



# Optimizing porcine donor kidney preservation with normothermic or hypothermic machine perfusion: A systematic review

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## Abstract

We present an updated overview of the literature comparing normothermic with hypothermic machine perfusion in porcine kidneys. We conducted a systematic literature review in Embase, Medline Epub (Ovid), Cochrane Central, Web of Science, and Google Scholar on studies comparing normothermic (NMP) to hypothermic machine perfusion (HMP) in porcine kidneys. A meta-analysis was judged inappropriate because of heterogeneity in study design and perfusion methods. The quality of evidence of each included study was assessed. We included 8 studies. One out of 5 studies reported a significant difference in peak renal blood flow in favor of NMP. Oxygen consumption was significantly higher in NMP kidneys in 2 out of 5 studies. Peak creatinine clearance in NMP was significantly higher than that in HMP in 1 out of 6 studies. Two out of 4 studies reported a higher degree of epithelial vacuolation in kidneys receiving NMP over HMP. None of the studies found a significant difference between NMP and HMP in peak serum creatinine or graft survival after autotransplantation. The results need to be interpreted with caution in view of the diversity in perfusion protocols, the low quality of evidence, and the limited sample sizes.

## KEY WORDS

graft assessment, graft viability, hypothermic machine perfusion, normothermic machine perfusion, organ preservation

## 1 | INTRODUCTION

While static cold storage (SCS) is still the golden standard worldwide for kidney preservation prior to transplantation due to its easy availability and low costs, hypothermic machine perfusion (HMP) is increasingly being used and is already the standard of care in the Netherlands. HMP has been shown to reduce graft injury, lower delayed graft function (DGF) rates, and lead to better transplant outcomes.<sup>1</sup> HMP

can be applied both with and without the addition of oxygen (hypothermic oxygenated perfusion, HOPE); the addition of oxygen had a beneficial effect on early graft function in animals.<sup>2-5</sup> With HMP, limited viability assessment is possible, as cellular metabolism is still present.

Kidney preservation methods need to be improved to deal with the increasing number of marginal donor kidneys. Normothermic machine perfusion (NMP) is a promising alternative to HMP for kidney preservation, and the first clinical studies comparing NMP to HMP have already started.<sup>6</sup>

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NMP offers the unique ability to fully assess kidney function and viability by allowing the restoration of the renal aerobic metabolism, as it most closely resembles the physiological environment of the kidney.<sup>7</sup> This could theoretically result in less ischemia-reperfusion injury, and therefore a better survival after donation after circulatory death (DCD) and use of expanded criteria donors (ECD). Hosgood and colleagues have used NMP to assess and improve the function of declined kidney grafts and have successfully transplanted 4 of 10 initially declined kidneys,<sup>7</sup> proving that better preservation methods could help reduce the imbalance between supply and demand of suitable kidney grafts.

Limited data on human studies comparing HMP to NMP are available so far, with most studies focusing on NMP being conducted in porcine animal models as porcine kidneys are very similar to human kidneys in size, physiology, and anatomy.<sup>8,9</sup> Therefore, we performed a systematic qualitative review aimed to compare relevant outcomes of HMP and NMP of porcine kidneys.

## 2 | MATERIALS AND METHODS

This review adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.<sup>10</sup> Because study design and characteristics of outcome measures varied between included studies, we refrained from performing a meta-analysis and instead focused on a qualitative systematic review.

### 2.1 | Search strategy

A literature search was performed in the Embase, Ovid Medline, Cochrane Central, and Google Scholar databases. Searches were conducted using MeSH and Emtree keywords. Detailed search strategies are included in the Supplemental Digital Content Table 1. The final literature search was performed on November 13, 2020.

### 2.2 | Study selection

Studies were included if they compared outcomes of HMP to NMP in a porcine animal model. We applied the following predefined exclusion criteria: studies focusing on nonporcine kidneys, non-English studies, and specific types of studies (eg, conference abstracts, letters to the editor, replies, editorials, case reports, guidelines, and reviews).

