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Hypothermic Machine Perfusion as a National Standard Preservation Method for Deceased Donor Kidneys

Aukje Brat, MD,¹ Kirsten M. de Vries, MSc,² Ernst W. E. van Heurn, MD, PhD,³ Volkert A. L. Huurman, MD, PhD,⁴ Wim de Jongh, BSc,⁵ Henri G. D. Leuvenink, PhD,¹ Arjan D. van Zuijlen, MD, PhD,⁶ Bernadette J. J. M. Haase-Kromwijk, MSc,² Jeroen de Jonge, MD, PhD,⁷ Stefan P. Berger, MD, PhD,⁸ and Sijbrand H. Hofker, MD¹

Background. Recently, continuous nonoxygenated hypothermic machine perfusion (HMP) has been implemented as standard preservation method for deceased donor kidneys in the Netherlands. This study was designed to assess the effect of the implementation of HMP on early outcomes after transplantation. **Methods.** Kidneys donated in the Netherlands in 2016 and 2017 were intended to be preserved by HMP. A historical cohort (2010–2014) preserved by static cold storage was chosen as the control group. Primary outcome was delayed graft function (DGF). Additional analyses were performed on safety, graft function, and survival up until 2 y after transplantation. **Results.** Data were collected on 2493 kidneys. Analyses showed significantly more donation after circulatory death, preemptive transplantation, and retransplants in the project cohort. Of the 681 kidneys that were transplanted during the project, 81% were preserved by HMP. No kidneys were discarded due to HMP-related complications. DGF occurred in 38.2% of the project cohort versus 43.7% of the historical cohort ($P < 0.001$), with a significantly shorter duration within the project cohort (7 versus 9 d, $P = 0.003$). Multivariate regression analysis showed an odds ratio of 0.69 (95% confidence interval, 0.553–0.855) for the risk of DGF when using HMP compared with cold storage ($P = 0.001$). There was no significant difference in kidney function, graft survival, and recipient survival up until 2 y posttransplantation. **Conclusions.** This study showed that HMP as a standard preservation method for deceased donor kidneys is safe and feasible. HMP was associated with a significant reduction of DGF.

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INTRODUCTION

Organ preservation is essential to enable kidney transplantation, especially in situations where organs are shared, such as in the Eurotransplant region. For many years, static cold storage (CS), by “simply” submerging the donated kidney in a preservation solution at 0 °C–4 °C, provided a

safe way to preserve the kidney.^{1–3} The persisting demand for transplantable organs urged transplant professionals to expand the donor pool, especially for older and more comorbid recipients whose organs are preferably transplanted early as opposed to waiting for a better quality organ.^{4,6} This urge has, in part, been met by utilization

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W.d.J., and A.D.v.Z. participated in research design, performance of the research and review of the article. H.G.D.L. participated in research design, writing of the article, data analysis, and review of the article. B.J.J.M.H.-K. provided governance oversight to ensure the study adhered to all regulatory requirements and participated in review of the article. J.d.J. and S.P.B. provided governance oversight to ensure the study adhered to all regulatory requirements and participated in performance of the research and review of the article.

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of donation after circulatory death (DCD) donors and expanded criteria donors (ECD). However, with the use of these more vulnerable kidneys, the quest for better preservation methods has resurfaced.

With technical improvements and much more compact devices, hypothermic machine perfusion (HMP) regained interest in better preservation of kidneys between donation and transplantation. Entering the 21st century, multiple studies reported decreased delayed graft function (DGF) rates and an increased graft survival using HMP compared with static CS, of which the short-term results were confirmed in a recent Cochrane systematic review.⁷⁻⁹

Despite growing evidence of the beneficial effects of HMP in kidney preservation, static CS remains the default practice in many countries as the mode of preservation for deceased donor kidneys. On incidental base, or based on a specific donor type such as the uncontrolled DCD donors in France, kidneys are preserved by HMP, but no country has implemented HMP as standard care for the preservation of all types of deceased donor kidneys.

Based on the available evidence, the Netherlands started in 2016 a 2-y project to implement continuous nonoxygenated HMP as standard care for all types of deceased donor kidneys. The project was executed and monitored by a workgroup consisting of transplant professionals from different transplant centers and the Dutch Transplant Foundation.

