Systematic Review and Meta-Analysis

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Maximizing kidneys for transplantation using machine perfusion: from the past to the future

A comprehensive systematic review and meta-analysis

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Abstract

Background: The two main options for renal allograft preservation are static cold storage (CS) and machine perfusion (MP). There has been considerably increased interest in MP preservation of kidneys, however conflicting evidence regarding its efficacy and associated costs have impacted its scale of clinical uptake. Additionally, there is no clear consensus regarding oxygenation, and hypo- or normothermia, in conjunction with MP, and its mechanisms of action are also debated. The primary aims of this article were to elucidate the benefits of MP preservation with and without oxygenation, and/or under normothermic conditions, when compared with CS prior to deceased donor kidney transplantation.

Methods: Clinical (observational studies and prospective trials) and animal (experimental) articles exploring the use of renal MP were assessed (EMBASE, Medline, and Cochrane databases). Meta-analyses were conducted for the comparisons between hypothermic MP (hypothermic machine perfusion [HMP]) and CS (human studies) and normothermic MP (warm (normothermic) perfusion [WP]) compared with CS or HMP (animal studies). The primary outcome was allograft function. Secondary outcomes included graft and patient survival, acute rejection and parameters of tubular, glomerular and endothelial function. Subgroup analyses were conducted in expanded criteria (ECD) and donation after circulatory (DCD) death donors.

Results: A total of 101 studies (63 human and 38 animal) were included. There was a lower rate of delayed graft function in recipients with HMP donor grafts compared with CS kidneys (RR 0.77; 95% CI 0.69–0.87). Primary nonfunction (PNF) was reduced in ECD kidneys preserved by HMP (RR 0.28; 95% CI 0.09–0.89). Renal function in animal studies was significantly better in WP kidneys compared with both HMP (standardized mean difference [SMD] of peak creatinine 1.66; 95% CI 3.19 to 0.14) and CS (SMD of peak creatinine 1.72; 95% CI 3.09 to 0.34). MP improves renal preservation through the better maintenance of tubular, glomerular, and endothelial function and integrity.

Conclusions: HMP improves short-term outcomes after renal transplantation, with a less clear effect in the longer-term. There is considerable room for modification of the process to assess whether superior outcomes can be achieved through oxygenation, perfusion fluid manipulation, and alteration of perfusion temperature. In particular, correlative experimental (animal) data provides strong support for more clinical trials investigating normothermic MP.

Abbreviations: CI = confidence interval, CIT = cold ischemic time, CrCl = creatinine clearance, CS = cold (static) storage, DBD = donation after brain death, DCD = donation after circulatory death, DGF = delayed graft function, ECD = expanded criteria donor, EMS = exsanguinous metabolic support, FeNa = fractional excretion of sodium, HMP = hypothermic machine perfusion, HR = hazard ratio, KPS = kidney perfusion solution, MP = machine perfusion, MPS = machine perfusion solution, PGE1 = prostaglandin E1, PNF = primary nonfunction, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RR = risk ratio (relative risk), SMD = standardized mean difference, UW = University of Wisconsin, WIT = warm ischemic time, WP = warm (normothermic) perfusion.

Keywords: cold storage, DBD, DCD, ECD, kidney preservation, machine perfusion, warm perfusion

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1. Introduction

The most optimal long-term treatment option for end-stage renal disease remains kidney transplantation. On a worldwide basis, access and referral for transplantation is limited; in those patients referred for transplantation, there is an imbalance between the supply and demand for suitable organs.[1] In the United States alone, the median time to deceased donor renal transplantation is approximately 3 to 4 years.[2] This organ deficit has prompted the adoption of different strategies to increase the availability of kidneys for transplantation. One approach of considerable importance is the increasing utilization of donation after circulatory death (DCD) and expanded criteria donors (ECD), which must supplement the standard criteria, donation after brain death (DBD) kidneys.[1,3]

The growing demands for DCD and ECD kidneys must be balanced with their perceived suboptimal posttransplant function. There are higher rates of delayed graft function (DGF) for both DCD and ECD kidneys, and higher discard rates and by definition poorer survival in the ECD subset, when compared with standard criteria DBD kidneys.[4–10] Further improvements to the organ procurement and preservation process are therefore essential to improve marginal donor kidney quality.

Although cold static storage (CS) is still the most commonly utilized method for renal preservation, machine perfusion (MP) provides an important alternative. CS largely supplanted MP in the 1980s due to a lack of evidence with regards to improvement in transplantation outcomes and the large associated costs.[11–13] MP has seen a resurgence in the last decade due to the changing donor profile and advancements in perfusion solutions and technology.[14]

Indeed, application of MP is still not widespread, with conflicting evidence even in recent years regarding its utility.[15,16] Furthermore, there is minimal clinical data regarding the utility of evolving modifications to the MP process, and its mechanisms of action are also poorly understood. In particular, the use of warm (normothermic) perfusion (WP), oxygenation, or pharmacotherapies has largely been the subject of experimental (animal) studies.

The aims of this systematic review and meta-analysis were therefore to: describe ways in which MP is currently utilized; provide an updated and comprehensive analysis of the effect of hypothermic MP (HMP) on posttransplant graft function in deceased donor kidney transplantation; and explore experimental (animal) literature to investigate the utility of normothermic (WP) and/or oxygenated MP, and understand the mechanisms of action of MP preservation.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, http://links.lww.com/MD/B324) was utilized in the completion of this review (see Table, http://links.lww.com/MD/B325).[17] The review protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (March, 2016; registration number—CRD42016037100).[18]

2.1. Eligibility

2.1.1. Inclusion criteria. Clinical (human) studies consisted of randomized control trials (RCT) or prospective (nonrandomized) and observational studies, and were included in the presence of MP data. Experimental (animal) studies by their nature are prospective, and were included in the presence of comparative data either between different types of MP, and/or MP and an alternative form of preservation. Both English and non-English articles were considered, utilizing a translator if necessary. Only published works, and not conference abstracts, were included; although there is some evidence to suggest that gray literature exclusion can contribute to publication bias,[19] these abstracts were all assessed and deemed to have either insufficient data or quality for inclusion.

