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Normothermic machine perfusion of kidneys: current strategies and future perspectives

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Purpose of review
This review aims to summarize the latest original preclinical and clinical articles in the setting of normothermic machine perfusion (NMP) of kidney grafts.

Recent findings
Kidney NMP can be safely translated into the clinical routine and there is increasing evidence that NMP may be beneficial in graft preservation especially in marginal kidney grafts. Due to the near-physiological state during NMP, this technology may be used as an ex-vivo organ assessment and treatment platform. There are reports on the application of mesenchymal stromal/stem cells, multipotent adult progenitor cells and microRNA during kidney NMP, with first data indicating that these therapies indeed lead to a decrease in inflammatory response and kidney injury. Together with the demonstrated possibility of prolonged ex-vivo perfusion without significant graft damage, NMP could not only be used as a tool to perform preimplant graft assessment. Some evidence exists that it truly has the potential to be a platform to treat and repair injured kidney grafts, thereby significantly reducing the number of declined organs.

Summary
Kidney NMP is feasible and can potentially increase the donor pool not only by preimplant graft assessment, but also by ex-vivo graft treatment.

Keywords
ex-vivo treatment, kidney preservation, normothermic machine perfusion

INTRODUCTION

In view of the ongoing organ shortage, novel strategies to increase utility of available donor organs are desperately needed. In 2021, 40 092 patients were added to the waiting list for a kidney transplant in the USA, and only 24 670, just over half the number of additions, receive a life-saving transplant [1]. A similar picture is seen in Europe, where, in the same year in the Eurotransplant region, only 2796 patients underwent kidney transplantation, while 4962 patients were added to the waiting list [2].

Apart from utilization of marginal donors, namely expanded criteria donors (ECDs) and donors after circulatory death (DCDs), novel strategies to store, assess and eventually repair and regenerate organs have been developed to diminish the gap between organ demand and supply and assure satisfactory outcome when using those types of grafts, as they are known to have high rates of delayed graft function, acute rejection and are generally associated with inferior outcome [3–5].

Perfusion devices – to either perfuse the organ(s) *in vivo* or *ex vivo* [6▪,7,8–11] – are a central element of these ongoing efforts. Static cold storage (SCS) was long regarded as the gold standard for donor organ storage, being simple, cheap and effective, especially in the setting of standard criteria donor (SCD) organs [12]. Due to an increasing number of

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KEY POINTS

- Several groups using RBC and non-RBC-based perfusion solutions demonstrated clinical translatability and safety of normothermic machine perfusion.
- Longer periods (>2 h) of NMP may be necessary to facilitate measurable beneficial effects in perfused kidney grafts.
- Prolonged ex-vivo normothermic perfusion is feasible and could serve as a platform for organ assessment, treatment and recovery.
- Ex-vivo treatment using mesenchymal stromal/stem cells, multipotent adult progenitor cells and microRNA during kidney NMP is feasible and demonstrates beneficial effects.
- Larger systematic trials are needed to clarify the benefit of NMP for preservation of marginal kidney grafts.

marginal donor kidneys, hypothermic machine perfusion was reintroduced as a first alternative storage strategy that eventually proved to be superior to SCS [10,11].

In the last two decades, interest in normothermic machine perfusion (NMP) has seen a resurgence. In contrast to HMP, NMP allows graft preservation under near-physiological conditions [13–15]. It may thereby enable pretransplant graft assessment and could serve as reconditioning, regeneration and treatment platform [16].

This review aims to summarize recent developments in the field of NMP with an emphasis on evidence for NMP in preserving kidney grafts, as well as the current state of biomarkers, ex-situ treatment and clinical translation.

NORMOTHERMIC MACHINE PERFUSION AS AN ORGAN PRESERVATION MODALITY

Donors after circulatory death represent an ever-growing source of organs. According to the Global Observatory on Donation and Transplantation, they represent 17.1% of deceased donor organs in the European Union, 36.5% in the USA and 29.5% globally [17]. In 2021 in the Netherlands, DCD kidney grafts represent, with more than 80%, even the main organ source [2].