Here we present the evaluation of the project. In particular, the retrospective assessment of the effect of the implementation of standard continuous nonoxygenated HMP started directly after organ retrieval up until transplantation compared with a historical cohort of static CS preserved kidneys on posttransplantation outcome.

MATERIALS AND METHODS

Hypothermic Machine Perfusion

Between January 11, 2016, and December 31, 2017, all deceased donor kidneys were included in this study. Excluded from the standard perfusion protocol but included in this study were DCD donors aged ≥ 50 y donating both kidneys for transplantation that were included in the COPE COMPARE study protocol, comparing oxygenated with nonoxygenated HMP.¹⁰ This led to 72 kidneys within this study being preserved by oxygenated HMP. All remaining kidneys were applicable for continuous nonoxygenated HMP started directly after organ retrieval up until transplantation as the standard method of preservation within this project. For kidneys from juvenile deceased donors, consultation occurred between procuring and transplantation surgeon leading to the preservation mode that seemed most appropriate depending on age and physique of the donor and their recipient.

The kidneys were randomly assigned to either perfusion using the LifePort Kidney Transporter 1.1 (Organ Recovery Systems, Belgium) or the Kidney Assist-transport (Organ Assist, Groningen, the Netherlands), in which both devices were used for nonoxygenated perfusion. Kidneys were assigned to the devices per donor, with one kidney connected to one machine and the contralateral kidney placed on the other device. This assignment was changed if due to anatomy or logistics certain

kidneys would not have been perfused. Both machines use a pulsatile perfusion pattern that was set on a mean pressure of 25 mm Hg. Belzer University of Wisconsin machine perfusion solution (UW-MPS) (Bridge to Life, Columbia, SC) was used as the perfusion fluid, while University of Wisconsin cold storage (UW-CS) solution (Bridge to Life) was used for the flush out. CS in UW-CS solution was used as backup when HMP was not possible. The UW-CS solution was also the standard preservation solution for both flush out and CS in the historical cohort. If kidneys were foreseen to be transplanted outside the Netherlands, CS was applied unless HMP was requested by foreign transplant centers as agreed upon within the Eurotransplant region.

Data Collection

Data were collected from the Dutch Organ Transplantation Registry, a national database containing donor and transplantation data from all Dutch donors and recipients. The audit committee of the Dutch Transplant Foundation has approved the collection and analysis of data as described within this article. Only kidneys donated and transplanted in the Netherlands were included in this retrospective study. A historical cohort was selected, from January 1, 2010, to December 31, 2014, in comparison with the project cohort. Data were collected on donor, preservation, transplantation, and follow-up data until 1 y after transplantation.

Medical Effectiveness

The primary endpoint of this retrospective study was DGF, defined as the need for dialysis within 7 d posttransplantation. DGF was used to evaluate the short-term effect of the implementation of HMP as standard preservation method on outcome after renal transplantation. Next to DGF, duration of DGF, serum creatinine levels, and estimated glomerular filtration rate (eGFR), calculated by the Chronic Kidney Disease Epidemiology Collaboration equation, at 3 mo were analyzed to assess the short-term functional outcome. eGFR, graft and recipient survival, and rejection rates at 1 and 2 y posttransplantation were used as assessment tools to evaluate the longer-term effects of the implementation of HMP. Duration of DGF was calculated as the number of days from transplantation up until the last dialysis session in case of DGF. They were limited to 90 d after transplantation. An eGFR of 10 mL/min/1.72 m² or lower was considered graft failure. For the analyses of graft failure and eGFR or serum creatinine in the follow-up data, an eGFR of 10 was imputed for failed grafts together with the associated serum creatinine level based on the Chronic Kidney Disease Epidemiology Collaboration equation.

All analyses were initially performed as intention-to-treat analyses, comparing HMP with CS. In addition, a per-protocol analysis was performed with a selected project cohort of all the actual perfused kidneys comparing the aforementioned variables with the historical cohort.

DGF rates were also assessed per donor type of the donated kidneys, enabling univariate comparison between the historical cohort and the project cohort for (a) DBD and DCD donors, and (b) standard criteria donors and ECDs, DCD donors aged <50 y, and DCD donors aged

≥50 y. ECDs are characterized as DBD donors aged ≥60 y or ≥50 y with 2 of the following conditions: a history of hypertension, cerebrovascular cause of death, or a terminal measured serum creatinine >1.5 mg/dL.

