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ORIGINAL ARTICLE

Machine perfusion versus cold storage for preservation of kidneys from expanded criteria donors after brain death

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Conflicts of Interest
Drs. Maathuis, Moers, Paul, and Leuvenink and Mrs. van Kasterop-Kutz report receiving one congress travel grant from Organ Recovery Systems; Dr. Pirenne, receiving 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; Dr. Ploeg, receiving consulting fees from Bristol-Myers Squibb and grant support from Nuts Ohra Trust; Dr. Moers, receiving grant support from the Dutch Kidney Foundation; Dr. Leuvenink, receiving grant support from the Dutch Kidney Foundation and the Eurotrans-Bio pro-donor project; and Drs. Ploeg and Leuvenink, having 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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Summary

The purpose of this study was to analyze the possible effects of machine perfusion (MP) versus cold storage (CS) on delayed graft function (DGF) and early graft survival in expanded criteria donor kidneys (ECD). As part of the previously reported international randomized controlled trial 91 consecutive heart-beating deceased ECDs – defined according to the United Network of Organ Sharing definition – were included in the study. From each donor one kidney was randomized to MP and the contralateral kidney to CS. All recipients were followed for 1 year. The primary endpoint was DGF. Secondary endpoints included primary nonfunction and graft survival. DGF occurred in 27 patients in the CS group (29.7%) and in 20 patients in the MP group (22%). Using the logistic regression model MP significantly reduced the risk of DGF compared with CS (OR 0.460, $P = 0.047$). The incidence of nonfunction in the CS group (12%) was four times higher than in the MP group (3%) ($P = 0.04$). One-year graft survival was significantly higher in machine perfused kidneys compared with cold stored kidneys (92.3% vs. 80.2%, $P = 0.02$). In the present study, MP preservation clearly reduced the risk of DGF and improved 1-year graft survival and function in ECD kidneys.

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Introduction

As a result of persistent donor organ shortage, kidneys from expanded criteria donors (ECDs) are nowadays accepted by many centers and successfully transplanted, thus shortening waiting times [1–3]. Unfortunately, kidneys from ECDs appear to have a higher rate of delayed graft function (DGF) and a more complicated postoperative course, resulting in an inferior long-term graft survival overall [2–6]. Although the use of kidneys from ECDs has an overall risk for graft failure of 1.7, it has also been shown that transplantation of these kidneys has a significant survival benefit compared with dialysis treatment [7].

To enhance the outcome of using ECD kidneys, it is important to analyze the risk factors, including the role of the preservation method. A recently published systematic review suggests that hypothermic machine perfusion (MP) might be superior compared with simple cold storage (CS), reducing the relative risk of DGF by up to 20% and increasing 10-year graft survival by 6% [8,9]. However, this evidence is based on studies that were limited by an uncontrolled patient selection, small patient numbers, the use of different and sometimes out-of-date preservation solutions, nonstandardized pumping modes and times, as well as inconsistent application of currently available pump technology.

We recently reported the overall results of an international multi-center randomized trial comparing MP versus CS in unselected consecutive donors ≥16 years of age, demonstrating the safety of MP and a significant reduction in both DGF and 1-year graft loss [10]. As this effect might be even more pronounced or clinically relevant in ECD kidneys [2,11], the purpose of this study was to provide an analysis of the possible effects of MP versus CS on DGF and early graft survival in ECD kidneys.

Materials and methods

As part of the previously reported multi-center randomized trial [10] all consecutively retrieved kidney pairs from heart-beating deceased ECDs in the Netherlands, Belgium, and the federal state of North Rhine-Westphalia in Germany between November 1, 2005 and October 31, 2006 were eligible for randomization. ECDs were defined according to the United Network of Organ Sharing (UNOS) definition [1,2], which includes: donor age ≥60 years or 50–60 years with at least two of the following criteria: history of hypertension, cerebrovascular cause of death and serum creatinine 132 μM (1.5 mg/dl) prior to retrieval.

