Paredes
M. Manyalich
Department of Transplant Coordination,
Hospital Clínic de Barcelona,
Villarroel 170, 08036 Barcelona, Spain

F. Oppenheimer · A. Alcaraz · R. Gutiérrez
Department of Urology,
Hospital Clínic de Barcelona,
Villarroel 170, 08036 Barcelona, Spain

Abstract Our aim was to analyze the short- and long-term function of kidneys procured from non- heart-beating donors (NHBD) by means of three techniques: in situ perfusion (ISP), total body cooling (TBC) and normothermic recirculation (NR). Fifty-seven potential NHBD were included. Mean warm ischemia time was 68.9 ± 35.6 min. Forty-four kidneys were obtained from donors perfused with ISP, 8 with TBC, and 8 with NR. Eighteen kidneys (32%) started functioning immediately, 29 (52%) showed delayed graft function (DGF) and 9 (16%) showed primary non function (PNF). The actuarial graft survival rate was 76.4% at 1 year and 56% at 5 years. The patient survival rate was 89.3% at 5 years. Incidence of DGF and PNF was significantly lower in kidneys perfused with NR than those with ISP or TBC ($P < 0.01$). Duration of DGF was shorter in kidneys obtained through TBC than in kidneys obtained with ISP ($P < 0.05$). In conclusion, NR reduces the incidence of DGF and may be considered the method of choice for kidney procurement from NHBD.

Key words Non-heart-beating donors · Kidney transplantation · Delayed graft function · Normothermic recirculation

Abbreviations *CPB* Cardiopulmonary bypass · *DGF* Delayed graft function · *ISP* In situ perfusion · *NHBD* Non-heart-beating donor · *NR* Normothermic recirculation · *PNF* Primary non-function · *TBC* Total body cooling

Introduction

Non-heart-beating donors (NHBD) have been widely introduced in the clinical practice and the use of organs, especially kidneys, from this type of donors has been reported in multiple series [7, 12, 13, 15, 22, 33, 37, 44, 45]. At our hospital, a program for identification and procurement of kidney grafts from asystolic donors has been in progress since 1986.

The main problem using NHBD kidneys arises from the increased incidence of impaired graft function due to long periods of warm ischemia. High rates of delayed graft function (DGF) and primary graft non-function (PNF) are the main complications in NHBD, in comparison with heart-beating donors. In order to improve this impaired graft function, Banowsky et al. [5] in 1971 and García-Rinaldi et al. [18] in 1975 introduced "in situ" perfusion as a preservation technique for kidney retrieval in NHBD. This perfusion technique is nowadays the most widespread method applied to perfuse these organs before their extraction. Nevertheless, high DGF rates have been reported using this technique [13, 14, 22, 33, 37, 46, 48, 54].

During the last few years, new techniques have been developed to improve the perfusion and post-transplant viability of organs obtained from NHBD. Total body cooling (TBC) through cardiopulmonary bypass (CPB) is a technique developed to minimise pre-existing ischemic damage, to ensure kidney viability in both the Maastricht category IV [32] and category II [2, 50] NHBD.

More recently, "normothermic recirculation" has been described in experimental studies [4, 19, 25, 39, 40, 51]. This method consist in the normothermic perfusion of the organs at 37 °C with hyperoxygenated blood by means of a cardiopulmonary bypass, before TBC. As far as we know, there are no references dealing with the use of normothermic recirculation in the clinical setting in kidney transplantation from NHBD. The aim of our study has been to analyze the clinical results of the normothermic recirculation technique for procurement of kidneys from NHBD in our hospital, as compared to in situ perfusion, and TBC.

Material and methods

The present study was carried out in accordance with the ethical standards set down in the 1964 Declaration of Helsinki and was approved by the ethical committee in our centre.

