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Oxygenated End-Hypothermic Machine Perfusion in Expanded Criteria Donor Kidney Transplant
A Randomized Clinical Trial

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IMPORTANCE Continuous hypothermic machine perfusion during organ preservation has a beneficial effect on graft function and survival in kidney transplant when compared with static cold storage (SCS).

OBJECTIVE To compare the effect of short-term oxygenated hypothermic machine perfusion preservation (end-HMPO_2) after SCS vs SCS alone on 1-year graft survival in expanded criteria donor kidneys from donors who are brain dead.

DESIGN, SETTING, AND PARTICIPANTS In a prospective, randomized, multicenter trial, kidneys from expanded criteria donors were randomized to either SCS alone or SCS followed by end-HMPO_2 prior to implantation with a minimum machine perfusion time of 120 minutes. Kidneys were randomized between January 2015 and May 2018, and analysis began May 2019. Analysis was intention to treat.

INTERVENTIONS On randomization and before implantation, deceased donor kidneys were either kept on SCS or placed on HMPO_2.

MAIN OUTCOME AND MEASURES Primary end point was 1-year graft survival, with delayed graft function, primary nonfunction, acute rejection, estimated glomerular filtration rate, and patient survival as secondary end points.

RESULTS Centers in 5 European countries randomized 305 kidneys (median [range] donor age, 64 [50-84] years), of which 262 kidneys (127 [48.5%] in the end-HMPO_2 group vs 135 [51.5%] in the SCS group) were successfully transplanted. Median (range) cold ischemia time was 13.2 (5.1-28.7) hours in the end-HMPO_2 group and 12.9 (4-29.2) hours in the SCS group; median (range) duration in the end-HMPO_2 group was 4.7 (0.8-17.1) hours. One-year graft survival was 92.1% (n = 117) in the end-HMPO_2 group vs 93.3% (n = 126) in the SCS group (95% CI, −7.5 to 5.1; P = .71). The secondary end point analysis showed no significant between-group differences for delayed graft function, primary nonfunction, estimated glomerular filtration rate, and acute rejection.

CONCLUSIONS AND RELEVANCE Reconditioning of expanded criteria donor kidneys from donors who are brain dead using end-HMPO_2 after SCS does not improve graft survival or function compared with SCS alone. This study is underpowered owing to the high overall graft survival rate, limiting interpretation.

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Kidney transplant has become the preferred standard form of treatment for most patients with end-stage kidney disease.[1,2] To cope with the growing demand for grafts in the setting of kidney transplant, nowadays most centers will accept kidneys that are retrieved from older and higher-risk donors with multiple comorbidities, the so-called expanded criteria donors (ECDs), in an attempt to shorten waiting times in transplant for patients with end-stage kidney disease.[3-5] While using grafts from ECDs may address the organ shortage, this policy has the secondary consequence of a higher rate of complications, such as primary nonfunction or delayed graft function (DGF) of the transplanted kidney and ultimately inferior long-term graft survival, when compared with organs retrieved from standard criteria donors.[5-8] On the other hand, and despite the overall risk for graft failure is approximately 1.7-times higher in ECD kidneys, the use and transplant of these higher-risk kidneys still offers a significant survival benefit for recipients compared with those patients continuing to receive dialysis.[9]

In the past decade, it has become clear that reduction of ischemia-reperfusion injury and optimized organ preservation are key in successful transplants, allowing better immediate function and prolonged graft survival, especially of more compromised donor organs.[10-12] To date, 2 methods of donor kidney preservation are widely used in the clinical setting of kidney transplant. First, the method of static cold storage (SCS), in which the kidney is flushed at time of procurement using a preservation solution, then submerged in cold preservation solution and kept on melting ice during transport to the recipient center until transplant. Second is the technique of hypothermic machine perfusion (HMP), which is a dynamic preservation method, in which the donor kidney is perfused with a cold machine perfusion solution using a device. SCS has remained the preferred technique worldwide owing to its perceived simplicity and low cost, although HMP has attracted considerable attention in the past decade and has led to changes in policy in some countries since clinical trials and multiple registry analyses found that function and outcomes for recipients are superior for HMP compared with SCS.[13,14] In 2009, our group was the first to report that continuous HMP of the donor kidney starting immediately after organ procurement until implantation in the recipient is associated with a reduced risk of DGF and improved kidney graft survival in the first year after transplant.[12] In addition, a subsequent subgroup analysis concerned kidneys from ECD donors after brain death and demonstrated a significantly reduced risk of DGF and higher 1-year graft survival in machine-perfused kidneys compared with cold-stored kidneys.[15]

More recently, a single-center study using SCS followed by a short-term preimplantation period of HMP (ie, end-HMP) suggested that end-HMP was able to reduce the risk for DGF in ECD kidneys. However, no clinical trial data have been available to provide evidence of a potential benefit.[16] This evidence is highly relevant because if the simplification by omitting the logistic complexity of sending out devices to donor hospitals could be confirmed, this would improve patient outcomes and cost-effectiveness.

