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Optimizing organs for transplantation; advancements in perfusion and preservation methods

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Introduction

Transplantation provides life-saving treatment for patients suffering from end-stage organ failure and consequently the demand for transplantable organs has grown substantially. Increased rates of transplantation have coincided with improvements in organ management and surgical techniques. However, despite remarkable advances, a discrepancy between demand and availability continues to grow and the shortage of donors for transplantation remains a worldwide problem.

In the United States 63,593 registrants and 58,664 candidates were added to the transplant waitlist in 2018, while only 36,529 patients were transplanted from living and deceased donors (based on OPTN data Jan. 2019). Due to the growing need for available organs, an interest has developed in the use of marginal organs from deceased donors. In order to predict a relative risk of posttransplant kidney failure with the use of marginal kidney organs, and to 'longevity match' these organs to recipients that can best be served by their use, the United Network for Organ Sharing (UNOS) has adopted a numerical score, called the Kidney Donor Risk Index (KDRI). Similar attempts are being made for other organs in order to judiciously use marginal organs to provide for patients with end-organ disease.

Marginal organs can be more susceptible to graft dysfunction and increased rates of rejection because they have preexisting disease that makes them prone to hypoxic injury¹⁻⁴. Thus,

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Conflicts of Interest

The authors report no conflicts of interest with the information reported in this manuscript.

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research into preservation methods that target molecular mechanisms of organ injury is being actively pursued.

Newer preservation methods, including targeted perfusion solutions and advanced machine perfusion methods may provide opportunities to treat, maintain, and assess marginal organs and ultimately improve transplant outcomes. This review summarizes recent advancements in preservation solutions and machine perfusion methods, including hypothermic, normothermic, and subnormothermic machine perfusion applicable to kidney, liver, pancreas, intestine, heart, and lung transplantation.

Methods

The comprehensive review of the literature was performed by systematic analysis of published literature to February, 2019. The PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed/>) was searched for variations of keywords: hypothermic machine reperfusion; normothermic machine reperfusion; subnormothermic machine reperfusion; kidney transplant perfusion; liver transplant perfusion; pancreas transplant perfusion; intestine transplant perfusion; heart transplant perfusion; lung transplant perfusion; and perfusion solution additions. Publication review included deceased and live donor types, cellular, animal and human studies. Prospective and retrospective clinical studies including center studies, meta-analyses and review articles were included. Waitlist and transplantation data was included from the Organ Procurement and Transplantation Network (OPTN; <https://optn.transplant.hrsa.gov/data/organ-datasource/>).

Preservation Solutions

Procured organs are routinely preserved in a solution containing constituents that slow molecular processes that would otherwise lead to cellular injury. Although the added constituents vary, the overall goal of the preservation solution is to prevent cell swelling, acidosis and oxygen radical formation. Numerous preservation solutions have been used for the static cold storage of organs. The most common solutions are described below.

In 1969, Collins developed the first static cold storage preservation fluid, which was later modified by the Eurotransplant Foundation to create the Euro-Collins solution in 1976⁵. The Euro-Collins solution was widely used until the 1980s when Folkert Belzer and James Southard developed the University of Wisconsin (UW) solution, which significantly reduced delayed graft function (DGF) and improved 1-year graft survival in kidney transplants⁵. The UW solution also allowed kidneys to be stored for up to 72 hours and thus became the dominant organ preservation solution⁶. However, the composition of the UW solution was changed when machine perfusion was developed because the UW solution was associated with high vascular resistance and RBC hyperaggregation when used with machine perfusion^{7,8,9}. The UW solution was modified to the Belzer MPS® UW Machine Perfusion Solution, also known as KPS1:UW Solution for machine perfusion of kidneys. Since the introduction of KPS1:UW, the modified UW solution has remained the dominant choice for organ preservation under hypothermic settings^{6,10,11}. Table 1 compares the ingredients between the UW and KPS1:UW solutions.