2.1.2. Exclusion criteria. Clinical/human studies were excluded if less than 10 patients were in the MP group, or there was significant data and/or patient overlap between 2 or more published studies, and/or there was insufficient data with regards to delayed graft function, primary nonfunction (PNF), or graft/patient survival. These parameters were chosen as they were the most commonly and uniformly reported in the studies analyzed. For animal studies, an article was excluded if there was no appropriate control group for comparison, and/or there was a lack of a reperfusion period (either ex vivo or in vivo) after MP preservation. All studies prior to 1980 were excluded. This publication year reflects a time after which there was a distinct shift in the type of perfusion machines and perfusion solutions used.

2.2. Search strategy

The EMBASE, Medline, and Cochrane (1980–December 2015) databases were searched using Ovid, with key search terms including "kidney or renal" and "machine perfusion" (see Table, Supplemental Digital Content 2, for complete strategy, http://links.lww.com/MD/B326). In an effort to include all eligible studies, a manual literature search was also conducted using any potential articles' bibliographies, in addition to reference lists from other reviews.

2.3. Data collection

Data was extracted from each article by 2 independent reviewers utilizing a predetermined template; a third reviewer was consulted if necessary for any disagreements.

2.3.1. Clinical (human) data. Human data was analyzed for the extraction of the following: date of publication and study period; study type (i.e., prospective or retrospective); kidney allocation; study center(s); patients in MP and CS groups; stratification of MP and CS patients by DBD, DCD, and ECD status; MP characteristics, including the use of oxygenation and preservation temperature; perfusion machine(s) used; and the preservation solution(s) used in CS and MP groups. Quantitative data was extracted for—the incidence of DGF and primary nonfunction (PNF), 1-year graft and patient survival in the whole cohort, acute rejection rates, and posttransplant renal function (CrCl in mL/min and serum creatinine in mg/dL). DGF was defined as the need for dialysis in the first week after transplantation.[20] Only 6 studies either utilized an alternate definition of DGF, or did not define DGF.

Hazard ratios (HR) for graft survival were calculated, when possible, using the methods described by Tierney et al.[21]

Although the "ECD" graft description is not as descriptively useful as a high Kidney Donor Profile Index donor kidney, ECD is used in this manuscript as it is the most commonly utilized term in the included literature.

2.3.2. Experimental (animal) data. Study parameters collected for animal data included: date of publication, institution(s) involved, animal/species employed, weight range of animals, experimental procedure(s)/model employed (study groups, DCD or DBD, ex vivo perfusion or transplantation after preservation, experimental period), number of animals in each group, cold/warm ischemic times, perfusion machine and settings used, preservation/perfusion solution(s) used, additives to preservation/perfusion solution(s), temperature of preservation/perfusion, and the use of oxygen. Study outcomes consisted of renal function parameters (peak creatinine in mg/dL, creatinine clearance (CrCl) in mL/min,), renal tubule parameters (fractional excretion of sodium (Na) (FeNa); enzymatic markers of tubular damage), glomerular parameters (proteinuria), endothelial injury parameters, markers of inflammation, oxidative stress markers, microcirculatory tissue perfusion post-preservation, oxygen consumption, histology, and animal survival.

The standardized mean difference (SMD) was calculated between comparator groups for peak creatinine, CrCl, FeNa, and survival using an effects size calculator.[22]

2.4. Bias assessment

2.4.1. Clinical (human) data. Bias assessment of prospective cohort studies included in the meta-analyses was performed using the Newcastle–Ottawa quality assessment scale for cohort studies.[23] RCT study quality was assessed using the Cochrane Collaboration's tool.[24]

2.4.2. Experimental (animal) data. Animal experimental studies have several important differences in comparison to clinical studies. As such, SYRCLE risk of bias tool for animal studies was instead utilized to assess the quality of animal data included in meta-analyses.[25]

2.5. Synthesis and analysis of results

Observational (retrospective) human studies, in conjunction with prospective studies, were collated to systematically summarize the current parameters of MP utilization clinically. Observational studies were not included in subsequent formal quantitative analyses.

Similarly, animal studies comparing HMP and CS were only utilized to explore mechanisms of MP preservation. As there are multiple human studies focusing on the comparison between HMP and CS, animal studies for this comparator group were not formally meta-analyzed to avoid additional heterogeneity.

2.6. Meta-analyses

In general, the HMP or WP groups were considered the intervention group when compared with CS; the intervention group was WP when compared with HMP, and oxygenated HMP when compared with nonoxygenated HMP. In the event of multiple experimental groups and 1 control group, each different experimental group was compared with the control group and analyzed as a separate study.

2.6.1. Human (clinical) data. Only prospective studies were included in meta-analyses. As only 1 study utilized WP[26] it could not be separately analyzed. Therefore, studies comparing HMP to CS were meta-analyzed. Further subgroup analyses for HMP versus CS in DCD and ECD donors were undertaken. In the event that 1 article presented the results from a subgroup of a larger study, the ECD or DCD donor results were only included in subgroup analyses. Forest plots denoting relative risk (RR) were constructed for DGF and PNF; HR was utilized in graft survival plots.

2.6.2. Animal (experimental) data. Meta-analyses were undertaken for studies comparing WP to CS or HMP, and oxygenated HMP to nonoxygenated HMP. All WP studies employed a DCD model so further subgroup analyses could not be undertaken. Forest plots were created for the SMD of relevant quantitative parameters.

Meta-analyses were performed for the above comparator groups using Comprehensive Meta-Analysis Version 2.2 (Biostat Inc, Englewood, NJ). The I^2 statistic was used to analyze study heterogeneity, with values $\geq 50\%$ indicating high levels of heterogeneity. In these cases, a random effects model was used; otherwise, a fixed effects model was employed. Publication bias was assessed using funnel plots. A P value <0.05 denotes statistical significance, and meta-analysis results are presented with 95% confidence intervals (CI).