Key Points

Question Does preimplantation short-term reconditioning of kidney grafts using oxygenated hypothermic machine perfusion for at least 2 hours after an initial period of static cold storage lead to an improvement of 1-year graft survival in kidneys retrieved from expanded criteria donors?

Findings In this randomized clinical trial of 305 kidneys, 1-year graft survival was equal between kidneys that were machine perfused following static cold storage and kidneys that remained on static cold storage prior to implantation without oxygenated hypothermic machine perfusion.

Meaning These findings suggest that the use of oxygenated hypothermic machine perfusion prior to implantation and following a period of static cold storage does not improve graft survival or kidney function in kidneys retrieved from donors who are brain dead meeting the expanded donor criteria.

To gain better insight and clarify the effectiveness of the combination strategy of SCS followed by short-term HMP immediately prior to transplant as well as to provide evidence of whether the addition of oxygen during HMP as an optimized form of perfusion enhances outcomes in kidney transplant, we have now compared the current standard SCS preservation of donor kidneys with the regimen propagated by many transplant centers to combine SCS and HMP including oxygenation in a randomized clinical trial using ECD kidneys after brain death.

Methods

Trial Design

This investigator-led, prospective, randomized, parallel group, participant-blinded, controlled, multicenter, superiority trial included 10 kidney transplant centers in 5 European countries (Belgium, Germany, Hungary, the Netherlands, and United Kingdom). Approval of the trial protocol, amendments, as well as consent forms was obtained from national research ethics committees for each trial country. The trial protocol and statistical analysis plan are available in Supplement 1. On arrival of the kidney at the trial center (eAppendix in Supplement 2), patients gave written informed consent for participation in the trial and use of follow-up data. The trial was funded by the European Union 7th Framework Programme (Theme Health.2012.1.4-1, grant agreement 305934) and conducted by the Consortium for Organ Preservation in Europe.

Eligibility and Consent

Kidneys fulfilling the ECD criteria as defined by the United Network for Organ Sharing were eligible for enrollment: a kidney donated for transplant from a donor who was brain dead and older than 60 years or from a donor older than 50 years with 2 of the following: a history of hypertension, the most recent serum creatinine 1.5 mg/dL or more (to convert to micromoles per liter, multiply by 88.4), or death resulting from an cerebrovascular injury.[3] Recipients were at least 18

years old and wait-listed for kidney-only transplant with either Eurotransplant or the National Health Service Blood and Transplant in one of the trial centers for a first or retransplant of a kidney. Participants received written and verbal information about the trial in advance while on the waiting list.

Randomization

Kidneys were randomized between January 2015 and May 2018. Once an eligible kidney had been allocated to a recipient in a trial center, written consent was obtained from the recipient of the organ. Using an online randomization tool, the kidney was randomly assigned to either standard SCS or the combination of SCS with subsequent oxygenated HMP after arrival at the recipient center (end-HMPO_2) with a 1:1 allocation per a computer-generated randomization scheme with random permuted block lengths, stratified by trial center.

SCS Group

All kidneys were placed on SCS following retrieval at the donor site and transported to the recipient center. Once a kidney was randomized to SCS on arrival, the kidney remained on SCS and transplanted according to standard local practice.

End-HMPO_2 Group

If the static cold-stored kidney was randomized for machine perfusion (end-HMPO_2) after arrival at the recipient transplant center, the kidney was first prepared for implantation and then placed on the Kidney Assist transport device (Organ Assist BV) to be perfused with actively oxygenated University of Wisconsin Machine Perfusion Solution (Bridge to Life) at 1 °C to 4 °C for at least 120 minutes with a set perfusion pressure of 25 mm Hg until implantation into the recipient. Oxygen (100%) was supplemented at 100 mL/min, resulting in partial oxygen tensions of about 600 mm Hg in the perfusate.