Both forms of UW solution contain hydroxyethyl starch, a synthetic colloid used to prevent tissue edema¹⁰. However, colloids, antioxidants and impermeants such as hydroxyethyl starch activate the complement system¹². The complement system protects against bacterial infections and links innate and adaptive immunity, but also generates anaphylatoxins C3a and C5a that form the membrane attack complex^{12–14}. Colloid solutions containing hydroxyethyl starch have been associated with osmotic nephrotic-like lesions in transplanted kidneys¹

An alternative to the UW solution is the Histamine Tryptophan Ketoglutarate (HTK) solution (Table 1). HTK is a low viscosity solution with an osmolality similar to plasma and an electrolyte composition comparable to extracellular fluid¹⁰. It contains low potassium concentrations and slows metabolism through extracellular sodium and calcium removal (Table 1)¹⁰

UW is still preferred for pancreas transplantation based on a meta-analysis by Hameed *et al*¹⁵ that showed UW *in situ* perfusion resulted in lower pancreatic enzyme release and higher graft survival rates compared to HTK³. However, they showed the perfusion solution type did not significantly affect transplant outcomes when cold ischemia times were minimized³

Perfusion Solution Additives

Recent laboratory-based studies have explored the benefits of preservation fluid additives. In 2017, Motayagheni *et al.* reviewed the effects of volatile anesthetics added to preservation solutions to improve donor kidney function. In pre- and post-conditioning studies sevoflurane and isoflurane were found to protect against ischemic kidney injury¹⁶. A preclinical study examining the effects of saturating the preservation solution Celsior® with argon and xenon found the addition of the gases improved early kidney function recovery, graft quality and graft survival (Table 1)¹⁷. Propofol, an intravenous anesthetic, has also been evaluated for its use in perfusion solutions. While preclinical studies indicated propofol protects organs from ischemic injury and may decrease acute kidney injury, clinical studies have shown better outcomes using volatile anesthetics such as desflurane^{18,19}

Additives such as hydrogen sulfide (H₂S) have also been found to decrease oxidative stress, apoptosis, inflammation and mitochondrial dysfunction in ischemic rodent kidneys^{20,21}. H₂S serves as an endogenous gasotransmitter with cytoprotective effects and has been shown in an ex vivo DCD porcine preservation model to improve graft function and survival after transplantation when added to UW solution²². A targeted, synthetic slow-releasing H₂S donor, AP39, was developed to better control H₂S concentrations in solution and, when compared to non-targeting H₂S donors, was found to offer 1000-fold more cytoprotection in a rodent kidney transplant model²¹. Juriasingani *et al.* found that AP39 using static subnormothermic perfusion improved porcine kidney viability in UW solution and mitigated the negative impacts of higher metabolic demands present at 21°C²²

A promising new advance in the studies of preservation solution additives has been immune inhibitors that target specific immunologic mechanisms of ischemic graft injury. Complement system activation is well known to play a role in the pathogenesis of ischemic

graft injury¹². Inhibiting complement activation in donation after brain death (DBD) donors improved organ quality and function by lowering inflammatory and pro-fibrotic gene expression in laboratory studies^{12,23}. Coskun and Baykal found that of 111 proteins found in preservation fluids after cold storage of kidneys, nine were complement system proteins²⁴. Bergamaschini *et al.* found that adding complement inhibitors to UW solution prevented complement activation in porcine livers²⁵. Other animal studies showed complement inhibition improved kidney graft survival and function^{12,26}. In other preclinical studies, complement system inhibition lessened renal tubular damage and increased graft survival^{27,28}.

Continued interest in immune regulators have led to studies of mesenchymal stromal cells, due to their reported immunomodulatory effects, as well as their low immunogenicity and regenerative properties⁴. These cells are multipotent adult stem cells that are isolated from bone marrow²⁹. In kidney transplants, mesenchymal stem cells have been used to minimize immunosuppressive medication dose; however, future research is needed in order to optimize their delivery⁴. Mesenchymal stem cells have also been investigated as a therapy against donor lung injury. One study using a porcine lung model found that these cells increased human endothelial growth factor and decreased levels of IL-8, a potent neutrophil attractant³⁰. Mesenchymal stromal stem cells have also been found to offer protection from ischemia reperfusion injury in murine intestines^{31,32}.

Several other preclinical studies have investigated methods of maintaining cellular processes in stored tissue. Addition of oxygen to preservation solutions has been found to restore cellular and mitochondrial homeostasis before reperfusion³³. Hypothermic oxygenated perfusion allows for additional oxygenation during organ perfusion and has been associated with improved renal function, increased ATP concentration, decreased tissue edema and lower inflammatory cytokine production^{11,34}. However, other groups were unable to find improvement after hypothermic oxygenated perfusion and therefore could not support wide use in clinical settings³⁴. Another form of oxygenation, called persufflation, adds oxygen during static cold storage. Animal studies showed improved tissue preservation, oxygenation, and ATP levels with persufflation; similarly, a study using human or paired porcine pancreases showed increased ATP levels and islet production comparable to that found in fresh pancreases¹⁰.