Two reviewers (SB and RCM) independently screened the titles and abstracts of retrieved studies, subsequently selected studies based on the inclusion and exclusion criteria, and read the full texts of the selected studies to determine relevance for the review.

Disagreements between SB and RCM were solved by consensus or by a third reviewer (JNMIJ). Studies focusing on NMP or sub-NMP only and not directly comparing with HMP were excluded.

### 2.3 | Data collection and extraction

The following study parameters were collected and included: date of publication, weight range of animals, experimental procedure or procedures/model employed (study groups, ex vivo perfusion or transplantation after preservation, experimental period), number of animals in each group, warm ischemia times, perfusion machine and settings used, preservation/perfusion solution or solutions used, temperature of preservation/perfusion, and oxygenated or nonoxygenated HMP. Study outcomes consisted of renal function parameters (peak serum creatinine in  $\mu\text{mol/L}$ , peak creatinine clearance (CrCl) in  $\text{mL/min}$ ), graft loss in studies describing transplantation after perfusion, oxygen consumption in case of oxygenation during perfusion, and histology of kidney biopsies. If a study presented data in a graph or graphs only, we extracted the data points with the use of DataThief III software.

### 2.4 | Quality of evidence assessment

SB and RCM independently assessed the risk of bias in each included study using SYRCLE's risk of bias tool for animal studies, which contains 10 entries.<sup>11</sup> These entries are related to 6 forms of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. A "yes" judgment indicates low risk of bias, a "no" judgment indicates high risk of bias, an "unclear" judgment stated as indicated that insufficient data could be retrieved from the study to properly assess the risk of bias.

## 3 | RESULTS

### 3.1 | Literature search

The database searches yielded 642 citations studies. After screening of titles and abstracts, 54 studies remained of which the full texts were assessed for eligibility. Eventually, 8 studies were included in this qualitative analysis (see Supplemental Digital Content Table 1 and Figure 1).<sup>12-19</sup>

### 3.2 | Study characteristics and study outcomes

The characteristics of the included studies are given in Table 1. The duration of perfusion, perfusion machine, and perfusion



TABLE 1 Study characteristics

Study	Year	Weight range of animals (kg)	Study groups (duration)	No. of animals	Perfusion machine brand	Perfusate	Warm ischemia time (min)	Oxygenated	Autotransplantation of graft
Bagul et al	2008	60-70	HMP (18 hours)	6	LP <sup>a</sup>	Kidney perfusion solution (KPS-1)	10	No	No
			HMP (16 hours) → NMP (2 hours)	6	IOPS <sup>b</sup>	NMP with whole autologous blood	10	Yes	Yes
Blum et al	2017	Not mentioned in the study	HMP (8 hours)	5	n/a	Belzer's Machine Perfusion Solution	45	No	No
Darius et al	2019	40	NMP (8 hours)	5	n/a	Erythrocyte-based solution	45	Yes	Yes
			SCS (20 hours) → HMP (2 hours)	7	LP <sup>a</sup>	Kidney perfusion solution (KPS-1)	30	Yes	Yes
Hosgood et al	2011	37.0-43.8	SCS (20 hours) → NMP (2 hours)	6	LP <sup>a</sup>	Autologous leukocyte-depleted blood	30	Yes	Yes
			HMP (22 hours)	6	LP <sup>a</sup>	Kidney perfusion solution (KPS-1)	32	No	Yes
Hoyer et al	2014	30	HMP (20 hours) → NMP (2 hours)	6	LP <sup>a</sup> and IOPS <sup>b</sup>	NMP with autologous leukocyte-depleted blood	33	Yes	Yes
			HMP (7 hours)	5	LP + HFox <sup>c</sup>	Custodiol-N solution including 5 g/dL of dextran 40	30	Yes	No
Metcalfe et al	2002	80-100	SNMP (7 hours) (20°C)	5	LP + HFox <sup>c</sup>	Custodiol-N solution including 5 g/dL of dextran 40	30	Yes	Yes
			SCS (2 hours) → HMP (16 hours)	6	RM3 system (Waters, Massachusetts, USA)	Belzer's Machine Perfusion Solution	8	No	No
Schopp et al	2015	25-30	SCS (2 h) → NMP (16 hours)	6	POPS <sup>d</sup>	Whole autologous blood	8	Yes	Yes
			HMP (18 hours)	6	n/a	Custodiol-N solution including 5 g/dL of dextran 40	n/a	No	No
Urbanellis et al	2020	30	SCS (18 hours) → COR (3 hours)	6	n/a	Custodiol-N solution including 5 g/dL of dextran 40	n/a	Yes	Yes
			HMP (16 hours)	5	LP <sup>a</sup>	Belzer's Machine Perfusion Solution	30	No	Yes
			NMP (16 hours)	5	n/a	Leukocyte-depleted blood	30	Yes	Yes

