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REVIEW

## Emerging concepts in liver graft preservation

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### Abstract

The urgent need to expand the donor pool in order to attend to the growing demand for liver transplantation has obliged physicians to consider the use of suboptimal liver grafts and also to redefine the preservation strategies. This review examines the different methods of liver graft preservation, focusing on the latest advances in both static cold storage and machine perfusion (MP). The new strategies for static cold storage are mainly designed to increase the fatty liver graft preservation *via* the supplementation of commercial organ preservation solutions with additives. In this paper we stress the importance of carrying out effective graft washout after static cold preservation, and present a detailed discussion of the future perspectives for dynamic graft preservation using MP at different temperatures (hypothermia at 4 °C, normothermia at 37 °C and subnormothermia at 20 °C-25 °C). Finally, we highlight some emerging applications of regenerative medicine in liver graft preservation. In conclusion, this review discusses the "state of the art" and future perspectives in static and dynamic liver graft preservation in order to improve graft viability.

**Key words:** Static cold preservation; Suboptimal liver grafts; Preservation solutions; Graft washout solutions; Machine perfusion and liver bioengineering

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**Core tip:** This review focuses on the latest advances in liver graft preservation, in both static cold storage and dynamic preservation by machine perfusion (MP). We describe some new trends for static cold preservation based on our experience; we stress the importance of developing washout solutions and the use of MP for suboptimal liver grafts. Finally, we discuss emerging applications of regenerative medicine in liver graft preservation.

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## INTRODUCTION

Liver transplantation is the definitive treatment option for end-stage liver diseases. Besides the immunological mechanisms of graft rejection, liver transplantation outcome is also limited by ischemia-reperfusion injury (IRI). IRI is a complex multifactorial process caused, principally, by the energy depletion during graft cold storage in preservation solutions (cold ischemia) and the subsequent production of oxidative stress and inflammatory events after graft revascularization in the recipient (reperfusion)<sup>[1]</sup>. IRI is associated with delayed graft function and primary graft failure, which remains one of the major clinical problems following liver transplantation.

A common strategy to reduce ischemic injury following explantation from the donor is the rapid cooling of the organs with the use of a preservation solution to minimize enzymatic activity and energy substrate depletion. In recent decades, major advances have been made in the area of liver preservation, including the development of new preservation solutions. Their emergence has helped to decrease hypoxic injury and has reduced graft vulnerability against reperfusion insult.

Currently, the high increase in demand for organs has obliged physicians to use suboptimal grafts in order to increase the organ supply for transplantation. Suboptimal or extended criteria donor (ECD) livers include organs characterized by steatosis, old donor age, prolonged cold ischemia or donation after cardiac death (DCD)<sup>[2,3]</sup>. It is well known that suboptimal livers present increased vulnerability to IRI, and are associated with graft dysfunction and long-term survival problems after surgery. For this reason, preservation methods for suboptimal livers need to be exhaustively explored in order to identify the ones that are the most suitable for graft conservation.

Machine perfusion (MP) has emerged as an alternative preservation strategy to static cold storage (SCS). MP is already routinely used for kidney transplantation, but a great deal is still to be done before it can be regularly used in clinical liver transplantation. In this review, we examine the SCS and MP techniques in detail, describing the latest advances in the development of preservation solutions for liver grafts and providing some proposals and new strategies in order to improve current graft preservation methods.

## STATIC COLD STORAGE

The main goal in organ preservation is to maintain

function of the organ and tissue during storage so that the graft will be viable at reperfusion. To date, the predominant organ preservation method used by most centers is SCS. The principles of SCS are based on the diminution of metabolism by hypothermia. The appropriate preservation solution is infused into the organ (the cooling phase) and then stored statically<sup>[4]</sup>.

### Cooling

SCS is the most widely used method for preserving organs for transplantation. Cooling is necessary to reduce cellular metabolism and the oxygen requirements in order to prevent tissue injury<sup>[5]</sup>.