Preservation Methods

Developments in preservation methods and perfusion solutions have been explored in parallel. Due to UW solution's early success, static cold storage became the standard means of organ preservation for human transplantation⁶. Preserving the organ between 0–4°C slows its metabolic rate and decreases edema and ischemic damage^{3,5}. However, organs from extended criteria donors (ECD), including donation after circulatory death (DCD) donors and DBD donors, are being increasingly used and are susceptible to higher rates of ischemic injury^{1,2,4}. Organs from these donor groups are also more sensitive to cold storage inflicted injury, which contributes to reduced graft function^{1–4}. Use of these organs has driven research into machine pulsatile perfusion (pumping) methods and new preservation

techniques. Table 2 highlights the preservation methods in preclinical and clinical studies that have been used for the different solid donor organs.

In contrast to static cold storage, hypothermic pumping allows for perfusion of preservation solution during organ storage. Hypothermic pumping has been shown in laboratory models to improve ATP levels and reduce endothelial damage and swelling^{3,6}. Several studies have demonstrated reduced DGF rates in organs from ECDs, DCDs, and DBDs and lessened IRI severity^{1,4,33}. However, while hypothermic pumping has been found to improve primary nonfunction (PNF) and 1-year graft survival rates, these results are not consistently supported across clinical studies¹

While hypothermic preservation techniques aim to slow metabolic processes during storage, normothermic pumping allows maintenance of cellular and metabolic processes at normal physiological rates. Normothermic pumping has been proposed to lessen injury associated with cold ischemia and to allow assessment of organ function prior to transplantation. It also has been used in preclinical studies of immune inhibitors, such as mesenchymal stem cells, complement inhibitors and anesthetics^{4,11,29,75}. To be successful, normothermic pumping requires oxygen carriers and nutrients to be added to the perfusate solution. One normothermic liver perfusion study found that solutions containing oxygen carriers, such as erythrocytes or whole blood, lowered markers of tissue injury, increased bile production and improved histology⁴⁴. Normothermic pumping has been shown to reduce DGF and ischemia reperfusion rates, restore ATP levels and increase blood flow and oxygenation^{6,33,75}. Furthermore, normothermic machine perfusion has been used to recover organ function following ischemic injury, which holds promise for increasing DCD organ viability^{29,75}

Subnormothermic machine perfusion similarly avoids cold ischemia but it reduces the need for oxygen carriers. In subnormothermic pumping, organs are stored at 20–25°C rather than at physiological temperatures; oxygen carriers are therefore not as essential to meet normal metabolic rate demands as they are in normothermic pumping¹¹. One study compared the use of static cold storage, oxygenated hypothermic pumping and subnormothermic pumping in porcine kidneys and found increased urine production, improved creatine clearance and improved blood flow in the subnormothermic group¹¹. Warmer temperatures in subnormothermic pumping yielded better oxygenation and subsequently improved repair and graft function, provided a better vascular environment and reduced endothelial cell injury compared to hypothermic pumping in preclinical studies³⁸. High oxygen consumption in the subnormothermic condition may also be associated with lower effluent protein levels³⁸. Berardo *et al.* associated machine pumping at 20°C with lower HIF-1 α RNA and protein expression and improved ATP levels offering better protection and functional recovery in comparison to static cold stored livers in rodents⁴³. Subnormothermic pumping at higher temperatures (32–34°C) also showed decreased serum creatinine and allowed for renal recovery after warm ischemia in dogs¹¹. Another group showed that adding human derived hemoglobin vesicles (HbV), a hemoglobin-based oxygen carrier, increased oxygen consumption but did not affect hepatocellular injury in a rodent model⁷⁶. Other studies have shown contradicting results with subnormothermic pumping⁶

Machine Perfusion in Abdominal Organs

Kidney perfusion

Perfusion kidney preservation was first used in clinical settings in the 1960s and, by the 1970s, hypothermic machine pumping was widely used to preserve and transport kidneys for transplantation⁶. Machine perfusion allows for graft optimization before transplant and increases the period of time, and therefore distance, in which an organ can be stored and transported. However, early renal machine pumping techniques were complex and yielded conflicting results, and therefore pumping was supplanted by static cold storage in 1980^{6,10}. The demand for more organs has led to increased use of DCD kidneys, which are susceptible to DGF, and are more sensitive to long cold ischemic times². Interest in hypothermic machine perfusion use has increased due to decreased DGF occurrence for ECD, DCD and DBD donor kidneys³³. Hypothermic pumping has also been found to allow the assessment of organ viability prior to transplant. Using terminal resistance and flow rates, Ding *et al.* developed an HMP scoring model to predict DGF risk and assess kidney quality pre-transplant⁷⁷. Machine pumping holds a variety of benefits for kidney preservation, and hypothermic machine pumping has therefore become a well-established practice in kidney transplantation. However, questions regarding the optimization and the economic benefits of machine perfusion remain.

