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The Prognostic Value of Renal Resistance During Hypothermic Machine Perfusion of Deceased Donor Kidneys

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Vascular renal resistance (RR) during hypothermic machine perfusion (HMP) is frequently used in kidney graft quality assessment. However, the association between RR and outcome has never been prospectively validated. Prospectively collected RR values of 302 machine-perfused deceased donor kidneys of all types (standard and extended criteria donor kidneys and kidneys donated after cardiac death), transplanted without prior knowledge of these RR values, were studied. In this cohort, we determined the association between RR and delayed graft function (DGF) and 1-year graft survival. The RR (mmHg/mL/min) at the end of HMP was an independent risk factor for DGF (odds ratio 21.12 [1.03–435.0]; p = 0.048) but the predictive value of RR was low, reflected by a c-statistic of the receiver operator characteristic curve of 0.58. The RR was also found to be an independent risk factor for 1-year graft failure (hazard ratio 12.33 [1.11–136.85]; p = 0.004). Determinants of transplant outcome are multifactorial in nature and this study identifies RR as an additional parameter to take into account when evaluating graft quality and estimating the likelihood of successful outcome. However, RR as a stand-alone quality assessment tool cannot be used to predict outcome with sufficient precision.

Key words: Deceased donor kidneys, delayed graft function, hypothermic machine perfusion, kidney transplantation, renal resistance, quality assessment, viability testing

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; DBD, donation after brain death; DCD, donation after cardiac death; DGF, delayed graft function; ECD, extended criteria donor; HMP, hypothermic machine perfusion; PNF, primary nonfunction; RR, renal resistance; SCD, standard criteria donor; UNOS, United Network for Organ Sharing.

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Introduction

Hypothermic machine perfusion (HMP) preserves kidney grafts by continuous or pulsatile administration of a recirculating cold (1–10°C) preservation solution. The Machine Preservation Trial (MP Trial) recently showed that HMP decreases the incidence of primary nonfunction (PNF) and delayed graft function (DGF), and increases 1-year graft survival compared to standard static cold storage (1). In addition, HMP offers the unique possibility to assess the graft in the interval between procurement and transplantation by monitoring perfusion dynamics and/or perfusate biomarkers that possibly correlate with graft outcome.

Since the early days of HMP in the 1960s, it has been assumed that perfusion dynamics, such as perfusion pressure, perfusate flow and intravascular renal resistance (RR), can reliably predict kidney graft outcome. To a certain extent, there is indeed evidence that perfusion parameters correlate with kidney graft function. However, this evidence originates almost exclusively from retrospective studies in which kidneys were preselected and discarded based on empirically defined perfusion parameter thresholds (2). Needless to say, systematically discarding kidneys introduced a major bias in these studies. Two of the earliest studies addressing the association between perfusion parameters and early graft function did not preselect kidneys based on these parameters. Henry et al. showed a correlation between early dysfunction and RR at the end

of HMP (3). However, the group of kidneys with early dysfunction was small (n = 10) and only one of those kidneys developed PNF. Sampson et al. found no difference in flow rates between immediately functioning kidneys and those that developed early graft failure (4). Noteworthy, 12 of the 18 graft failures in this study were related to acute or hyperacute rejection, and grafts were removed early after transplantation. The changed donor population and improved immunosuppression makes it even more difficult to interpret these results leaving the issue of the true prognostic value of perfusion parameters unresolved.

With the enduring donor shortage, kidneys of "uncertain" quality originating from extended criteria donors (ECDs) or donated after cardiac death (DCD) are increasingly used. As these kidneys have a higher incidence of PNF and DGF compared with standard criteria donor (SCD) kidneys (5,6), the need for specific and sensitive surrogates of their quality is becoming even more critical. The absence of prospective analyses of the association between perfusion parameters and kidney transplant outcome, and the increasingly urgent need for valid predictors of graft outcome led us to analyze the association between prospectively collected RR values and kidney graft outcome in a substudy of the MP Trial.