Safety

To monitor safety throughout the project, a safety monitoring committee was appointed, consisting of 2 transplant surgeons and a transplant coordinator/policy officer of the Dutch Transplant Foundation. Incidents regarding the perfusion devices were reported and assessed by the committee and classified as an adverse device-related event (ADE) or a serious adverse device-related event (SADE), depending on the consequences for the donated kidney and its assigned recipient.

Logistics and Costs

A nationwide logistical service system was introduced to optimize use of available machines, transport, and installation of the perfusion machines to assist the procurement and transplant teams. To cover the country geographically, perfusion hubs were used in which trained professionals, called transplant technicians (TTs), specialized in preparing and handling of the perfusion devices were used. TTs were responsible for delivery and setup of the perfusion devices at the donor sites (there were approximately 88 potential donor sites in the Netherlands at that time) and collection from the 8 different transplant centers after the preservation period for servicing in the perfusion hub. Logistical procedures were continuously evaluated throughout the project to improve efficiency. The implementation project was financially covered by the Dutch health insurance companies and monitored by the Dutch Transplant Foundation.

Statistical Analysis

SPSS version 24 was used to perform all analyses. Continuous data, given as median (range), were compared using the Mann-Whitney U tests, whereas categorical data were compared between the 2 groups using chi-square tests. The impact of continuous nonoxygenated HMP as a standard preservation method on the risk of occurrence of DGF was calculated by a multivariate logistic regression model, correcting for confounding factors based on

literature. For the effect of the implementation of HMP on graft failure within 2 y after transplantation, a univariate Cox logistic regression analysis was performed. For all analyses, a *P* value <0.05 was considered statistically significant.

RESULTS

Overview and Demographics

Figure 1 shows the flowchart of all deceased donor kidneys in the 2 cohorts that were transplanted in the Netherlands. Of the 1518 potential donors who were reported within the historical cohort, 2403 kidneys were procured, of which 1812 (75.4%) were transplanted in the Netherlands, and transplantation follow-up data were collected. For the project cohort, 614 potential donors were reported, leading to the procurement of 934 kidneys, of which 681 (72.9%) were transplanted within the Netherlands. Compared with the number of reported kidneys, proportions of all transplanted kidneys (transplanted within the Netherlands and abroad) were similar between the historical and project cohort, respectively, 75.3% (2182 transplants out of 2897 reported kidneys) and 73.0% (826 transplants out of 1131 reported kidneys) (*P*=0.144). Of the kidneys transplanted in the Netherlands within the project cohort, 81.5% (555 kidneys) were preserved by HMP. As mentioned, 72 of these kidneys from donors aged ≥50 y were perfused with the addition of oxygen to the UW-MPS in the context of the COPE COMPARE study.

Of the 268 kidneys not preserved by HMP, most were cold stored due to a foreign recipient (47.0% [126 kidneys]). 18.3% (49 kidneys) due to anatomy and respectively 7.8% (21 kidneys) and 90% (24 kidneys) due to logistical reasons or at the request of the transplant center. Only 6.7% (18 kidneys) were not perfused due to device-related problems. For 11.2% (30 kidneys), the reason for placing them on ice is unknown. Of the kidneys that were not perfused due to anatomical difficulties, approximately in one quarter, the main reason for CS was atherosclerosis, one quarter was not connected due to patch size problems, one quarter due to multiple arteries, and in one quarter, the exact anatomical anomaly was not registered. For multiple kidneys, >1 of the aforementioned reasons was reported. When looking at all the kidneys donated in the