Donors

Potential NHBD admitted to the hospital were included in the study. In our series, only II and IV Maastricht NHBD categories [29] were considered. The procedure for non-heart-beating organ procurement begins after death is diagnosed. To consider a dead patient as a potential NHBD, the criteria included, in addition to the general criteria for donor selection, an age under 65 and a warm ischemia time lower than 150 min with a period of warm ischemia without cardiopulmonary resuscitation manoeuvres less than 30 min. Donor demographic characteristics (gender, age), warm ischemia time, as well as Maastricht categories and cause of death, were recorded. Initially, basic cardiopulmonary resuscitation manoeuvres (cardiac massage and mechanical ventilation at $FiO_2 = 1$) were set in motion and the donors were heparinized ($3 mg \cdot kg^{-1}$). Subsequently, vascular access was attained by surgical dissection and cannulation of the femoral vessels, and a Fogarty catheter was introduced through the other femoral artery to block the diaphragmatic aorta and reduce the perfused territory to the splacnic area.

Three different perfusion techniques were used along the years:

"In situ" perfusion was achieved by means of cold perfusion of Collins' solution through a multiperforated catheter in the femoral artery. A catheter was placed into the cava vein through the femoral vein to allow blood drainage. In our early cases, liquid infusion was produced by gravity. In the later cases, a non-pulsatile perfusion pump was used to maintain a constant Collins' solution perfusion flow of $500 ml \cdot min^{-1}$ until a clear solution through the vein catheter was obtained and then reduced to $200 ml \cdot min^{-1}$.

"Total body cooling" through cardiopulmonary bypass was used in other cases. Cannulation was carried out using a 16–18F cannula for the femoral artery and a 20–24F cannula for the femoral vein, and these were then connected to a blood oxygenator (Bard Quantum Oxygenator and Venous reservoir, HF6000–H6770VR, CR Bard Inc; Haverhill, MA 01832, USA), a heat exchanger (Módulo Normohipotermia Palex S. A., Barcelona, Spain) and a non-pulsatile roller pump (Stöckert-Shiley, Munich, Germany). The circuit was primed with saline solution 500 ml, mannitol $0.5 g \cdot kg^{-1}$ and Hemoce (saline solution of polygeline) 500 ml. Oesophagic temperature was also monitored (Mon-A-Therm; Mallinckrodt Medical Inc; St Louis, MO 63134, USA). Bypass was begun with a progressively increasing flow (1 to $2 l \cdot min^{-1}$) in an attempt to achieve $2.2 l \cdot min^{-1} \cdot m^{-2}$ body surface. Sodium bicarbonate was added to the circuit to correct metabolic acidosis. TBC continued until the donor reached a core temperature of 15–20 °C and was maintained until permissions were obtained; kidney procurement was then performed. The kidneys were then cooled with 1–2 l University of Wisconsin solution perfusion through the aorta and preserved at 4 °C until transplantation. As described elsewhere [50], when difficulties in obtaining good venous blood return appeared, TBC was aborted and "in situ" perfusion was started.

"Normothermic recirculation" through CPB, was the technique used in the later cases. In these cases, extracorporeal circulation was maintained at 37 °C, using the same technique above described for TBC. After cannulation of the femoral artery and vein, cannulas were connected to the blood oxygenator, the heat exchanger and the non-pulsatile roller pump. "Normothermic recirculation" was supported at the maximum pump flow rate for 60 min with a progressively increasing flow (1 to $2 l \cdot min^{-1}$), in an attempt to achieve $2.2 \cdot min^{-1} \cdot m^{-2}$ body surface and the temperature exchanger was set at 37 °C to maintain donor temperature. Sodium bicarbonate was added to the circuit to correct metabolic acidosis. After the 60 min period of "normothermic recirculation", cooling through the extracorporeal circulation was run until the donor reached a core temperature of 15–20 °C and was maintained until permissions were obtained and organ extraction was finished. Time needed to reach that temperature depended on the donor size and the blood flow rate maintained during the period.

Recipients

Kidneys obtained from NHBD were transplanted into blood group-compatible and negative cross-match recipients, in order to reduce cold ischemia time. Immunosuppression therapy varied according to the transplant era. However, most patients were treated with a sequential induction therapy with antithymocite globuline or OKT3 antibodies, steroids, azathioprine or mycophenolate mophetil and cyclosporin A. Incidences of family or coroner refusal and clinical contraindications for transplantation were recorded.

