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Machine perfusion versus cold storage for the preservation of kidneys from donors ≥65 years allocated in the Eurotransplant Senior Programme

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Abstract

Background. In the Eurotransplant Senior Programme (ESP), kidneys from donors aged ≥65 years are preferentially allocated locally and transplanted into patients aged ≥65 years on dialysis. The purpose of this study was to analyse whether the results of transplantation in the ESP can be improved by preservation of organs by hypothermic machine perfusion (MP) compared with simple cold storage (CS).

Methods. Overall, 85 deceased heart-beating donors ≥65 years of age were included in this analysis with follow-up until 1 year post-transplant. For each donor, one kidney was randomly assigned to preservation by CS and the contralateral kidney to MP from organ procurement until transplantation. Delayed graft function (DGF), primary non-function (PNF) and 1-year patient and graft survival rates were evaluated as primary and secondary endpoints.

Results. The median recipient age was 66 years in both groups and the median cold ischaemia time was 11 h for MP and 10.5 h for CS (P = 0.69). The DGF rate was 29.4% for MP and 34.1% for CS (P = 0.58). Only extended duration of cold ischaemia time was an independent risk factor for the development of DGF (odds ratio 1.2, P < 0.0001). PNF was significantly reduced (3.5% MP versus 12.9% CS, P = 0.02). The 1-year patient and graft survival rates were similar for MP and CS (94% versus 95% and 89 versus 81%, P > 0.05). The 1-year graft survival rate was significantly improved after MP in recipients who developed DGF (84% MP versus 48% CS, P = 0.01).

Conclusions. Continuous pulsatile hypothermic MP for kidneys from donors aged ≥65 years can reduce the rate of never-functioning kidneys and improve the 1-year graft survival rate of kidneys with DGF. In this small cohort, the known advantage of MP for the reduction of DGF could not be confirmed, possibly due to relatively short cold ischaemia times.

Keywords: cold ischaemia time; delayed graft function; Eurotransplant Senior Programme; graft survival; kidney transplantation

Introduction

Eurotransplant started the Eurotransplant Senior Programme (ESP) in 1999. Kidneys from donors aged ≥65 years are matched with recipients aged ≥65 years [1]. Kidneys are allocated without Human Leukocyte Antigen (HLA) matching in order to keep cold ischaemia times as short as possible. If allocation to this group of recipients is not possible, these kidneys are offered via the regular Eurotransplant Kidney Allocation System to recipients <65 years. If this also fails, the organs are finally offered to centres that are free to choose one or two potential recipients from their local waiting list [2].

The effectiveness of this allocation system has been demonstrated on the basis of 5-year analysis of ESP data by Frei *et al*. [3]. Cold ischaemia times and rates of delayed graft function (DGF) were markedly reduced compared with standard allocation based on HLA matching. Five-year graft survival rates are similar or inferior to those of standard criteria donor kidney transplantation in this age group, but are considered acceptable as long-term

results in the ESP are better than the expected results after dialysis-only treatment [3–5].

The first successful kidney transplant after 17 h of machine perfusion (MP) was performed >40 years ago by Belzer and Kountz [6]. Despite initial encouraging results, MP was abandoned in favour of simple cold storage (CS), mainly for logistical reasons when more effective CS preservation solutions were introduced. However, the utilization of non-heart-beating and expanded criteria donor (ECD) kidneys has resulted in a need for improved organ preservation, leading to a renewed interest in MP.

A meta-analysis published in 2003 concluded that hypothermic kidney MP reduced the risk of developing DGF by up to 20% and the 10-year graft survival rate could be increased by up to 6% [7]. Randomized studies to clarify the exact influence of MP were not available at that time. Our recently published randomized multicentre study, which examined the effect of MP compared with CS for all donors aged ≥16 years, showed an advantage for MP, with less DGF in kidneys recovered from all common types of deceased donors. In addition, we found an improved 1-year graft survival rate, which was most pronounced for ECD kidneys. [8–10]. So far, no data are available for kidneys preserved by MP and transplanted in the ESP setting. The objective of this study was to analyse the effects of MP compared with CS for kidneys from donors aged ≥65 years allocated in the ESP.