Materials and Methods

Study design

Study data were prospectively collected in the HMP arm of the MP Trial. This randomized controlled trial compared HMP with static cold storage for the development of DGF in all types of deceased donor kidneys within part of Eurotransplant: Belgium, the Netherlands, and the federal state of North Rhine-Westphalia in Germany. The MP trial showed that HMP significantly reduces the incidence of DGF (adjusted odds ratio [AOR] 0.57 [0.36-0.88]; p = 0.01) and 1-year graft failure (hazard ratio 0.52 [0.29-0.93]; p = 0.03; Ref. 1).

Briefly, all kidneys from eligible consecutive deceased donors (SCD, ECD and DCD), aged 16 years or older, were included. We defined ECD kidneys according to criteria of the United Network for Organ Sharing (UNOS; Ref. 6). Among the DCD kidneys, only those from Maastricht category III donors were included (7). One kidney from each donor was assigned to HMP and the contralateral kidney to static cold storage, according to regional and computer generated randomization lists. When a reliable connection to the perfusion machine was impaired either by an aortic patch that was too small or by too many renal arteries, randomization for this kidney pair was changed and the preservation methods switched. Kidneys were allocated according to standard Eurotransplant allocation rules without revealing the preservation method at the time of organ offer. A strictly paired design was maintained, in which both kidneys from one donor needed to be transplanted into different recipients. Both kidneys of a pair were excluded when one or both recipients died within 1 week after transplantation. For this analysis, only the data prospectively collected in the HMP arm of the MP Trial was used. Informed consent from recipients was not required, as kidneys were randomized before organ allocation. Ethical approval was obtained from the Eurotransplant Ethical Advisory Committee, the Kidney Advisory Committee and ethics review boards in each trial region.

Preservation method

Kidneys were flushed *in situ* with the University of Wisconsin solution (64%) or histidine–tryptophan–ketoglutarate (32%); in 4% of cases the flush solution was not reported. Pulsatile HMP was provided by LifePort® Kidney Transporter machines (Organ Recovery Systems, Itasca, IL, USA). All kidneys were perfused with Belzer's machine perfusion solution, available as Kidney Preservation Solution-1® (1–8°C; Ref. 8). Perfusion was started immediately after organ recovery and was continued until transplantation. The systolic perfusion pressure was set at 30 mmHg and the machine continuously recorded the perfusion parameters. The LifePort® was used as a stand-alone preservation technique: changing the perfusion pressure or adding pharmacologic agents to the perfusion solution was not allowed. The HMP kidney was transported to the recipient hospital without any monitoring. Because the transplantation team was blinded to the perfusion parameters, the decision to accept or reject a kidney could not be biased by these parameters. The RR data were downloaded by the perfusionist at the end of HMP, to be evaluated at a later time.

Follow-up

Recipient centers provided follow-up data to a secure online Eurotransplant database and were financially compensated to ensure maximal data completeness. No relevant irregularities were found during an external audit of a random sample of 10% of all patient follow-up data.

Study endpoints

DGF was defined as the need for dialysis in the first week after transplantation, preceding return of graft function. PNF was defined as the permanent lack of graft function. Death censored graft survival was the outcome measure for graft performance until 1-year posttransplantation. Because the LifePort® software calculates RR every 10 s (mmHg/mL/min), we chose to analyze RR data at 30 min, 1, 2 and 4 h and at the end of HMP. These time points were chosen before disclosure of RR values.

Statistical methods

We performed univariable logistic regression analysis for DGF and then constructed a multivariable logistic regression model to find independent risk factors of DGF. The RR was entered as a covariate in these models. Other covariates were prespecified in the protocol before the MP Trial started. Because of a limited number of events in this subgroup analysis, we only included those prespecified factors that were significantly associated with DGF in the MP Trial: cold ischemic time, donor type (donation after brain death [DBD] vs. DCD), donor age, retransplantation versus first transplantation and duration of pretransplant dialysis (1). A receiver operator characteristic (ROC) curve was constructed to investigate the predictive accuracy of RR for DGF. Because the number of PNF was low, an association between PNF and RR could not be studied and PNF cases were excluded from further analysis. We performed unadjusted and adjusted Cox regression analysis for 1-year graft failure. Because of the low number of graft losses, we could only correct for two variables; we therefore chose RR, the variable of interest and donor age, the variable that was the strongest independent risk factor for graft failure in the MP Trial. To exclude a potential bias introduced by kidneys in which randomization needed to be switched, the logistic and Cox regression analyses only included kidneys that were randomized to and effectively preserved by HMP.