Abbreviations: COR, controlled oxygenated rewarming; HMP, hypothermic machine perfusion; (s)NMP, (sub)normothermic machine perfusion; SCS, static cold storage.

<sup>a</sup>LifePort hypothermic preservation machine (Organ Recovery Systems, Des Plaines, Illinois, USA).

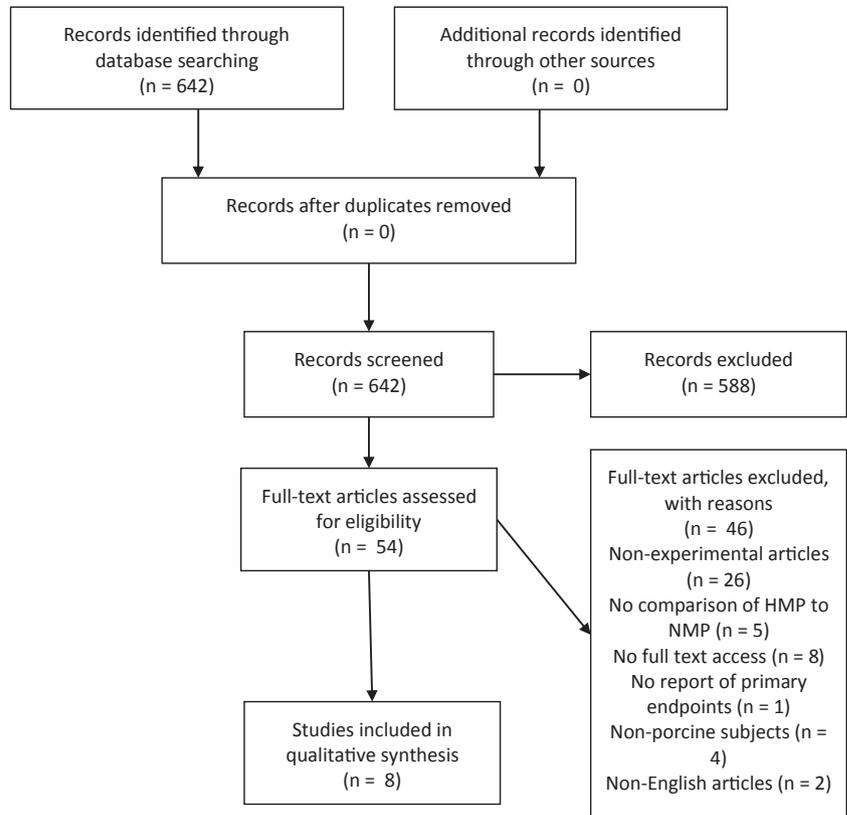
<sup>b</sup>Isolated organ perfusion system (Medtronic 550 Bio-console system; Medtronic, Watford, UK).

<sup>c</sup>LifePort hypothermic preservation machine (Organ Recovery Systems, Des Plaines, Illinois, USA) with hollow fiber oxygenator (Minimax; Medtronic; Minneapolis, Minnesota, USA).

<sup>d</sup>POPS (pulsatile organ perfusion system) (Transmedics, Boston, Massachusetts, USA).