Normothermic pumping and subnormothermic pumping are being explored as alternatives for kidney preservation due to injury associated with cold ischemia. Normothermic pumping uses physiological temperature, which has shown promise for functional kidney recovery and direct management of cellular processes via therapeutic additions⁷⁵. Normothermic pumping has also been shown to lower peak creatinine, improve graft survival and allow organ recovery after periods of cold ischemia as noted in several human and animal studies^{33,75}. Prolonged normothermic pumping is also being explored, as one study established the feasibility of kidney preservation for 24 hours using urine recirculation in discarded human kidneys, effectively maintaining perfusate composition and stability³⁵. Though normothermic pumping typically requires oxygen carriers to support physiologic metabolic rates, short periods of pumping following static cold storage have been found to avoid reperfusion tissue alteration and dysfunction without adding erythrocytes in an autotransplant model in pigs³⁶.

Liver perfusion

Liver transplantation provides life-saving therapy for patients with end-stage liver disease. Use of ECD, DCD, and DBD donor livers is therefore being encouraged to meet the unmet demand for liver transplants. Marginal organs are however susceptible to tissue injury, especially DCD livers. Liver grafts from DCD donors experience higher risks of DGF, primary non-function (PNF), and biliary complications, which contribute to higher rates of morbidity, graft loss, patient mortality and necessity for retransplantation^{6,33,78}. DCD livers are prone to ischemic-type biliary lesions, also known as ischemic cholangiopathy, leading to greater risk of retransplantation and death^{6,33}.

Liver machine pumping began in 1935 when Alexis Carrel and Charles Lindbergh developed the first liver perfusion machine; however, this technique was abandoned after unsuccessful use with human livers in 1967⁶. Static cold storage has since served as the primary means of liver preservation. However, due to poor graft outcomes, DCD livers have a higher rate of discard. Increased need for their use has therefore renewed interest in machine pumping techniques⁵³. Due to high demand for oxygen in the liver, hypothermic machine perfusion fluids are often oxygenated in order to slow metabolic rates while providing oxygenation and metabolic support during organ storage and preventing endothelial damage^{6,39,79,80}. Compagnon *et al.* found that the hypothermic machine perfusion Airdrive™ system, a portable, disposable oxygenated hypothermic pumping system, offered improved graft function, histology and metabolism. It also lessened hepatocellular and endothelial damage, inflammatory responses, oxidative load, ER stress, mitochondrial harm and apoptosis in a pig transplant model⁴⁰. Hypothermic oxygenated perfusion (HOPE) following static cold storage has been shown to lower acute rejection and increase 5-year graft survival rates compared to untreated DCD livers in a human trial⁵². Though the HOPE-treated DCD livers were higher risk, they showed similar reperfusion injury and hemodynamic stability and displayed better lactate clearance and lower international normalized ratio values on the first day, and lower occurrence of non-tumor-related graft loss, ischemia cholangiopathy, vascular complications and PNF compared to untreated DCD livers⁵². Oxygenation with hypothermic perfusion has also been found to downregulate pro-reactive oxygen species pathways in mitochondria and allow succinate metabolism, lowering succinate accumulation that has been found to initiate mitochondrial dysfunction; and therefore, leads to better hepatic function upon normothermic reperfusion in both human and animal studies^{39,41}. HOPE treatment has also been associated with restored ATP levels, at rates higher than normothermic oxygenated perfusion^{42,81}. In two clinical cases using octogenarian grafts, Rayar *et al.* found that HOPE shortened hospital stays to eight and twelve days and enabled graft function recovery in a graft with 20% steatosis, more than 10 hours of ischemia, and significant ischemia-reperfusion lesions⁵¹. Another group found combining dual hypothermic oxygenated machine perfusion and normothermic pumping offered graft resuscitation after being previously rejected for transplantation⁵⁰. Out of seven DCD livers, five were transplanted and had a 100% graft survival rate at three months⁵⁰.