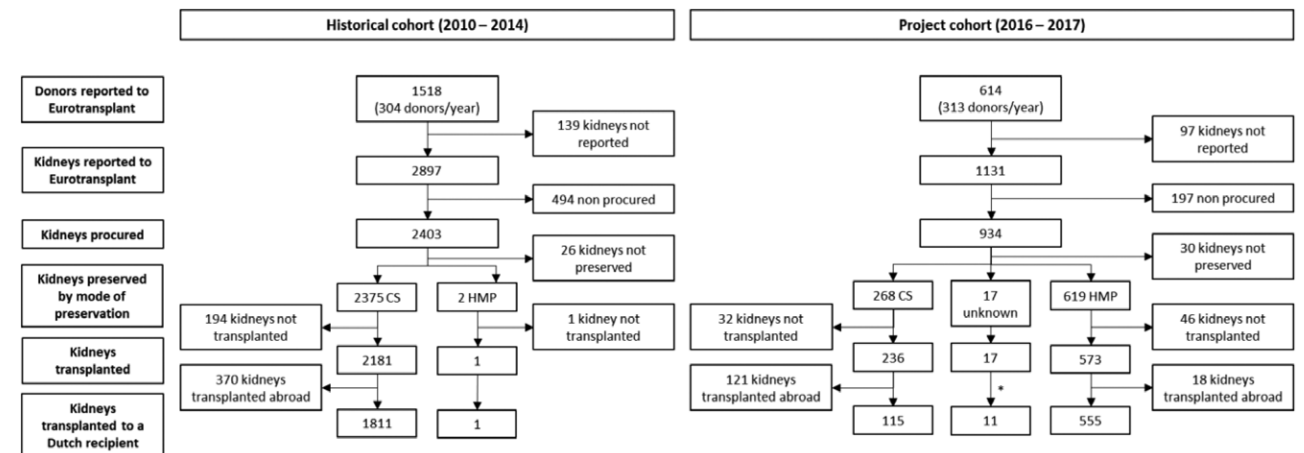


FIGURE 1. Flowchart of all deceased donor kidneys included in this study. CS, cold storage; HMP, hypothermic machine perfusion.

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project cohort, it shows that the more renal arteries present, the smaller the portion being perfused. Of the kidneys with only 1 artery, 86.3% (442) kidneys were preserved by HMP. When 2 arteries were present, this decreased to 74.6% (103), with 3 arteries to 55.6% (10), and both kidneys with 4 reported arteries were placed on ice. Analysis showed that kidneys with multiple arteries were significantly more often stored by CS than kidneys with just 1 artery ($P < 0.001$).

Table 1 shows a detailed comparison of donor, preservation, and recipient/transplantation characteristics between the historical and project cohort. The proportion of DCD kidneys in the project cohort was slightly larger than in

the historical cohort. No other significant differences were seen between the historical and project cohort when observing donor characteristics of transplanted kidneys.

For the preservation characteristics, a significant decrease in both warm ischemia time (only for DCD donors, defined as time from start of circulatory arrest to start cold flush) and cold ischemia time (CIT, defined as start of cold flush to start of anastomosis) was shown in the project cohort compared with the historical cohort. In contrast, anastomosis time increased significantly in time.

Recipient age was significantly higher in the project cohort compared with the historical cohort. In the project

TABLE 1.
Characteristics of donors and recipients, and the univariate differences between the historical cohort and project cohort