Donors were only included in the study for analysis if both organs were transplanted into two different recipients. Donors accepted for combined organ transplantation (e.g., liver–kidney transplantation) by the recipient center were excluded from the trial.

Recipient centers were blinded to the method of preservation (MP or CS) at the time of acceptance of the kidney for a specific recipient.

The study protocol was approved by ethics committees in each trial region. The study was sponsored by the Deutsche Forschungsgemeinschaft (DFG TR 811/1-1) and by Organ Recovery Systems (Itasca, IL, USA).

Randomization and logistics

From each donor, one kidney was randomized to MP and the contralateral kidney to CS. The randomization process and logistic management have been described in an earlier publication [10].

Preservation methods

All kidneys underwent *in situ* vascular washout with cold preservation solution (histidine–tryptophan–ketoglutarate or University of Wisconsin solution). Kidneys assigned to hypothermic MP were connected to a LifePort Kidney Transporter® (Organ Recovery Systems) shortly after procurement and machine perfused until transplantation. A pulsatile flow of machine preservation solution (Kidney Preservation Solution-1®; Organ Recovery Systems, Itasca, IL, USA) at 1–8 °C and a fixed systolic perfusion pressure of 30 mmHg were maintained. The transplant team was blinded to MP intravascular resistance and flow data. Kidneys assigned to CS were submerged in preservation solution and stored on melting ice.

Endpoints and data collection

The primary endpoint of this ECD study was DGF defined as the need for dialysis during the first week post-transplant. Secondary endpoints were: functional delayed graft function (f-DGF), which is defined as the absence of a decrease in serum creatinine levels of at least 10% per day for at least three consecutive days in the first week after transplantation [12]; duration of DGF; primary nonfunction (PNF) of the transplanted kidney; serum creatinine levels at 1–14 days and one, three and 12 months; creatinine clearance at 1 and 2 weeks and 1, 3 and 12 months; biopsy-proven acute rejection and calcineurin inhibitor toxicity within the first 2 weeks; recipient hospital stay length; graft and patient survival; and the number of biopsy-proven rejection and calcineurin inhibitor toxicity episodes up to 1 year post-transplant.

In addition, standard donor and recipient data and the type of induction immunosuppression therapy were

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recorded. Follow-up data were collected in a secure online database hosted by Eurotransplant and were provided by each of the 60 participating transplant centers.

Statistics

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 82 pairs of ECD kidneys. The primary analysis of the DGF endpoint consisted of a logistic regression model with the covariates shown in Table 3.

Secondary endpoint variables were assessed for univariate differences between groups by the McNemar or the Wilcoxon signed rank test. Differences between survival curves were determined by the log rank test. A Cox proportional hazards model was applied to examine which variables significantly influenced the risk of graft failure. All *P*-values are two-sided and not adjusted for multiple testing. Analyses were conducted using SPSS (IBM Corporation, Somer, NY, USA), SAS (SAS Institute Inc., Cary, NC, USA) and R software packages (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Between November 1, 2005 and October 31, 2006, 336 out of 654 deceased donors 16 years of age and older were included in the overall study. Of these 654 donors, 200 were ECDs. There were 109 ECDs who were not studied, thus 91 donors were included in the subgroup analysis. The reasons for exclusion are described in Table 1. The main reason was that one or both kidneys were not transplantable (42/109). Preservation methods were switched in five donors. In two cases this was attributable to aberrant vascular anatomy, whereas in three cases no reason could be found.

Table 1. Reasons for exclusion of donors.

Reported after procurement	1
Could not be reached in time	8
Donor center refusal	0
Donor family refusal	0
Donor procedure canceled	5
One or both kidneys not transplantable	42
Combined organ offer	7
Other reasons	32
Kidney rejected at transplant center	4
Technical failure MP	2
Not assessed by mistake	0
Unknown	8

Potential donors *N* = 200.
Donors included *N* = 91.
Reasons for excluding *N* = 109.
MP, machine perfusion.