The use of physiological temperature in normothermic pumping allows for normal metabolic rates and it minimizes cold ischemia⁶. Normothermic pumping has been associated with lower ischemia reperfusion injury occurrence and improved bile production in large animal and clinical studies⁶. Nasralla *et al.* showed that normothermia reduced peak serum aspartate transaminase (AST) and early allograft dysfunction (EAD) levels, which are biomarkers used to predict long-term patient and graft survival in clinical settings⁵⁵. However, they found that differences in graft and patient survival could not be seen in comparison to static cold stored livers likely due to study size⁵⁵. Additionally, no differences in biliary stricture occurrence were found for DCD or DBD livers⁵⁵. Peak AST rates were lower in DCD normothermic pumped livers than in DCD and DBD livers preserved via static cold storage and DBD livers after normothermic pumping⁵⁵. Normothermic pumping also allowed longer preservation times without compromising organ quality, resulted in fewer discarded livers and lowered non-anastomotic biliary strictures in

DCD livers compared to static cold storage in a randomized clinical trial⁵⁵. Similarly, another group found decreased peak AST levels and ischemia reperfusion injury occurrence in DBD livers treated with normothermic pumping one-week post-operation⁵⁴. Normothermic pumping was found to promote tissue repair, growth, and metabolism gene expression, while static cold storage yielded increased immune response related gene expression in a clinical trial comparing normothermic pumping to cold storage⁵⁴. Though both static cold storage and normothermic pumping encouraged healing, differentiation, and regeneration pathways, only normothermic pumping downregulated inflammation pathways⁵⁴. Currently, normothermic perfusion provides the best means to predict ischemic biliary complications by measuring bile pH⁸². Criteria for assessing organ viability such as concentration of lactate, bile production and vascular flow patterns have also been introduced and successfully tested in a clinical study using discarded livers⁸³. Although normothermic pumping shows promise, there are additional requirements of oxygen carriers and nutrients and implementation into clinical practice has been complicated^{6,40}. Therefore, studies have also explored subnormothermic pumping effects on liver preservation. Subnormothermic pumping offers cold perfusion to replenish ATP stores and has been shown to increase tissue energetics, peroxidation, production of bile, recovery of homeostasis, oxygen metabolism, and histology in animal and human studies^{6,48,49}. One study in a pig model developed an *ex vivo* reperfusion model to assess machine pumping utility and demonstrated that subnormothermic perfusion yielded decreased hepatic artery pressure and AST concentrations⁴⁷. Kakizaki *et al.* explored subnormothermic oxygenated perfusion use in a dripping system that excluded the need for perfusion machinery in porcine livers⁴⁶. They found improved survival rates, increased microcirculation, and reduced PNF occurrence; however, AST and ALT levels were still higher than in livers supported by a beating heart⁴⁶. However, subnormothermic pumping benefits have not been consistently supported across studies⁴⁵.

Pancreas perfusion

Pancreas transplantation, using either whole organ or isolated islets is performed routinely in the United States³. Due to improvements in non-transplant treatments for diabetes mellitus, increased donor risk and reduction in referrals, the number of isolated pancreas transplants performed has recently decreased in the US, however there were more combined kidney/pancreas transplants done in the US with a three year increase noted¹⁰. Those needing a pancreas transplant make up just 2.2% of candidates on the waitlist (based on OPTN data Feb. 2019). While preservation techniques have been explored for other organs, perfusion methods for donated pancreases have been slow to develop. However, rates of organ failure in the first days following a pancreas transplant are higher when compared to other solid organ transplants and optimization is needed⁵⁶. Like other donated organs, static cold storage is the traditional and standard means of pancreas preservation. However, in 1988, Kuroda *et al.* developed in a model of isolated islets from rats using the “Two-Layer Method” (TLM) in which the pancreas is cold-stored in two layers of solutions with varying densities (Surgery, Vol. 134, Issue 3, p437–445)¹⁰. Perfluorocarbons, which allow oxygenation in solution, make up the bottom layer, while less dense UW or Euro-Collins solution forms the top layer Surgery, Vol. 134, Issue 3, p437–445. The utility of this method, however, in human pancreas transplantation is still being evaluated¹⁰. To supply oxygen

more directly, persufflation of perfusate has also been considered. This method has been shown to increase ATP concentration and produce islet levels comparable to living tissue in human and porcine pancreata^{10,62}