Variable	Historical cohort	Project cohort	P
Donor characteristics of reported donors			
Number reported donors	1518	614	
Age (y), median (range)	55 (0–85)	56 (0–87)	0.024*
Sex male, % (number)	56.1 (852)	54.7 (336)	0.587
Type of donation, % (number)			
After brain death	43.6 (662)	39.4 (242)	0.084
After circulatory death	56.4 (856)	60.6 (372)	–
Standard criteria	24.2 (368)	20.8 (128)	0.518
Expanded criteria	19.4 (294)	18.6 (114)	–
Terminal serum creatinine ($\mu\text{mol/L}$), median (range)	66 (3–1007)	66 (15–502)	0.371
Donor characteristics of transplanted kidneys in Dutch recipients			
Number transplanted kidneys in Dutch recipients	1812	681	
Age (y), median (range)	55 (7–82)	55 (2–84)	0.834
Sex male, % (number)	53.8 (975)	53.9 (367)	1.000
Type of donation, % (number)			
After brain death	46.3 (839)	39.6 (270)	0.003*
After circulatory death	53.7 (973)	60.4 (411)	–
Standard criteria	25.1 (455)	21.4 (146)	1.000
Expanded criteria	21.2 (384)	18.2 (124)	–
Terminal serum creatinine ($\mu\text{mol/L}$), median (range)	65 (3–411)	65 (29–426)	0.240
Preservation			
Number preserved kidneys	2377	904	
Static cold storage, % (number)	99.9 (2375)	29.6 (268)	<0.001*
Hypothermic machine perfusion, % (number)	0.1 (2)	68.5 (619)	<0.001*
Unknown, % (number)	0.0 (0)	1.9 (17)	
Ischemia times			
Number transplanted kidneys in the Netherlands	1812	681	
Warm ischemia time (min), median (range)	17 (0–66)	15 (0–54)	<0.001*
Total cold ischemia time (h), median (range)	14 (2–42)	12 (2–43)	<0.001*
Anastomosis time (min), median (range)	30 (10–105)	33 (3–153)	0.002*
Recipient characteristics			
Number of Dutch recipients	1812	681	
Age (y), median (range)	58 (2–81)	60 (3–82)	<0.001*
Sex male, % (number)	62.4 (1130)	60.5 (412)	0.466
Preemptive transplantation, % (number)	4.6 (84)	8.1 (55)	0.001*
Duration of pretransplantation dialysis (y), median (range)	3.4 (0.01–20.9)	2.4 (0.04–16.0)	<0.001*
Retransplants, % (number)	10.2 (185)	14.2 (97)	0.005*
Panel reactive antibody level, % (number)			0.009*
0–5%	93.2 (1688)	91.6 (624)	–
6–84%	5.8 (106)	6.3 (43)	–
≥85%	0.1 (2)	0.9 (6)	–
No HLA mismatches (A, B, or DR), % (number)	2.5 (45)	3.8 (26)	0.094

*P value indicating statistical significance <0.05.

cohort, significantly more preemptive transplantations were performed, whereas when excluding preemptive transplantations, the duration of dialysis before transplantation has significantly decreased from 3.4 to 2.4 y. The number of retransplantations and proportion of people in groups with higher panel reactive antibody levels showed a statistically significant increase in the project cohort. The number of HLA mismatches was similar.

Posttransplantation Results

Primary outcome was DGF, which was decreased in the project cohort as compared with the historical cohort (38.2% versus 43.7%, $P < 0.001$) as shown in Table 2. In addition, the duration of DGF decreased significantly, with a medium duration of 7 d posttransplantation within the project cohort against 9 d within the historical cohort ($P = 0.003$). Serum creatinine and eGFR values showed no significant differences at 3 mo and 1 and 2 y posttransplantation. Also, no significant differences were seen for graft and recipient survival up until 2 y posttransplantation.

Next to the intention to treat analyses, per-protocol analyses were performed, with only the HMP kidneys included in the project cohort (Table 2). Comparing this HMP-only project cohort with the historical cohort, DGF was decreased in the perfused kidney group (37.8% versus 43.7%, $P < 0.001$), with a significant decrease again in DGF duration (7 versus 9 d, $P = 0.005$). No significant functional or survival differences were seen after 3 mo and 1 and 2 y, with exemption of rejection rates 2 y posttransplantation (16.6% versus 13.1%, $P = 0.048$).

To adjust for the effect of different donor-, preservation-, and recipient-related variables on the results of the implementation of HMP as a standard preservation method, a multivariate regression analysis was performed.

The odds ratio for DGF was 0.69 (95% confidence interval, 0.553-0.855) for the project cohort with a P value of 0.001 favoring machine perfusion above the use of static CS. The included variables and results of this intention to treat analysis are shown in Table 3.

When specifying the occurrence of DGF for different types of deceased kidney donors (Figure 2), DBD donors showed a similar occurrence of DGF of 25.0% in the historical cohort compared with 22.2% in the project cohort ($P = 0.186$). Comparing the DCD donors within the historical and project cohort, DGF is present in 59.7% compared with 48.7%, respectively ($P < 0.001$). Further in-depth analysis of standard criteria donor, ECD, DCD <50 y, and DCD donors aged ≥ 50 y shows a numerical decline of DGF in all subgroups, with significant differences in both DCD subgroups ($P < 0.001$).

A univariate analysis was also performed for the effect of HMP as standard preservation mode on the risk of death-corrected graft failure 2 y after transplantation; this showed no significant difference (hazard ratio of 0.991 [95% confidence interval, 0.733-1.340] with a P value of 0.955).