Donor and recipient characteristics are summarized in Table 2. The median donor age was 66 years (50–81 years) and the median recipient age was 65 years in both groups. There were no significant differences between the two groups concerning relevant baseline characteristics.

Further subset analysis showed no differences concerning median cold ischemia time between MP and CS for donors older than 65 years (9 h vs. 10 h, $P = 0.61$) or the subset of transplants with more than three HLA mismatches (10 h vs. 10 h, $P = 0.92$).

In this ECD subgroup, DGF occurred in 27 patients in the CS group (29.7%) and in 20 patients in the MP group (22%). This difference was not statistically significant in the univariate analysis ($P = 0.27$) (Table 2). The analysis using the logistic regression model showed that MP significantly reduced the risk of DGF compared with CS (adjusted odds ratio 0.460, $P = 0.047$) (Table 3).

The number of kidney pairs from the same donor for which both kidneys developed DGF after transplantation was nine.

There was no significant difference in the incidence of DGF in the ECD subgroup compared with the main data [10] set in neither machine perfused kidneys (22% vs. 20.8%) nor in cold stored kidneys (29.7% vs. 26.5%). Further significant factors affecting the risk for DGF were cold ischemia time, duration of pretransplant dialysis, and whether it was a retransplant versus a first transplant.

Secondary endpoints

The incidence of PNF in the CS group (12%) was four times higher than in the MP group (3%) ($P = 0.04$). Of the cold stored kidneys with PNF in the main dataset, 68% were from ECDs; however, only 42.5% of machine perfused kidneys with PNF came from ECDs ($P = 0.52$). The PNF in cold stored ECD kidneys was significantly more frequent than in the whole group of cold stored kidneys ($P = 0.025$), whereas there was no difference in the occurrence of PNF in the machine perfused kidneys when ECDs were compared with all donors. The incidence of f-DGF was 29.7% after CS and 20.8% after MP ($P = 0.31$) (Table 2).

There were no significant differences between the two groups concerning creatinine clearance up to 3 months, daily creatinine values up to day 14, the incidence of biopsy-proven calcineurin inhibitor toxicity, acute rejection episodes, and the length of hospital stay. Creatinine clearance after 1 year was significantly higher in the MP group compared with the CS group (78 ± 41 ml/min vs. 69 ± 48 ml/min, $P = 0.01$) (Table 2).

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Table 2. Donor and recipient characteristics, results of univariate analysis.

	MP arm	CS arm	*P*-value
Donor			
Age (years)		66 (50–81)	
Gender		M/F (49/42)	
BMI		27 (21–42)	
Days on ICU prior to procurement		2.5 (0.1–17)	
Serum creatinine			
Mean		96 μmol/l	
Max		310 μmol/l	
Median (range)		86 (50–310)	
(Nor)adrenalin Y/N/U		72/19/0	
Preservation solution			
UW		50	
HTK		40	
Other		1	
Recipient			
Age (years)	65 (20–79)	65 (32–79)	0.75
Gender: M/F	55/36	57/34	0.88
Pre-RTX dialysis duration (days)	1728 (149–3866)	1728 (137–5154)	0.68
Previous transplants	0/1/2 (69/19/3)	0/1/2/3 (64/19/6/2)	0.29
Current PRA (%)	0–5/6–84/85+ (85/5/1)	0–5/6–84/85+ (81/9/1)	0.43
HLA-A, -B, -DR mismatches (% of 0 MM)	12.1	8.8	0.63
CIT (h)	13 (3–23)	13 (4–29)	0.97
Endpoints			
DGF, Y/N (%)	20/71 (22)	27/64 (29.7)	0.27
Duration of DGF (median, days)	14 (3–31)	15 (4–41)	0.45
Duration of DGF <7 days, Y/N (%)	5/15 (33.3)	4/23 (17.4)	0.22
f-DGF, Y/N (%)	15/57 (20.8)	22/52 (29.7)	0.31
PNF, Y/N (%)	3/88 (3)	11/80 (12)	0.04
CNI intoxicity, Yes/No/U (%)	5/78/8	3/81/7	0.63
Acute graft rejection, Yes/No/U (%)	17/64/10	16/67/8	0.98
Creatinine clearance at 1 year (mean ± SD ml/min)	78 ± 41	69 ± 48	0.01