Trial End Points

The primary end point of the study was defined as the difference in 1-year graft survival between the 2 treatment arms. Secondary end points included (1) DGF (the need for dialysis within the first 7 days after transplant and preceding the return of kidney function); (2) kidney function at day 7 and months 3, 6, and 12 after transplant, determined by the estimated glomerular filtration rate (measured using the 4-variable Modification of Diet in Renal Disease formula[17] and Chronic Kidney Disease Epidemiology Collaboration equation[18]); (3) functional DGF (the absence of a decrease in serum creatinine levels of at least 10% each day for 3 consecutive days within the first week after transplant, not including patients with biopsy-proven acute rejection or established calcineurin inhibitor toxicity); (4) primary nonfunction (defined as the continued need for dialysis until 3 months after transplant); (5) patient and (death-censored) graft survival; and (6) biopsy-proven acute rejection episodes up to 12 months after transplant. Graft loss was defined as the return to permanent dialysis or the need for retransplant.

Statistical Analysis

In our published previous analysis, we reported that use of HMP vs SCS increases 1-year graft survival for ECD kidneys from 80% to 92%.[15] For this trial to have a power of 80% with type I error (α) of 5% in a 2-sided statistical model, the required sample size to detect an improvement in 1-year graft survival from 80% to 92% was 262 kidneys in total, with 131 kidneys in each treatment arm.

Results are reported as an intention-to-treat analysis comparing intervention (end-HMPO_2) against control (SCS) for the primary outcome and all secondary outcomes. Kidneys randomized but not transplanted to the consented recipients were excluded from the analysis. Differences between treatment groups are presented as mean and standard deviation, median and range, or percentages. Outcomes are reported with 95% CIs and 2-sided *P* values. *P* values less than .05 were regarded as statistically significant.

The treatment effect is described as absolute difference in proportions as well as odds ratio, which is presented together with confidence intervals. Kaplan-Meier curves and log-rank tests were performed for the assessment of time to graft failure and patient death. Any missing creatinine values within the first week of transplant have been imputed using linear interpolation. Here, a total of 10 values were imputed. For statistical analysis, SAS statistical software version 9.4 (SAS Institute) and Stata version 15 (StataCorp) were used. Kidney donor risk index as well as kidney donor profile index were calculated using the respective formula and mapping table provided by Organ Procurement and Transplantation Network.[19,20]

No interim analyses of end points were carried out. At regular intervals, an independent data monitoring committee reviewed recruitment, accruing data and confidential safety reports. Transplant participants were blinded, and care clinicians were not blinded to the treatment arm. Analysis began May 2019.

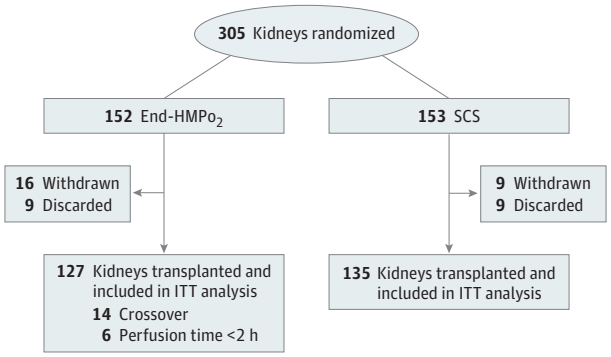
Results

Recruitment

A total of 305 kidneys were randomized, with 53 subsequently being excluded (**Figure 1**). A similar discard and withdrawal rate between the 2 trial arms resulted in 127 end-HMPO_2 and 135 SCS kidneys available for primary and secondary outcome analysis (Figure 1; eTable 1 in Supplement 2). Fourteen kidneys of the end-HMPO_2 group were cold stored because machine perfusion was found to be impossible (eTable 2 in Supplement 2), and 6 kidneys received machine perfusion for less than 2 hours (for logistical reasons). All these organs are included in the end-HMPO_2 arm on an intention-to-treat basis.

Donor and recipient characteristics were well balanced in both treatment arms (**Table 1**). To summarize donor factors that influence transplant outcome and the relative risk for graft failure after transplant, we calculated both the kidney donor risk index and kidney donor profile index for the transplanted kidneys. In our trial, the kidney donor risk index and the kidney donor profile index were comparable among treatment arms.