**FIGURE 1** Flow diagram of included studies



fluid differed between studies. The overview in Table 2 shows the outcomes analyzed in the individual studies.

### 3.3 | Peak renal blood flow

In five studies, peak renal blood flow was measured during perfusion. Hoyer et al<sup>16</sup> found a significant difference in peak renal blood flow between NMP (212.82 mL/min) and HMP (176.37 mL/min),  $P = .007$ . Urbanellis et al<sup>19</sup> did not perform a statistical analysis on peak renal blood flow but reported a peak renal blood flow of 215 mL/min during NMP and 53.6 mL/min during HMP.

### 3.4 | Oxygen consumption

In 5 studies, the oxygen consumption during perfusion was measured, although in 2 studies only during NMP. Two studies, Bagul et al<sup>12</sup> and Schopp et al,<sup>18</sup> found a significant difference in oxygen consumption between the 2 perfusion methods, respectively, 40 versus 35.1 kPa mL/min/g in NMP versus HMP and 6.28 versus 3.93 mL/min/100 g in NMP versus HMP.

### 3.5 | Intrarenal resistance

In 8 studies, the intrarenal resistance was measured. Only Darius et al<sup>14</sup> found a significant difference of 0.96 mm Hg/

mL/min in the NMP group compared with 0.38 mm Hg/mL/min in the HMP group,  $P < .05$ .

### 3.6 | Peak serum creatinine

In both the study of Bagul et al<sup>12</sup> and that of Hosgood et al,<sup>15</sup> peak serum creatinine was measured. Bagul et al reported a peak serum creatinine of 1756  $\mu\text{mol/L}$  in the NMP group versus 2156  $\mu\text{mol/L}$  in the HMP group, without significant difference. Hosgood et al reported a peak serum creatinine of 1553  $\mu\text{mol/L}$  in the NMP group versus 1736  $\mu\text{mol/L}$  in the HMP group, without significant difference.

### 3.7 | Peak creatinine clearance

In 6 studies, peak creatinine clearance was measured. Only Schopp et al<sup>18</sup> reported a significant increase in peak creatinine clearance in grafts treated with NMP and 16.95 mL/min versus 9.58 mL/min,  $P < .05$ , respectively.

### 3.8 | Graft survival after autotransplantation

In 3 studies, an autotransplantation was performed after graft perfusion. Darius et al<sup>14</sup> measured graft recovery but did not



TABLE 2 Overview of study outcomes

Study	Year	Perfusion method	Peak renal blood flow (mL/min)	Oxygen consumption (mL/min/100 g)	Intrarenal resistance (mm Hg/mL/min)	Peak serum creatinine (μmol/L)	Peak creatinine clearance (mL/min)	Graft survival after autotransplantation (%)	Epithelial vacuolation (grade)	Tubular dilatation (grade)	Epithelial shedding (grade)
Bagul et al	2008	NMP	90	40 <sup>b,*</sup>	0.4	1756	1.8	n/a	1.5*	No	No
		HMP	Not reported	35.1 <sup>b</sup>	Not reported	2156	2.5	n/a	0.8	significant difference <sup>c</sup>	significant difference <sup>c</sup>
Blum et al	2017	NMP		4.4	0.18		6.5 <sup>a</sup>	n/a	1.7 [0.9-2.3]*	1.6 [0.1-2.3]	1.1 [0.6-1.9]
		HMP		n/a	1		9.3 <sup>a</sup>	n/a	0 [0-0.5]	0.9 [0.1-2.2]	1.3 [1.2-1.9]
Darius et al	2019	NMP	73.35 <sup>a</sup>		0.96 <sup>a,*</sup>			Not reported			
		HMP	49.03 <sup>a</sup>		0.38 <sup>a</sup>			Not reported			
Hosgood et al	2011	NMP	55.33	28.3	0.45	1553	2.3	66.67	1.1	1.9	
		HMP	55.33	n/a	0.46	1736	Not reported	83.33	1.2	2.2	
Hoyer et al	2014	sNMP	212.82 <sup>a,*</sup>	3.67	0.46		18.18 <sup>a</sup>	n/a	[2-3] <sup>c</sup>	[2-2.5] <sup>e</sup>	Not observed
		HMP	176.37 <sup>a</sup>	3.5	1.08		12.29 <sup>a</sup>	n/a	[2-3] <sup>c</sup>	[2-3] <sup>e</sup>	Not observed
Metcalfe et al	2002	NMP			No significant difference <sup>c</sup>		No significant difference <sup>c</sup>	n/a			
		HMP			No significant difference <sup>c</sup>		No significant difference <sup>c</sup>	n/a			
Schopp et al	2015	COR		6.28 <sup>b,*</sup>	1.13		16.95 <sup>b,*</sup>	n/a			
		HMP		3.93 <sup>a</sup>	1.45		9.58 <sup>a</sup>	n/a			
Urbanellis et al	2020	NMP	215 <sup>d</sup>		0.45			100		[1-1.5]	
		HMP	53.6		0.45			100		[1-1.5]	