3. Results

3.1. Summary clinical and experimental study characteristics

Both human and animal studies were analyzed in the formulation of this systematic review, with human studies used in comparisons between HMP and CS, and animal articles utilized for the analysis of oxygenated HMP, WP, and the mechanisms of MP. In total, 63 human and 38 animal studies met inclusion criteria for which data was extracted for both quantitative and qualitative analyses. Figure 1 outlines the study selection process. Baseline study characteristics are outlined in Supplemental Digital Content 3, http://links.lww.com/MD/B327 and 4, http://links.lww.com/MD/B328 (Tables), while Table 1 summarizes preservation and perfusion parameters for all studies.[27,28]

3.2. Human (clinical) data

3.2.1. MP parameters for deceased human donor kidney preservation (all studies). University of Wisconsin (UW)-based MP solutions were the most commonly utilized preservation solutions in human MP (Table 1). Perfusion fluid was pumped through kidneys using Waters or LifePort MP apparatus in most cases (Table 1). Pulsatile perfusion was employed in the vast majority of studies; only 2 (3.2%) articles specified the use of nonpulsatile MP.[29,30] Median perfusion pressure was 50 mm Hg (range 30–60 mm Hg) in HMP articles, while the 1 WP study used pressures of 52 to 70 mm Hg.[26]

Pharmacologic manipulation of the perfusate was minimal, with only 8 (12.7%) human studies entertaining the addition of nonstandard additives (Table 1), and 4 (6.3%) of articles utilizing oxygenated MP. All but 1 human study utilized HMP; in the WP study the perfusate was warmed to a temperature of 32° to 36°C.[26]

The duration and location of placement of kidneys on the machine varied between centers. In particular, 18 of 63 (28.6%) of articles specified the use of CS in conjunction with MP; in these cases, MP was usually commenced upon arrival to the recipient center. Kidneys that underwent MP tended to have greater median CITs compared with CS kidneys (23.4 vs 19.5 hours, respectively) (see Table, Supplemental Digital Content 3, http://links.lww.com/MD/B327), largely reflecting the use of MP as a possible means to extend preservation times.

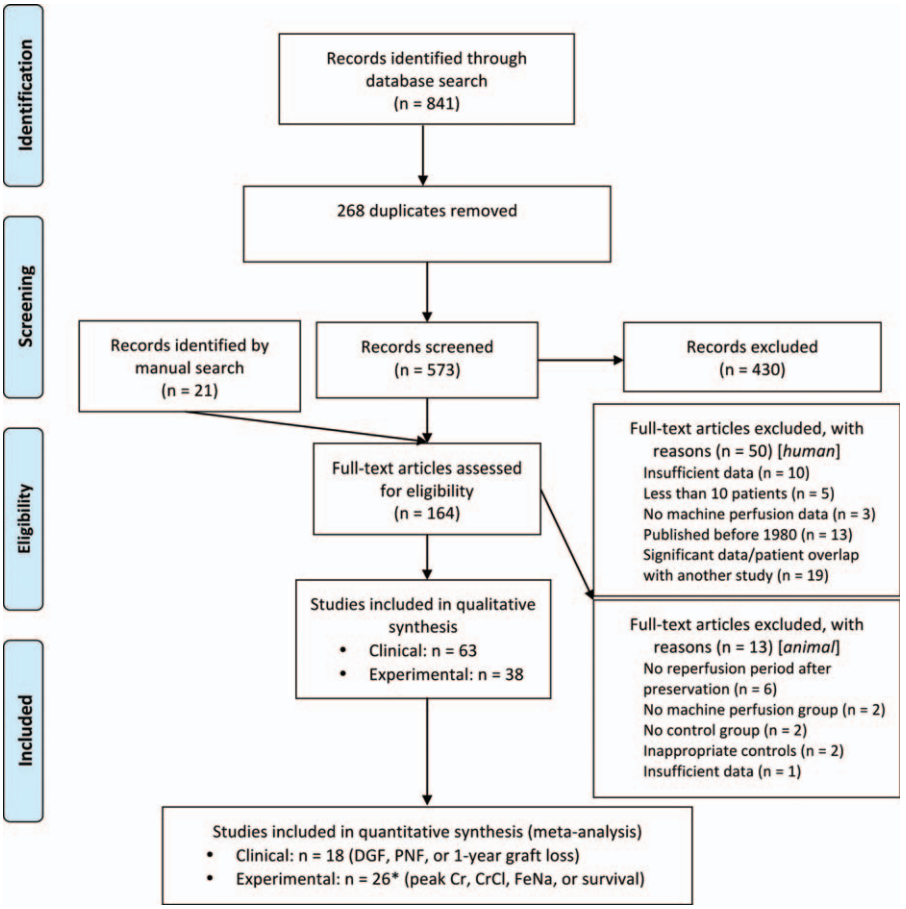

Figure 1. Study selection flow diagram.

3.2.2. Meta-analyses (prospective studies). Eighteen studies were included in the human meta-analysis, out of which 11 (61.1%) articles were RCTs, and 7 (38.9%) studies were prospective but nonrandomized (prospective cohorts). As there was only 1 study comparing WP to CS, WP could not be directly compared with other preservation methods using the human studies.

Forest plots of selected meta-analyses are shown in Figure 2, with all results tabulated in Supplemental Digital Content 5, http://links.lww.com/MD/B329.

Human studies displayed the short-term advantages of MP when compared with CS. The RR (unadjusted) of DGF for HMP versus CS studies was 0.77 (95% CI 0.69–0.87; $P<0.001$). Within the DCD kidney subgroup, the RR of DGF was 0.78 (95% CI 0.66–0.91; $P=0.002$), while it was 0.67 for ECD donors (95% CI 0.42–1.08; $P=0.097$). It should be noted that only 2 studies were available for the ECD comparison. A significant difference in PNF rates between HMP and CS was only detected in the ECD cohort (RR 0.28, 95% CI 0.09–0.89; $P=0.031$).

The medium to long-term effects of MP were less clear. With respect to graft failure rates within the first year, there was no difference between HMP and CS overall (HR 1.25, 95% CI 0.20–7.62; $P=0.81$). Insufficient data precluded HR calculations for further subgroup analyses, or for the comparison of patient survival between the HMP and CS groups.