Figure 1. Enrollment of Kidneys in the Trial



end-HMPO$_2$, hypothermic machine perfusion preservation; ITT, intention-to-treat; SCS, static cold storage.

Cold ischemia time refers to the total preservation time in both groups. In the end-HMPO$_2$ treatment arm, the median SCS time prior to placement on the perfusion device was 7.97 hours, followed by a median of 4.67 hours of hypothermic oxygenated machine perfusion.

Graft Survival

The primary end point of this trial was graft survival at 1 year after transplant. In the end-HMPO$_2$ group, 92.1% (117 of 127) of kidney grafts were functioning at 1 year, which is similar to 93.3% (126 of 135) of functioning grafts in the control group (SCS) (95% CI, −7.5 to 5.1; P = .71) (**Table 2**). Death-censored graft survival was similar in both groups at 1 year (**Figure 2**). Graft losses were due to immunological reasons (n = 3), viral or bacterial infection (n = 3), arterial or venous thrombosis and complications (n = 5), or other reasons (n = 8) (eTable 3 in Supplement 2). To account for the number of crossovers, we performed a per-protocol analysis, which also did not yield any significant difference in terms of graft survival (eTable 4 in Supplement 2).

Kidney Function

Estimated GFR was comparable between both treatment groups at all assessed time points and showed a steady increase for both groups over time until 1 year after transplant (Table 2; eTable 5 in Supplement 2). The rates of DGF were numerically lower within the end-HMPO$_2$ group compared with the SCS group (30 [23.6%] vs 38 [28.1%]); however, this did not reach statistical significance (95% CI, −15.1 to 6.1; P = .40). Similar results were also found for occurrence of functional DGF, with lower rates in the end-HMPO$_2$ group vs the SCS group (76 [59.8%] vs 93 [68.9%]; 95% CI, −22.5 to 2.7; P = .13). Rates of primary nonfunction were the same in both groups (Table 2).

Other Secondary End Points

Rates of patient death were higher in the end-HMPO$_2$ group compared with the control group (9 [7.1%] vs 2 [1.5%]; 95% CI, 0.07-10.5; P = .03) (Table 2; eFigure 1 in Supplement 2). Reasons for death over the course of 12 months were myocardial infarction (n = 5), wound infection and subsequent sepsis (n = 3), multiorgan failure (n = 1), unintentional cerebrovascular injury (n = 1), and malignant neoplasms (n = 1) (eTable 6 in Supplement 2). Patients in the end-HMPO$_2$ group who did not survive died with a functioning graft, except for 1 patient. Rates of biopsy-proven acute rejection did not show a significant difference between patients of the end-HMPO$_2$ and SCS groups (Table 2). The rates of patients for whom at least 1 adverse event was reported were similar in both arms (62 [54.9%] in the end-HMPO$_2$ group vs 99 [66.4%] in the SCS group; 95% CI, −23.4 to 0.03) (eTable 7 in Supplement 2). The incidence of at least 1 serious adverse event was also similar in both treatment groups (76 [67.3%] in the end-HMPO$_2$ group vs 93 [62.4%] in the SCS group; 95% CI, −6.8 to 16.5), with none of the serious adverse events being attributable to the storage method (eTable 8 in Supplement 2).

Further exploratory analysis showed that when stratifying graft failure according to study group and the incidence of DGF, once DGF occurred, graft survival was almost identical between kidneys that were either cold stored or machine perfused (eFigure 2 in Supplement 2).

For kidneys that were randomized to the end-HMPO$_2$ group, the duration of machine perfusion did not correlate with kidney function at 12 months (eFigure 3 in the Supplement 2). This was also shown for the length of cold storage time prior to machine perfusion, in which the duration of storage time in general did not show a significant effect on kidney function at 12 months after transplant (eFigure 4 in Supplement 2). The incidence of DGF as well as biopsy-proven acute rejection episodes were also not affected by the length of end-HMPO$_2$ or previous SCS time (eTable 9 in Supplement 2). Extreme hours of machine preservation (ie, >10 hours of machine preservation) did not show differences in outcome (eTable 10 in Supplement 2). For a detailed description of number of kidneys per length of preservation per trial arm, see eTable 11 in Supplement 2.

Discussion

In the past decades, many transplant centers have adopted the policy of placing donor kidneys on the pump using HMP for a few hours immediately prior to implantation and after a period of SCS during transport to the recipient center.[16] To our knowledge, this is the first multicenter randomized clinical trial to evaluate this often-applied strategy that in general is perceived as beneficial and enhancing donor kidney function.