Due to a variable time of organ hypoperfusion and cardiocirculatory arrest, retrieved organs from DCD donors might present as inadequately perfused after retrieval [18,19]. To assess the potential of NMP in salvaging grafts subjected to prolonged warm ischemic injury, the Toronto Group explored the use of NMP in comparison to HMP and SCS in a 30 min warm ischemic time (WIT) porcine kidney auto-transplant model using 16 h preservation time [20]. This clinically relevant model demonstrated that NMP kidney grafts displayed a significantly improved recovery compared with HMP and especially SCS organs, evidenced by a reduced mean peak serum creatinine [NMP: 3.6 mg/dL {postoperative day (POD) 1} vs. HMP: 8.8 mg/dl (POD 2) vs. SCS: 12.9 mg/dl (POD 3)] and an increased creatinine clearance on POD 3 (NMP: 63.6 ml/min vs. HMP: 13.5 ml/min vs. SCS: 4.0 ml/min) [20].

A second study investigated the effect of NMP in the setting of prolonged WIT [21]. Using the same porcine auto-transplant model, the group subjected kidneys to 120 min of WIT followed by 8 h of SCS or NMP. Although all surviving animals (four out of six) in the SCS group developed significant renal dysfunction (SRD = POD 4 oliguria <500 ml/24 h with serum K^+ >6.0 mmol/l), only one out of five animals in the NMP group did and no animal was lost postoperatively. In contrast to SCS, NMP grafts displayed decreased peak serum creatinine levels, a higher creatinine clearance on POD 4 and a return of serum creatinine to baseline on POD 7 [21]. Together, these two preclinical studies seem to support a beneficial effect of NMP in an experimental model of warm ischemic injury and suggest its superiority compared with HMP after moderate WIT [20,21].

In 2021, the Toronto Group published a study comparing NMP with oxygenated HMP (oxHMP) and anoxic HMP. Grafts were retrieved following 30 min of WIT and subsequently pumped for 16 h followed by porcine auto-transplantation after contralateral nephrectomy [22▪▪]. In the 8 days of follow-up, the group demonstrated that NMP resulted in a significant reduction of preservation injury compared with oxHMP and HMP that translated in a reduced peak serum creatinine (NMP: 3.7 mg/dl vs. oxHMP: 8.8 mg/dl vs. HMP: 9.0 mg/dl), an increased creatinine clearance on POD 3 and lower neutrophil gelatinase-associated lipocalin (NGAL) ratios (urine NGAL/ urine creatinine; NMP: 0.5 vs. oxHMP: 1.4 vs. HMP: 1.8) [22▪▪].

The group from Imperial College London compared NMP (25 min WIT + 24 h CIT + 4 h NMP; autologous whole blood based perfusate) and HMP (25 min WIT + 24 h CIT + 4 h HMP) preserved porcine DCD grafts to SCS kidneys (28 h CIT) by an additional 2 h of NMP for graft assessment [23▪]. In contrast to the findings of the Toronto group, they demonstrated that HMP kidneys had higher urinary output (5.3 vs. 2.4 ml/min), oxygen consumption (22.7 vs. 11.8 ml/min) and perfusate flow

rates (46.2 vs. 26.2 ml/min) and lower apoptosis rates than kidneys after NMP [23▪].

Finally, the group from Aarhus explored the benefit from a short oxHMP duration (SCS 150 min + 90 min oxHMP using Belzer's Machine Perfusion Solution) compared with SCS (240 min) followed by NMP [2 h; red blood cell (RBC)-based] in a porcine DCD model (75 min WIT) [24]. oxHMP-preserved grafts maintained a significantly lower renal resistance, a higher mean renal blood flow and a higher oxygen consumption compared with SCS grafts during NMP. They concluded that oxHMP before NMP significantly improved initial perfusion haemodynamics [24].

To better understand the protective effect of NMP in DCD graft preservation, the Toronto group performed a proteomics analysis of graft biopsies (three timepoints; baseline prior to WIT, 30 min postreperfusion and POD 3) using their well established porcine auto-transplantation model (30 min WIT, 8 h NMP or SCS). After identifying differentially expressed proteins in NMP compared with SCS, they could demonstrate that NMP preservation was associated with an increase in proteins mediating key metabolic processes, including fatty acid-ß-oxidation, tricarboxylic acid cycle and oxidative phosphorylation [25]. Using the same porcine auto-transplantation model (30 min WIT, 8 h NMP or SCS) with an additional nonstorage group (NS; 30 min WIT with immediate auto-transplantation), they also performed a transcriptomic analysis. NMP and NS kidney grafts had a closely resembling expression profile. Similar to the proteomics analysis, the NMP group showed an increased transcription of key mitochondrial metabolic pathways. In contrast, the SCS group expressed genes particularly involved in mechanism of IRI [26].

