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Effect of machine perfusion preservation on delayed graft function in non-heart-beating donor kidneys – early results

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Abstract The functioning of non-heart-beating (NHB) donor kidneys upon transplantation is often delayed. To evaluate the effect of preservation by machine perfusion (MP) on early post-transplant function, 37 NHB donor kidneys were compared to 74 matched heart-beating (HB) donor kidneys preserved by cold storage (CS). The NHB donor kidneys were subject to 49 ± 34 min of warm ischemia. Delayed function (DF) and primary nonfunction (PNF) rates were significantly higher for NHB than for HB donor kidneys (49 % and 19 % vs 34 % and 7 %, respectively). Consequently, renal function was impaired but recovered within 6 months. MP could not eliminate the differences in DF rate between NHB and HB donor kidneys. However, NHB donor kidneys preserved by MP showed less DF than that reported in kidneys preserved by CS. This suggests that MP has a beneficial effect on ischemically damaged kidneys. The similar results observed with category 2 and category 3 NHB donors also suggest this effect. The high PNF rate emphasizes the need for viability tests that prevent the transplantation of nonviable organs. We conclude that MP alone is not sufficient to reduce DF and PNF rates in NHB donor kidneys.

Key words Non-heart-beating donor, machine perfusion · Machine perfusion, non-heart-beating donor · Kidney transplantation, non-heart-beating donor

Introduction

Organs for transplantation procured from non-heart-beating (NHB) donors sustain a period of warm ischemia once the blood stops circulating. This warm ischemic period leads to rapid loss of high-energy metabolites, altered calcium metabolism, and vascular blockage, which consequently damage the organs. Basic cell functions are distorted and reactive oxygen species are generated when the blood flow is subsequently restored [37]. As a result, upon reperfusion, organ function after transplantation may be impaired or even lost. Transplanted NHB donor kidneys show high rates of delayed onset of function [16, 35, 38]. The impact of delayed function (DF) on the outcome of transplantation is negative and considered undesirable for both clinical and economic reasons.

Preservation by machine perfusion (MP) is thought to be advantageous for the preservation of ischemically damaged kidneys [23] and for improving immediate post-transplant graft function [39]. Experiments have confirmed this; in fact, MP preservation of kidneys damaged by warm ischemia has been shown to be superior to preservation by simple cold storage (CS). In a recent study, MP resulted in better survival rates and improved preservation of microcirculatory integrity [6, 7].

In an attempt to improve the early post-transplant function and reduce the DF rate, we selected MP as the

Table 1 Matching criteria (*CS* cold storage, *UW* University of Wisconsin preservation solution, *PRA* panel reactive antibodies, *HLA* human leukocyte antigen)

- Same transplant center
- CS preservation with UW
- Number of transplant (1st, 2nd, 3rd)
- Current level of PRA (≤ 5 %, 5 %–85 %, ≥ 86 %)
- HLA-DR mismatches (0, 1, 2)
- Donor age (± 10 years)
- Date of transplantation (± 5 years)
- Recipient age (5–50, > 50 years)

Table 2 Donor characteristics. Values given represent mean ± SD

	NHB donors	HB donors	*P* value
Age (years)	45 ± 16	41 ± 15	0.23
Gender (M/F)	16 : 21	51 : 23	0.009
Serum creatinine (μmol/l)	111 ± 58	87 ± 31	0.009
Diuresis (ml/last 24 h)[a]	3319 ± 2493	5337 ± 3291	0.003
Warm ischemia time (min)	49 ± 34	0 ± 0	< 0.001

[a] Whenever available in NHB donors

preferred method for kidney preservation in our NHB donor program. In this study, we evaluate the early post-transplant function of grafted NHB donor kidneys preserved by MP and compare the short-term results with those of matched heart-beating (HB) donor kidneys preserved by CS.