Materials and methods

Out of 132 potential deceased heart-beating donors, 85 donors with a median age of 70 (65–83) years were included in this analysis (Figure 1). In three donors (3.4%), the preservation method was switched because of the vascular anatomy of the kidney assigned to MP. Initially,

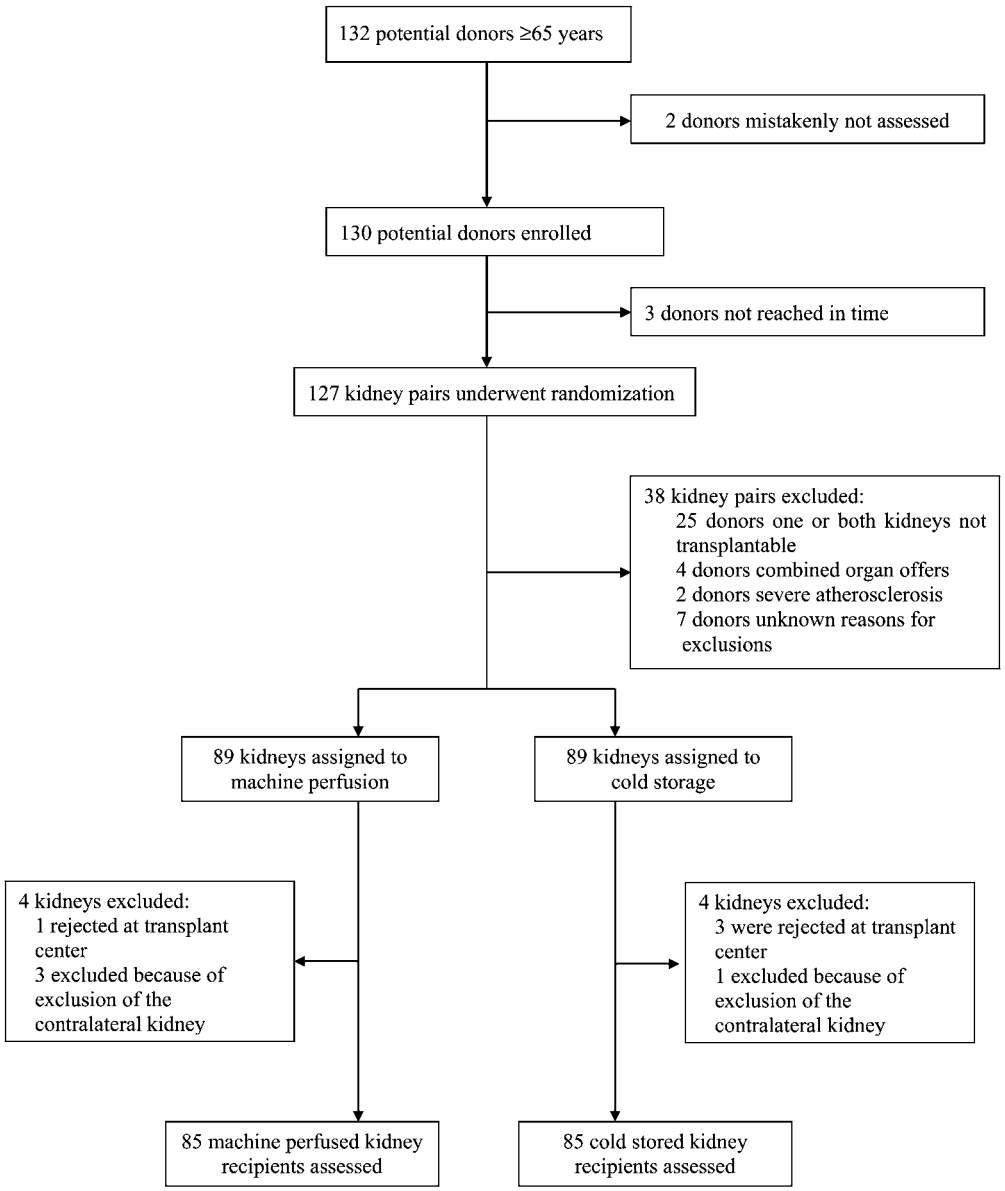

Fig. 1. Trial profile: enrolment, assignment and assessment of kidney pairs to MP or CS.

39 donors were included as part of the previously reported multicentre randomized trial [8]. Prior to completion of patient enrolment of the main study, it became evident that the number of ESP patients included would not be sufficient for a separate ESP subgroup analysis. Therefore, the steering committee decided to continue enrolment of donors aged ≥65 years until at least 82 ESP donors had been included. This was achieved for 85 donors by exactly following the main trial protocol in the ensuing 9-month period.