Demographic characteristics (age, gender) of the kidney recipients were collected. Delayed graft function was defined as the need for dialysis within the first week post transplantation. Duration of DGF was defined as the interval between the transplantation and the date of the last post-transplantation dialysis. The incidence of PNF kidneys was also recorded. Days necessary to recover plasmatic creatinine values inferior to $3 mg \cdot dl^{-1}$ were also registered. Finally, graft and patient survival analysis was made.

A comparative analysis was made of the results of kidney-function following the technique used for organ preservation (in situ perfusion, TBC and normothermic recirculation).

Statistical analysis was carried out according to Student's t test and ANOVA for the analysis of quantitative variables and Chi square and Fisher's exact probability test were used for the analysis of qualitative variables. Results are expressed as mean and standard deviation (SD). Graft- and patient survival were analyzed by means of the Kapplan Meier method and Logrank for comparison of survival curves. We considered a value of $P < 0.05$ to be statistically significant.

Table 1 Demographic characteristics, Maastricht categories (according to the perfusion technique), and death etiology of non-heart-beating donors in our series. Results are expressed as mean ± standard deviation, and as the number of cases and percentage

Age (years)	39.5 ± 15.6	
Gender (male/female)	43/14	
Maastricht categories (I-II-III-IV)[a]	0–51–0–6	
In situ	0–31–0–6	
Total body cooling	0–11–0–0	
Normothermic recirculation	0–6–0–0	
Etiology of death:		
Cardiac disease	23	40%
Multiple trauma	21	37%
Stroke	4	7%
Anoxia	2	3%
Isolated cranial trauma	3	5%
Other	4	7%

[a] In three cases the procedure was aborted before any perfusion procedure was started

Results

Donors

Between October 1986 and March 1999, 57 potential NHBD were included in our study. Demographic characteristics, Maastricht categories, and death etiology of donors are described in Table 1. Mean warm ischemia time was 68.9 ± 35.6 min, with a mean period of warm ischemia without effective cardiopulmonary resuscitation manoeuvres of 6 ± 7 min.

The procedure was aborted due to family refusal in 9 cases (15%) and, due to coroner refusal, in 2 cases (3%). Sixteen donors (27%) were rejected due to a clinical contraindication, either for deficient donor perfusion technique (9 cases; 16%), deficient organ perfusion noticed during organ explantation (2 cases; 3%), or a positive virus serology or other risk factor for disease transmission (5 cases; 9%).

Perfusion was achieved by means of in situ perfusion with cold Collins' solution by gravity in 29 cases (51%), and in situ perfusion was achieved by means of a non-pulsatile pump in 8 cases (14%). TBC was performed in 11 cases (17%) but in 3 cases, due to a limited venous blood return, TBC was aborted and in situ perfusion by gravity was started. In the remaining 6 donors (11%), normothermic recirculation technique was used. In 3 cases procedure was aborted before any perfusion procedure was started.

In the end, 30 donors could be used. Forty-four kidneys were obtained from donors perfused with in situ perfusion. Two kidneys were not transplanted due to intraoperative recipient problems, and two were transplanted in other center and not subsequently followed up. Eight kidneys were obtained from donors perfused with TBC technique and 8 from donors with normothermic recirculation.

Recipients and grafts

The kidney recipients' mean age was 44.2 ± 16.5 years old. Thirty-six were male and 20 female. Eighteen kidneys (32%) started functioning immediately, 29 (52%) showed DGF and 9 (16%) never functioned. Mean duration of delayed graft function was 20.1 ± 14.6 days. The actuarial graft survival rate was 76.4% at 1 year and 56% at five years. The graft survival rate is shown in Fig. 1. The patient survival rate was 90% at one year and 89.3% at five years.

Kidney function was analyzed according to the organ perfusion technique used in the organ procurement. No differences were found in age, sex, HLA matching, cold ischemia time or immunossupresion therapy between the three groups (Table 3). The percentage of polytraumatic patients in the in situ group was statistically higher than in the other two groups ($P = 0.02$). Warm ischemia time was significantly lower in the in situ group compared to the other groups ($P = 0.02$) (Table 3). Incidence of DGF and PNF kidneys, according to the organ perfusion technique used, are shown in Table 2. Incidence of DGF and PNF was significantly lower in kidneys perfused with normothermic recirculation than in those perfused with in situ perfusion ($P = 0.0003$) or TBC ($P = 0.04$). The incidence of DGF and PNF was not significantly different in kidneys perfused with TBC compared with those perfused in situ. However, the duration of DGF was significantly shorter in kidneys obtained through TBC than kidneys obtained