The results of this multicenter trial do not show any improvement in 1-year graft survival or function when higher-risk ECD kidney grafts are first statically cold stored and then exposed to oxygenated HMP prior to implantation. This finding is in contrast to the widespread clinical assumption on the superiority of continuous HMP over SCS in donors with brain death and donation after cardiac death donor kidneys.[16,21,22] There are a number of potential explanations for this different outcome we would like to summarize.

First, in our previous report, an improvement of graft survival by 12.1% (from 80.2% to 92.3%) was observed when ECD kidneys were exposed to (nonoxygenated, continuous) HMP

Table 1. Donor, Recipient, and Transplant Characteristics

Characteristic	No. (%)		
	End-HMPO_2	SCS	Total
Donor			
No.	152	153	305
Age, median (range), y	64.0 (50.0-82.0)	65.0 (51.0-84.0)	64.0 (50.0-84.0)
Sex			
Female	67 (44.1)	86 (56.2)	153 (50.2)
Male	73 (48.0)	60 (39.2)	133 (43.6)
Missing	12 (7.9)	7 (4.6)	19 (6.2)
BMI, median (range)	26.3 (17.6-47.8)	26.2 (18.4-56.2)	26.2 (17.6-56.2)
Cause of death			
Unintentional cerebrovascular injury	95 (69.9)	114 (78.1)	209 (74.1)
Trauma	20 (14.7)	11 (7.5)	31 (11.0)
Hypoxia	12 (8.8)	15 (10.3)	27 (9.6)
Other	9 (6.6)	6 (4.1)	15 (5.3)
Arterial hypertension	79 (58.1)	98 (67.1)	177 (62.8)
Diabetes	14 (10.3)	26 (17.8)	40 (14.2)
Creatinine at admission, median (range), mg/dL	0.81 (0.37-2.12)	0.83 (0.24-2.1)	0.81 (0.24-2.12)
Last creatinine, median (range), mg/dL	0.86 (0.32-5.69)	0.79 (0.32-3.4)	0.82 (0.32-5.69)
Kidney donor risk index			
All trial sites	1.48 (1.1-2.5)	1.51 (1.1-2.6)	1.50 (1.1-2.6)
Missing	25 (8.2)		
Kidney donor profile index			
All trial sites, median (range), %	84 (50-100)	86 (60-100)	85 (50-100)
Missing	25 (8.2)		
Recipient			
No.	127	135	262
Age, median (range), y	63.8 (30.7-81.2)	60.9 (22.0-76.8)	63.0 (22.0-81.2)
Sex			
Female	46 (36.2)	63 (46.7)	109 (41.6)
Male	81 (63.8)	72 (53.3)	153 (58.4)
Kidney disease			
Congenital, rare familial, metabolic disorders	3 (2.4)	2 (1.5)	5 (1.9)
Diabetic nephropathy	24 (18.9)	16 (11.9)	40 (15.3)
Glomerular diseases	18 (14.2)	20 (14.8)	38 (14.5)
Hypertensive nephroangiosclerosis	14 (11.0)	8 (5.9)	22 (8.4)
Polycystic kidney disease	20 (15.7)	19 (14.1)	39 (14.9)
Renovascular and other kidney vascular diseases	1 (0.8)	7 (5.2)	8 (3.1)
Tubular and interstitial diseases	10 (7.9)	5 (3.7)	15 (5.7)
Uncertain cause	1 (0.8)	10 (7.4)	11 (4.2)
Other	36 (28.3)	48 (35.6)	84 (32.1)
No. of previous transplants			
0	108 (85.0)	110 (81.5)	218 (83.2)
1	15 (11.8)	24 (17.8)	39 (14.9)
2	2 (1.6)	1 (0.7)	3 (1.1)
3	2 (1.6)	0 (0.0)	2 (0.8)
Transplant			
No.	113	149	262
Cold ischemic time, median (range), h	13.2 (5.1-28.7)	12.9 (4.0-29.2)	13.0 (4.0-29.2)
Missing	5 (1.9)	NA	NA
Warm ischemic time, min	34.0 (17.0-92.0)	32.0 (11.0-80.0)	33.0 (11.0-92.0)
Missing	6 (2.3)	NA	NA
Cold storage time prior to machine perfusion, h	7.97 (2.0-28.4)	NA	NA
Total perfusion time, h	4.67 (0.8-17.1)	NA	NA
Kidneys perfused <2 h	5 (4.4)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); end-HMPO_2, hypothermic machine perfusion preservation; NA, not applicable; SCS, static cold storage.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