CS, cold storage; DGF, delayed graft function; MP, machine perfusion; PNF, primary nonfunction; CIT, cold ischemia time; HTK, histidine–tryptophan–ketoglutarate; UW, University of Wisconsin solution; MM, mismatch; PRA, panel reactive antibodies.

Table 3. Logistic regression model – dependent variable delayed graft function (DGF).

	Odds ratio (95% CI)	*P*-value
Treatment arm MP versus CS	0.460 (0.213–0.989)	0.047
CIT	1.151 (1.057–1.254)	0.001
HLA MM	1.905 (0.454–8.000)	0.379
Recent PRA	1.004 (0.980–1.029)	0.742
Recipient age	1.586 (0.569–4.424)	0.378
Donor age	1.036 (0.957–1.122)	0.385
First/re-transplant	2.307 (1.257–4.234)	0.007
Duration of pretransplant dialysis	1.001 (1.000–1.001)	0.021

CIT, cold ischemia time; CS, cold storage; MP, machine perfusion; MM, mismatch; PRA, panel reactive antibodies.

Patient and graft survival

No patient deaths occurred in the first 14 days after transplantation. Patient survival after 1 year was 93.4% in the MP group and 96.7% in the CS group ($P = 0.30$). One-year death censored graft survival was significantly higher in machine perfused kidneys compared with cold stored kidneys (92.3% vs. 80.2%, $P = 0.02$) (Fig. 1a). This difference was even more pronounced if DGF had occurred. Although in the MP group there was a difference of nearly 10% for 1-year graft survival if DGF occurred compared with kidneys with immediate function, this difference was not statistically significant (94% vs. 85%, $P = 0.164$). In the CS group, graft survival was impressively reduced if DGF occurred (41% vs. 97%, $P < 0.0001$). If only recipients of grafts that developed DGF were analyzed, there was a significant difference in 1-year graft survival between machine perfused kidneys and cold stored kidneys (85% vs. 41%, $P = 0.003$) (Fig. 1b).

Cox regression analysis showed that MP significantly reduced the risk of graft failure in the first year with a hazard ratio of 0.353 ($P = 0.022$) (Table 4). As a relevant

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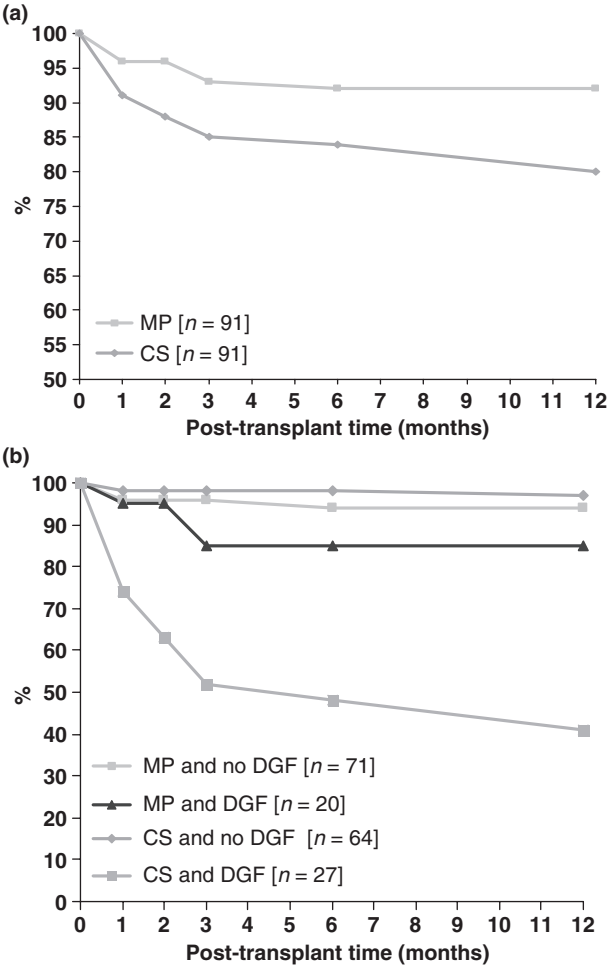