In order to obtain viable organs after long-term preservation, various methods have been proposed, ranging from organ freezing and vitrification<sup>[6,7]</sup> to “supercooling” (subzero non-freezing at 0 °C to -5 °C)<sup>[8-11]</sup>. In general, long-term survival rates after transplantation using these methods are disappointing.

However, in a recent study by Berendsen *et al.*<sup>[12]</sup>, the combination of “supercooling” (cold preservation at -6 °C) with other parameters achieved effective preservation of liver grafts for 4 d. This promising new technique comprises three steps: first, “supercooling” of the organ at -6 °C to reduce the cellular metabolism; second, subnormothermic MP at 21 °C (see the dynamic preservation section below), which reinitiates the metabolism and replenishes ATP levels, and third, the use of two preservatives, 3-O-methyl-D-glucose (3-OMG) and polyethylene-glycol 35 (PEG35). Each of these conditions is necessary to achieve successful liver transplantation<sup>[13]</sup>. With this in mind, supercooling techniques may be a potentially useful tool for suboptimal livers which are currently discarded for transplantation purposes, and may have great impact on global organ sharing.

### Preservation solutions

Although cold is a fundamental requirement for tissue preservation, it has harmful repercussions due to the induction of cell swelling<sup>[14]</sup> and cytoskeletal alteration<sup>[15]</sup>. This was in part the reason for the development of commercial organ preservation solutions able to prevent many of the cellular alterations associated with hypothermia and to mitigate the harmful effects of cooling.

Euro-Collins (EC) solution was developed in the 1970s as a high potassium-sodium solution (intracellular composition) which does not contain oncotic agents but does contain glucose. Given that glucose is impermeable to renal cells, this preservation solution was suitable for kidney preservation when relatively short times were needed or DCD organs were used. However, the permeability of the liver and pancreatic cells to glucose leads to the loss of the osmotic effect, and also causes the subsequent anaerobic metabolism of glucose, inducing intracellular acidosis and thus limiting cell preservation. This is why glucose was later substituted by other larger sugar molecules such as lactobionate and raffinose in

**Table 1 Additives for improving static cold storage in University of Wisconsin and Institute Georges Lopez preservation solutions**

Additive	Preservation solution	Ref.
TMZ	UW, IGL-1	[25,30]
EGF + IGF-1	UW	[45]
IGF-1	IGL-1	[44]
EGF	IGL-1	[46]
ML	IGL-1	[43]
BZ	UW, IGL-1	[51,117]
SV	UW	[64]
BZ, MG132	UW	[50]
ML + TMZ	IGL-1	[38]
CAII	IGL-1	[54]

TMZ: Trimetazidine; EGF: Endothelial growth factor; IGF: Insulin growth factor 1; ML: Melatonin; BZ: Bortezomib; SV: Simvastatin; CAII: Carbonic anhydrase II; UW: University of Wisconsin; IGL-1: Institute Georges Lopez.

University of Wisconsin (UW) solution, which remains in the extracellular space and preserves its beneficial effect. The use of the UW preservation solution improved organ preservation time from 6 to 16 h<sup>[16]</sup>.

The efficacy of UW solution is based on the prevention of edema by impermeants (raffinose, lactobionate), and the addition of an ATP precursor (adenosine) and anti-oxidant components (allopurinol, reduced glutathione). Drawbacks include the presence of hydroxyethyl starch (HES) as oncotic support, which has been associated with high blood viscosity and consequent tissue saturation with the preservation solution. As a result, washout of blood from the graft and blood flow during reperfusion may be reduced<sup>[17,18]</sup>. In addition, the high K<sup>+</sup> concentration is associated with cellular depolarization and activation of voltage-dependent channels<sup>[19]</sup>. The problems caused by HES and K<sup>+</sup> led to the development of other preservation solutions without oncotic agents such as Celsior and HTK (Custodiol) and others with PEG as oncotic agent, such as Institute Georges Lopez solution (IGL-1) and Tissue and Organ Conservation Solution (SCOT).