FROM HYPOTHERMIC TO NORMOTHERMIC PERFUSION: CONTROLLED REWARMING

Another interesting approach was explored by the Essen Group: they hypothesized that controlled rewarming by ex-vivo machine perfusion with gradual elevation of perfusate temperature prior to implantation might prevent mitochondrial dysfunction upon reperfusion [27,28]. For these experiments, a porcine DCD (15 min WIT) model was used. Kidney grafts were subjected to 18 h of SCS followed by 2 h of controlled oxygenated rewarming (COR) using two different rewarming protocols. In comparison to SCS grafts, kidneys subjected to both COR protocols displayed a significantly increased glomerular filtration rate, higher tubular sodium reabsorption, less glucose loss, reduced AST levels and better mitochondrial coupling efficiency during perfusion [27]. In a second study, the Essen group compared SCS (8 h) with COR (SCS for 6 h + 2 h COR) or upfront NMP (8 h) in a porcine DCD (30 min WIT) autotransplant model with 7 days of posttransplant follow-up [28]. Both perfusion protocols ameliorated microcirculatory tissue perfusion 10 min after reperfusion and displayed significantly lower serum creatinine and urea levels compared with SCS grafts. Overall, proinflammatory cytokine expression and tissue injury score were lowest in the COR group [28].

GRAFT ASSESSMENT DURING NORMOTHERMIC MACHINE PERFUSION

By keeping kidney grafts under near-physiologic conditions, NMP may enable graft monitoring and quality assessment. Thus far, haemodynamic parameters such as intrarenal resistance have been linked to the occurrence of delayed graft function in kidney NMP; however, only limited knowledge on the real predictive potential of biomarkers and other novel assessment tools is available to date [29].

The Oxford group investigated renal injury and inflammatory biomarkers during NMP of 12 discarded human kidney grafts at 1 and 6 h of NMP with ($n = 8$) and without ($n = 4$) urine recirculation (URC). They demonstrated a link between donor factors (kidney function parameters), metabolic and haemodynamic parameters (perfusate lactate, perfusate pH, urine output) as well as biomarkers (especially NGAL and KIM-1) underlining the need for an integrated approach to assess the quality of a perfused kidney graft [30].

Not only the heterogeneity of grafts, but also the composition of the perfusion solution may have an impact on organ assessment. This was shown by the Groningen group by evaluating four different RBC-based perfusion solutions in a porcine NMP model (20 min WIT, 7 h NMP). They demonstrated that perfusion compositions significantly affected perfusion parameters and injury markers, potentially limiting intergroup comparability in light of absence of a standard perfusate for NMP [31]. Together, these findings stress the importance of correcting any new perfusion-based biomarker for other, standard clinical variables that are already known to evaluate whether this new biomarker remains independently predictive of outcome.

Wang *et al.* [32] investigated the predictive value of flavin mononucleotide (FMN), which is released upon damage of complex I in electron transport chain, on posttransplant graft function. They demonstrated increased FMN perfusate levels in kidneys

developing a delayed graft function or primary non-function (PNF).

Apart from donor factors, haemodynamics and biomarkers, imaging techniques may also serve as valuable tools for graft assessment. Sommer *et al.* [33] used hyperspectral imaging (HSI) data of 26 kidney grafts to train KidneyResNet, a convolutional neural network (CNN), to generate an algorithm of automated ROI selection in order to predict inulin clearance behaviour of the assessed kidney graft. After optimization and decision based on all ROIs of a kidney, a high accuracy of predicting kidney function was achieved [33]. The Groningen group used MRI to characterize regional perfusion distribution during NMP. For this study, nine porcine kidneys and four human discarded kidneys were perfused normothermically for 3 h with scans being performed every 15 min. They could demonstrate that only after 1–2 h of NMP, kidneys reached an *in vivo* like perfusion state. Before that, the renal cortex appeared under-perfused, suggesting that functional assessment at the beginning of perfusion may not reflect a physiological state and should be interpreted with caution [34▪▪].

FEASIBILITY OF PROLONGED NORMOTHERMIC MACHINE PERFUSION

The potential of NMP as an ex-vivo platform for organ assessment, regeneration and treatment is in many instances linked to the possibility of prolonged perfusion. The Oxford group has previously published a protocol to successfully perfuse porcine and human kidney grafts normothermically for up to 24 h using a blood based perfusate [35]. Key factor for maintaining a stable perfusion was the application of URC. Porcine kidneys with URC displayed higher arterial flow rates and lower perfusate sodium and lactate levels [36]. In a second study, they investigated why URC might be superior to urine replacement with ringer's lactate. Data from a proteomics analysis using mass spectrometry from 16 kidney biopsies showed an upregulation of enzymes involved in glucose metabolism and pH-stabilization as well as an increase in anti-inflammatory molecules in kidneys with URC [37].