Figure 1 (a) Post-transplant graft survival rates. All consecutive renal transplants from heart beating (HB) expanded criteria donor (ECD) $N = 182$. Logrank test of equality machine perfusion (MP) versus cold storage (CS) $P = 0.02$. (b) Post-transplant graft survival rates. All consecutive renal transplants from HB ECD $N = 182$ – Logrank test of equality. Within CS group delayed graft function (DGF) versus no DGF $P < 0.0001$. Within MP group DGF versus no DGF $P = 0.164$. Within no DGF group MP versus CS $P = 0.48$. Within DGF group MP versus CS $P = 0.003$.

defining factor for ECDs, donor age had no significant influence on DGF in this analysis. However, even in this older group of donors, it did significantly influence 1-year graft survival (hazard ratio 1.103, $P = 0.016$).

Discussion

In the context of this randomized trial [10] we have now focused on the effect of MP in kidneys from ECDs. This effect was even more pronounced than in the overall study, with an odds ratio (OR) of 0.46 for the risk of developing DGF (overall OR of 0.57). Nevertheless, direct comparison of the treatment effects on DGF between expanded criteria donation and standard criteria donation that also included deceased donation after cardiac death showed no significant difference.

Table 4. Cox 'proportional hazards model' – dependent variable 1 year graft function.

	Hazards ratio (95% CI)	*P*-value
Treatment arm MP versus CS	0.353 (0.145–0.862)	0.022
CIT	1.082 (0.994–1.179)	0.068
HLA MM	4.070 (0.484–34.208)	0.196
Recent PRA	1.006 (0.983–1.030)	0.600
Recipient age	0.629 (0.219–1.805)	0.388
Donor age	1.103 (1.018–1.195)	0.016
First/re-transplant	0.938 (0.480–1.832)	0.851
Duration of pretransplant dialysis	1.000 (1.000–1.001)	0.495

CIT, cold ischemia time; CS, cold storage; MP, machine perfusion; MM, mismatch; PRA, panel reactive antibodies.

It is interesting to see that in this study, the incidence of DGF in ECD kidneys is only slightly higher than in the main data set, irrespective of the preservation method. The incidence of DGF found in this trial is clearly lower than that reported in previous studies using ECD [13,14]. One explanation for this might be the relatively short cold ischemic times in this study.

The hazard ratio for graft failure was also more reduced for ECDs with a value of 0.35 than in the overall study with 0.52. The number of recipients receiving an ECD kidney with PNF was fourfold higher in the CS group compared with the MP group. Such early graft failure, in addition to subsequent graft failures, puts a severe burden on patients and waiting lists for kidney transplantation. The effect we observed was much stronger than described in a recent meta-analysis [8].

For ECDs, we also show for the first time that at 1 year post-transplant, the function of the surviving grafts was better if the kidney was preserved by MP compared with CS. These results differ from retrospective studies as these studies show only short term beneficial effects of MP with a reduction of DGF but no improvement in graft survival [15–17].

Although donor age is already part of the ECD definition, it was the only significant predictive factor in the Cox proportional hazard model for graft survival after 1 year, apart from the treatment modality MP versus CS (Table 4).