Ideal perfusion parameters have been difficult to determine for the pancreas, as high pressures lead to endothelial damage and increased rates of thrombosis¹⁰. While hypothermic pumping has been shown to reduce levels of islet and acinar cell damage, edema, even at low flow rates, has been shown to be unavoidable in a porcine model⁵⁹. Another study preserved 20 human pancreases using oxygenated hypothermic pumping and found adequate good quality islet concentrations and no indication of cellular injury, edema or reactive oxygen species production⁵⁷. Additionally, ATP levels increased in both DCD and DBD pancreases with no resulting significant difference⁵⁷. Branchereau *et al.*, utilized hypothermic pulsatile machine perfusion at 25mmHg in discarded human pancreases for 24 hours and found no edema or necrosis in whole pancreas parenchyma⁵⁶. Short-term use (5 hours) of hypothermic pumping after 24 hours of static cold storage has also shown promise as a model developed in porcine pancreases and tested in human pancreases resulting in little edema at low pressures⁵⁸. Limited normothermic machine perfusion research has been done for pancreases, although Barlow *et al.* was able to assess functionality by measuring markers in perfusate and exocrine excretions using five discarded human pancreases⁶¹. Although edema was found in all five pancreases, the study showed promise for assessing pancreas function and viability prior to transplant⁶¹. Another study using an *ex vivo* normothermic porcine pancreas perfusion model found 4 hours of viability at low pressure (20 mmHg), although difficulties in interpreting amylase levels may act as a limitation⁶⁰.

Intestine perfusion

Patients needing an intestinal transplant make up just 0.2% of waitlist candidates (based on OTPN data Feb. 2019), and for this reason improvements in procurement and storage have been slow to develop. Optimization of organ preservation techniques is crucial for intestinal transplants, as it is among the most sensitive organ to ischemic injury⁶³. Additions to *in situ* luminal solutions such as polyethylene glycol (PEG) have been considered to lessen intestinal preservation injury incidence. Casselbrant *et al.* found that medium and large molecular mass PEG solutions delayed onset and occurrence of intestinal preservation injury in rats, although this was not performed in a transplant model⁸⁴. Due to success in other organs, machine perfusion is also seen as a possible means of improving intestinal graft storage. Muñoz-Abraham *et al.* tried to optimize preservation using the intestinal preservation unit (IPU), which they developed with students from the Yale Schools of Medicine and Engineering and Applied Sciences⁶³. They found that the IPU group human jejunal segments received better pathologist classification using the Park Chiu classification for intestinal-reperfusion injury than the control group, while the IPU ileum and control groups received equal grading⁶³. However, as this study was done on only five grafts, statistical power could not be reached⁶³. They indicated a need for further research in normothermic machine perfusion use, therapeutic treatment additions and preservation solutions. While UW solution is most commonly utilized and has been beneficial in intestinal preservation, questions remain about its efficacy in machine perfusion use^{63,85,86}

MP in Thoracic Organs

Heart perfusion

For those experiencing end-stage heart failure, transplantation provides life-saving treatment²⁹. Increased use of deceased donor organs has required means of optimizing these grafts for transplantation. Hypothermic machine pumping has been found to offer improved left ventricular function recovery, cardiac myocyte integrity, and improved graft energy stores, including hearts from DCD donors^{29,64}. Normothermic pumping use is also being explored as it has been shown in preclinical studies to allow normal metabolic rates and, subsequently, organ quality and functional assessment²⁹. Using normothermia, one group found that elevated lactate levels at the end of perfusion signaled graft failure (Hassanein J thorac cardiovasc surg 1998 Nov 16:821.²⁹). Currently, the Organ Care System (OCS™) is the only machine developed to warm perfuse the heart²⁹. One multicenter, open-label, randomized non-inferiority study held in centers in the USA and Europe found similar short-term outcomes for OCS and static cold stored hearts ([ClinicalTrials.gov](https://clinicaltrials.gov) Number). However, another single-center, non-randomized study found OCS improved recipient survival and reduced rates of primary graft dysfunction and acute rejection²⁹.

As with other organs, the possibility of organ quality assessment has incentivized research into machine perfusion for heart graft optimization. In a case study, Messer *et al.* utilized normothermic regional perfusion after a 15-minute cold ischemic period to restore contractile ability. This restoration allowed the ability to determine direct pressure, thermodilution cardiac output, and echocardiography, and afterward the heart was returned to static cold storage before successful transplantation⁶⁵. Another form of assessment was developed by a group at Papworth Hospital, Cambridge, UK using normothermic regional perfusion to determine heart quality in DCD donors²⁹. These methods are being developed in the hopes that through assessment pre-transplantation the use of costly perfusion techniques might be minimized or avoided.