Table 2 Kidney function according to the perfusion technique used for non-heart-beating donors organ procurement. Values expressed as number and percentage of kidneys with respect to the technique group, or mean and standard deviation

	In situ	Total body cooling	Normothermic recirculation
Total transplanted kidneys	40	8	8
Immediately functioning kidneys	9 (22.5%)	2 (25%)	7 (87.5%)[a]
Delayed graft functioning kidneys	22 (55%)	6 (75%)	1 (12.5%)[a]
Primary non functioning kidneys	9 (22.5%)	0	0
Duration of delayed graft function (days)	22.3 ± 16.1	13.4 ± 4.4[b]	7
Days before plasmatic creatinine < 3 mg · dl^{-1}	46.5 ± 66.7	29.1 ± 6.9	13.4 ± 7.8[a]

[a] $P < 0.05$ compared to other groups; [b] $P < 0.05$ compared to in situ group

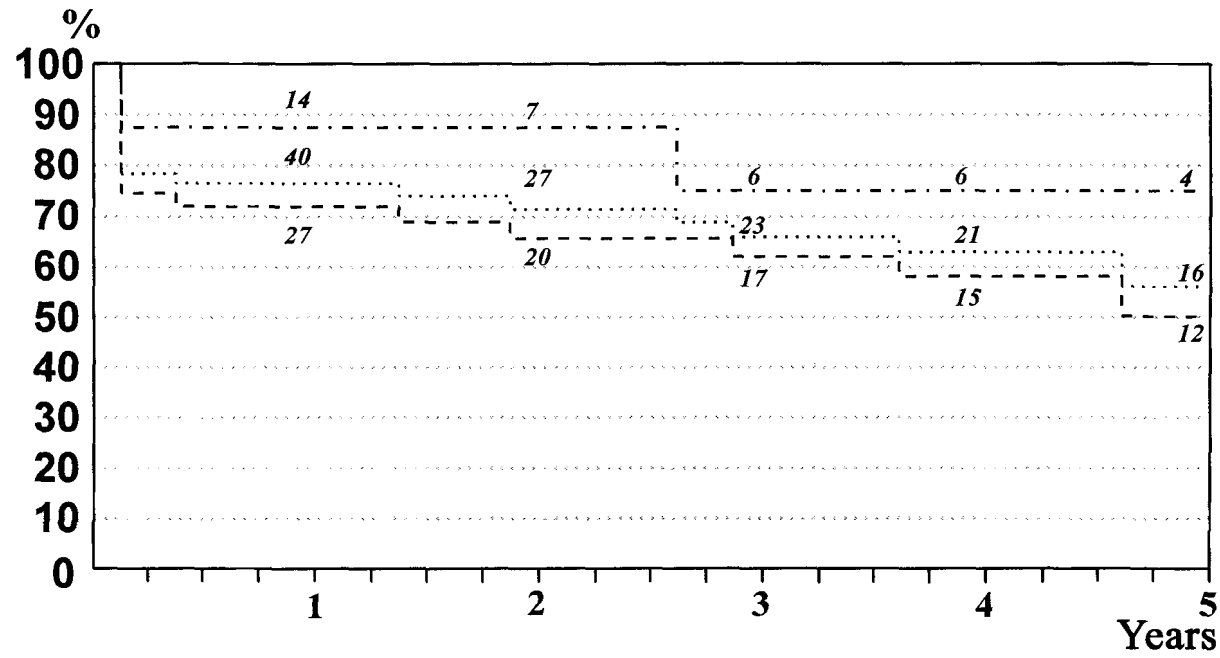

Fig. 1 Actuarial graft survival rate of kidneys transplanted from non-heart-beating donors in our series, according to the technique used: in situ perfusion technique and techniques using cardiopulmonary bypass (CPB) (including total body cooling and normothermic recirculation). Values on each line: Number of grafts at risk for each technique (at one to five year-period). (In situ: ------, CPB: · · · · · · · · · ·, Overall: - - - - - - -)

with in situ perfusion ($P < 0.05$). Serum creatinine levels lower than 3 mg · dl^{-1} were achieved in fewer days in the normothermic recirculation group than in the others, these differences being statistically significant ($P = 0.029$). The graft survival rate was separately analyzed, according to the perfusion technique, but no statistical differences were found (Fig. 1).

