Review Article

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A Review of Machine Perfusion Strategies in Liver Transplantation

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The acceptance of liver transplantation as the standard of care for end-stage liver diseases has led to a critical shortage of donor allografts. To expand the donor organ pool, many countries have liberalized the donor criteria including extended criteria donors and donation after circulatory death. These marginal livers are at a higher risk of injury when they are preserved using the standard static cold storage (SCS) preservation techniques. In recent years, research has focused on optimizing organ preservation techniques to protect these marginal livers. Machine perfusion (MP) of the expanded donor liver has witnessed considerable advancements in the last decade. Research has showed MP strategies to confer significant advantages over the SCS techniques, such as longer preservation times, viability assessment and the potential to recondition high risk allografts prior to implantation. In this review article, we address the topic of MP in liver allograft preservation, with emphasis on current trends in clinical application. We discuss the relevant clinical trials related to the techniques of hypothermic MP, normothermic MP, hypothermic oxygenated MP, and controlled oxygenated rewarming. We also discuss the potential applications of ex vivo therapeutics which may be relevant in the future to further optimize the allograft prior to transplantation. (J Clin Exp Hepatol xxxx;xxx:xxx)

As worldwide acceptance of liver transplants grew, the 1990s witnessed an expansion of liver transplant programs. This was further fueled by the development of live donor techniques, making this surgery acceptable in Asian countries where brain death donation was not yet culturally acceptable. Now, liver transplantation is firmly established as a standard of care for end-stage liver diseases as opposed to an experimental therapeutic option. The indications have progressively increased, and the many contraindications have gradually been overcome as our technology, and ancillary support has improved.

This rapid increase in liver transplant programs across 80 countries globally created its own set of problems like donor organ shortage. While the advent of split liver transplantation has potentially doubled the number of available allografts, technical challenges and a shortage of grafts suitable for splitting hinder its universal use.[1] The lack of organs available for liver transplantation in many countries has led to liberalization of the selection criteria for acceptable organ donors. More research is now focused on optimizing organ preservation techniques and implementing salvage strategies for organs considered marginal or unsuitable for transplantation.[2]

The concept of ex vivo machine perfusion (MP) of isolated organs is not new and dates back to the Lindbergh Apparatus in the 1930s.[3] Continuous perfusion of liver allografts was described by Brettschneider *et al.* as early as the 1960s.[4] At that time, the lack of availability of a suitable perfusate, and the inherent logistic and financial challenges of a continuous perfusion system prevented widespread acceptance. Moreover, organ preservation using static cold storage (SCS) after *in situ* perfusion with the University of Wisconsin (UW) preservation solution in the 1980s provided a safe and effective method of preservation of standard criteria livers procured on donation after brain death (DBD). So, the strategy of continuous perfusion was largely abandoned.[2,5] Then, as the acceptance of liver transplantation grew, demand for allografts far

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Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine transaminase; ASO: Antisense oligonucleotides; AST: Aspartate transaminase; CIT: Cold ischemia times; COPE: Consortium for Organ Preservation in Europe; COR: Controlled oxygenated rewarming; DBD: Donation after brain death; DCD: Donation after circulatory death; DHOPE: dual hypothermic oxygenated machine perfusion; EAD: Early allograft dysfunction; ECD: Extended criteria donors; ETC: Electron transport chain; GGT: Gamma glutamyl transferase; HCV: Hepatitis C virus; HMP: Hypothermic machine perfusion; HOPE: Hypothermic oxygenated machine perfusion; ICU: Intensive care unit; IGL: Institute George Lopez-1; INR: International normalized ratio; IRI: ischemia reperfusion injury; LDH: Lactate dehydrogenase; MP: Machine perfusion; MELD: Model for end-stage liver disease; NAS: Non-anastomotic biliary strictures; NMP: Normothermic machine perfusion; NO: Nitric oxide; PNF: Primary nonfunction; ROS: Reactive oxygen species; RT-PCR: Reverse transcription polymerase chain reaction; SNMP: Sub-normothermic machine perfusion; UW: University of Wisconsin; WIT: Warm ischemia times

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outstripped their supply, and many countries introduced extended criteria donors (ECD), including donation after circulatory death (DCD), in an attempt to bridge the shortage. These included organs from donors aged >80 years, organs with cold ischemia times (CITs) of >8–10 h, and warm ischemia times (WITs) of >30 min, organs with graft macrosteatosis >30%, poor *in situ* perfusion, prolonged retrieval, and extensively elevated donor liver function tests.[6] These marginal organs are at a higher risk of injury using the SCS protocol as sudden rewarming causes considerable damage to ECD allografts with increased susceptibility to ischemia reperfusion injury (IRI), primary nonfunction (PNF), early allograft dysfunction (EAD), and biliary complications.[2,7–10] So, researchers looked at other avenues for organ preservation. They found that MP techniques using an appropriate perfusate limited allograft damage and led to better preservation of the liver, thereby optimizing the organ before implantation. This has led to a renewed interest in using (and optimizing) MP techniques to protect and preserve these marginal livers. Therefore, global trends in liver transplantation have been towards introducing MP strategies for organ preservation.