All donors were heart-beating donors and were included in this study only if both kidneys were transplanted into two different recipients. Donors for combined organ transplantation were excluded. All organs were allocated according to the ESP allocation system. At the time of organ offer, recipient centres were blinded for the preservation method (MP or CS) and pump parameters.

Trial logistics, randomization and preservation methods, as well as the data collection method have been previously described in detail [8, 9]. Briefly, one kidney from each donor was randomized to MP and the contralateral kidney to CS prior to the start of organ procurement. After *in situ* flush-out, kidneys assigned to MP were connected to a LifePort Kidney Transporter® (Organ Recovery Systems, Itasca, IL). A hypothermic pulsatile flow of Kidney Preservation Solution-1® (Organ Recovery Systems) at a fixed maximum systolic perfusion pressure of 30 mmHg was maintained during the entire cold ischaemia period. Kidneys assigned to CS were submerged in preservation solution (either University of Wisconsin solution or histidine–tryptophan–ketoglutarate) and stored on melting ice.

The primary endpoint of this study was DGF, defined as the need for dialysis during the first post-transplant week. The main secondary endpoints were functional DGF (f-DGF, defined as the absence of a decrease in serum creatinine level of at least 10% per day for at least 3 consecutive days in the first week after transplantation), primary non-function (PNF), episodes of acute rejection and 1-year graft and patient survival rates. Patients were treated post-transplant according to local standards per recipient centre, which included induction and maintenance immunosuppression. As in the main study, the follow-up data were collected in a secure online database hosted by Eurotransplant and were provided by the 60 participating transplant centres.

The analysis was powered to detect a reduction in DGF of at least 20%, based on the assumption of a 40% incidence of DGF in recipients with kidneys preserved by CS. With a power of 0.8 and a type I error of 0.05, the required sample size was at least 82 pairs of ECD kidneys. The primary analysis of the DGF/PNF endpoint consisted of a logistic regression model performed in an intention-to-treat and per-protocol fashion with the covariates shown in Table 3. Differences between groups were examined with Fisher's exact test or the Mann–Whitney *U*-test. Secondary endpoints were assessed using the Wilcoxon signed-rank test or McNemar's test. Variables that had a significant influence on graft failure were included in a Cox proportional hazards model. Graft and patient survival rates were plotted in Kaplan–Meier curves and analysed with the log-rank test. All calculations were performed with SPSS, SAS and R software.

An independent scientific steering committee was responsible for all aspects of this study. The study protocol was approved by the Eurotransplant Ethical Advisory Committee and ethics committees in each trial region. The study was sponsored by the Deutsche Forschungsgemeinschaft (DFG TR 811/1-1) and by Organ Recovery Systems.

Results

Eighty-five donors resulting in 170 kidney transplants allocated according to ESP guidelines were included in this study. Donor and recipient details are summarized in Table 1. For baseline characteristics, there were no differences between the two study groups. Re-transplantation was performed in 23.5% of the recipients in the MP group and 14.1% in the CS group (P = 0.30). The median cold ischaemia times were similar in the two groups (MP versus CS: 11 versus 10.5 h). None of the six kidneys (three donors) where random assignment was switched, because of technical reasons, developed DGF or PNF.

Primary endpoint

DGF occurred in 25 recipients (29.4%) in the MP group and in 29 recipients (34.1%) in the CS group (P = 0.58; Table 2). Logistic regression analysis also showed no difference in DGF between the study groups. Only cold ischaemia time [odds ratio (OR): 1.2, P < 0.0001) and re-transplantation (OR: 3.99, P = 0.007) were significantly associated with the development of DGF (Table 3).

Analysis of DGF in an intention-to-treat model and per-protocol fashion produces similar results (per-protocol results not shown).

Secondary endpoints

There was a significant difference in never-functioning kidneys (PNF) between the two study groups. PNF occurred in 3 recipients (3.5%) in the MP group and in 11 recipients (12.9%) in the CS group (P = 0.02). The reasons for PNF in the MP group were vascular thrombosis in one case and never achieving sufficient function in the absence of rejection/vascular thrombosis in two cases.