3.2.3. Meta-analysis publication bias and heterogeneity (prospective studies). Visual assessment of funnel plots displayed no significant asymmetry when comparing HMP to CS for the DGF parameter. There was only mild asymmetry in favor of positive studies for studies comparing PNF (see Figure, Supplemental Digital Content 6, for funnel plots, http://links.lww.com/MD/B330). Study heterogeneity was low for a majority of parameters (see Table, Supplemental Digital Content 5, http://links.lww.com/MD/B229).

3.2.4. Trends in 1-year graft loss and patient survival (prospective studies). Meta-analyses for graft loss/survival at 1 year could only be conducted in 2 studies. In 1 of these studies by Moers et al, graft loss at 1 year was significantly higher in the CS group compared with HMP (HR 0.52; $P=0.03$); this finding was maintained in the ECD (HR 0.35; $P=0.02$) but not DCD subgroups (HR 1.29; $P=0.7$) in subsequent expansions of the study cohorts.[16,31,32] Graft loss (survival) data for the 1 year time-point were available in 8 further prospective studies. Although there were no statistically significant differences between HMP and CS, there was a trend toward higher survival after HMP in 4 studies, including 1 article investigating ECD kidneys.[33–36] In contrast, although still underpowered to produce statistical significance, 2 studies indicated higher survival in CS kidneys, with 1 of these studies analyzing DCD kidneys.[37,38]

There were 7 prospective studies with results available for patient survival 1 year posttransplant.[15,16,31–34,36] Median survivals were 94.9% (range 80.6–97%) for HMP kidneys, and 96.7% (range 77.7–100%) for CS kidneys. No study reported

Table 1

Summary human and animal study perfusion and preservation characteristics[‡].

Humans	Preservation solution [*n* studies][*,†]	Additives to perfusion solution[§,*]	Perfusion machine [*n* studies][*]	Storage/perfusion temperature [range, °C][*]	Use of oxygen, *n* studies[*]
CS	EC [14] HTK [3] Other [4] UW [15]	N/A	N/A	Hypothermic	Nil
MP	Plasma/albumin-based [16] Other [3][‖] UW[#] [32]	α-Ketoglutarate L-Arginine N-Acetylcysteine Papaverine PEG-SOD Phentolamine Prostacyclin PGE1 Verapamil	Gambro [4] LifePort [16] Other [5] Waters (RM3 or MOX-100) [31]	Hypothermic [1–8] Normothermic [34.6][**]	4 [3 × HMP; 1 × WP]

Animals	Preservation solution [*n* studies][*,†]	Additives to perfusion solution[*,§]	Perfusion machine [*n* studies][*]	Storage/perfusion temperature [range, °C][*]	Use of oxygen, *n* studies [pO_2 mm Hg][*]
CS	HTK [9] HOC [3] Other [2] UW [11]	N/A	N/A	Hypothermic	Nil
HMP	Albumin-based [3] Custodiol-N/dextran[##] [5] HTK [3] Other [4] UW[#] [21]	Alanine[‡‡] Aspartate[‡‡] Deferoxamine[‡‡] Glycine[‡‡] L-arginine[‡‡] PEG[§§]	Belzer [2] Gambro [3] LifePort [10] Other [5] Waters (RM3 or MOX-100) [8]	Hypothermic [0–8]	19 [150–800]
WP	Blood [6][††] Custodiol-N/dextran [2] EMS medium [5] Other [1]	Components of EMS media[¶¶] FGF Sodium nitroprusside	EMS technology [4] IOPS[‖‖] [4] Other [3]	Subnormo/normo-thermic [20–38]	14 [150–700]

CS = cold (static) storage, EC = Euro-Collins, EMS = exsanguinous metabolic support, FGF = fibroblast growth factor, HMP = hypothermic machine perfusion, HOC = hyperosmolar citrate, HTK = histidine–tryptophan–ketoglutarate, IOPS = isolated organ perfusion system, MP = machine perfusion, PEG = polyethylene glycol, PEG-SOD = polyethylene glycol-superoxide dismutase, PGE1 = prostaglandin E1, UW = University of Wisconsin, WP = warm (normothermic, machine) perfusion.

[*] Where recorded.

[†] Each study may have used >1 perfusion/preservation solution (for different experimental groups).

[‡] Excluding subgroups in study counts.

[§] In addition to "standard" additives such as insulin, penicillin and dexamethasone, as instructed by manufacturers of UW solution—see UW product sheet.[28]

[‖] Plasma-free packed red cells + Ringer solution used in WP study.

[¶] Excludes any potential CS solution used prior to MP.

[#] UW solution developed for MP (in contrast to UW used in CS); includes kidney perfusion solution (KPS) 1, and Belzer machine perfusion solution (MPS).

[**] n = 1 study.

[††] In some cases leukocyte-depleted.

[‡‡] Part of Custodiol-N solution.

[§§] As part of Institut Georges Lopez (IGL)-1 solution (substitute for hydroxyl ethyl starch in extracellular UW solution).[138]

[‖‖] Based on pediatric cardiopulmonary bypass apparatus.

[¶¶] See Brasile et al.[27]

[##] Modified form of HTK.

statistically significant differences between either preservation method.

Nicholson and Hosgood[26] presented the only human study exploring the use of WP for renal preservation. The WP cohort impressively had 100% 1 year graft and patient survival rates, although there were only 18 patients in the WP group.