Celsior was developed initially in the 1990s as a cardiac preservation solution with a low potassium and high sodium composition. Due to its extracellular composition, Celsior was also adopted for the preservation of abdominal organs as an alternative to UW. Other solutions without oncotic agents such as histidine-tryptophan-ketoglutarate solution (HTK) were also developed. HTK presents low viscosity and for this reason provides more rapid cooling and better washout of blood elements during organ procurement than UW. Celsior and HTK solutions have been extensively used for liver transplantation<sup>[20-22]</sup>. However, some limitations for HTK use have recently been described. Stewart *et al.*<sup>[23]</sup> reported that HTK is associated with reduced graft survival in case of additional risk factors such as DCD, cold ischemia time over 8 h, and donors over 70 years when compared to UW solution.

In IGL-1 preservation solution, HES was substituted by a PEG with a molecular weight of 35 kDa (PEG35), and the high K<sup>+</sup>/low Na<sup>+</sup> ratio was reversed. Both experimental<sup>[24,25]</sup> and clinical<sup>[26-28]</sup> studies of liver and kidney transplantation have shown the beneficial effects of IGL-1 against apoptosis, endoplasmic reticulum stress, microcirculation dysfunction and immune response. Moreover, in previous studies of cold preservation and *ex vivo* perfusion, we have reported that IGL-1 contributes to a more efficient preservation of both non-steatotic and steatotic rat liver grafts compared to UW<sup>[29-31]</sup>. The beneficial effects of IGL-1 include prevention of hepatic damage, oxidative stress and mitochondrial injury, and are mediated through nitric oxide (NO) production. So IGL-1 is the first solution reported to be advantageous in SCS of suboptimal livers.

Moreover, a PEG of smaller size, PEG20, is the basic component of another solution for organ preservation: the SCOT, which furthermore contains low K<sup>+</sup>/high Na<sup>+</sup> concentrations. SCOT was reported to show a higher renal protection against the immune response, mainly due to the “immunocamouflage” process provided by PEG20<sup>[32]</sup>. PEG20 at 15 g/L has been found to reduce alloantigen recognition after liver reperfusion in comparison to UW solution<sup>[33]</sup>. Even so, the use of PEG35 as oncotic agent has been shown to be more effective than PEG20 for liver graft preservation<sup>[34]</sup>.

### Modification of static preservation solutions

The extended use of commercial preservation solutions has improved the conditions of liver graft preservation, but with the increasing use of suboptimal grafts it seems necessary to explore new alternatives in order to prolong the ischemia times and increase graft quality during cold storage. Along these lines, new additives have been proposed to improve static liver graft preservation when UW and IGL-1 solutions are used (Table 1). Although these alternatives are promising and have been successfully applied in animal models, they require further investigation before they can be implemented in clinical transplantation.

**Anti-ischemic drugs:** Previous work in kidney<sup>[35,36]</sup>, liver<sup>[37,38]</sup> and heart<sup>[39-41]</sup> models has demonstrated the anti-oxidant action of trimetazidine (TMZ), an anti-ischemic drug. The addition of TMZ to UW solution was tested in both steatotic and non-steatotic rat livers after cold storage and *ex vivo* perfusion<sup>[25]</sup>. The enrichment of UW solution with TMZ reduced hepatic injury by diminishing microcirculatory dysfunction, oxidative stress, and mitochondrial damage. In the same experimental conditions, supplementation of IGL-1 solution with TMZ offered better liver graft preservation than IGL-1 solution alone and induced significant activation of hypoxia inducible factor-1 $\alpha$  (HIF1 $\alpha$ ) and increased NO production<sup>[30]</sup>. The benefits of TMZ have been shown clinically in patients undergoing hepatic surgery under vascular clamping<sup>[42]</sup>. This would suggest that TMZ has

potential for use as an additive in commercial preservation solutions for clinical transplantation purposes.