Continuous variables are expressed as median and range, categorical variables as number and percentage. Two-sided p-values ≤ 0.05 were considered to indicate statistical significance. Endpoint interim analyses were not performed. All data analyses were performed using SPSS, SAS and R software.

Table 1: Population characteristics, early graft function, 1-year patient and graft survival of machine-perfused kidneys in the Machine Preservation Trial

Variable	All (n = 336)	SCD (n = 203)	ECD (n = 91)	DCD (n = 42)	p-Value
Donor characteristics					
Age[1] (year)	51 (16–81)	46 (16–59)	66 (50–81)	42 (17–60)	0.001[2]
Cold ischemic time[1] (h)	15 (3–30)	15 (5–30)	13 (3–23)	16 (4–25)	0.001[2]
Recipient characteristics					
Age[1] (year)	53 (11–79)	51 (11–76)	62 (20–79)	50 (24–69)	0.001[2]
Duration pretransplant dialysis[1] (year)	4.5 (0.2–18)	4.5 (0.2–14)	4.7 (0.4–11)	4.7 (1.1–18)	0.11[2]
Early graft function, n (%)					
Immediate function	266 (79)	178 (87)	68 (75)	20 (48)	0.001[2]
Primary nonfunction[1]	7 (2)	3 (1)	23 (3)	1 (2)	0.61[2]
Delayed graft function[3]	63 (19)	22 (11)	20 (22)	21 (50)	0.001[2]
Graft survival, n (%)					
Death censored					
At 3 months	320 (95)	194 (96)	85 (93)	41 (98)	0.61[4]
At 6 months	317 (94)	193 (95)	84 (92)	40 (95)	0.61[4]
At 1 year	317 (94)	193 (95)	84 (92)	40 (95)	0.61[4]
Including patient death					
At 3 months	319 (92)	194 (96)	84 (92)	41 (98)	0.35[4]
At 6 months	314 (94)	192 (95)	82 (90)	40 (95)	0.32[4]
At 1 year	309 (92)	189 (93)	80 (88)	40 (95)	0.22[4]
Patient death, n (%)					
At 3 months	1 (0.3)	0 (0)	1 (1)	0 (0)	–
At 6 months	6 (2)	2 (1)	4 (4)	0 (0)	0.08[4]
At 1 year	11 (3)	5 (2)	6 (7)	0 (0)	0.08[4]

All values of donor and recipient characteristics are median (range). SCD = standard criteria donor; ECD = extended criteria donor as defined by UNOS criteria (7); DCD = donation after cardiac death = Maastricht category III (8).
[1]Primary nonfunction: permanent lack of allograft function.
[2]Wald test.
[3]Delayed graft function: need for dialysis in the first week after transplantation.
[4]Log-rank test.

Results

Three hundred thirty-six deceased donor kidneys were preserved by HMP between November 1, 2005 and October 31, 2006. We included 42 DCD kidneys (13%) and 294 DBD kidneys (87%), of which 203 were SCD and 91 were ECD. Table 1 shows donor and recipient characteristics, early graft function and 1-year graft and patient survival. Overall, 19% of machine-perfused kidneys developed DGF; PNF occurred in seven cases (2%). The incidence of DGF was highest in DCD kidneys; PNF did not differ between SCD, ECD and DCD kidneys. One-year patient and death censored graft survival was 97% and 94% and comparable between all donor types. The RR data was available in 326 cases (Figure 1 and Table 2). The RR of PNF kidneys were intermediate between RR of DGF and immediately functioning kidneys. Because of the low number of events, these PNF cases were excluded from further analyses. Randomization was switched in 24 donors (7%) because of aberrant vascular anatomy, making the connection to the LifePort® difficult. Switching randomization had no significant effect on the incidence of DGF; of these 24 kidneys, 8 developed DGF whereas 16 had immediate graft function (p = 0.12). To avoid an impact on the outcome of the logistic and Cox regression models, these 24 kidneys were excluded from the regression analyses.