Lung perfusion

Similar to the heart, lung transplantation is a life-saving procedure for patients suffering from end-stage lung disease²⁹. In 2001, Steen and colleagues were the first to successfully perform a lung transplant after using *ex vivo* lung perfusion for organ assessment (EVLP)^{87,88}. Due to the success of static cold storage for lung storage, this technique has primarily been used as a method to assess non-standard graft viability before transplantation acceptance^{3,88–92}. However, an international, multi-center, randomized controlled, non-inferiority clinical study assessed EVLP effectiveness via OCS™ Lung, a normothermic perfusion machine, and found significantly reduced primary graft dysfunction compared to the static cold storage group⁷³. Additionally, EVLP may help to recondition marginal lungs and was found to produce similar outcomes compared to conventional grafts after 4–6 hours of acellular perfusion⁷⁴. Charles *et al.* found in a porcine model that four hours of normothermic EVLP allowed DCD lung grafts to meet transplant criteria after up to 120 minutes of warm ischemia⁶⁶. In a separate porcine lung perfusion study, EVLP showed upregulated expression of genes involved in inflammatory suppression, cell proliferation and apoptosis regulation, energy metabolism, tissue remodeling and oxidative stress response.

reaching its peak expression after 6 hours of perfusion compared to static cold storage⁶⁷. However, longer EVLP periods may be beneficial as downregulation of injury and pro-inflammatory gene expression continued until 12 hours to levels lower than pre-transplantation⁶⁷. Spratt *et al.* developed a porcine model using 24-hour normothermic blood-based EVLP to predict organ function⁶⁸. While at 24 hours perfusion, allograft oxygenation was predictive of lung function after transplant, they noted that poor allograft oxygenation could be anticipated from assessing allograft edema and early hemodynamics and that graft function could likely be predicted after 8 hours of perfusion⁶⁸. Alternatively, static normothermic perfusion has shown promise for improving oxygenation and reducing rates of edema when performed for 12 hours following prolonged periods of cold ischemia (12 hrs) in comparison to 24-hour static cold storage in porcine lungs⁷¹

EVLP also offers the opportunity to administer treatments during storage. In a porcine model, *ex vivo* treatment with surfactant improved acid-injured lung function⁷². While canine lung function was improved after ventilation using a bronchodilator, argon gas ventilation did not influence porcine lung function^{69,93}. Stone *et al.* found that EVLP human lung recipients experienced reduced donor leukocyte transfer and T cell infiltration compared to non-EVLP lungs⁷⁰. Similarly, Noda *et al.* determined in a rodent model that the addition of leukocyte filters significantly lowered interleukin-6 levels, improved graft function, and lessened inflammation²⁹

Conclusion

Organ transplantation provides life-saving treatment for patients suffering from end-stage organ failure. Due to the existing gap between organ supply and demand, marginal organs are increasingly being considered in order to expand the available donor pool. There is intense interest in research into methods that hold promise to improve preservation of marginal organs in order to optimize their use. New preservation solutions and machine perfusion methods now provide an opportunity for *ex vivo* treatment and maintenance of organs that would have otherwise been discarded. The addition of therapies in perfusion fluids holds promise to lessen tissue injury, inhibit immune responses and maintain cellular homeostasis. Machine perfusion advancements offer means of functional maintenance, restoration and assessment while reducing damage associated with static cold storage. Though questions for further optimization remain, such enhancements may allow for an inclusion of more grafts for donation and serve to lessen the severe shortage of donor organs available for transplantation

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Highlights

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Table 1.