Abbreviations: COR, controlled oxygenated rewarming; HMP, hypothermic machine perfusion; (s)NMP, (sub)normothermic machine perfusion; SCS, static cold storage.

<sup>a</sup>Data originally published as a graph; extracted using DataThief III.

<sup>b</sup>in kPa.mL/min/g.

<sup>c</sup>Exact measurements not reported; no significant difference between groups.

<sup>d</sup>No statistical analysis performed.

<sup>e</sup>A 5-point scale was used instead of a 3-point scale.

\*Significant difference.



analyze graft loss per study group. Of the 46 autotransplants performed in this study, 8 were excluded from analysis due to death related to complications other than renal failure. Hosgood et al<sup>15</sup> and Urbanellis et al<sup>19</sup> measured graft survival until postoperative day 10 and day 8, respectively, and concluded that there was not a significant difference in this respect between HMP and NMP, respectively, 66.67% versus 83.33%,  $P = 1.00$  and 100% versus 100%,  $P = 1.00$ .

### 3.9 | Histology

In 5 studies, histological analysis was performed of the kidney grafts after perfusion. None found a significant difference in tubular dilatation or epithelial shedding between the perfusion methods. Two out of 4 studies analyzing epithelial vacuolation found a significant difference, with NMP receiving higher grades than HMP.

### 3.10 | Risk of bias assessment

We performed a study bias assessment with the SYRCLE's risk of bias tool for animal studies.<sup>11</sup> There was a high risk of bias in few domains. However, due to the lack of available data, sections of the bias assessment were judged "unclear" (see Figure 1 of Supplemental Digital Content).

## 4 | DISCUSSION

We performed a qualitative systematic review to investigate the potential benefits of NMP over HMP in porcine kidneys and provided an updated overview of the current published literature comparing experimental HMP to NMP.

Two out of the 5 studies that measured oxygen consumption found that it was significantly higher in NMP compared with HMP and 1 out of the 6 studies that measured peak creatinine clearance found that it was significantly higher in NMP compared with HMP. None of the respective significant differences were found between peak serum creatinine or graft survival after auto-transplantation between NMP and HMP.

Our findings overall expand on those of the systematic review performed by Hameed et al.<sup>20</sup> Other than Hameed et al, we narrowed our literature search to porcine kidneys, excluding studies performing experiments on canines and rodents. By only focusing on studies that directly compared HMP with NMP, we attempted to homogenize the data from the included studies. Nevertheless, we were unable to perform a meta-analysis due to the considerable heterogeneity in perfusion methods and durations applied in the individual studies. The differences in perfusion protocols may be explained