In their latest publication, Weissenbacher *et al.* [38] further expanded the timespan of NMP to 48 h in a declined human kidney graft. Using the kidney assist device and URC, they were able to demonstrate the feasibility of substantially expanding the time of ex-vivo perfusion without adding significant histological damage to the perfused organ. The possibility of prolonged ex-vivo preservation might pave the way for regeneration of damaged donor organs that require a longer time span [39]. The Oxford group is currently testing the feasibility of prolonged perfusion in the clinical setting in a phase II safety study using the OrganOx kidney device. Thirty-six kidneys will be perfused for up to 24 h and the trial has recruited about one-third of the total participants.

EX-VIVO RECONDITIONING AND ORGAN TREATMENT: CURRENT STATUS

In the last decades, regenerative medicine in the setting of organ transplantation has gained substantial momentum [40]. Proposed interventions range from administration of cellular components to infusion of genetic, biological or pharmacological agents. Dynamic preservation platforms such as machine perfusion offer the opportunity to deliver therapies and execute interventions on isolated grafts in an anaerobic or aerobic environment. Ex-vivo perfusion facilitates direct targeting of interventions to the perfused organ without the need for systemic application in the recipient [16,41–44].

From the various therapies that have been explored, we will give a brief overview on recent ones that were delivered or assessed by NMP.

Mesenchymal stromal/stem cells (MSCs) have emerged as a potential cellular therapy in NMP. These multipotent cells, which can easily be isolated and expanded *in vitro*, display strong immunomodulatory, anti-inflammatory and regenerative properties [45–47].

Brasile *et al.* [46] used 10^8 human MSCs to treat ischemically damaged human kidney grafts via 24 h NMP using an exsanguinous metabolic support platform. Their data showed that intra-arterial MSC application resulted in reduced inflammatory cytokine synthesis, an increase in adenosine triphosphate and growth factors synthesis as well as an increase in mitotic active renal cells compared with EMS perfusion alone [46].

Moers *et al.* [48] explored the feasibility of administration of MSCs during NMP (RBC-based). They administered 0, 10^5, 10^6 or 10^7 human adipose tissue derived MSC (A-MSC) and fluorescent prelabelled bone-marrow derived MSCs (BM-MSC) after 1 h of stable perfusion of porcine kidneys grafts. They demonstrated that infused MSCs were localized within the lumen of glomerular capillaries, but only after infusion of the highest number of cells. Numbers of circulating MSCs declined after infusion, and only approximately 10% of cells could be detected after 6 h NMP. The authors explained the decline by exposure to nonphysiological stress during perfusion that contributes to MSC death [48].

In a second study, the groups explored the cytokine profile secreted by MSCs during NMP of porcine

kidney grafts [49]. Porcine grafts with 20 min of WIT were initially subjected to HMP followed by NMP for 7 h and administration of 0 or 10^7 cultured human A-MSCs, or 10^7 BM-MSCs. Administration of MSCs did not alter arterial flow dynamics, but resulted in reduced NGAL and lactate dehydrogenase (LDH) levels as well as increased human hepatocyte growth factor, interleukin (IL)-6 and IL-8 levels compared with untreated controls. Interestingly, MSC treatment in the absence of an injured kidney did not lead to an increase of IL-6 and IL-8 expression [49].

The Aarhus group demonstrated the safety and feasibility of MSC infusion during NMP in a porcine auto-transplant model with a follow-up of 14 days [50]. Porcine kidneys subjected to 75 min of WIT followed by 14 h of oxHMP and 4 h of NMP (RBC-based) or oxHMP alone were infused with 10^7 porcine or human A-MSCs. They demonstrated that MSCs did not affect posttransplant plasma creatinine levels, GFR, NGAL concentrations or kidney damage assessed by histology. Nevertheless, they showed MSCs retention in the renal cortex after 4 h of NMP and on POD 14 [50].

Thompson *et al.* [51] reported the use of multipotent adult progenitor cells (MAPC; 50×10^6 cells) in five human kidney pairs that were subjected to NMP (RBC-based) for delivery (60 min after NMP start) and graft assessment for 7 h. Compared with untreated control kidneys, their MAPC-treated counterparts demonstrated improved urine output, decreased NGLA expression, improved microvascular perfusion as well as downregulation of IL-1b and upregulation of IL-10 during NMP [51].