Discussion

The main handicap of NHBD kidneys as opposed to heart-beating donors lies in the high incidence of DGF and a high percentage of never functioning grafts, which has been widely documented. In the most experienced groups, DGF varies from 48–78.4% and PNF kidneys from 4–19% [13, 14, 22, 33, 37, 46, 48, 54]. Our overall results, with a DGF rate of 52% and PNF rate of 16%, are very similar to the above data. DGF not only increases the duration of hospital admission but has been related to an impairment of the long-term graft function [11, 41]. Ojo et al found a significant and robust relationship between DGF and decreased cadaveric renal function, DGF being an independent risk factor for long and short-term graft survival. Some other authors [48, 49, 53], however, have failed to find a relationship between DGF and long term survival, acute graft rejection being the only risk factor identified.

Different techniques of organ perfusion and preservation before and after graft extraction have been developed. The use of the pulsatile perfusion preservation reduces the incidence of DGF [8, 23], and it has been described as a useful test for distinguishing whether or not a kidney is suitable for transplantation [28, 36]. With regard to organ perfusion in the cadaver, different perfusion techniques have been developed. Several modifica-

Table 3 Donor's cause of death, cold and warm ischemia time, recipients characteristics and HLA-A, B, DR matching according to the perfusion technique used for organ procurement. Values expressed as mean and standard deviation, and as the number of cases (*M* male, *F* female, *PLT* politraumatism)

	In situ	Total body cooling	Normothermic recirculation
Donor's cause of death: PLT/Non PLT	9/13[a]	1/3	0/4
Cold ischemia time (h)	18.5 ± 6.2	15.3 ± 4.6	17.8 ± 6.7
Warm ischemia time (min)	58 ± 41[a]	81 ± 15	82 ± 11
Recipients age (years)	36.7 ± 16.4	36 ± 5.9	46.7 ± 8.1
Recipients sex (M/F)	26/14	3/5	7/1
HLA-A, B, DR matching	1.9 ± 1.3	1.6 ± 1.1	1.3 ± 1.6

[a] $P = 0.02$ compared to other groups

tions of the in situ perfusion technique have been introduced to improve viability results: various types of catheters [3, 34], different types of perfusion liquid [9, 26, 44], or the addition of drugs, such as trifluoroperazine [3], tolazoline [27], or phentolamine [7] to the perfusate. However, the results with the use of this technique are far from optimal. Although PNF was slightly higher in our series (22.5%), the DGF rate (55%) and graft survival (71, 8% at 1 year and 50% at 5 years) in kidneys harvested through in situ perfusion was similar to other groups. Other techniques, such as intraperitoneal surface cooling [3, 33, 42] and isolated mechanical ventilation combined with cardiac massage until organ extraction [20] have also been applied for the same purpose.

After the favourable results obtained with the total body perfusion through extracorporeal circulation in the preservation of the heart and lungs, and in cases of multiorganic extraction [6, 10], several groups have used the technique of TBC through CPB in non-heart-beating human donors with good results, either for procurement of kidneys [2, 32, 50], livers [24, 31] or other organs [16]. Between 1990 and 1996, we have used a portable CPB device for TBC to improve kidney viability. With this technique we were not able to reduce the rate of DGF, compared to in situ perfused kidneys, but we could significantly reduce the delay in the recovery of graft function from 22.3 ± 16.1 days in the in situ group to 13.4 ± 4.4 days in the TBC group. Moreover, all kidneys functioned in this group, compared to 9 out of 40 kidneys which never functioned in the in situ group. Better quality hypothermia, induced progressively and smoothly, compared with simple perfusion, has been hypothesised as the main factor for improving viability [10]. Higher pressure perfusion of the preservation liquid has been related to an improvement in post-transplant renal function [30], since low perfusion pressure would cause an increase in the renal vascular resistance, and thereby a reduction in renal flow and inadequate hypothermia [3]. Moreover, temperature decrease is more rapid and effective when perfusion pressure is over 70 mm Hg [3]. Besides these factors, TBC provides the additional benefit of continuously oxygenating the organs during the cooling period [24].