Patients and methods

NHB donor kidneys were procured from patients who had suffered irreversible cardiac arrest. Patients were considered potential donors if circulatory arrest lasted less than 30 min (excluding the time of resuscitation) and if cardiopulmonary resuscitation did not exceed 2 h. The donors were not older than 65 years of age and had no history of uncontrollable hypertension, kidney disease, or malignancies other than nonmetastasizing primary brain tumors. The donors also had no signs of systemic infection or intravenous drug abuse. The kidneys were preserved in situ by inserting a femoral cooling catheter and applying large volumes of cold preservation solution as soon as possible after death had been established and consent for organ donation obtained [20]. All kidneys were preserved by MP in Gambro PF-3B organ perfusion machines (Gambro, Lund, Sweden). University of Wisconsin (UW) solution for MP was used as the perfusate [5]. Flow was set to an initial perfusion pressure of 60 mmHg and kept constant thereafter; the kidneys were perfused continuously until transplantation. Organs not procured locally were initially preserved in CS and sent to our institution. Kidneys offered by Eurotransplant were transplanted to patients at several transplant centers, according to the uniform Eurotransplant allocation policy.

As controls for each recipient of a NHB donor kidney, we selected two recipients of HB donor kidneys from Eurotransplant files. The control group was stratified for transplant center to prevent bias due to differences in post-transplant management. To prevent bias due to the effect of different preservation solutions, all HB donor kidneys were preserved with UW in simple CS. The controls were matched for the number of transplant (first, second, third), current level of panel reactive antibodies (PRA; 5 % or less, 6 %–85 %, or > 85 %), number of HLA-DR mismatches (0,1,2), donor age (< 10 years difference), date of transplantation (< 5 years difference), and recipient age (15–50, over 50 years of age; Table 1). Transplant centers were approached for cooperation, and data were collected by questionnaire.

Relevant donor and recipient characteristics were analyzed to ascertain the efficiency of matching. Early post-transplant function was classified as (1) immediate function (IF), i.e., life-sustaining renal function without any post-transplant dialysis; (2) delayed function (DF), i.e., ultimately life-sustaining renal function but at least one post-transplant dialysis treatment necessary; or (3) primary nonfunction (PNF), i.e., failure of renal function and constant dialysis. Renal function was estimated at 1, 3, and 6 months post-transplant by measuring serum creatinine levels. Grafts with DF were analyzed further. The number of postoperative days until the patient was without dialysis and the number of dialysis sessions within this period were registered. Rejection episodes in the first 3 months were defined as the number of rejection treatments implemented, whether proven by biopsy or not.

Finally, the outcome of renal grafts from NHB donors who died after an unsuccessful resuscitation attempt (category 2 NHB donors) was compared to that of renal grafts from NHB donors who sustained irreversible cardiac arrest after intentional withdrawal of life-support treatment (category 3 NHB donors). Categorization is described in detail elsewhere [24].

The results are given as percentages or as mean ± SD. The differences between the groups were calculated with the Pearson chi-square test and Yates' correction for discrete variables. The Mann-Whitney U-test was used for unrelated continuous variables, where appropriate. *P* values less than 0.05 were considered statistically significant.

Results

Between August 1993 and July 1995, 39 NHB donor kidneys were preserved by MP at the University Hospital Maastricht and subsequently transplanted within the Eurotransplant organization. Two grafts that were successfully transplanted outside this area were not available for matching purposes and were excluded from the study [29]. Thus, 37 kidneys with a follow-up period of at least 6 months (mean 13 ± 7 months) were included in the NHB group. Consequently, 74 HB controls were matched and selected for comparison. The donor data are given in Table 2. The main causes of death among the NHB donors were myocardial infarction (35 %), cerebral bleeding (30 %), and cerebral trauma (19 %). HB donor death was caused mainly by cerebral bleeding (58 %) and cerebral trauma (34 %; $P < 0.001$). Seventeen kidneys from category 2 and 17 from category 3 NHB donors were transplanted. Three (8 %) kidneys were procured from NHB donors who had sustained irreversible cardiac arrest after brain death had been diagnosed (category 4 NHB donors). The NHB donors died either in the emergency room (41 %) or the Intensive Care Unit (ICU; 59 %), so that none of