**Hormones:** Melatonin (ML), a hormone produced by the pineal gland in a circadian manner, has been shown to be highly beneficial for enhancing resistance of both steatotic and non-steatotic livers against IRI when added to IGL-1. ML decreased hepatic injury by overexpression of endothelial NO synthase (e-NOS) and Heme Oxygenase-1, and reduced mitochondrial damage and oxidative stress<sup>[43]</sup>. These protective effects of ML in fatty liver graft preservation were further potentiated by addition of TMZ to IGL-1 + ML solution<sup>[38]</sup>. Protective mechanisms were dependent on AMPK activation. Furthermore, UW and IGL-1 solutions enriched with trophic factors like epidermal growth factor and insulin-like growth factor-1 enhanced the resistance of steatotic livers to IRI, partly due to Akt and eNOS signaling activation, and reduced cytokine release<sup>[44-46]</sup>.

**Proteasome inhibitors:** The ubiquitin proteasome system (UPS) is an energy-dependent system that degrades misfolded proteins and regulates various cellular processes<sup>[47]</sup>. It has been established that proteasome activation is a pathophysiologically relevant mechanism of cold ischemic myocardial injury. A subset of 26S proteasomes appears to be a cell-destructive protease that is activated as ATP levels decline<sup>[48]</sup>. The addition to UW solution of epoxomicin, a proteasome inhibitor, reduced cardiac edema and preserved the ultrastructural integrity of the post-ischemic cardiomyocyte<sup>[49]</sup>. In liver, we have recently demonstrated that the addition of the reversible UPS inhibitors bortezomib (BRZ) and MG132 to UW solution improved steatotic and non-steatotic liver preservation, and that the protective effect of BRZ was superior to that of MG132<sup>[50]</sup>. Supplementation of IGL-1 solution with BRZ also showed protective effects which were partially mediated through the activation of AMPK and Akt/mTOR signaling<sup>[51]</sup>.

**Carbonic anhydrase II:** Carbonic anhydrase (CA) are Zn-metalloenzymes that catalyze the reversible reaction between carbon dioxide hydration and bicarbonate dehydration. Recently the function of CAs has aroused great interest, as they contribute to the transport of CO<sub>2</sub> and protons across the biological membranes and are involved in pH regulation, CO<sub>2</sub> homeostasis and biosynthetic reactions such as gluconeogenesis, lipogenesis and ureagenesis. In mammals 16 different CAs are found, with different amino acid sequences, enzymatic properties and sites of expression<sup>[52]</sup>. Since carbonic anhydrase II (CA II) also contributes to acid-base homeostasis<sup>[53]</sup>, we suggest that it could be modulated in conditions of liver preservation and that its addition to the preservation solution could be an efficient strategy for reversing pH alterations provoked by cold ischemia. Indeed, in preliminary studies at our laboratory,

we have observed that fatty livers preserved in IGL-1 solution supplemented with CA II showed lower injury, better function and major reductions in liver apoptosis parameters<sup>[54]</sup>. So CA enrichment of preservation solutions is an up-and-coming approach for improving the preservation of suboptimal liver grafts.

**Statins:** Statins, or the 3-hydroxyl-3-methylglutaryl coenzyme A inhibitor family, are a group of drugs known to decrease cholesterol levels and treat dyslipidemias<sup>[55]</sup>. They also have a variety of anti-inflammatory, antioxidant and immunoregulatory effects<sup>[56,57]</sup> and they maintain the endothelial barrier by activation of eNOS and subsequent production of NO<sup>[58-60]</sup>. Due to their various effects, statins have been proposed as effective pharmacological agents against IRI in both normal and steatotic livers<sup>[61-63]</sup>. UW supplementation with simvastatin (a synthetic analog of statin) prevented the deleterious effects of cold storage in endothelial cells, due to the enhancement of vasoprotective pathways, thus improving liver viability<sup>[64]</sup>. With this in mind, the supplementation of IGL-1 with simvastatin could promote the NO generation induced by IGL-1 solution alone, and may contribute to preventing the exacerbated microcirculation complications existing in fatty liver grafts after revascularization. In addition, increased levels of NO could contribute to stabilize cytoprotective factors such as HIF- $\alpha$ , which are generated as an adaptive response to the hypoxic conditions that characterize cold preservation<sup>[30]</sup>.