Table 1. Donor and recipient baseline characteristics

	MP arm	CS arm	P-value
Donor			
Age (years)	70 (65–83)		
Gender (M/F)	40/45		
BMI (kg/m^2)	26 (21–40)		
Days on ICU before Tx	2.5 (0.2–16.8)		
Serum creatinine			
Mean (mg/dL)	0.99		
Max (mg/dL)	2.4		
Median (range)	0.9 (0.57–2.4)		
Preservation solution			
HTK (*n*)	57		
UW (*n*)	27		
Other (*n*)	1		
Recipient			
Age (years)	66 (39–79)	66 (37–79)	0.61
Gender (M/F)	55/30	59/26	0.31
Dialysis pre-Tx (years)	4.4 (0.5–9.1)	4.2 (1.14–8.0)	0.60
First/re-transplantation (*n*)	65/20	73/12	0.30
PRA pre-Tx ≤5% (*n*)	80	83	0.70
No HLA-A, -B, -DR mm (%)	1.2	1.2	0.93
Cold ischaemia time (hours)	11 (4–24)	10.5 (3–24)	0.69
Hospital stay (days)	21 (8–92)	23 (8–131)	0.19

MP, machine perfusion; CS, cold storage; Tx, transplantation; HTK, histidine–tryptophan–ketoglutarate; UW, University of Winsconsin solution; PRA, panel reactive antibodies; HLA mm, HLA mismatches.

Table 2. Results of univariate analysis

	MP	CS	P-value
Delayed graft function (DGF; %)	29.4	34.1	0.58
Duration delayed graft function (days)	12.5 (3–31)	13.0 (3–92)	0.33
f-DGF (%)	18.8	23.5	0.84
PNF (%)	3.5	12.9	0.02
CNI toxicity (%)	8.2	7.06	0.61
Acute rejection (%)	22.5	16.5	0.25

f-DGF, functional delayed graft function; PNF, primary non-function; CNI, calcineurin inhibitor.

Table 3. The logistic regression model—dependent variable delayed graft function (intention-to-treat analysis)

	Odds ratio (95% CI)	P-value
MP versus CS	0.68 (0.32–1.43)	0.315
CIT	1.20 (1.10–1.31)	<0.0001
HLA mm	1.33 (0.98–1.83)	0.072
PRA	1.03 (0.99–1.07)	0.184
Recipient age	1.04 (0.98–1.12)	0.204
Donor age	1.06 (0.98–1.15)	0.125
First versus re-transplantation	3.99 (1.49–11.13)	0.007
Length of dialysis	1.22 (0.98–1.52)	0.076

CI, confidence interval; MP, machine perfusion; CS, cold storage; CIT, cold ischaemia time; HLA mm, HLA mismatches; PRA, panel reactive antibodies

In the CS group, PNF was caused by vascular thrombosis in two cases, rejection in two cases never achieving sufficient function in the absence of rejection/vascular thrombosis in five cases and unknown in two cases. Serum creatinine levels and creatinine clearance did not differ between the two groups at any time point (data not shown). There were also no differences in the duration of DGF, in f-DGF or in the occurrence of calcineurin inhibitor toxicity. 22.4% of recipients in the MP group and 16.5% in the CS group developed at least one episode of acute rejection during the follow-up period (P = 0.25; Table 2).

Patient and graft survival rates

One patient in the CS group and none in the MP group died within the first month after transplantation. Overall, the 1-year patient survival rate was 95%. Within the first year after transplantation, five patients (5.8%) died in the MP group and four patients (5%) in the CS group (P = 0.79). The 1-year graft survival rate was 89% in the MP group and 81% in the CS group (P = 0.139; Figure 2). When DGF occurred, the 1-year graft survival rate was significantly better after preservation with MP compared with CS (84% versus 48%, P = 0.01; Figure 3). Among the recipients with immediate graft function, 1-year graft survival rates were 92% in the MP group and 98% in the CS group (P = 0.109). In the Cox proportional hazards model, only donor age significantly influenced the graft survival rate (OR: 1.12, P = 0.038; Table 4).

Discussion

The Eurotransplant Senior Programme (ESP) facilitates timely kidney transplantation for elderly recipients while effectively utilizing marginal donor organs [1]. Short- and long-term results of ESP are acceptable, although inferior compared with those of standard donors and recipients [3, 4, 11]. One of the reasons for this is that aged ECD kidneys are known to have decreased functional capacities and are more susceptible to ischaemia-related damage [12, 13]. Therefore, kidneys from elderly donors have the potential to profit most from improved preservation methods.