The same group pioneered ex-vivo oligonucleotide delivery [52]. After human microRNA expression profiling 1 h after initiation of NMP, Thompson *et al.* [52] identified miR-24-3p as a possible target of blockade during NMP. NMP (RBC-based) was carried out for 6 h and grafts were treated with either miRNA-24-3p antagomir or scramble sequence oligonucleotide (1 mg each). They did not only prove endosomal antagomir uptake during NMP but also showed engagement of the miRNA target that was only seen under normothermic but not hypothermic ex-vivo conditions. Treatment resulted in increased expression of genes controlled by this microRNA, while gene expression otherwise remained unchanged [52].

DiRito *et al.* [53] described microvascular obstruction due to the accumulation of fibrinogen within tubular epithelium in human kidneys that was aggravated by normoxic conditions. By combined delivery of plasminogen and tissue plasminogen activator during NMP (90 min; RBC-based), they were able to lyse these obstructions with subsequent significant reduction in renal injury markers and improved renal function [53].

Hameed *et al.* [54] investigated ischemia-reperfusion injury mitigating properties of αCD47Ab in the setting of porcine DCD kidney NMP (1 h; RBC-based). The group showed renal binding of the agent and an improvement of some renal perfusion and injury parameters [54].

Huijink *et al.* [55] analysed the role of the anti-hyperglycemic drug metformin in pre and postconditioning in a rat (90 min; William's Medium-based perfusate) and porcine (4 h; RBC-based perfusate) NMP model. Although metformin preconditioning of rat kidneys led to decreased perfusate injury biomarkers and reduced proteinuria, postconditioning resulted in a dose-dependent decrease of histologic damage. In contrast, NMP of porcine kidneys did not lead to differences in urinary protein excretion, LDH and aspartate aminotransferase (AST) levels or graft damage [55].

NORMOTHERMIC MACHINE PERFUSION AS A PLATFORM FOR COMPOUND TESTING

Apart from direct drug administration, NMP has the potential to assess drug safety and toxicity as demonstrated by Kassimatis *et al.* [56]. Inspired by a lack of efficacy in a clinical phase IIa trial, they used a porcine NMP (3 h, RBC-based) model to perform a dose-finding study for Mirococept treatment, a potent membrane-localizing complement inhibitor. After studying reagent tissue distribution following perfusion and readjustment of dosing, NMP was successfully applied to evaluate its safety and lack of toxicity [56].

OPTIMIZATION OF NORMOTHERMIC MACHINE PERFUSION PROTOCOLS

After establishing reproducible perfusion protocols, Hosgood *et al.* [57] further investigated the use of a Cytosorb adsorber to optimize perfusion conditions and lower inflammatory responses caused by ex-vivo perfusion. The group used the adsorber in a porcine kidney NMP (22 h CIT, 6 h NMP) model. Although a positive effect in terms of a reduced inflammatory response and an improved renal blood flow was observed, no effect on renal function could be seen [57]. As the Cytosorb adsorber is not cytokine specific and might even eliminate important anti-inflammatory mediators, the group further explored the use of a hemoadsorber to selectively remove pro-inflammatory cytokines. The use of a hemoadsorber resulted in a reduced expression of DGF-associated genes [58▪].

Another group propagated a short period of hyperthermic perfusion (10 min at 42°C) of porcine kidneys (20 h SCS; 2 h perfusion with gradual increase of temperature to 35°C), as this led to a 50% increase of heat shock proteins, potentially inducing repair mechanism and tolerance against subsequent cellular injury [59].

Due to aggressive anticoagulation and ureteral manipulation, haematuria is a relevant problem during kidney NMP. Hosgood *et al.* [60] reported on their positive experience with the use of double-J ureteric stents during NMP. These universally available and cheap stents not only enabled accurate monitoring of urine output, but they also decreased visible haematuria compared with the previously used soft Nelaton catheters [60].