#### **New potential additives: Some considerations**

**Sirtuin activators:** Sirtuin1 (SIRT1) is a deacetylase that regulates the activity of various non-histone and histone proteins and as a result is involved in various cell processes such as apoptosis and oxidative stress<sup>[65-68]</sup>. SIRT1 induces AMPK activation through LKB1 deacetylation, and favors NO production by e-NOS activation<sup>[69,70]</sup>. Further, in a recent study published by our group, we mentioned that SIRT1 is involved in the beneficial effects of ischemic preconditioning, partly *via* AMPK and eNOS activation<sup>[68]</sup>. Consequently, addition of SIRT1 activators in preservation solutions may be a promising strategy for prolonging storage periods; SIRT1 activators may activate AMPK and maintain the cell energy status, and may also increase NO levels and alleviate microcirculation disturbances, especially in fatty livers. Preliminary data obtained from our laboratory showed that SIRT1 is a differential marker in steatotic and non-steatotic livers during cold preservation. Since SIRT1 activity requires high NAD<sup>+</sup> levels, NAD<sup>+</sup> activators may also contribute to better liver graft preservation by activating not only SIRT1, but also other members of sirtuin-family such as Sirtuin3 (SIRT3). SIRT3 is located in the mitochondria and affects the acetylation status of various mitochondrial proteins<sup>[71]</sup>. Enhancement of SIRT3 activity could thus achieve better mitochondrial preservation and prevent reactive oxygen

species (ROS) production during reperfusion.

**Nrf2 activators:** Moreover, recent studies have demonstrated the importance of Nrf2 in IRI models<sup>[72-74]</sup>. Nrf2 is activated under conditions of oxidative stress and induces the transcription of anti-oxidant enzymes in order to eliminate redox stress. Nrf2-deficient livers exhibit enhanced liver injury upon IRI<sup>[75]</sup>. Consequently, we propose the use of Nrf2 activators in preservation solutions in order to alleviate oxidative stress during reperfusion.

All in all, extensive studies in experimental models have proposed modified preservation solutions in order to extend cold storage and to maintain graft viability as far as possible. Since IRI is a multifactorial process, preservation solutions could incorporate various pharmacological agents in order to combine different protective mechanisms and thus improve liver preservation. Nonetheless, the use of pharmacological agents may be limited by their potential toxicity and side effects or their unsuitability for suboptimal grafts, and so novel strategies of preservation should be developed.

### Liver graft wash out

After cold storage, the liver grafts preserved in commercial preservation solutions need to be washed out to remove the solution before reperfusion and also to obtain the most suitable conditions for graft revascularization and viability after transplantation. Although research into rinse solutions is limited, recent data from our laboratory show that washing out the liver grafts preserved in UW for 24 h, with a rinse solution containing PEG35, is an effective tool for reducing liver graft injury after two hours of *ex vivo* perfusion<sup>[76]</sup>. PEG35 in the rinse solution was associated with decreased oxidative stress and mitochondrial damage, increased activation of AMPK, and enhanced NO generation. In addition, it contributed to restoring cytoskeleton integrity following IRI. In contrast, when livers were preserved in IGL-1 solution, these benefits were not evident, probably due to the presence of PEG35 as oncotic agent (unpublished data).

It is well known that PEG molecules are water-soluble polymers of various molecular weights which are non-immunogenic and non-toxic<sup>[77]</sup>. In general, PEGs prevent the generation of ROS<sup>[78,79]</sup>, enhance cell survival pathways in hypoxia/reoxygenation conditions and repair endothelial cell damage during post-ischemic reperfusion<sup>[80,81]</sup>. PEG exerts its cytoprotective role through the restoration of membrane integrity<sup>[15,78,81,82]</sup> or by entering the cell through the disrupted membranes and interacting with cellular organelles<sup>[83]</sup>. In hypothermic hepatocyte preservation, PEG8 (8 kDa) prevented cell swelling through a mechanism that was independent of its osmotic properties<sup>[14]</sup>.