This review aims to address the topic of MP in liver allograft preservation, with emphasis on current trends in clinical applications and future perspectives.

NEED FOR MACHINE PERFUSION STRATEGIES

SCS aims to reduce the allograft metabolism and oxygen demand thereby increasing the preservation time.[11] However, this strategy merely delays the graft damage. As demonstrated by some researchers, the metabolism does not cease entirely during SCS. A low rate, but significant amount of anaerobic metabolism continues, which depletes the intracellular ATP pool leading to dysregulation of cellular metabolism.[11–13] Ultimately, the depleted ATP stores result in the failure of ATP-dependent Na+/K+ and Ca2+ pumps and lead to cell death. SCS also fails to address the physiological effects of blood flow in the liver. The lack of blood flow derived shear stress leads to a disruption of nitric oxide (NO) production, which impairs the functioning of the sinusoidal endothelial cells.[14,15]

When such a SCS-preserved organ is implanted, there is a sudden reperfusion of oxygen-rich blood. This results in a cascade of cellular events, which ultimately lead to the massive production of reactive oxygen species (ROS). The mitochondrial electron transport chain (ETC) is a significant source of ROS under these reperfused conditions.[16–18] During periods of ischemia, the lack of oxygen inhibits the ETC and leads to the accumulation of succinate in the cells. This accumulated succinate drives further ROS production during reperfusion and leads to IRI.[19] The liver sinusoidal endothelial cells are especially vulnerable during the cold ischemic phase. On reperfusion and exposure to the ROS, these cells express a multitude of proinflammatory cytokines, which activate the Kupffer and Stellate Cells, eventually resulting in fibrosis and the loss of organ function.[20] These deleterious effects of IRI are more pronounced in ECD allografts as they exhibit impaired microcirculation and an increased susceptibility to oxidative stress.[21,22]

MP strategies have shown promise to not only limit the damage sustained by the allograft but also reverse some of the harmful effects of cold ischemia.[5] The way MP does this is quite simple: Continuous circulation prevents dysregulation of NO homeostasis and preserves endothelial function while also washing out metabolic waste. Supplementation of oxygen, nutrients, and other metabolic substrates may allow for a recovery of the oxygen debt and may preserve the physiologic function of the liver.[8] Several researchers have also demonstrated reduced levels of proinflammatory cytokines (TNFα and IL-6) during MP preservation techniques compared with SCS-preserved controls.[20,23]

The preservation temperature is often not monitored in SCS preservation. MP strategies involving hypothermic temperatures may also allow for better core cooling of the allograft.

BASIC CONCEPTS OF MACHINE PERFUSION

The term "machine perfusion" includes a variety of dynamic, continuous perfusion techniques, which aim to preserve, and possibly improve, the outcomes in liver transplantation.[24–27] Depending on the temperature of the perfusate, modern MP techniques include the hypothermic machine perfusion (HMP) (2–10 °C), subnormothermic machine perfusion (SNMP) (20–25 °C) and normothermic machine perfusion (NMP) (35–37.5 °C).

HMP is the dynamic counterpart of SCS, and it aims to combine the technical simplicity and relative safety of SCS with the positive effects of continuous perfusion. In HMP, the perfusate is not actively oxygenated. Techniques like hypothermic oxygenated machine Perfusion (HOPE) implement active oxygenation of the hypothermic perfusate. Now, if this oxygenated perfusate is circulated via the portal vein alone, it is termed HOPE. When the oxygenated perfusate is perfused using both the portal vein and hepatic artery, researchers have termed it dual HOPE or DHOPE.[28,29] Most machines deliver continuous flow through the portal vein and pulsatile flow through the hepatic artery to mimic their physiology.

In contrast to HMP, NMP aims to maintain a near-normal metabolism of the allograft by perfusing it with oxygenated blood-based solutions at body temperatures. It also provides a unique theoretical opportunity for intervention during ex vivo MP by the addition of therapeutic substances into the perfusate.[30]

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Table 1 Summary of Machine Perfusion Techniques.

Strategy	Temperature	Main characteristics	Limitations
HMP	4–12 °C	Reduced metabolism and washout of metabolic waste	No viability testing
HOPE D-HOPE	4–12 °C	Oxygenated perfusate via the portal vein alone (HOPE) or via a dual portal vein and hepatic artery setup (DHOPE) Surrogate markers used for organ quality assessment	Limited data on viability testing
SNMP	<37 °C	Lowered metabolism, surrogate markers used for organ quality assessment, a bridge between HMP and NMP	Limited data available on the use of this technique
NMP	37 °C	Mimics *in vivo* conditions, allows for organ viability assessment, potential ex-vivo therapeutics	Logistic challenges to maintain temperature, nutrition, etc. Failure of perfusion during transportation may jeopardise the graft without immediate conversion to SCS
COR		Combination of the above techniques to achieve gradual rewarming	Limited data available on the use of this technique

HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; DHOPE, dual hypothermic oxygenated machine perfusion; SNMP, sub-normothermic machine perfusion; NMP, normothermic machine perfusion; COR, controlled oxygenated rewarming.