The effect of MP on the reduction in serum creatinine levels in the first 14 days compared with cold stored kidneys could not be demonstrated in the ECD group, although, this was shown in the main data set. This is probably because of the smaller sample size of the present study.

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The f-DGF was chosen instead of creatinine reduction ratio (CRR) since the CRR only takes into account days 1 and 2 post-transplant. The f-DGF has a scope of 7 days after Tx and has also been validated by Boom *et al* [12]. The scope of the classical DGF definition (in terms of hemodialysis requirement) is also 1 week, so in our view f-DGF is a more functional definition which uses the same time frame.

Parameters characterizing the individual kidney during perfusion – such as vascular resistance, and flow and perfusate viability markers – were not used as potential predictors of outcome. In a separate analysis, renal resistances during MP were shown to correlate with DGF and 1 year graft survival (univariate analysis), but not with PNF [18]. Hence, further analysis of these parameters and perfusate biomarkers might help to identify kidneys at risk for DGF and PNF, also recently shown in an experimental study [19–21]. Interestingly, but not fully analyzed yet, was that kidneys with DGF after MP and after CS were seldom from the same donor in this study. This could imply that parameters of MP providing a prognosis for the development of DGF in the perfused kidney will in most cases not help to identify renal grafts at risk for DGF after CS.

A striking fact is that the proportion of ECDs in Germany, where donation is only allowed after brain death, is almost 50% (47.7% in 2006 and 48.2% in 2007) (Eurotransplant analysis). The proportion of ECDs in the main study was 27.9% (94/336) when donation after cardiocirculatory death was included and 30.9% (91/294) when only donation after brain death was considered. This relatively small proportion of ECDs is an effect caused by the procurement policy in Belgium and the Netherlands and could imply a strong bias toward better-quality ECD categorized donors in the present study. It can be assumed that ECD populations in other countries are not fully comparable to our study's inclusions and, therefore, the effect of MP versus CS as described in this article could be somewhat different.

The high rate of exclusion could represent a possible bias, but is explained by the early randomization process and high exclusion rate because one or both kidneys were eventually not transplanted. Exclusion for a combined organ transplantation was rare. This too could provide a bias toward the 'better' extended criteria donor, and perhaps effects of MP could be even more pronounced in a series with more marginal ECD kidneys.

There were no kidney pairs that could not be randomized. All consecutive ECD donor kidney pairs were assessed for inclusion, randomized if they met the initial inclusion criteria, and only if vascular anatomy of the kidney randomized for MP prevented a reliable connection of the kidney to the perfusion machine, could the preservation methods for this pair be switched, thus indeed frustrating randomization. We checked whether the presence of vascular anomalies had any relevant influence on post-transplant outcome, and this was not the case. Therefore, the few cases in which preservation methods were switched did not introduce any bias to our results.

The recent review of Yuan *et al.* critically describes the possibilities and developments in the field of MP over the last decades. The authors emphasize the importance investigating the relevance of MP for marginal donor organs. We feel that the present study adds important new data which support the benefit of MP for the preservation of such donor organs [22].

In summary, this study shows that MP reduces the risk of DGF and improves 1-year graft survival and function in ECD kidneys. The development of better pretransplant predictors for DGF [23] could increase the cost-effectiveness of MP in extended criteria donation. We believe that as long as there are no such reliable predictors, every ECD kidney should be machine perfused, because in the first year after transplantation alone, 12% more grafts could be saved as a result of MP.

Authorship

JT, CM, JMS, RJP and AP: designed study, performed study, analyzed data and wrote paper. AG and M-HJM: performed study and collected data. MvK-K: performed study, collected data and analyzed data. IJ: participated to data analysis. JJHvdH: designed study and performed study. J-PS and HGDL: designed study, performed study and collected data. EvH and JP: designed study, performed study, collected data and analyzed data. GRK: designed study, performed study and analyzed data. AR: performed study and collected data.

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