## DYNAMIC PRESERVATION: MACHINE PERFUSION TECHNIQUES

For standard liver grafts, SCS with different preservation solutions remains highly successful. However, with the increasing need for organs in recent years, the use of novel techniques for optimizing suboptimal graft preservation is arousing interest.

MP consists of creating a controlled recirculating flow of preservation solution through the organ using a pump. This continuous perfusion permits better penetration of the preservation solution, a thorough washout of blood and equilibration of the interstitium with the perfusate medium, delivery of oxygen and nutrients (if the perfusate is oxygenated), and removal of toxic metabolites (when the perfusate is renewed or filtered). In addition, it allows real-time monitoring of the functional and biochemical performance of the graft and the provision of metabolic support during preservation<sup>[84]</sup>.

Unlike the kidney, the MP protocol for the liver is determined mainly by the temperature of preservation: hypothermic (HMP) at 4 °C, normothermic (NMP) at 37 °C and subnormothermic (SNMP) at 20 °C-25 °C. Also, several flows and pressures (pulsatile or not), single or dual perfusion (hepatic artery and portal vein), oxygenation or non-oxygenation, and different MP solution compositions have been tested in various liver graft experimental models<sup>[85]</sup>.

### HMP

HMP is a dynamic cold preservation method at 4 °C which ensures homogeneous and continuous supply of metabolic substrates to the graft during the *ex vivo* period<sup>[86]</sup>. During HMP, aerobic metabolism decreases but does not stop completely and the provision of metabolic substrates allows the reduction of the cellular insults seen during reperfusion.

HMP offers several advantages over SCS. Guarrera *et al.*<sup>[87]</sup> were the first to compare HMP to SCS in human liver transplantation, and showed that HMP improves graft function and attenuates classical biochemical markers of liver preservation injury. Given the fact that ROS accumulation during ischemia can lead to significant hepatocyte toxicity, HMP has been shown to protect the rodent liver from ROS by a reduction in glutathione depletion and superoxide anion release when compared with SCS<sup>[88]</sup>. And in the case of suboptimal livers, Bessems *et al.*<sup>[89]</sup> showed that HMP improved both hepatocellular and endothelial function while reducing damage in a diet-induced rat fatty liver model.

In contrast to the kidney, in which successful HMP does not necessarily depend upon oxygenation, oxygenated HMP (HOPE) has been developed as a means of improving the quality of liver preservation in normal

or ECD livers<sup>[90]</sup>. Oxygenated preservation enables grafts to restore tissue homeostasis and to maintain the functional integrity of hepatocytes during ischemia. In a recent study, Schlegel *et al*<sup>[91]</sup> also described a protective effect on the rodent biliary system using HOPE in DCD grafts that underwent transplantation. As expected, perfusion with the HOPE system decreased the parameters of hepatocellular injury and lowered immunogenic upregulation.

**Perfusates for HMP:** In general, the composition of perfusate solutions used for HMP is based on a reformulation of UW solution, in which lactobionate is replaced by gluconate. This solution, named Belzer-MP solution (Belzer-MPS), continues to be the predominant perfusion solution.

Bessemis *et al*<sup>[92]</sup> described a new HMP solution, Polysol, which contains amino acids, histidine, glutamine, tryptophan, ascorbic acid and  $\alpha$ -tocopherol. Their studies show that Polysol improved liver preservation compared to Belzer's MPS, with lower enzyme release and increased bile production. Vasosol has also been proposed as an efficient alternative for HMP<sup>[87]</sup>. Its composition is based on Belzer-MPS but it is supplemented with antioxidants (N-acetyl-cysteine), metabolic substrates ( $\alpha$ -ketoglutarate, L-arginine) and vasodilators (prostaglandin E1 and nitroglycerin). Recently, the benefits of Vasosol have been improved by the addition of  $\alpha$ -tocopherol to further enhance antioxidant properties when HMP is used<sup>[93]</sup>.