Univariable analysis showed that RR was a risk factor for the development of DGF at 30 min, 2 and 4 h and at the end of HMP (Table 3). In multivariable analysis, only RR at the end of HMP proved to be an independent risk factor of DGF in addition to donor type (DBD vs. DCD), donor age and retransplantation (Table 4). The RR data at 4 h showed a trend towards significance in the multivariable analysis for the risk of DGF (AOR 9.68 [0.79–118.39]; p = 0.076). The c-statistic of the ROC curve for RR at the end of HMP was 0.58. The RR was also a risk factor for 1-year graft failure in both unadjusted and adjusted Cox regression analysis (Tables 3 and 4).

Discussion

This analysis of prospectively collected RR values of kidneys stored by HMP showed that RR is an independent risk factor for both DGF and 1-year graft failure. These findings suggest that RR is an important additional

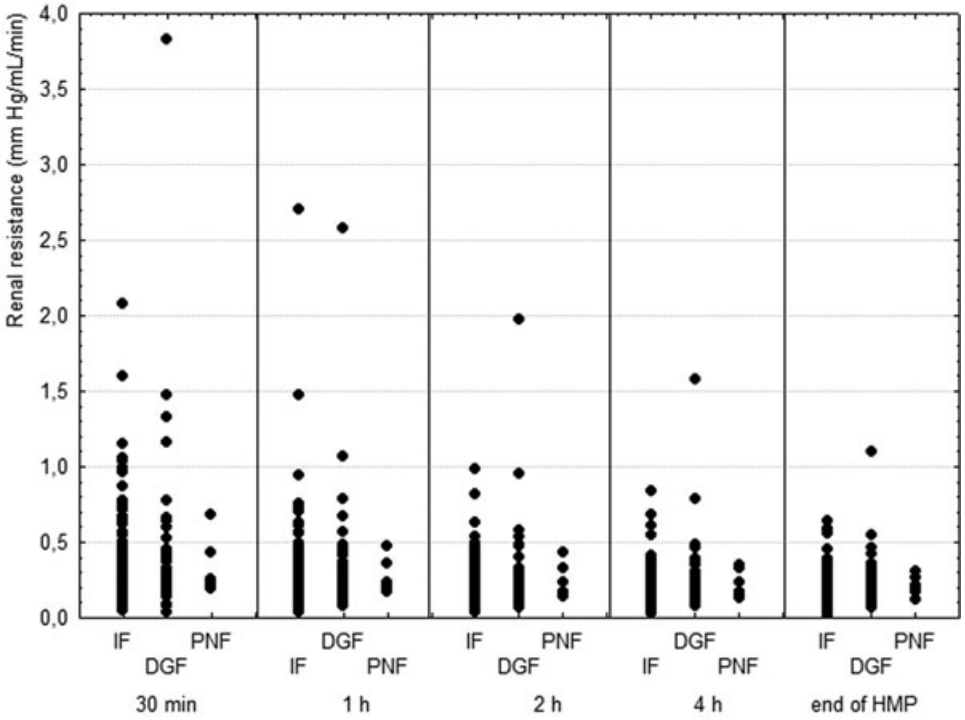

Figure 1: Dot plot representing the individual renal resistance values in function of perfusion time during hypothermic machine perfusion and early graft function. PNF, primary nonfunction defined as permanent lack of graft function (n = 6); DGF, delayed graft function defined as dialysis in the first week after transplantation, preceding return of graft function (n = 63); IF, immediate function (n = 257); HMP, hypothermic machine perfusion.