Table 3 Recipient characteristics. Values given represent mean ± SD

	NHB donors	HB donors	*P* value
Age (years)	48 ± 14	47 ± 12	0.36
Gender (M : F)	24 : 13	47 : 27	0.89
Retransplantations	4 (11 %)	15 (20 %)	0.37
Current panel reactive antibodies > 5 %	6 (17 %)	12 (16 %)	0.87
HLA-DR mismatches	0.5 ± 0.5	0.4 ± 0.5	0.52
Cold ischemia time (hours)	30 ± 6	25 ± 9	0.001

Table 4 Early post-transplant function. Values given represent mean ± SD

	NHB donors	HB donors	*P* value
Immediate function	12 (32 %)	44 (59 %)	
Delayed function (DF)	18 (49 %)	25 (34 %)	0.02
Primary nonfunction	7 (19 %)	5 (7 %)	
Diuresis post-transplant (ml/1st 24 h)	1511 ± 2341	1911 ± 2392	0.09
Duration DF (days)	18 ± 10	14 ± 11	0.82
Dialyses post-transplant (number)	6 ± 4	5 ± 3	0.74
Hospital stay (days)	33 ± 17	33 ± 32	0.28
Rejection episodes (number/1st 3 months)	0.6 ± 0.9	0.7 ± 1.0	0.88

Table 5 Serum creatinine levels (μmol/l) in functioning kidneys. Values given represent mean ± SD

Months post-transplant	NHB donors	HB donors	*P* value
1	292 ± 184 (26)[a]	185 ± 114 (61)	0.01
3	217 ± 126 (27)	152 ± 52 (62)	0.02
6	196 ± 117 (24)	152 ± 69 (63)	0.22
Lowest creatinine level	155 ± 64	124 ± 42	0.04

[a] Number of grafts evaluated

the in situ preservation procedures took place in the operating room under controlled circumstances [14].

The recipient characteristics are given in Table 3. There were no differences between the NHB and HB donor groups for blood type, original renal disease, type of dialysis (hemodialysis in 70 % vs 64 %, $P = 0.83$), or duration of pretransplant dialysis (36 ± 39 vs 45 ± 43 months, $P = 0.32$). The immunosuppressive protocols were similar for both groups. Cyclosporin was used for 32 (86 %) of the NHB donor kidneys and for 68 (92 %) of the HB donor kidneys ($P = 0.93$). It was introduced preoperatively or immediately postoperatively in 23 (72 %) and 47 (68 %) cases, respectively. Recipients of NHB donor grafts received cyclosporin and steroids 14 times (38 %) and triple immunosuppression (cyclosporin, azathioprine, and steroids) 17 times (46 %). These regimens were prescribed for 46 (62 %) and 18 (24 %) recipients in the HB donor group, respectively ($P = 0.08$). Induction protocols using OKT3, ATG/ALG, or other agents for rejection prophylaxis were used for 8 (22 %) NHB donor kidneys and for 15 (20 %) HB donor kidneys ($P = 0.56$).

Early post-transplant function of NHB donor kidneys was significantly different from that of HB donor kidneys (Table 4). Renal function was impaired but recovered within 6 months (Table 5). As a result of the high PNF rate, the survival of NHB donor grafts was reduced. Additionally, two grafts failed within the 1st month due to untreatable acute rejection. Thus, graft survival at 6 months was 72 % for the NHB donor grafts and 90 % for the HB donor grafts. No patients died within 6 months post-transplant in either group.