### SNMP

Recently it has been suggested that the use of SNMP systems may be suitable for *ex vivo* preservation and recovery of human liver for transplantation. SNMP is an intermediate status for graft conservation, using sub-thermic conditions (20 °C-25 °C), taking advantage of the lower metabolic demand in sub-physiological temperature conditions, while still maintaining sufficient metabolism for viability testing and improvement of graft function. SNMP has already proven advantageous in reducing markers of biliary injury during preservation and in restoring normal biliary physiology<sup>[94]</sup>. A recent study by Bruinsma *et al*<sup>[95]</sup> is the first demonstration of the capacity of SNMP to sustain human livers. This group showed that SNMP effectively supports the human liver *ex vivo* with minimal injury, and normalizes physiological post-ischemia disturbances.

### NMP

The principle of normothermic perfusion is the maintenance of normal cellular metabolism in a physiological environment throughout the preservation period by maintaining normal temperature (37 °C) and providing oxygen and essential substrates<sup>[96]</sup>. This ensures large-scale metabolic activity and the maintenance of energy reserves such as ATP content. NMP has the advantage of allowing viability assessment prior to transplantation. As the liver metabolism is maintained during preservation,

markers including bile production and liver enzymes can be measured.

NMP is an emerging technology whose potential in liver preservation has been described in several animal studies, which have shown its superiority over SCS in the preservation of liver grafts<sup>[96-98]</sup>. Interestingly, porcine and murine models of DCD livers are significantly improved by NMP compared to organs preserved by SCS<sup>[99,100]</sup>.

Recently, Ravikumar *et al*<sup>[101]</sup> reported the first clinical trial of transplanted livers with NMP. Their study included 10 transplanted patients with relatively low risk donors and recipients, and showed that NMP is safe and feasible in human applications. This study opens up new avenues for research into liver graft preservation with NMP.

Recently, NMP has emerged as a novel tool for decreasing steatosis in a process named "defatting". In a preliminary study using porcine livers, *ex vivo* normothermic perfusion for 48 h led to a 50% reduction in lipid droplet size in perivenous hepatocytes, reaching the size found in control lean livers<sup>[102]</sup>. Moreover, NMP of steatotic livers from Zucker ob rats using a "defatting cocktail" decreased the intracellular lipid content by 50% over 3 h of perfusion<sup>[103]</sup>. Decreasing steatosis prior to transplantation by short term NMP would allow the transplantation of severely steatotic livers and thus alleviate the donor liver shortage.

**Perfusates for NMP:** NMP requires advanced metabolic support since the organ is fully metabolically active. Therefore, typically diluted blood-based perfusates are used. More recently, a solution initially described for lung perfusion has also been applied to liver grafts<sup>[104]</sup>. Steen is a buffered extracellular solution containing dextran and albumin at an optimized colloid osmotic pressure.

For defatting purposes, the perfusate developed contains different compounds to activate nuclear receptors such as PPARs, pregnane X receptor, and constitutive androstane receptor in order to exert an insulin-mimetic effect and to stimulate intracellular cAMP. This liquid was added into Minimum Essential cell culture medium as a perfusate to stimulate the lipid metabolism of obese rat liver grafts preserved using NMP. With this cocktail, a significant decrease (50%) in steatosis was observed after 3 h of NMP<sup>[103]</sup>. A recent study showed that the supplementation of this cocktail with L-carnitine, together with hyperoxic exposure, abolished the sensitivity of macrosteatotic hepatocytes to hypoxia reoxygenation (H/R)<sup>[105]</sup>.