Safety

While implementing continuous nonoxygenated HMP as a standard preservation method, 68 ADEs were reported within the first year. Six of these were defined as serious with a potential risk for the kidney due to the use of the devices. Of these 6 SADEs, 3 were related to temperature control, which led to a stricter regime of refilling ice after 18 h when CIT was prolonged. Two other events were related to changing perfusion flows that could not be clinically explained, after which the kidney was subjected to CS, and the devices were checked by their manufacturer. In the last SADEs, a device

TABLE 2.

Univariate analysis of differences in short-term and longer-term outcome posttransplantation between the historical and project cohort and the per-protocol project cohort

Outcome	Historical cohort (N=1812)	Project cohort intention to treat (N=681)	P	Project cohort per protocol (N=555)	P ^a
Short-term outcome					
DGF	43.7 (791)	38.2 (260)	<0.001*	37.8 (210)	<0.001*
Duration of DGF (d)	9 (0–90)	7 (0–90)	0.003*	7 (0–90)	0.005*
PNF	4.0 (73)	4.1 (28)	0.896	4.7 (26)	0.820
Serum creatinine 3 mo	145 (41–621)	141 (34–603)	0.329	143 (34–603)	0.775
eGFR 3 mo	44 (10–178)	43 (10–196)	0.924	43 (10–196)	0.512
1-y outcome					
Serum creatinine	136 (40–625)	136 (47–610)	0.751	138 (47–610)	0.944
eGFR	45 (10–180)	44 (10–141)	0.633	43 (10–141)	0.426
Rejection	12.4 (225)	15.0 (102)	0.105	15.3 (85)	0.089
Patient death	5.3 (96)	3.7 (25)	0.114	4.0 (22)	0.249
Graft failure ^b	6.8 (123)	7.3 (50)	0.692	7.9 (44)	0.411
2-y outcome					
Serum creatinine	136 (44–625)	136 (28–610)	0.213	140 (47–610)	0.384
eGFR	45 (10–170)	45 (10–147)	0.763	43 (10–136)	0.850
Rejection	13.1 (238)	16.2 (110)	0.061	16.6 (92)	0.048*
Patient death	9.2 (116)	6.9 (47)	0.086	7.4 (41)	0.227
Graft failure ^b	8.6 (155)	8.5 (58)	1.000	9.0 (50)	0.805

^aCompared with the historical cohort.

^bCorrected for patients who died with a functioning graft.

* P value indicating statistical significance < 0.05 .

DGF, delayed graft function; eGFR, estimated glomerular filtration rate; PNF, primary nonfunction.

TABLE 3.
Multivariate analysis of independent risk factors for development of delayed graft function posttransplantation

Variable	Odds ratio (95% CI)	P
Age donor	1.02 (1.015-1.030)	<0.001*
DCD vs DBD	5.33 (4.359-6.522)	<0.00*
CIT (h)	1.03 (1.015-1.053)	<0.00*
Standard care: HMP vs CS	0.69 (0.553-0.855)	0.00*
Age recipient	1.00 (0.991-1.006)	0.662
Panel reactive antibody level (%)	1.00 (0.993-1.012)	0.592
HLA mismatches (number)	1.00 (0.920-1.079)	0.921
Duration of pretransplant dialysis (y)	1.12 (1.072-1.176)	<0.00*
Retransplant vs first transplant	1.53 (1.105-2.118)	0.010*

*P value indicating statistical significance <0.05.

CI, confidence interval; CIT, cold ischemia time; CS, cold storage; DBD, donation after brain death; DCD, donation after circulatory death; HMP, hypothermic machine perfusion.

had been handled improperly during transport, leading to conversion to CS and more strict instructions on how to fixate the device during transport. The adverse events reported were primarily related to the use of the devices, were without clinical consequences, and solved within the same procedure. Examples are problems with de-airing the system, a kidney with multiple arteries that could not all be connected to the device, and parts that became accidentally nonsterile while setting up the device before connecting the kidney. For the purpose of the implementation process, the process was continuously being improved by analyses of all (serious) adverse events. This resulted in only 1 SADE occurring in the second year. The reported issue was due to fluid leakage of a disposable, leading to a change of the disposables and extra checks of the machine before transportation.