3.2.5. Graft rejection (prospective studies). Acute graft rejection rates were not statistically comparable owing to variable definitions and immunosuppression. Rejection rates were no different in the multicenter trial by Moers et al[16] (13.7% for CS vs 13.1% for MP). In contrast, 3 prospective studies showed a strong trend toward lower rates of acute rejection in the HMP group, although this did not reach significance.[15,39,40]

3.2.6. Risk of bias assessment (prospective studies). The risk of bias assessment of cohort studies is summarized in Supplemental Digital Content 7, http://links.lww.com/MD/B331 (Figure). Six out of 8 domains in the assessment scale were adequately covered in at least 60% of studies. Comparability of cohorts in study design or analysis was less adequately covered, as a proportion of studies did not appropriately account for factors such as organ ischemic times. Supplemental Digital Content 8, http://links.lww.com/MD/B332 (Table) displays the risk of bias assessment for the included RCTs upon utilization of the Cochrane

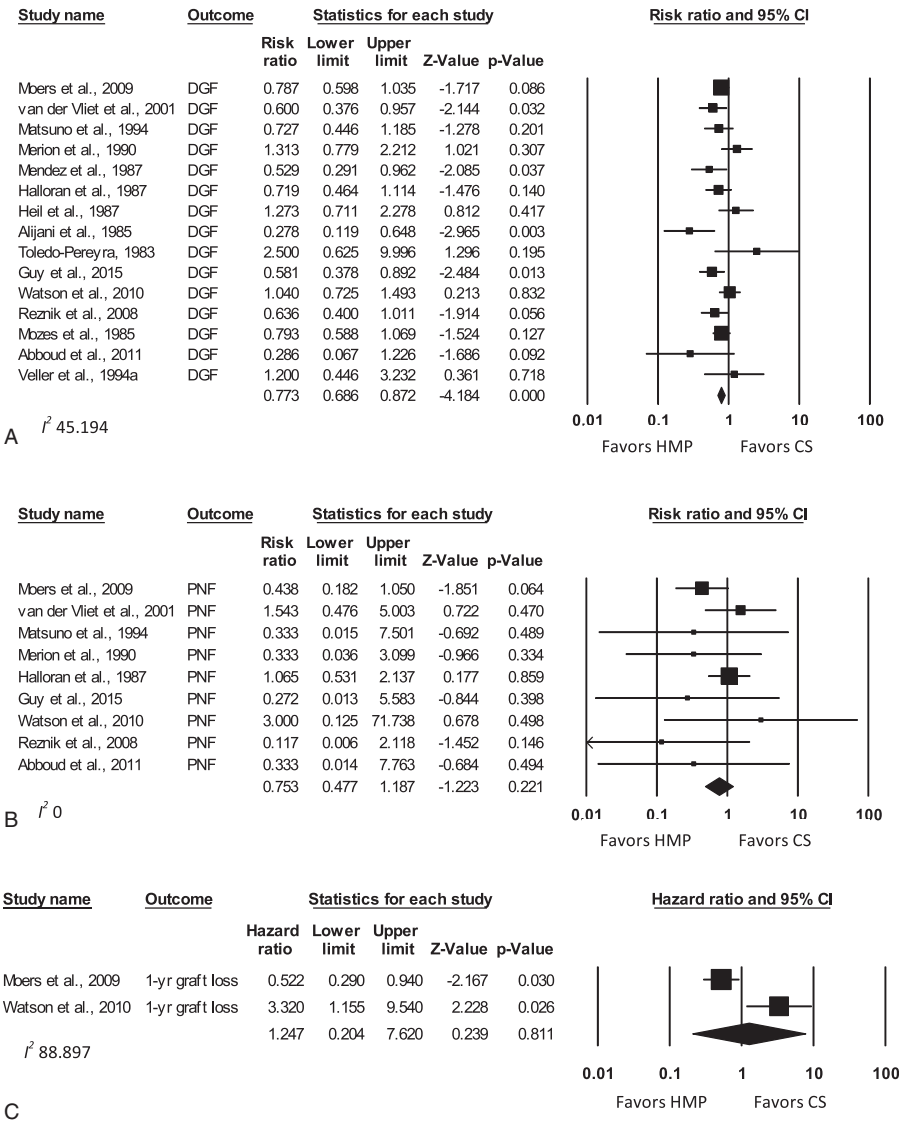

Figure 2. Forest plots comparing DGF (A), PNF (B), and 1-year graft loss (C) for all studies comparing HMP to CS—human studies. Data expressed as RR (for DGF and PNF) and HR (for graft loss) ± 95% CI. Different analyses within the same study are denoted by an alphabetical letter suffix (e.g., "a"). CI = confidence interval, CS = cold (static) storage, DGF = delayed graft function, HMP = hypothermic machine perfusion, HR = hazard ratio, PNF = primary nonfunction.

Collaboration bias tool.[24] Across studies, it can be seen that there is a low risk of bias in at least 3 of the domains. Within the domains of blinding and allocation concealment, however, at least half of the studies were at risk of selection and performance bias.

4. Animal (experimental) data

4.1. MP characteristics (all studies)

In stark contrast to human studies, 30 of 38 (78.9%) animal articles utilized oxygenated MP. Furthermore, WP, including subnormothermic MP, was used in 14 (36.8%) of the included animal studies (see Table, Supplemental Digital Content 4, http://links.lww.com/MD/B328). As such, further quantitative analyses regarding oxygenated and/or WP were undertaken in animal studies.

4.2. Meta-analyses (oxygenated HMP and WP studies)

There were 10 distinct animal data-sets utilized in the meta-analyses that compared CS to WP, while 11 studies were included that compared HMP with WP and 5 studies were available for the comparison between oxygenated and nonoxygenated HMP.

Figure 3 displays forest plots of selected meta-analyses, with results tabulated in Supplemental Digital Content 9, http://links.lww.com/MD/B333.

Postpreservation renal function in animal experiments was assessed using the parameters of peak creatinine, CrCl and FeNa, and animal survival during the experimental period. Peak creatinine values were significantly lower in animal groups utilizing WP (SMD −1.72, 95% CI −3.09 to −0.34; $P=0.014$) when compared with CS. The SMD of peak serum creatinine levels in the WP group was also significantly lower when compared with the HMP group (−1.66, 95% CI −3.19 to −0.14; $P=0.033$). There was no significant difference however between peak creatinine levels in the oxygenated HMP versus non-oxygenated HMP group (SMD −0.39, 95% CI −1.85 to 1.08; $P=0.60$); however, there were only 2 studies eligible for this comparison.[41,42] However, the SMD of peak CrCl between the WP and HMP (0.83, 95% CI −0.50 to 2.15; $P=0.22$) and CS