by the different strategies for which NMP can be employed. As mentioned before, NMP can be used as a tool to assess graft viability, as it mimics physiological conditions. Another option is to employ NMP to optimize kidney graft function, possibly with the addition of therapeutic agents. These different applications can result in differences in protocol (end-ischemic or continuous machine perfusion) and perfusion components. Hamelink and colleagues have recently published an overview of the current renal NMP protocols used globally, demonstrating the diversity in perfusion protocols.<sup>21</sup> Elliot and colleagues have published a review on the rationale of NMP protocols and perfusate components necessary for a clinically viable protocol.<sup>22</sup> For NMP to be clinically viable, perfusate must contain at least: a (red blood cell) based oxygen carrier, a crystalloid-/colloid-based solution to maintain volume, mannitol, a vasodilator, corticosteroids to reduce inflammation, support of metabolism through glucose and amino acids, insulin to increase absorption of glucose, and a buffer to maintain pH (usually sodium bicarbonate).

For many years, hypothermic techniques have been the golden standard for organ preservation, based on the observation that cooling overcomes the detrimental effects of anoxia by diminishing the metabolic rate of the organ.<sup>23</sup> Nonetheless, cold preservation affects tissue integrity and predisposes subsequent reperfusion injury.<sup>24</sup> Prolonged cold ischemia directly correlates with the inflammatory process after reperfusion, and the associated inhibition of cellular metabolism eliminates the possibility of any substantial repair process that could occur with warm preservation.<sup>25</sup>

Since 2016, all donor kidneys in the Netherlands are placed on a hypothermic ex vivo kidney perfusion device designed to maintain a sterile, pulsating circulation of cold fluid (4°C) through the kidney. This approach allows for a better distribution of glucose and more efficient removal of waste compared with SCS. The COMPARE study compared HOPE to nonoxygenated HMP in a clinical setting and found that HOPE reduced the risk of acute rejection and graft loss in DCD kidneys from donors of age 50 or older.<sup>26</sup> This has led to a change in protocol in the Netherlands, where all kidney grafts from DCD donors age 50 or older are transported using HOPE. Another randomized controlled trial compared the effect of short-term oxygenated HMP after SCS to SCS alone in ECD-DBD donor kidneys.<sup>27</sup> They did not find a significant difference in 1-year graft survival, incidence of DGF, or incidence of PNF.

The underlying mechanisms of oxygenated HMP have been explored by Darius and colleagues, in a preclinical study wherein they compared the timing of oxygenation (start or end of perfusion, continuous or nonoxygenated HMP).<sup>28</sup> They found that the groups receiving oxygenated HMP at the start of perfusion or continuous oxygenated HMP had better graft recovery. This was associated with a better metabolic profile (eg, lower concentrations of lactate and succinate).



They suggest that brief oxygenation at the start of HMP can lead to protection of mitochondria and better renal graft function compared with nonoxygenated HMP. Without the addition of oxygen, tissue oxygenation is only possible through diffusion. This eventually leads to hypoxia and the accumulation of metabolites that hinder the resynthesis of ATP. Early addition of oxygen during HMP appears to negate this mechanism, promoting physiological mitochondrial processes.

NMP has several benefits compared with cold storage methods such as SCS or HMP. First, aerobic metabolism can be completely restored by oxygenation of the perfusion fluid, allowing the kidney to regain function (eg, replenish adenosine triphosphate, control of pH). Second, the kidney can be maintained in a stable state allowing close observation and assessment of viability and function.<sup>7</sup> Last, it provides the opportunity to add therapeutic agents to improve the kidney's condition, reduce ischemia/reperfusion injury, and repair the kidney with cellular therapies.<sup>29,30</sup> This is especially important as there has been an increased demand for donor's kidneys and more marginal organs are used for transplantation. Using methods that can improve the quality of donor's kidneys will lead to a larger pool of usable kidneys and shorter waiting lists. Recently, a randomized controlled multicenter trial in the United Kingdom has been conducted, which compares DGF rates in SCS to end-ischemic NMP in a DCD kidney transplantation setting. Results of this trial are expected to be published soon.<sup>31</sup>

Machine preservation has also been a topic of discussion in regard to liver transplantation, as there is also a substantial gap between liver graft supply and demand. An overview on the topic of porcine *ex vivo* liver machine perfusion has been published, although this review does not directly compare HMP to NMP.<sup>32</sup>

Several underlying mechanisms that are not yet fully understood could underlie the outcomes of NMP as compared with HMP that we found in this review. The difference in renal blood flow may be explained by the higher pressure usually employed during NMP compared with HMP (~75 mm Hg compared with ~30 mm Hg). During NMP, the kidney graft is generally more metabolically active compared with HMP, which could explain the difference in oxygen consumption.