A comparison of transplants from category 2 ($n = 17$) and category 3 ($n = 17$) NHB donors revealed no differences in early post-transplant outcome or renal function, despite increased age (52 ± 14 vs 41 ± 13 years, respectively; $P = 0.01$), increased serum creatinine (133 ± 52 vs 93 ± 62 μmol/l, respectively; $P = 0.003$), and longer warm ischemia time (WIT; 79 ± 26 vs 21 ± 11 min, respectively; $P < 0.001$) for category 2 NHB donors. Five grafts (29 %) from the category 2 NHB donors and one (6 %) from the category 3 NHB donors had PNF. The difference, however, was not statistically significant ($P = 0.12$).

Discussion

The success of transplantation has made it the treatment of choice for patients with end-stage renal disease. Yet, the increasing demand for kidneys has created a gap between the organs available and the organs needed. In renal transplantation, NHB donors are valuable in reducing this organ shortage and the waiting lists, and organ procurement from these donors is gaining more attention. However, NHB donors sustain cardiac arrest, and warm ischemia subsequently damages the kidneys. This may, in turn, cause acute tubular necrosis (ATN) and impaired clinical function after grafting. Thus, there is often no immediate life-supporting function, and dialysis must be continued until the transplanted kidney has recovered and regained its function.

There is much controversy about the effect of DF on graft survival [4, 8, 9, 36]. It is thought to increase the incidence of acute rejection [22] and to reduce graft survival. Without rejection, graft survival may not be influenced by DF [34]. This suggests that, while ischemic and immunological factors may both result in ATN and DF of the transplanted kidney, DF with an immunological component will reduce graft survival [18]. Although it may have multiple causes, DF is a serious post-transplant complication for a number of reasons. Post-transplant management is more difficult, symptoms of early

rejection are disguised, and costs are increased due to a longer hospital stay and continued dialysis. Furthermore, the prolonged dependence on dialysis and the initial failure of the transplant are frustrating to both recipient and physician. Therefore, DF is a major concern in kidney transplantation, especially with NHB donor kidneys.

It has been reported that preservation by MP reduces DF rates and increases the rate of prompt function of renal grafts [1, 17, 25, 28]. Moreover, MP with the synthetic UW solution (Belzer's perfusate) has been found to be superior to MP with plasma-based perfusate [2]. Nevertheless, the effect of MP on graft survival remains controversial [25, 30]. Because MP preservation is labor-intensive, logistically demanding, and costly, and because CS solutions are becoming increasingly safe and effective, most transplant centers have abolished the use of preservation machines, and nowadays organ preservation in simple CS is the standard. Kidney preservation by MP may still be preferable for prolonged preservation times [27] and for preservation of ischemically damaged kidneys. However, the observed prolonged cold ischemia time (CIT) in the NHB donor group, and thus in the MP preservation group, should be avoided, as it is known to lead to DF [10]. It is also reported to have a detrimental effect on graft survival in combination with DF, HLA-DR mismatch, and acute rejection [11]. In the case of organs already damaged by warm ischemia, as in NHB donor kidneys, prolonged hypothermic ischemia has an additional negative effect on transplant outcome, even if the kidneys are preserved by MP. Therefore, preservation time should be kept to a minimum.

MP for preserving NHB donor kidneys has been reported to be more advantageous than CS in a study in which each kidney was compared with its own contralateral as a control [26]. The procedures, however, were fully controlled and the WIT was extremely short. The excellent transplant results with NHB donor kidneys reported by D'Alessandro et al. [14] and Orloff et al. [31] are at least partially attributable to preservation by MP.

Since no group of NHB donors was available as a control group for this study, the impact of MP on transplantation results with NHB donor kidneys had to be compared to HB donor controls. The groups were adequately matched and were comparable. Increased donor serum creatinine and decreased diuresis are typical for NHB donors and reflect the hemodynamically unstable agonal phase. MP could not correct for the differences in early post-transplant function between NHB and matched HB donor grafts. Although DF still occurred significantly more often in the NHB MP group, our results with MP in this study suggest a reduction in DF in comparison to the previously reported DF rates of 60 %–90 % with NHB grafts preserved by CS [15, 16, 38]. Others have reported considerably lower DF rates with CS; however, the donors differed with respect to age, cause of death, CIT, and WIT [33]. Excellent outcome with DF rates of merely 19 %–22 % have been obtained with category 3 NHB donors and preservation by MP [14, 31]. In those series, however, many viable grafts have been lost due to the extreme selection.