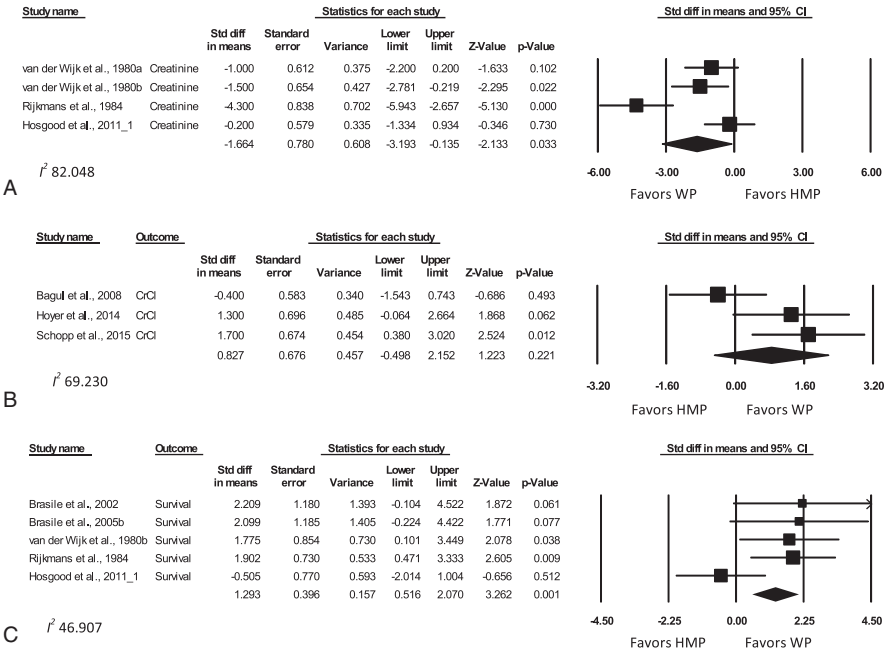

Figure 3. Forest plots comparing peak creatinine (A), peak CrCl (B), and survival (C) for WP compared with HMP—animal studies. Data presented as SMD ± 95% CI. Different analyses within the same study are denoted by an alphabetical letter suffix (e.g., "a"). HMP = hypothermic machine perfusion, SMD = standardized mean difference, WP = warm (normothermic) perfusion.

(2.08, 95% CI −1.83 to 6.00; $P=0.22$) groups was not significantly different.

FeNa could not be compared between WP and other groups due to an insufficient number of studies. Importantly, pooled FeNa was significantly lower in studies comparing oxygenated to nonoxygenated HMP (SMD −1.54; 95% CI −2.54 to −0.54; $P=0.002$).

Animal survival in such studies is a reflection of maintenance of renal function as opposed to actual survival per se as the vast majority of deaths reflected euthanasia after manifestation of features of renal failure. Importantly, WP once again demonstrated its superiority over HMP (SMD 1.29; 95% CI 0.52–2.07; $P=0.001$). There was not enough data to analyze this parameter for WP compared with CS groups.

4.3. Meta-analysis publication bias and heterogeneity (WP studies)

Analysis of funnel plots did not display significant asymmetry when comparing peak creatinine between WP and the HMP or CS groups (see Figure, Supplemental Digital Content 10, for funnel plots, http://links.lww.com/MD/B334). Study heterogeneity was high for most parameters (see Table, Supplemental Digital Content 9, http://links.lww.com/MD/B333).

4.4. Mechanisms of action of MP—tubules, glomeruli, and endothelium (all studies)

The animal studies outlined comparisons between experimental and control groups for a wide range of parameters that could not be meta-analyzed due to significant variability in reporting between different studies. These functional indicators are displayed in Table 2,[41–61] and can broadly be characterized into those relating to tubular, glomerular, or endothelial function or damage, oxidative stress, levels of inflammation, microcirculatory tissue perfusion, and oxygen consumption. Histology was not included in this analysis due to wide variability in the reporting of histological criteria. Broadly, improved tubular function with a reduction in tubular injury, improved glomerular function, and reduced endothelial injury seemed to be evident after the utilization of HMP compared with CS. Furthermore, HMP appeared to improve renal cortical microcirculation. There was no obvious advantage for any experimental group regarding markers of inflammation or oxidative stress. Furthermore, with the exception of higher oxygen consumption in all 3 studies comparing WP with CS, no clear differences could be elucidated between the other experimental and control groups (Table 2).

4.5. Risk of bias assessment (all studies)

Animal study bias assessment was performed using SYRCLE assessment tool[25] and is summarized in Supplemental Digital Content 11, http://links.lww.com/MD/B335 (Figure). Overall, there were very few domains in which there was clearly a high risk of bias. In 6 out of the 10 parameters however, bias assessment was largely unclear as the domains could not be analyzed from the available study data.

5. Discussion

This systematic review and meta-analysis provides a comprehensive and up-to-date insight into the current published literature regarding MP preservation of renal grafts prior to transplantation in the clinical setting. Animal data was included to explore modifications to MP that are as yet grossly under-explored in human studies, namely WP and oxygenated MP, in addition to allowing the development of a greater mechanistic understanding of MP.

Table 2

Tubular, glomerular, and endothelial function and damage in animal studies*.