Table 2. Primary and Secondary End Points

Variable	No. (%)		Risk difference (95% CI)	*P* value
	End-HMPO_2 (n = 127)	SCS (n = 135)		
Primary end point				
Graft survival at 1 y	117 (92.1)	126 (93.3)	−1.2 (−7.5 to 5.1)	.71
Secondary end points				
Posttransplant estimated GFR, MDRD equation, mean (SD), mL/min/1.73m^2				
7 d	27.1 (16.2)	26.0 (17.6)	1.08 (−3.38 to 5.55)	.63
3 mo	38.1 (13.9)	39.8 (15.8)	−1.74 (−5.44 to 1.96)	.36
6 mo	38.0 (13.3)	39.6 (15.4)	−1.61 (−5.21 to 2.00)	.38
1 y	39.9 (14.4)	41.2 (17.1)	−1.31 (−5.36 to 2.75)	.53
Delayed graft function	30 (23.6)	38 (28.1)	−4.5 (−15.1 to 6.1)	.40
Functional delayed graft function	76 (59.8)	93 (68.9)	−9.9 (−22.5 to 2.7)	.13
Primary nonfunction	8 (6.3)	8 (5.9)	0.4 (−5.4 to 6.2)	.90
Patient death	9 (7.1)	2 (1.5)	5.6 (0.07 to 10.5)	.03[a]
Biopsy-proven acute rejection episodes	23 (18.1)	18 (13.3)	4.8 (−4.0 to 13.6)	.29

Abbreviations: end-HMPO_2, hypothermic machine perfusion preservation; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCS, static cold storage.

[a] Fisher exact test was used owing to low event rate.

instead of SCS.[15] The data presented in this recent trial show similar results of graft survival for SCS and end-HMPO_2, which exceed 92% in both arms of the trial. This implies that in the past years in the same clinical environment and centers, a substantial improvement of graft survival has occurred compared with our initial publication dating back to 2011.[15] Exploring the reasons for improved graft survival at this stage requires much larger sample sizes than the numbers included and on which this analysis is based. A possible trial-specific influencing factor could be the donor age limit that was set in this trial to be 85 years, which was not defined in our underlying studies. Also, only kidneys that were able to be placed on pump were ultimately perfused via end-HMPO_2. Extreme anatomical variants or the mere fact of not achieving a perfect perfusion circuit were reasons to not place graft on the perfusion machine. Immunosuppression was documented from all kidney transplant recipients and was similar in all trial sites. The immunosuppression regimen was consistent and comparable within the past decade, minimizing the likelihood as being attributable to the overall outcome of the trial.

Second, HMP has repeatedly been shown to decrease the incidence of DGF and improve graft survival up to years after transplant,[23-26] especially in donor kidneys 65 years and older,[27] when HMP was applied throughout the entire preservation period, ie, donor kidneys were perfused immediately after procurement and until transplant at the recipient center. End-HMPO_2 is a strategy that hopes to facilitate logistics during organ procurement and transportation, using valuable time on arrival at the recipient center to recondition a statically cold-stored organ, while avoiding prolongation of cold ischemia time.[28] However, the exact time when to start the reconditioning, and thus estimating the exact balance between the duration of kidneys being cold stored and then machine perfused with (or without) oxygen required to maintain the positive effect on transplant outcomes, is difficult to determine. Some experimental data suggest a beneficial effect of end-ischemic (nonoxygenated) machine perfusion of as little as 1 hour.[29] Other data in a porcine model by Hosgood et al[30] did not find functional improvement when kidneys were subjected to 4 hours of HMP following 14 hours of SCS vs 18 hours of SCS alone without HMP. In a 2017 study that reported paired analysis of ECD kidneys, (nonoxygenated) end-HMP with a mean preservation time of 6.15 hours proved to be an independent factor for the prevention of DGF, which in turn was the strongest risk factor for 1-year graft failure.[16] In our current trial, a mandated minimum machine preservation time of 2 hours and a mean preservation time of 4.67 hours using end-HMPO_2 did not improve clinical outcomes after transplant, suggesting that either a longer period of oxygenated HMP or an earlier supply of oxygen and/or HMP is required to maintain a clinically relevant improved outcome. Further in-depth analysis of our cohort regarding the balance of SCS and HMP did not reveal any possible improvement in graft survival, not even in kidneys that were perfused for the longest time after a relatively shorter period of SCS. The accurate timing of HMP administration either at the beginning (preconditioning) or at the end (reconditioning) can be discussed. In parallel to this trial in ECD kidney transplant, another prospective randomized clinical trial by Consortium for Organ Preservation in Europe has directly compared continuous oxygenated vs nonoxygenated HMP in paired donor kidneys from the moment of procurement until implantation.[31] This study found that prolonged oxygenated HMP provides significantly better results in donation after circulatory death kidneys compared with standard HMP, showing a lower rate of graft failure, reduction in incidence of acute rejection, and better estimated glomerular filtration rate at 12 months after kidney transplant.[32]