Table 2: Renal resistance of machine-perfused kidneys in function of donor type and early graft function

Variable	RR at 30 min HMP	RR at 1 h HMP	RR at 2 h HMP	RR at 4 h HMP	RR at end HMP
All	0.28 (0.04–3.83) n = 325	0.22 (0.04–2.70) n = 324	0.20 (0.04–1.97) n = 323	0.18 (0.03–1.58) n = 302	0.17 (0.02–1.10) n = 325
Donor type					
SCD	0.25 (0.05–3.83) n = 202	0.21 (0.04–2.70) n = 202	0.19 (0.04–1.97) n = 202	0.18 (0.03–1.58) n = 193	0.16 (0.02–1.10) n = 202
ECD	0.26 (0.04–1.47) n = 82	0.23 (0.07–0.79) n = 81	0.21 (0.06–0.66) n = 80	0.20 (0.05–0.57) n = 69	0.18 (0.03–0.51) n = 82
DCD	0.29 (0.08–3.4) n = 41	0.23 (0.09–2.62) n = 41	0.21 (0.09–1.72) n = 41	0.20 (0.08–0.79) n = 40	0.18 (0.07–0.88) n = 41
Early graft function					
IF	0.24 (0.05–2.08) n = 257	0.21 (0.04–2.7) n = 256	0.19 (0.04–0.99) n = 254	0.17 (0.03–0.84) n = 234	0.16 (0.02–0.64) n = 256
DGF	0.28 (0.04–3.83) n = 62	0.23 (0.08–2.58) n = 62	0.21 (0.07–1.97) n = 63	0.20 (0.08–1.58) n = 62	0.18 (0.07–1.10) n = 63
PNF	0.25 (0.12–0.68) n = 6	0.22 (0.17–0.47) n = 6	0.21 (0.14–0.43) n = 6	0.21 (0.11–0.35) n = 6	0.20 (0.12–0.31) n = 6

All values are median (range). RR = renal resistance in mmHg/mL/min; SCD = standard criteria donor; ECD = extended criteria donor as defined by UNOS criteria (7); DCD = donation after cardiac death = Maastricht category III (8); IF = immediate function; DGF = delayed graft function defined as dialysis in the first week after transplantation, preceding the return of graft function; PNF = primary nonfunction defined as permanent lack of graft function; HMP = hypothermic machine perfusion.

Table 3: Univariable analysis for delayed graft function and 1-year graft failure in 302 machine-perfused kidneys

Variable	Odds ratio (95% CI)	Hazard ratio (95% CI)	p-Value
Delayed graft function			
RR at 30 min of HMP	2.41 (1.02–5.71)		0.046
RR at 1 h of HMP	2.28 (0.86–6.04)		0.097
RR at 2 h of HMP	8.88 (1.39–56.59)		0.021
RR at 4 h of HMP	16.30 (1.67–158.95)		0.016
RR at end of HMP	44.43 (2.79–706.79)		0.007
Graft failure			
RR at end of HMP		12.970 (1.20–140.74)	0.035

Logistic regression model for delayed graft function and Cox regression model for graft failure.
CI = confidence interval; RR = renal resistance expressed in mmHg/mL/min; HMP = hypothermic machine perfusion.

objective tool to be used in kidney graft quality assessment. Nevertheless, our analysis also indicates that RR, given its low predictive accuracy, cannot be used as a stand-alone viability parameter to accept or discard a given kidney, unlike current practice in some centers.

We showed that RR at the end of HMP was an independent risk factor for the later development of DGF. A potential important benefit of RR could therefore be the ability to estimate the risk of a particular kidney to develop DGF. This information may help clinicians in the postoperative management of their patients (e.g. delaying or lowering exposure to calcineurin inhibitors, additional information to institute dialysis, etc.). The RR at the end of HMP is not a fixed point in time but depends on the duration of HMP. Knowing the risk profile of a particular kidney earlier in the preservation process might be of greater benefit, because it would provide a time window necessary for selecting a particular recipient for a particular kidney. In fact, RR data at 4 h showed a trend towards significance in the multivariable analysis for the risk of DGF and RR values remained stable after 4 h until the end of HMP.