	CS vs HMP [*n* studies/total]	HMP vs WP [*n* studies/total]	CS vs WP [*n* studies/total]	HMP No-O_2 vs HMP-O_2 [*n* studies/total]
Tubules	Lower FeNa: CS—0/8 HMP—8/8 Higher serum/urine tubular damage markers†: CS—7/11 HMP—0/11	Lower FeNa: HMP—0/2 WP—1/2 Higher serum/urine tubular damage markers†: HMP—0/3 WP—1/3	Lower FeNa: CS—1/4 WP—3/4 Higher serum/urine tubular damage markers†: CS—2/4 WP—1/4	Lower FeNa: No-O_2—0/2 O_2—0/2 Higher serum/urine tubular damage markers†: No-O_2—2/5 O_2—0/5
Glomeruli	Lower proteinuria: CS—1/6 HMP—4/6	Lower proteinuria: HMP—0/1 WP—0/1	Lower proteinuria: CS—NR WP—NR	Lower proteinuria: No-O_2—0/1 O_2—1/1
Endothelium	Higher injury markers ‡: CS—3/5 HMP—1/5	Higher injury markers ‡: HMP—0/1 WP—0/1	Higher injury markers ‡: CS—1/3 WP—0/3	Higher injury markers ‡: No-O_2—1/1 O_2—0/1
Inflammation	Increased inflammatory markers§: CS—1/5 HMP—2/5	Increased inflammatory markers§: HMP—0/2 WP—1/2	Increased inflammatory markers§: CS—0/2 WP—1/2	Increased inflammatory markers§: No-O_2—0/1 O_2—0/1
Oxidative stress	Elevated markers of oxidative stress‖: CS—2/4 HP—2/4	Elevated markers of oxidative stress‖: HMP—1/1 WP—0/1	Elevated markers of oxidative stress‖: vCS—0/1 WP—1/1	Elevated markers of oxidative stress‖: No-O_2—1/2 O_2—2/2¶
Microcirculation#	Better cortical microcirculation**: CS—0/4 HMP—4/4	Better cortical microcirculation**: HMP—NR WP—NR	Better cortical microcirculation**: CS—NR WP—NR	Better cortical microcirculation**: No-O_2—0/1 O_2—0/1
O_2 consumption	Higher O_2 consumption††: 1 HMP—0/5	Higher O_2 consumption††: HMP—0/2 WP—1/2	Higher O_2 consumption††: CS—0/3 WP—3/3	Higher O_2 consumption††: No-O_2—0/3 O_2—0/3

CS = cold (static) storage, HMP = hypothermic machine perfusion, NR = not recorded, WP = warm (machine) perfusion.

* Number of studies for each respective outcome included only if statistically significant difference recorded in each study (see meta-analyses for pooled outcomes for FeNa); in studies where there were >2 study groups, study outcome(s) only included for comparable groups.

† Markers measured (references): alanine aminopeptidase[45,54]; aspartate aminotransferase[42,52,57]; gamma-glutamyl transpeptidase[48]; lactate dehydrogenase[41,48,49,52,56,58,59,61]; liver fatty acid binding protein[46,47]; N-acetyl-β-D-glucosaminidase.[45,54]

‡ Endothelial injury markers (references): endothelin-1[46,52,53,59,61]; thrombomodulin[41]; von Willebrand factor.[45,55,57]

§ Inflammatory markers (references): high mobility group protein B1[55]; intercellular adhesion molecule 1[55]; interleukin-6[59,60]; myeloperoxidase activity[52]; nuclear factor kappa B1[53]; toll-like receptor 4[55]; tumor necrosis factor α.[48,60]

‖ Free radical damage/oxidative stress markers (references): 8-isoprostane[52,56,59]; malondialdehyde[51]; oxidized to total glutathione ratio[54]; thiobarbituric acid reactive substances[45,50]; unspecified lipid peroxidation products.[41]

¶ In Gallinat et al,[41] lipid peroxidation products significantly lower in the no oxygen group during preservation (perfusion), with the opposite true after transplantation; in Hoyer et al,[50] markers of oxidative damage were also measured during preservation (perfusion), and were lower in the no oxygen group.

Assessed as mean cortical erythrocyte flux 10 minutes postreperfusion by Laser Doppler flowmetry.

** Studies included.[41,43,45,46,55]

†† Studies included.[44,47–49,52,56,59,61]

We show a definite reduction in DGF post-HMP preservation for renal allografts in humans when compared with CS, including in DCD and ECD kidneys. PNF appeared to be reduced in the ECD subset. There was not enough data to give sufficient power to comparisons of 1 year graft survival by meta-analysis, and subgroup analyses could not be conducted for this parameter. One-year patient survival was comparable among the different studies. We obtained mixed results regarding the benefits of oxygenated HMP. Furthermore, although there was only 1 human study that employed WP,[26] multiple animal studies showed its advantages over both CS and HMP kidneys in terms of posttransplantation creatinine levels and animal survival. Animal study results showed mechanisms for improved allograft function in MP kidneys, including better tubular and glomerular function, and less endothelial damage.

Increased demands for donor kidneys have necessitated the use of more marginal organs for transplantation. Indeed, any method such as MP that will increase the pool of usable kidneys can benefit developing and developed countries alike, especially due to the often prohibitively high costs associated with long-term dialysis, and should be explored further.[1] A detailed economic analysis by Wight et al,[62] albeit from 2003, showed that MP is likely to be more effective than CS in the long-term, with an economic benefit more pronounced when MP preservation is applied to DCD kidneys. While Groen et al[63] in 2012 could not make the same conclusion for DCD transplants due to insufficient numbers, these authors found reduced costs after MP in the ECD subset, largely due to a reduced need for post-transplantation dialysis and hospital bed-stays.

Mechanistically, MP reduces preservation-related damage and aids renal recovery through a variety of mechanisms. ATP levels, and thus energy homeostasis, are better preserved in perfused kidneys.[43,44] Tubular and glomerular integrity seems to be aided by MP, an assertion that is supported by the reduction in markers of tubular damage and improved tubular and glomerular function seen after MP as compared with CS (Table 2). Furthermore, MP ensures better reperfusion of grafts as measured by cortical microcirculation; this is likely related to a reduction in endothelial damage and swelling[43,45] (Table 2). The flow cessation itself in CS as compared with MP likely

contributes to the increased endothelial dysfunction in CS grafts.[64] The pulsatile aspect of MP likely has an important effect on the maintenance of endothelial integrity, as pulsatile-perfused kidneys compared with nonpulsatile MP have been shown to have higher renal vascular flow, reduced expression of endothelin-1, and increased expression of the vasoprotective kruppel-like factors and nitric oxide.[46] We did not however find significant support for less inflammation and oxidative stress in the HMP group (Table 2), although recent evidence suggests that apoptosis and inflammation may be reduced in HMP through up-regulation of aldehyde dehydrogenase 2 and reduction in expression of nuclear factor-κB and matrix metalloproteinase 9.[65,66]