Whenever DF occurred, the severity did not differ among the groups. This is reflected in the equal duration of postoperative dialysis and the number of dialyses needed. After initial impairment due to more DF in the NHB donor group, renal function recovered, and within 6 months it was equal for both groups. Similarly, the lowest serum creatinine reported in the NHB donor group (155 ± 64 μmol/l), as an indication of potential renal function, was higher than the lowest level for the HB donor group but acceptable. The higher DF rate did not result in more acute rejection episodes in the NHB donor group, confirming the suggestion that DF based on ischemia does not predispose the patient to acute rejection. Although there was a slight tendency to treat recipients in the NHB donor group with triple immunosuppressive therapy more often, induction therapy was equally employed. To prevent cyclosporin nephrotoxicity in the early post-transplant period, especially in recipients of NHB donor kidneys with a high risk of DF, induction therapy with ATG, ALG, or OKT3 and sequential delayed introduction of cyclosporin may be beneficial [19].

The PNF rate of 19 % for NHB donor kidneys in our study is unacceptable. Analysis of the contralateral kidneys of the grafts with PNF, revealed one pair failing and three kidneys with not transplanted contralaterals. Excessive ischemia might have played a role in the failure of these five kidneys. The other two PNF grafts had functioning contralaterals. This high PNF rate also had a major impact on graft survival in the NHB donor group, which was reduced considerably. When considering functioning grafts only, the 6-month graft survival was similar (92 % and 97 %) for both groups. The increased failure rate of NHB donor kidneys underlines the importance of parameters that may give an indication of the warm ischemic damage sustained and the expected post-transplant function. Especially in category 2 NHB donors, warm ischemic damage is unknown and may vary considerably. An adequate viability test might indicate whether post-transplant tubular necrosis in a graft is reversible; it might also be of help in discarding nonviable kidneys [13].

In the present study, the beneficial effect of MP on warm ischemic damage in NHB donor kidneys was demonstrated by the similar results obtained with grafts from category 2 and category 3 NHB donors. Despite the older age of, and increased WIT for, category 2 NHB donors, transplanted kidneys functioned as well as the obviously less damaged kidneys from category 3 NHB donors. Apparently, MP is especially beneficial

after prolonged warm ischemia, which confirms earlier suggestions [12, 32]. In addition to the direct effect on the organs, MP provides access to the organ for graft evaluation and intervention during preservation. Although proposed "rescue agents" did not affect the transplant outcome of canine kidneys damaged by prolonged hypothermia [32], the effect of such agents on the post-transplant function of NHB donor kidneys is worth evaluating. Furthermore, in ischemically damaged kidneys, reperfusion injury might be reduced by preventing free oxygen radical formation during preservation [3, 21].

From this study, we conclude that early post-transplant function of NHB donor kidneys preserved by MP is impaired vs. that of matched HB donor controls preserved by CS. Still, the results suggest a beneficial effect of MP on NHB donor kidneys as the DF rates are lower than those reported in NHB donor kidneys preserved by CS. Moreover, the transplant outcome is similar for category 2 and category 3 NHB donors. Apparently, MP does not repair NHB donor kidneys but merely minimizes additional damage. However, our study group was rather small, and our findings need to be confirmed in the long term. Since NHB donor kidneys are already ischemically damaged, further insults that threaten graft function, i.e., prolonged CIT and cyclosporin nephrotoxicity, should be avoided to obtain optimal transplant results. MP plays a key role in improving the preservation of ischemically damaged organs and in developing viability tests that will prevent transplantation of nonviable kidneys. Although MP is useful for preservation of NHB donor kidneys, in itself it is not sufficient to obtain optimal transplant results.

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