Although it would be appealing to use the RR value as a stand-alone parameter to assess the risk of DGF, we found that the c-statistic of the ROC curve of RR for predicting DGF was 0.58. This c-statistic implies that any determined RR threshold would result in a relatively poor predictive capacity for DGF. To illustrate this, we attempted a posthoc analysis to define a RR threshold value in our data set. The calculated discriminative capacity of this threshold (RR = 0.28 mmHg/mL/min) was weak (specificity 93%, sensitivity 17%, positive predictive value 40% and negative predictive value 81%). These results are not surprising given the multifactorial nature of the pathogenesis of DGF. Several donor, procurement and recipient-related risk factors (age, donor type, warm and cold ischemic time, inotropy, hypertension, hypovolemia, number of previous transplants, etc.) influence DGF (9) and it would be too simplistic to believe that one single new risk factor, RR, would replace all the others.

Our observations are in concordance with previous reports that recommend caution in using RR in the assessment of kidney quality. Indeed, Sonnenday et al. stressed the importance of considering not only the perfusion parameters but all donor factors when assessing graft quality. These authors could successfully transplant 11 of 14 kidneys with favorable donor characteristics that had been turned down by other centers due to "poor" perfusion parameters (10). Mozes et al. analyzed 336 consecutive machine-perfused ECD kidneys and showed that the outcome of kidneys with "poor" perfusion parameters (0.40 mmHg/mL/min < RR < 0.60 mmHg/mL/min) was similar to the kidneys with "good" perfusion parameters (11). More recently, Guarrera

Table 4: Multivariable risk analysis for delayed graft function and 1-year graft failure in 302 machine-perfused kidneys

Variable	Odds ratio (95% CI)	Hazard ratio (95% CI)	p-Value
Delayed graft function			
RR at end of HMP (mmHg/mL/min)	38.1 (1.56–934)		0.026
Donor age (year)	1.03 (1.00–1.06)		0.036
Donor type[1]	0.10 (0.04–0.25)		<0.0001
Retransplant versus first transplant	2.29 (1.37–3.83)		0.002
Duration of pretransplant dialysis (year)	1.07 (1.00–1.16)		0.065
Cold ischemic time (h)	1.05 (0.90–1.24)		0.57
Graft failure			
RR at end of HMP (mmHg/mL/min)		12.33 (1.11–136.85)	0.004
Donor age (year)		1.01 (0.98–1.05)	0.5

Logistic regression model for delayed graft function and Cox regression model for graft failure. CI = confidence interval; RR = renal resistance; HMP = hypothermic machine perfusion.
[1]Donor type was stratified to either donation after brain death (standard criteria donors and extended criteria donors) or donation after cardiac death.

et al. reported acceptable short- and long-term results in a small series of deceased donor kidneys with "poor" perfusion parameters (flow < 80 mL/min/100g and RR > 0.40 mmHg/mL/min/100g) but no other high donor risk factors (12).

The necessity to cautiously interpret RR data is also illustrated by the unexpected finding that all the PNF cases in our cohort had RR values intermediate between functioning and DGF kidneys. Because only seven cases of PNF were encountered, statistically sound conclusions regarding a possible association between RR and PNF could not be drawn. However, it is remarkable that when RR criteria, commonly used to discard kidneys likely to fail (RR > 0.40 mmHg/mL/min; 11), were to be applied in our study population, no single PNF case would have been prevented, but eight viable kidneys (2.5%) would have been erroneously discarded (four kidneys with immediate function, four with DGF).