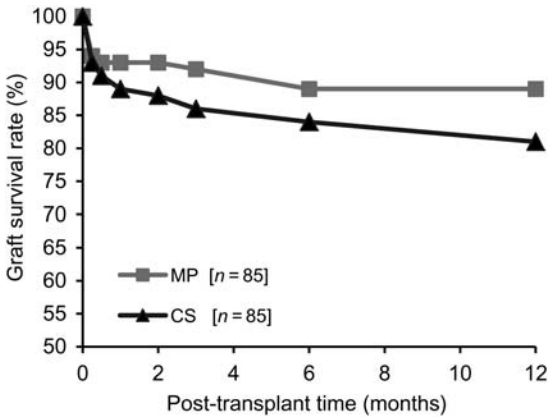

Fig. 2. The 1-year graft survival rate. MP, machine perfusion; CS, cold storage; the log-rank test of equality: MP versus CS, P = 0.14.

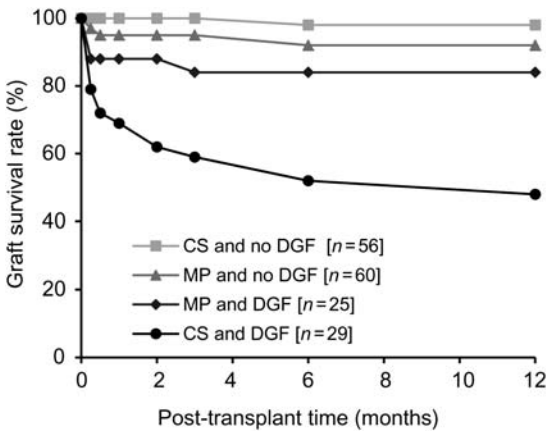

Fig. 3. The 1-year graft survival rate of kidney grafts with and without DGF. MP, machine perfusion; CS, cold storage; DGF, delayed graft function; the log-rank test of equality: MP versus CS in kidneys without DGF, P = 0.11; MP versus CS in kidneys with DGF, P = 0.01; DGF versus no DGF within CS group, P < 0.0001; DGF versus no DGF within MP group, P = 0.27.

Table 4. The Cox proportional hazards model—dependent variable graft failure within 1 year after transplantation (intention-to-treat analysis)

	Hazard ratio (95% CI)	P-value
MP versus CS	0.48 (0.21–1.11)	0.887
Recipient age	1.02 (0.93–1.13)	0.610
Donor age	1.12 (1.01–1.24)	0.038

CI, confidence interval; MP, machine perfusion; CS, cold storage.

In our recently reported randomized controlled trial, MP reduced the risk of developing DGF in standard and extended criteria donors, as well as in controlled non-heart-beating donors [8–10]. The 1- and 3-year graft survival rates were improved for MP kidneys from DBD donors, but not for DCD kidneys [8, 9, 14]. To date, no information about the effect of MP in programmes such as the ESP had been available.

The overall results of the present study concur with the ESP data published so far. However, the DGF rate of 34.1% in the CS arm was somewhat higher than the previously reported rates [3, 15, 16]. On the other hand, the DGF rate in the CS arm was also lower than the originally estimated 40% that had been used to calculate the required sample size for this study. The exclusion of potentially high-risk kidneys derived from donors of whom only one kidney had been accepted for transplantation may have led to an under-estimation of DGF rates in both the arms of our study. Compared with the overall study, this potential bias by exclusion of high-risk donor kidneys was less counterbalanced by exclusion of low-risk donor kidneys that were transplanted together with another organ into the same recipient, as these procedures are not part of the ESP programme.

In retrospective analyses, Matsuoka and Stratta showed that MP can significantly reduce DGF in ECD kidneys compared with cold storage. PNF was not reduced in these studies, but the overall rate of PNF after MP in our study was comparable [17, 18].

In the present study, MP reduced DGF by 4.7% from 34.1 to 29.4%. This difference was not statistically significant in univariate or multivariate analysis. This may be due to the relatively small number of patients included in this study, but it may also be explained by the relatively short median cold ischaemia time. Due to the method of allocation in ESP, the median cold ischaemia time in this study (10.8 h) was much lower than that in the retrospective analyses of Matsuoko and Stratta (19–24.5 h) [17, 18]. It was also lower than in the overall study (15 h) [8], still lower than in the analysis focusing on ECD results (13 h) [9]) and even lower than in the ESP report by Frei *et al.* (11.9 h) [3].