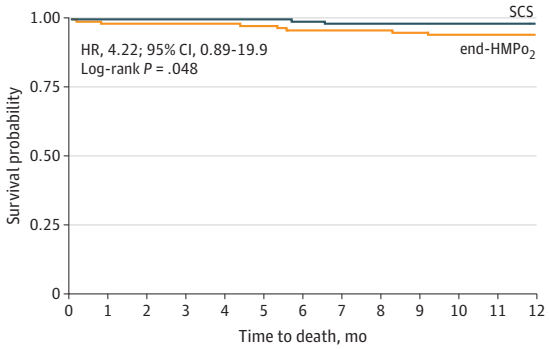
In concordance with those results, recent experimental analyses have shown that oxygenation during HMP increases kidney flow during HMP preservation and suggest that an early application of oxygenated HMP may be a more effective method than end-HMPO_2.[33,34] In addition, it remains unclear whether an initial potentially more damaging period of SCS can be overcome by offering a subsequent shorter or longer duration of (oxygenated) HMP. Another aspect of HMP is the possible assessment of perfusion characteristics, such as kidney

resistance, that has been found to predict DGF, when assessed at the end of HMP.[35] In our study, we have observed a decrease of kidney resistance and subsequent increase in kidney artery flow during the perfusion period (data not shown), and the presence or absence of any correlation with clinical outcome has to be investigated.

While cold storage is currently the most widely applied technique in organ preservation, a brief period of normothermic machine perfusion has been increasingly tested in an experimental setting. By choosing normothermic conditions, especially in higher-risk donors, it is thought to avoid cold ischemic injury and allow a better assessment of organ viability.[36] While a first trial in a donation after circulatory death setting comparing SCS alone with 1-hour end-normothermic machine perfusion immediately prior to transplant after SCS is underway and results have to be evaluated (ISRCTN15821205), current experimental data using oxygenated end-HMP after prior HMP (and without any SCS) have shown that this combination can improve early graft function.[33] First-in-man data on controlled rewarming of a cold-stored kidney graft have recently shown good results in a clinical setting.[37]

This international clinical trial aimed to increase insight on the question of relevance and if so, on duration and initiation of oxygenated HMP when following SCS preservation in kidney transplant, which is widely perceived as beneficial. Although this study is statistically underpowered owing to the improved graft survival rates achieved today in this high-risk group of ECD kidneys, we have failed to find any clinically beneficial effect by hypothermically machine perfusing donor kidneys for a brief period including oxygenation in the recipient center after a prior prolonged period of SCS preservation. Our current data do not support the use of a noncontinuous, brief period of $HMPO_2$ placed at the final stage of organ preservation in ECD kidneys, which appears to be clinically ineffective while generating additional cost.

Figure 2. Kaplan-Meier Curve for Death-Censored Graft Survival



No. at risk

SCS	135	134	134	134	133	132	130	129	129	129	129	120	72
end-$HMPO_2$	127	124	124	124	123	122	119	119	119	118	117	112	78

end-$HMPO_2$, hypothermic machine perfusion preservation; HR, hazard ratio; SCS, static cold storage.

Limitations

The baseline assumption of 80.2% 1-year graft survival in ECD kidneys has been exceeded by far in the control group of the present study. This study is statistically underpowered owing to the improved graft survival rates achieved today in comparison with clinical trial data used for the statistical analysis plan.

Conclusions

Reconditioning of higher-risk ECD kidneys from donors after brain death using short-term oxygenated HMP immediately prior to transplant after a period of SCS does not lead to improved graft survival or graft function when compared with simple SCS alone.

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