Most groups use RBC-based perfusates for NMP. Especially in the preclinical setting, however, only limited quantities of autologous blood are available. The Groningen group compared autologous and allogenic porcine, and human RBCs as perfusion solution in a porcine NMP model (20 min WIT, 1.5-2.5 h HMP, 7 h NMP). Regardless of RBC source, all kidneys were functional and produced urine during NMP. AST levels and histologic examination showed significantly more damage in the human RBCs group compared with both autologous and allogeneic porcine RBC groups, concluding that allogeneic porcine RBCs should be used preferably in case of insufficient amounts of autologous RBCs [61]. Trying to find an alternative to blood-based solution in NMP, van Leeuwen *et al.* [62] tested the serum-like preservation solution (Aqix) enriched with different additives, with and without RBCs in a porcine NMP model (WIT 30 min, HMP 3 h, NMP 4 h). Although the Aqix solution alone was able to support metabolism and renal function, their results indicated a superiority of RBC supplementation [62].

CLINICAL REALIZATION OF NORMOTHERMIC MACHINE PERFUSION: CURRENT STATUS

Since its clinical translation in 2011, when the first clinical case of NMP was reported by Nicholson and Hosgood, increasing evidence exists that shows superior preservation of marginal kidney grafts using NMP [63,64]. Although Hosgood and Nicholson demonstrated a significant reduction of delayed graft function (DGF; 5.6 vs. 36%) in marginal kidney grafts subjected to NMP in a single-centre clinical study and the potential of this technology to expand the donor pool by pretransplant assessment and reconditioning of otherwise declined human kidneys [65], they also reported that NMP may only have limited ability to predict PNF in grafts after uncontrolled DCD [66].

Following these promising results in marginal donor organs from England, the Rotterdam group initiated a randomized, controlled open-label trial to assess 2 h of NMP (RBC-based) in addition to standard care (anoxic HMP) within recipients of organs in the Eurotransplant Senior Program [67]. Eleven patients were included in the NMP arm of the study, and 53 patients were included as controls. No significant improvement of DGF was seen in NMP compared with HMP-preserved grafts (NMP: 36 vs. HMP: 60%, $P = 0.14$) [68].

In 2022, the Toronto group reported their clinical experience with kidney NMP and reported on the outcome of 13 patients who received kidney grafts subjected to 1–3 h of NMP after initial anoxic HMP. Similar to the results of the Rotterdam group, they reported comparable DGF rates for NMP and HMP-preserved kidney grafts (NMP: 30.8% vs. HMP: 46.2%) and equivalent 1-year patient and graft survival rates [69▪▪].

Together, these studies demonstrated the safety and feasibility of NMP for clinical kidney preservation, yet they concluded that better powered studies are required to further explore its full clinical potential.

Building on the favourable results of their preclinical work, the Essen group reported the first clinical use of controlled rewarming of an ECD kidney graft using STEEN solution without oxygen carriers prior to transplant. After 12.5 h of SCS, the kidney was subjected to 120 min of COR and was subsequently transplanted in a 61-year-old male recipient. The graft displayed immediate graft function and the patient was discharged after an event-free postoperative course [70]. In 2022, they published their first case series of six ECD kidneys that were transplanted after COR and compared with matched kidneys after SCS. Patients who received kidney grafts after COR had a significantly better creatinine clearance on POD 7 (COR: 66.1 ml/min vs. SCS: 27.0 ml/min) and 3-month GFR (COR 70 vs. 45 ml/min), although similar numbers of postoperative complications occurred [71▪▪].

CONCLUSION

Machine perfusion, regardless of applied temperatures (HMP, NMP, COR), has often resulted in a superior organ preservation capacity compared with SCS. Depending on the clinical setting and graft type, different temperature ranges might be preferred. In the setting of controlled DCD grafts, NMP has already demonstrated some potential in graft salvage. Preclinical data suggest that NMP

could be more effective in DCD graft preservation than HMP. Several groups have shown clinical translatability and safety of renal NMP. Even though similar results were seen in a direct comparison of clinical HMP and NMP, this might be attributed to the rather short NMP duration and low power. New evidence suggests that longer perfusion durations are needed in order to achieve sufficient global renal perfusion. To clarify the benefit of NMP for the preservation of marginal kidney grafts, larger randomized controlled clinical trials are needed.

Apart from its potential to expand the organ pool, NMP may offer the unique possibility for ex-vivo graft assessment prior to transplant under near-physiological conditions. A combination of donor factors, perfusion and metabolic parameters as well as kidney injury and inflammation markers are crucial to determine graft quality and viability. However, compared with the already available data on HMP and its positive impact on outcome after kidney transplantation, clear convincing clinical evidence for any of NMP's promises, that is improved organ preservation, pretransplant organ assessment and treatment, is still missing. Therefore, a new integrated approach is needed to establish reliable and reproducible perfusion-based kidney graft assessment in a (pre)clinical setting.

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There are no conflicts of interest.

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