Normothermic recirculation has shown the best results in our series, reducing DGF and improving viability. All organs perfused with this technique are functioning, and DGF appeared in only 1 out of 8 kidneys transplanted. This dramatic reduction in the DGF rate can be explained by various reasons: firstly, blood has been shown to be a better preservation solution than crystalloids for recovering from tissue damage [24, 35, 38, 43, 52]. In previous studies, Van der Wijk et al [52] improved preservation and viability of 3-day cold preserved kidneys by means of an *ex vivo* organ perfusion with normothermic blood for 3–4 h. These results were confirmed by other authors [17, 35]. Mayfield et al [38] demonstrated an improvement in the capacity of the blood perfused kidneys to control tissue oedema and ion pump activity, suggesting better membrane integrity than in kidneys not preserved with this technique.

Since cell metabolism decreases rapidly at temperatures below 37 °C, Schon et al, in an experimental study with ex-vivo perfused pig livers, postulate that normothermic oxygenated perfusion after extraction could offer the possibility of restoring metabolic processes and repairing damaged cells, thus resuscitating ischemically injured livers [47]. Some other experimental studies in liver and kidney transplantation have demonstrated the utility of normothermic recirculation to recover adenine nucleotide levels after warm ischemia [4, 21, 25, 40], to increase reduced glutathione levels in both the liver and the kidney before cold storage [4] and to improve post transplant viability [19, 25, 51]. In this way, Rijkmans et al state that it is possible to prevent irreversible damage through normothermic blood perfusion [43]. In accordance with these studies, we have found a clear improvement in graft function after a period of normothermic recirculation during organ procurement.

The results of our study, however, must be carefully analyzed since some limitations are clear. Donors' groups were not randomly distributed. The choice of the perfusion technique, has evolved over the years in our hospital. In situ perfusion was the only technique used from 1986 to 1989, TBC was incorporated from 1990 to 1996 and, lastly, normothermic recirculation has been used from 1997 till now. Other factors influenced the choice of the technique: in situ perfusion was the only technique used in the IV-Maastricht category-NHBD. This factor would enhance the results in this group since "controlled" NHBD have shown better results than "non controlled" NHBD [12]. On the other hand, when difficulties in obtaining good venous blood return appeared, TBC was aborted and in situ perfusion was started. For this reason, since 1995, we have not used either TBC or normothermic recirculation when the cause of death was a polytraumatism. The higher number of polytraumatisms in the in situ group could alter the results. In spite of this, there are authors who obtain similar or even better rates of graft function and graft survival in kidneys harvested from non-heart-beating trauma donors [1, 13].

In situ perfusion requires a high volume of perfusate, at least initially, to perfuse the organs and wash out the deleterious blood constituents. For this reason, Collins' solution was used for this purpose in our series. In contrast, University of Wisconsin solution was used to wash out the organs prior to cold storage when TBC or normothermic recirculation were used. This difference could affect the results since several authors [9, 26, 44] have pointed out the benefits of Wisconsin solution over Collins solution.

Finally, the small number of patients, especially in the groups using CPB could also explain the lack of differences in survival rate between the groups (in spite of statistical differences which appeared in the comparison of the DGF rate).

Ethical concern exists about when death may be pronounced. Although there is no universal consensus about how long the heart has to be stopped to assure the death of the brain, and about when cardiac function has been "irreversibly" lost, the "ten-minute rule" has been widely accepted. According to the "Maastritcht recommendations" the diagnosis of death in our NHBD series was made by physicians independent of the procurement team. On the other hand, category III NHBDs, where statement of death is rather more difficult, are not permitted in Spain, so none of these donors were included in our series.

In conclusion, kidneys obtained through normothermic recirculation showed a lower degree of DGF, a zero incidence of PNF kidneys, and a trend towards an improvement in long-term survival. Consequently, extracorporeal circulation with a period of normothermic recirculation may be the method of choice for the procurement of organs from NHBD, although further studies have to be performed to validate our results.

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