No SADEs led to the loss of a kidney for transplantation.

Logistics and Costs

The logistical service was adapted from the randomized controlled trial COPE COMPARE.¹⁰ In this RCT, only 2 perfusion hubs were operational to offer support at the donation and transplant sites. In March of 2017, the number of perfusion hubs was increased to 3, allowing a more efficient coverage of the country. Initially, both procuring and transplant teams were supported on-site by the TTs from the perfusion hubs. To reduce costs, local TTs were

introduced, being responsible for assisting the transplant team and returning the machines to the perfusion hub by regular courier service.

During the 2-y course of this project, costs were covered by the Dutch health insurance companies for the amount of 1.2 million euros per year. These costs can be separated into variable (€996 000.–) and fixed costs (€204 000.–). A total of 934 kidneys were procured, of which 619 were perfused by HMP, resulting in 573 transplanted kidneys. This means that within this project, the total HMP preservation costs per transplanted kidney were €4188.48.

DISCUSSION

Supported by numerous studies showing a beneficial effect of HMP on the risk of DGF and graft survival for deceased donor kidneys, the Netherlands is the first country worldwide to implement continuous nonoxygenated HMP starting directly after organ retrieval up until transplantation as standard mode of preservation for all types of deceased donor kidneys. Previous studies compared HMP against the current default practice of CS under strictly regulated research protocols. This is the first study evaluating HMP when used as standard mode of preservation on a national level in a clinical setting and confirming results shown earlier in randomized controlled trials.^{8,9}

When reviewing the inclusions within this study, both cohorts showed a comparable number of kidneys being reported per year. Of the 904 kidneys preserved within the project cohort, 68.5% were preserved by HMP, with 92.6% of these HMP preserved kidneys being transplanted in their allocated recipient. For the CS-preserved kidneys within the project cohort, 88.1% were transplanted. Proportions of transplantations between the historical and project cohort were otherwise similar. This might represent a beneficial effect of HMP but more likely reflects a selection bias at the donor site, with less qualitative kidneys being more prone to preservation by CS due to, for example, extensive arteriosclerosis and the subsequent difficulty to adapt the organ to the device. With similar transplantation rates between both cohorts, the implementation of HMP is not likely to have led to an increased acceptance of marginal kidneys. However, because this was an implementation of standard care, clinicians were not blinded, and although protocols did not change, we cannot exclude

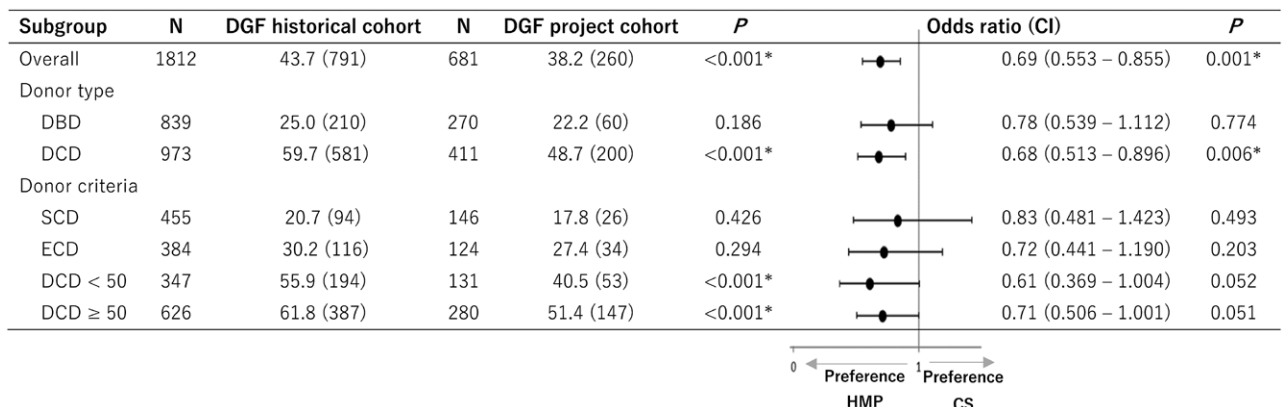


FIGURE 2. Forest plot of the effect of the implementation of nonoxygenated HMP on the prevalence on DGF in different donor subgroups. CI, confidence interval; CS, cold storage; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; ECD, expanded criteria donor; HMP, hypothermic machine perfusion; SCD, standard criteria donor.

individual changes in acceptance or posttransplantation care due to physician expectations toward the effect of machine perfusion.