In congruence with previous systematic reviews[8,67–69] our data shows that DGF is undoubtedly reduced in patients undergoing MP compared with CS. We additionally showed the possibility of reduced PNF after HMP preservation of ECD kidneys. In contrast to Jiao et al[70] however, we could not find statistical evidence for improved graft survival in the ECD cohort, due to a lack of available HR data that could subsequently be pooled. Furthermore, statistical methods in the former study are flawed, with survival analyses conducted using OR instead of HR; in addition, 2 out of the 3 studies in their survival analysis had significant patient overlap.[70] Perhaps most pertinently however, the pivotal large-scale and multicenter RCT performed by Moers et al showed significantly improved graft survival in HMP patients, with this survival advantage still present after 3 years in DBD and especially ECD kidneys, but not in kidneys from DCD donors.[16,71,72]

While Moers et al study provides evidence regarding the efficacy of machine perfusion as it is utilized currently, our analysis of all retrospective and prospective MP studies in humans to date show that it is still employed in a very limited fashion, with considerable room for modification to maximize the potentials of this technique. In particular, temperature modification, oxygenation, and pharmacologic manipulation of perfusion solutions are all in their infancy with regard to human renal preservation via MP.

The inclusion of animal data has allowed this review to capture the possible future of MP, as this experimental work has not yet caught up with application to the clinic. In particular, a reasonable deduction can be made regarding the applicability and potential success of WP, which currently has little human data. WP reverses the pivotal concept of hypothermia in organ preservation, sustaining normal metabolic rates with an oxygenated red blood cell-based perfusate. Compared with CS and HMP kidneys, WP kidneys had significantly lower peak creatinine and better survival (Fig. 3; also see Table, Supplemental Digital Content 9, http://links.lww.com/MD/B333). Nicholson and Hosgood[26] utilized WP in human ECD kidney grafts, and also reported lower rates of DGF compared with CS. WP potentially reduces the possibility of irreversible cold-induced metabolic disruption in addition to reducing ischemia-reperfusion injury upon commencement of normothermic reperfusion in vivo.[27,65,73]

An alternative to WP at body temperature is the concept of subnormothermic MP, successfully utilized here in 2 studies.[47,48] Subnormothermic perfusion helps avoid the injuries induced by cold ischemia without necessitating a significant change in perfusion equipment or solutions.[48] In addition, it guards against the pitfalls inherent to an immediate temperature shift from hypothermia to body temperature upon postanastomotic reperfusion.[47]

The perfusion solution and its additives potentially have a major impact on the effectiveness of kidney preservation. UW or a modified form of UW was the most commonly employed solution for CS and MP in both animal and human studies (Table 1), which is not surprising considering its proven efficacy.[66] Although there is considerable ongoing research into pharmacological manipulation of organ preservation solutions, surprisingly few studies utilized additives to try and change graft outcomes (Table 1). Pathophysiological targets for these additives include free-radical injury, endothelial damage, and vasoconstriction, the complement cascade, and apoptosis.[74–78] These processes were in some cases targeted as part of new perfusion solutions, including Custodiol-N, Vasosol, and Exsanguinous Metabolic Support (EMS) media.[74,76,78,79] It is difficult to ascertain individual effects of each pharmacologic agent, as few studies undertook direct comparisons between them. Guarrera et al[78] compared Vasosol solution, which contains vasodilatory agents such as prostaglandin E1 (PGE1) and nitroglycerin, and the antioxidant N-acetylcysteine, to UW (Belzer MPS), and showed significant lower DGF rates in the Vasosol group. The addition of PGE1 to UW was also shown to be effective in another study.[76] Other pharmacological therapies that may be incorporated into renal preservation are reviewed by Chatauret et al.[80]

Oxygenation is also a pharmacologic intervention that can be applied to HMP. Its use was much more prevalent in animal studies, with comparisons showing significantly lower FeNa in the oxygenated HMP compared to nonoxygenated HMP group (see Table, Supplemental Digital Content 9, http://links.lww.com/MD/B333). The absence of a statistical difference with regards to peak creatinine may be explained by the fact that there were only 2 studies for comparison.[41,42] Active oxygenation of the perfusate may potentially increase the generation of reactive oxygen species (see Table 2), although this was not supported posttransplantation in the study by Gallinat et al.[41] In contrast, the use of oxygen during HMP is purported to restore adequate mitochondrial and cellular homeostasis prior to reperfusion.[49,50] An alternative to oxygenated MP is the use of persufflation, through which oxygen can be delivered to the kidneys directly through its vasculature. Suszynski et al[81] summarize the utility of persufflation for renal preservation; this technique was compared to CS and HMP by Treckmann et al,[51] with persufflated kidneys having significantly lower creatinine levels posttransplantation compared with HMP.

Limitations of this review include the suboptimal comparability of HMP and CS cohorts within the human studies. This was largely due to the fact that CIT for human MP kidneys was higher than that for CS kidneys (see Table, Supplemental Digital Content 3, http://links.lww.com/MD/B327), which is not surprising given that MP is often used as a means to extend the period of preservation. Furthermore, a not insignificant proportion of RCTs suffered from features of selection bias due to poor blinding and allocation concealment. Additionally, it is difficult to tease out the impact of MP solutions on the overall effect of MP, as a variety of solutions were utilized that were usually different to the CS control. Animal studies, although informative, were quite heterogeneous and difficult to formally assess for bias. We attempted to minimize bias by excluding all retrospective studies from the meta-analyses, and in order to account for any study heterogeneity a random effects model was employed to help reduce type I error.

In summary, we have shown distinct short-term advantages in the use of MP over CS for the preservation of renal allografts,

especially with regards to the reduction of DGF. ECD graft recipients may benefit further from a reduction in PNF rates. In the medium to long-term, there is likely a survival and cost advantage for ECD kidneys that have undergone MP in this way. Although results from animal studies should be interpreted with more caution, they show some mechanistic advantages to the use of oxygenated MP, and distinct functional improvements upon the use of normothermic perfusion; this should provide a further stimulus for MP oxygenation and WP human trials. We strongly encourage additional exploration and enhancement of the MP preservation technique, through a variety of modifications based on the presented experimental evidence, which may improve its short and long-term efficacy.

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