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## BIOENGINEERING IN LIVER GRAFT PRESERVATION

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In the context of liver graft preservation, bioengineered human livers represent an opportunity to test new solutions and liver preservation methods, thus potentially bypassing the requirement of precious and scarce human organs. Bioengineering allows quicker and cheaper

**Table 2 Advantages and disadvantages of machine perfusion preservation**

Advantages	Disadvantages
Continuous nutrients and oxygen supply	Logistically complex
Continuous monitoring of organ viability	High cost
Removal of metabolic waste products	No optimized conditions
Extended preservation time	Need for trained personnel
Better preservation of microcirculation	
Potential "rescue" of suboptimal organs	

development and transfer to the clinic<sup>[106]</sup>.

Over the past few years, organ bioengineering has come of age. The seminal study by Ott *et al.*<sup>[107]</sup> in 2008 on heart decellularization and recellularization paved the way for whole organ bioengineering. After this initial study of the heart, many other organs followed. In 2009, Baptista *et al.*<sup>[108]</sup> described the first methods for liver, pancreas and kidney decellularization and recellularization, and their paper was followed by an exponential growth of publications by many other authors.

Currently, with several solid organs already successfully bioengineered and under further development by several groups around the world, this technology has huge potential. However, bioengineered organs are still not available to the transplant surgeon as alternative grafts. There are already several applications that can be addressed and extended with the current generation of bioengineered organs and their acellular scaffolds. Most of these applications, like drug metabolism<sup>[106]</sup>, organ/tissue physiology<sup>[106,107,109,110]</sup>, matrix biology<sup>[111]</sup>, developmental biology<sup>[111,112]</sup>, and stem cell biology<sup>[113]</sup> are perfectly complemented by these novel bioengineered human tissues which will open up exciting new experimental avenues.

In the particular context of normothermic perfusion, the enabling bioreactor and culture media technology developed in the bioengineering process of livers may constitute a new body of knowledge that can help further the development of NMP for liver preservation, due to the similarities of the conditions used<sup>[114]</sup>. Finally, the use of normothermic perfusion bioreactors in liver preservation and bioengineered human livers may also provide a better route and environment for *ex vivo* administration of mesenchymal stem cells. The use of these cells has been proposed as a novel way to attenuate IRI and to downregulate the alloimmune response (adaptive immunity) and promotes engraftment after transplantation<sup>[115]</sup>. This has been demonstrated for rat kidneys, thus raising the hope that it may also work in the liver and other solid organs<sup>[116]</sup>.

## CONCLUSION

Due to its low cost and simple technical and logistical requirements, SCS is still preferred to MP as the standard method of preservation in liver transplantation. SCS is probably unsuitable for suboptimal liver grafts,

because they have already suffered severe tissue damage secondary to hypoxia during the initial period of warm ischemia. Additional damage to the organ due to hypothermic conditions may limit the ability to restore cellular function, because metabolic activity is decreased at low temperatures.

The growing need to use suboptimal livers and to expand donor pool is accompanied by the drive to improve current preservation techniques before transplantation. In this situation, there has been renewed interest in liver graft preservation using machine perfusion. Both HMP and NMP have been found to be beneficial in preserving normal and suboptimal livers, and their relative merits are currently being debated. More basic research and randomized controlled trials are needed. As for SNMP preservation, it remains relatively unexplored at present.

Studies on the cost-effectiveness of MP and SCS will continue over the coming years, but considerable support for MP is beginning to emerge. Table 2 summarizes its advantages and disadvantages for liver preservation. It seems clear that MP strategies will play an increasing role and that their use should be optimized, including the subsequent development of new perfusion solutions. With this in mind, the future of liver MP preservation will also depend on the composition of perfusion solutions. At present, little attention is being paid to the potential advantages of adding cytoprotective, immunomodulating, pro-regenerative components to the MP solutions.

It is well known that PEG protects cell membranes; it has already been used as a colloid in machine perfusion, just as it was previously in SCS. The development of different PEG molecules could establish new frontiers in the design of new perfusion solutions for application in MP techniques and may increase graft conservation in the future. The revitalization of steatotic livers through defatting agents represents another interesting future application, given that the worldwide incidence of severely steatotic livers is expected to rise together with the increase in obesity rates.

Finally, bioengineering is another area with great potential for graft preservation in clinical transplantation.

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