Although the overall cohorts of reported donors showed a significant increase in donor age, the median age of transplanted kidneys was similar. The ongoing increase of the proportion of DCD donors is reflected within these cohorts. For the ischemia times, warm ischemia at the donor site was restricted, and beneficial shorter CITs were seen in the HMP group.^{11,12} Anastomosis time, however, slightly increased. Although we cannot retrieve the exact cause, we speculate that this increase is related to the increased recipient age and proportion with retransplants with related vascular complexity. The analysis of recipient characteristics of the project cohort compared with the historical cohort shows older recipients within the project cohort and illustrates trends toward increased occurrence of preemptive transplantation.¹³ Also, when pretransplant dialysis was inevitable, its duration was decreased. In the HMP cohort, a higher proportion of retransplants took place, and recipients had a higher overall panel reactive antibody level.

Comparison of DGF as primary outcome measurement shows a significantly decreased occurrence of DGF in the project cohort, comparable with the effect seen in the earlier machine perfusion trial of Moers et al.⁹ Multivariate analysis confirms the individual positive effect of the implementation of HMP on the reduction of the occurrence of DGF. In addition, the duration of DGF was also significantly reduced. As mentioned in the *Materials and Methods* of this evaluation, the COPE COMPARE trial was conducted in the same period, and 72 kidneys that were perfused with the addition of oxygen by the COPE COMPARE protocol were included in our analysis because the outcome of DGF was not different between the 2 study arms.¹⁰

One could question whether machine perfusion of all types of deceased donor kidneys is the most economic choice to make. In light of this discussion, different subgroups were analyzed on the basis of donor characteristics to compare DGF rates per group with their respective subgroup within the historical cohort. Although all project subgroups showed a lower DGF rate, only both DCD groups (< and ≥ 50 y of age) showed a significant difference in comparison with their historical counterpart. It could be that because the DBD kidneys already showed a lower DGF rate within the historical cohort, it is more difficult to reach a significant difference, also given their smaller sample size, although it is debatable whether the investment will be cost-efficient for DBD grafts. Groen et al¹⁴ showed that most financial benefits of HMP are not obtained by the decrease in DGF but in the improved graft survival, especially for ECD kidneys.¹⁵ Therefore, analysis of graft failure and function up until 2 y posttransplantation results was also performed. Despite research showing DGF as a negative prognostic factor for graft function and survival of both grafts and recipients,^{16,17} we could not show a significant impact of HMP on graft survival 2 y posttransplantation. A possible explanation for this discrepancy despite otherwise comparable results is that the relations between occurrence of DGF and long-term results are most pronounced for DBD kidneys, whereas the largest effect on DGF within this study was shown in the DCD group. Another factor in play could be the heterogeneity of the 2 cohorts and the significant differences in

donor and recipient characteristics with known opposite effects on outcome after transplantation.¹¹⁻¹³ Where randomized controlled trials can be designed to show (small) differences in outcomes that are infrequent, the variability within and between these cohorts could result in the fact that these groups are too small for analysis, and further follow-up of a larger cohort is required.

Because HMP proved a safe mode of preservation in which no kidneys were lost, HMP is continued in the Netherlands as standard care in all deceased donor renal grafts. From 2021 onward, all costs related to HMP of kidneys are no longer financed by a project financing structure but incorporated in the normal financing structure for kidney transplantation issued by the Ministry of Health.¹⁸

In many aspects, the results shown here are in line with the results shown in earlier machine perfusion trials, adding to the body of evidence for the use of continuous non-oxygenated HMP.^{8,9} However, the use of HMP as standard care does not only optimizes preservation but also gives opportunities to future therapeutic interventions. In line with the results from the COPE COMPARE, for example, addition of oxygen with the older DCD kidneys has already been implemented.¹⁰

In summary, continuous nonoxygenated HMP preservation as a nationwide standard mode of preservation of deceased donor kidneys was shown to be feasible and safe. As a result of this introduction, DGF rates and duration of DGF decreased significantly compared with a historical cohort.

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