Importantly, we also found that RR is a risk factor for 1-year graft failure. As there were only 18 graft losses, we could only correct for one additional factor, donor age. Nevertheless, our observation is in line with a recent retrospective analysis of 454 preselected HMP kidneys in the donor service area of New York showing that a RR > 0.3 mmHg/mL/min at 3 and 5 h of HMP is a significant predictor of 1-year graft survival in Cox regression analysis (13). In analogy with the carotid intima–media thickness that reflects a person's cardiovascular risk profile (14), we hypothesize that RR of perfused kidneys may reflect their intrinsic morphological "quality" and subsequent likelihood of successful outcome after kidney transplantation. Correlation studies between RR and renal histology parameters are warranted to determine which particular morphological features of the kidney graft are mirrored by RR. In comparison to single biopsies, that are subject to sampling error and interobserver variability, RR may reflect the overall quality of a given kidney better.

Although our study clearly shows that RR is an independent risk factor for both DGF and graft failure, the determinants of transplant outcome are multifactorial and it remains elusive to predict outcome based on RR data (or other parameters) alone. Numerous risk scores, implementing several independent donor, procurement and recipient risk factors have already been proposed. For example, Irish et al. have constructed a "composite DGF score" that has a moderate predictive power for DGF (c-statistic 0.70; Refs. 15,16). Rao et al. recently developed the kidney donor risk index to estimate the risk of graft failure (17). Adding RR to such risk scores will likely increase their predictive accuracy and provide better tools to evaluate kidney quality. Another parameter that may also improve the predictive value of these multifactorial scoring systems is the concentration of certain biomarkers in the perfusate because, like the RR, they have been shown to independently correlate with DGF (18).

The aforementioned data on the impact of RR on transplant outcome apply to all deceased donors with the exception of uncontrolled DCD donors (Maastricht category I, II). Such donors were not included in our trial. In most centers within Eurotransplant, kidneys recovered from uncontrolled DCD donors are already routinely preserved by HMP and when designing the study, it was felt unethical to randomize these kidneys to static cold storage because of their particularly high risk of PNF (up to 13.5% for category II kidneys; 19). The exclusion of uncontrolled DCD donors may account, at least in part, for the low incidence of PNF in our study.

A potential bias in our study is the change of randomization in 25 cases because of vascular anomalies of a right or left kidney that prevented connection to the machine perfusion device. In these cases, the other kidney was machine perfused. This could have led to the exclusion of kidneys with a higher risk of DGF. Vascular anomalies had no significant effect on the development of DGF in our trial. However, to minimize for a possible bias, we performed the logistic and Cox regressions only with kidneys that were allocated to and effectively underwent HMP.

An important technical point for the interpretation of our data and their possible application in the clinics is that all kidneys were perfused with LifePort® machines whereas many previously reported studies used different systems, among them the RM3 machine (Waters Medical Systems, Rochester, MN, USA). This is noteworthy because the LifePort® uses a pressure controlled roller pump to deliver the perfusate creating sinusoidal flow curves whereas the RM3 has a flow controlled pumping system. This gives rise to different wave pressure forms and different calculated RR values. Although absolute RR values calculated by the two devices cannot be compared directly, the association of RR and DGF/1-year graft failure found in our analysis remains valid since only one pump type was used. We believe that similar conclusions would have been reached if another system had been used, albeit probably with different RR values.

In conclusion, this study shows that RR during HMP of all common types of deceased donor kidneys is an independent risk factor for the development of DGF and for 1-year graft failure. Therefore, RR represents an additional and objective source of information that can assist clinicians in their decision making process. However, DGF and graft failure have a complex pathogenesis and cannot be predicted with precision based on RR as a stand-alone assessment tool. More accurate prediction of graft outcome will require integration of perfusion parameters into multifactorial graft quality scoring systems.

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Disclosure

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Commercial organizations

An independent scientific steering committee composed of clinicians and scientists from each trial region was responsible for the design, conduct, data analysis and manuscript preparation of this study. The sponsor was not involved in the study design, follow-up data acquisition, data analyses or writing of the manuscript. During the course of this trial, the sponsor provided the trial regions with HMP devices and disposables free of charge and operated a 24-h helpline that could be consulted in case of perfusion device-related technical issues.

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