Darius et al<sup>14</sup> propose that higher renal blood flow and lower intrarenal resistance associated with NMP could be the consequence of the synthesis of nitric oxide, a vasodilator that is synthesized as a result of an oxidation process.<sup>33</sup> The higher grades of epithelial vacuolation in the NMP kidneys could be caused by the sudden temperature shift in NMP—leading to ischemia-reperfusion injury. Ischemia-reperfusion injury would occur in HMP kidneys after kidney implantation, as evidenced by the similar vacuolation grades between HMP and NMP after autotransplantation.<sup>15</sup> It is therefore uncertain whether the higher grades of epithelial vacuolation after NMP is of any clinical significance.

We hypothesize that aerobic metabolism occurring during normothermic machine perfusion leads to repair mechanisms that improve the quality of the graft and lead to higher creatinine clearance and lower peak serum creatinine level, counteracting the inflammatory processes started during warm ischemia. This hypothesis is supported by the finding of Urbanellis and colleagues that the neutrophil gelatinase-associated lipocalin (NGAL) serum levels in NMP kidneys were lower than those in SCS kidneys.<sup>19</sup> Ferdinand et al<sup>34</sup> compared the effect of NMP with that of SCS on the global kidney transcriptome; and determined that SCS was associated with a reduction in gene expression, whereas NMP was associated with upregulation of oxidative phosphorylation genes as well as immune and inflammatory pathways. Hameed et al,<sup>35</sup> too, compared the effects of NMP to SCS in paired kidneys. Their gene expression analyses included an analysis after simulated transplantation, which revealed highly disparate gene signatures—indicating that the changes in gene expression persist and could affect clinical outcomes.

So far, no study has compared gene expression in kidneys perfused using NMP with that of kidneys perfused using HMP. It would be valuable to undertake this and to determine if the changes in gene expression also persist after graft implantation. These gene expression changes should be correlated to clinical outcomes, such as the incidence of DGF and/or primary nonfunction.

Our review has some limitations. Most of the studies included in this review analyzed different parameters in several technical ways. Even if the studies described similar parameters, the units used for those parameters were defined differently. Perfusion protocols differed, with some using end-ischemic NMP, whereas other studies used continuous normothermic machine perfusion. With this limited number of studies and small sample size data, a significant difference between HMP and NMP cannot be demonstrated. Similarly, an association between NMP and improvements in outcomes cannot be established.

While some studies used HOPE, others did not add oxygen during preservation. The small number of included studies did not allow for a subgroup analysis comparing HOPE to nonoxygenated HMP.

We used SYRCLE's risk of bias tool for animal studies in which some domains were difficult to formally assess due to the lack of available data. However, few domains showed a high risk of bias, which means that results should be interpreted with caution.

In conclusion, this systematic review gives an updated overview of the current published literature comparing HMP with NMP in porcine kidneys. Results need to be interpreted with caution because of the low quality of the evidence and the limited sample sizes. More experimental and human studies are needed to determine the optimal technique of organ preservation for enhancing the quality and number of donor organs.



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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## AUTHOR CONTRIBUTIONS

*Study design:* Bouari, Eryigit, Minnee

*Data collection and analysis:* Bouari, Eryigit, Minnee

*Drafting the article:* Bouari, Eryigit

*Critical revision and approval of the study:* de Bruin, IJzermans, Minnee

## ETHICAL APPROVAL

No ethical approval was sought for this manuscript as this is a systematic review.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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