Preservation solutions used for solid organ transplantation

Belzer UW Cold Storage Solution			Custodial HTK Solution		
Ingredient	g/L	mmol/L	Ingredient	g/L	mmol/L
Hydroxyethyl starch (Pentafraction)	50.0	N/A	Sodium chloride	0.8766	15.0
Lactobionic Acid (as Lactone)	35.85	105.0	Potassium chloride	0.6710	9.0
Potassium dihydrogen phosphate	3.4	25.0	Potassium hydrogen 2-ketoglutarate	0.1842	1.0
Magnesium sulfate heptahydrate	1.23	5.0	Magnesium chloride* 6 H ₂ O	0.8132	4.0
Raffinose pentahydrate	17.83	30.0	Histidine * HCl * H ₂ O	3.7733	18.0
Adenosine	1.34	5.0	Histidine	27.9289	180.0
Allopurinol	0.136	1.0	Tryptophan	0.4085	2.0
Total Glutathione	0.922	3.0	Mannitol	5.4651	30.0
Potassium hydroxide	5.61	100.0	Calcium chloride * 2 H ₂ O	0.0022	0.015
Sodium hydroxide/Hydrochloric acid (adjust to pH 7.4)			Sterile water for injection		
Water for injection q.s.			Anion Cl ⁻ – 50 mval		
Celsior Flushing and Cold Storage Solution for Heart Preservation			KPS-1: UW Solution for machine perfusion of kidneys		
Ingredient	g/L	mmol	Ingredient	g/L	mM
Mannitol		60.0	Calcium chloride (dehydrate)	0.068	0.5
Lactobionic Acid		80.0	Sodium hydroxide	0.70	
Glutamic Acid		20.0	HEPES (free acid)	2.38	10.0
Histidine		30	Potassium phosphate (monobasic)	3.4	25.0
Calcium Chloride		0.25	Mannitol (USP)	5.4	30.0
Potassium Chloride		15.0	Glucose, beta D (+)	1.80	10.0
Magnesium Chloride		13.0	Sodium gluconate	17.45	80.0
Sodium Hydroxide		100.0	Magnesium gluconate D (–) gluconic acid, hemimagnesium salt	1.13	5.0
Reduced Glutathione		3.0	Ribose, D (–)	0.75	5.0
Water for injection q.s.		Up to 1 L	Hydroxyethyl starch (HES)	50.0	N/A
			Glutathione (reduced form)	0.92	3.0
			Adenine (free base)	0.68	5.0
			Sterile water for injection (SWI)	To 1000 mL	N/A

Table 2.

Preservation methods used in preclinical and clinical studies for solid donor organs.

Organ	Study type	Reference	Year Published	Perfusion Type	Model
Kidney	Preclinical	Weissenbacher et al ³⁵	2019	NMP	Human
		Von Horn et al ³⁶	2018	NMP	Pig
		Hoyer et al ³⁷	2014	SMP	Pig
Liver	Preclinical	Morito et al ³⁸	2018	HMP; SMP	Pig
		Yoshikawa et al ³⁹	2018	Oxygenated HMP	Pig
		Compagnon et al ⁴⁰	2017	HMP	Pig
		Kron et al ⁴¹	2017	Oxygenated HMP	Rat
		Schlegel et al ⁴²	2014	HMP; NMP	Rat
		Berardo et al ⁴³	2017	NMP; SMP	Rat
		Liu et al ⁴⁴	2016	NMP	Pig
		Nassar et al ⁴⁵	2016	NMP; SMP	Pig
		Kakizaki et al ⁴⁶	2018	SMP	Pig
		Yoshikawa et al ⁴⁷	2018	SMP	Pig
		Knaak et al ⁴⁸	2014	SMP	Pig
		Minor et al ⁴⁹	2013	SMP	Pig
	Clinical	de Vries et al ⁵⁰	2018	Dual HMP & NMP	Human
		Rayar et al ⁵¹	2018	Oxygenated HMP	Human
		Schlegel et al ⁵²	2018	Oxygenated HMP	Human
		Guarrera et al ⁵³	2009	HMP	Human
		Jassem et al ⁵⁴	2018	NMP	Human
		Nasralla et al ⁵⁵	2018	NMP	Human
Pancreas	Preclinical	Branchereau et al ⁵⁶	2018	HMP	Human
		Leemkuil et al ⁵⁷	2018	Oxygenated HMP	Human
		Hamaoui et al ⁵⁸	2017	HMP	Pig, Human
		Karcz et al ⁵⁹	2010	HMP	Pig
		Kumar et al ⁶⁰	2018	NMP	Pig
		Barlow et al ⁶¹	2015	NMP	Human
		Scott et al ⁶²	2010	TLM	Rat, Pig, Human
Intestine	Preclinical	Muñoz-Abraham et al ⁶³	2016	HMP	Human
		Van Caenegem et al ⁶⁴	2016	HMP	Pig
Heart	Clinical	Messer et al ⁶⁵	2018	NRP	Human
Lung	Preclinical	Charles et al ⁶⁶	2018	NMP	Pig
		Dromparis et al ⁶⁷	2018	NMP	Pig
		Spratt et al ⁶⁸	2018	NMP	Pig
		Hijiya et al ⁶⁹	2017	NMP	Dog

Organ	Study type	Reference	Year Published	Perfusion Type	Model
		Stone et al ⁷⁰	2016	NMP	Pig
		Cypel et al ⁷¹	2009	NMP	Pig
		Inci et al ⁷²	2008	NMP	Pig
	Clinical	Warnecke et al ⁷³	2018	NMP	Human
		Cypel et al ⁷⁴	2012	NMP	Human