Our data contrast with previously published data by Schold *et al.* [19], who did demonstrate a significant effect of MP on the incidence of DGF, even with median cold ischaemia times under 12 h. Re-transplantation was a strong and significant risk factor for the development of DGF compared with primary transplantation. The re-transplantation rate was higher in the MP group than that in the CS group. Although this difference was not significant, it could still have exerted a relevant negative influence on the DGF rate in the MP group. The high rate of exclusions may also partially explain why the anticipated DGF risk reduction of 20% could not be shown. Our study finally demonstrated a relative risk of 0.68.

The rate of never-functioning grafts (PNF) of almost 13% in the CS group in this study was much higher than the 7.3% reported earlier by Frei *et al.* [3], even though the median cold ischaemic time of 10.5 h was much lower. This indicates the urgent need for viability testing and improved preservation methods in these high-risk donor organs.

One of the most interesting and clinically relevant findings of this study is that the rate of PNF was significantly lower in the MP group than that in the CS group. While the PNF rate of 3.5% in the MP arm is comparable to rates reported for well-selected ECD kidneys [17, 18], the 12.9% PNF rate in the CS arm exceeds PNF rates previously reported for the ESP in 1999–2004 by 5.6% [3]. Compared with UNOS registry data and single-centre retrospective analysis of PNF rates of kidneys from older donors in North America, the PNF rates in the CS arm of our study are much higher than expected, even though reported cold ischaemia times were usually much longer [17, 18]. The most likely explanations for this discrepancy are the high discard rate of up to 50% of kidneys from donors ≥65 years of age in the UNOS region [20], the use of MP for preservation in some cases [21, 22] and the routine use of histopathology analysis for selecting kidneys, which is usually not available within the Eurotransplant region [20, 23].

The overall frequency of acute rejection in this study was not significantly different in the MP versus the CS arm and similar to the donor and recipient age-corrected UNOS data [24]. HLA matching has the potential to reduce acute rejection [25, 26]. Possibly due to the recently recognized more severe immune response in grafts from older donors, acute rejection rates in the ESP are much higher than previously anticipated. The rationale for the ESP was that local allocation and short CIT are more important than HLA matching. Based on our findings, one could argue that a component of HLA matching should be included in the allocation algorithm, when these very old kidneys are preserved by MP, even if this would lead to a slightly longer CIT.

The mechanisms of the clinically relevant benefit of MP remain unclear. In theory, the elimination of toxins, protective endothelial gene expression during pulsatile perfusion, decrease of vasospasm and several other mechanisms are discussed but not yet fully understood [27]. Nevertheless, the application of MP in kidneys from donors ≥65 years of age could be a valuable tool to safely decrease the discard rate of those marginal kidneys.

The 1-year patient survival rate of nearly 95% in ESP kidney recipients was similar to that in the overall study (97%) with much younger donors and recipients. ESP results published so far have reported patient survival rates ranging between 80 and 95%, confirming that higher recipient age is not a contraindication *per se* [3, 15, 28, 29].

While a significant advantage in the graft survival rate up to 1-year post-transplant could be shown in the overall study (94 MP versus 90% CS, $P = 0.04$) [8], the analysis of this smaller series of patients could not demonstrate a similar advantage. There was, however, a statistically significant and highly clinically relevant difference in the graft survival rate if DGF occurred.

One possible shortcoming of this analysis is that the design of the overall study did not anticipate subgroup analysis and that the ECD and ESP donor population are partly overlapping. Furthermore, even though an additional 46 donors ≥65 years were enrolled, the overall number of included patients only allows for detection of larger differences. However, we feel that this study underlines the importance of very short cold ischaemia times for kidneys recovered from very old donors. Although we could not show a significant effect of MP on DGF, the reduced rate of PNF, as well as the improved graft survival rate of kidneys that developed DGF indicates that MP is a valuable tool for addressing the forthcoming challenges in kidney transplantation from donors of advanced age.

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Conflict of interest statement. C.M., J.-P.S. and H.G.D.L. have each received congress travel grants from Organ Recovery Systems; J.P. has received a research grant from the government of Flanders, Belgium, in cooperation with Organ Recovery Systems to study machine perfusion of liver grafts, for which he receives no salary; R.J.P. has received consulting fees from Bristol-Myers Squibb; C.M. has received grant support from the Dutch Kidney Foundation, H.G.D.L. has received grant support from the Dutch Kidney Foundation and the Eurotrans-Bio pro donor project; R.J.P. and H.G.D.L. have a patent on a portable preservation apparatus for donor organs. No other potential conflict of interest relevant to this article was reported.

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