Since MP protocols are still largely experimental, with only a small number of transplant centers having access to commercially available perfusion machines, literature still lacks guidelines for its use.[6,31] Varying compositions of perfusate, temperatures, perfusion devices, the degree of oxygenation, perfusion route and pressure also hamper evidence-based comparisons between the available methods (Table 1). In this review article, we provide the relevant clinical evidence available for different MP techniques. A detailed description of the basic science of perfusion biology is beyond the scope of the present review.

Probably the benefit of MP techniques could be optimized by using it from the time of graft retrieval in the donor hospital until its implantation in the recipient hospital. However, this poses several logistic challenges related to transportation of the machine itself. Therefore, several strategies are currently in use, using these techniques (Table 2).

A quick mention in the role of liver enzymes for assessment of graft function is appropriate at this point before we look into the clinical evidence of MP strategies. The use of peak enzyme levels as a primary endpoint in MP trials has been criticized by Dutkowski *et al.*, arguing that perfusion could potentially "washout" liver enzymes and, therefore, lead to lower peak levels in the postoperative period. Czigany and colleagues, on the other hand, are of the opinion that a potential "washout" of transaminases in perfused livers is relevant only in trials using NMP and/or long perfusion times.[32] The present authors are of the opinion that other outcome parameters such as a reduction in acute kidney injury or a reduction in biliary complications, serve as more informative indicators of better preservation.

HYPOTHERMIC MACHINE PERFUSION

While the technique of HMP is well established in renal transplants, relatively few studies have investigated the benefits of HMP in liver transplants (Table 3). The first, prospective cohort study was conducted by Guarrera *et al.* in 2010 when they transplanted 20 livers preserved by a non-oxygenated HMP device using both portal vein

Table 2 Strategies Using Machine Perfusion Techniques.

Procurement	Pre-transport	Transport	Pre-implantation	Name
Cold flush out	Cold storage	Cold storage	Cold storage	Static cold storage
Cold flush out	Cold storage	Cold storage	HMP/HOPE/DHOPE/NMP	Back to base technique or End ischemic technique
Cold flush out	Cold storage	Cold storage	Controlled rewarming	COR
Cold flush out	NMP	NMP	NMP	Continuous NMP
NMP	NMP	NMP	NMP	*In situ* perfusion or ischemia free technique

HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; DHOPE, dual hypothermic oxygenated machine perfusion; NMP, normothermic machine perfusion; COR, controlled oxygenated rewarming.

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Table 3 Summary of Relevant Hypothermic Machine Perfusion Trials.

Author	Trial	Design	n	Machine	Key findings
Guarrera *et al.*[33] in 2010	HMP vs. SCS	Prospective cohort study, Case-matched 1:1	20 vs. 20	Modified Medtronic PBS® Perfusate: Vasosol®	No significant difference in PNF, EAD and survival Shortened hospital stay, reduced peak serum aspartate transaminase levels and improved renal function
Henry *et al.*[34] in 2012	HMP vs. SCS	Prospective, cohort study Case-matched 1:1	18 vs. 15	Modified Medtronic PBS® Perfusate: Vasosol®	Reduced proinflammatory cytokine expression, Reduced downstream activation of adhesion molecules Fewer ultrastructural damage to the liver compared with SCS controls
Guarrera *et al.*[35] in 2015	HMP vs. SCS (Declined donor grafts)	Prospective, nonrandomized clinical trial Case-matched 1:1	31 vs. 30	Modified Medtronic PBS® Perfusate: Vasosol®	Similar EAD and 1-y patient survival Lower incidence of biliary complications within the first year Reduced hospital stay

HMP, hypothermic machine perfusion; SCS, static cold storage; PNF, primary nonfunction; EAD, early allograft dysfunction; PBS, portable bypass system.
Listed perfusion devices: Medtronic PBS®, Minneapolis, MI, USA.
Listed perfusate: Vasosol®, Preservation Solutions Inc., Elkhorn, WI, USA.

and hepatic artery cannulation. They included patients with model for end-stage liver disease (MELD) scores less than 35, and who were not in the ICU at the time of organ offer. Patients were excluded if the expected CIT was less than 4 h or if the estimated total travel time from the donor hospital was greater than 3 h. These patients were compared with 20 controls who were transplant recipients of allografts preserved using the standard SCS organ preservation protocols. Patients who had met all the inclusion criteria but declined to participate as HMP subjects were identified as potential control subjects. Control subjects were matched for donor and recipient age, MELD score, and cold and WITs. They used similar surgical techniques and peri-operative protocols in both the study groups. In this study, the major endpoints like PNF, EAD, graft and patient survival did not differ significantly between the two groups. However, the HMP cohort showed a significantly reduced peak of liver enzyme levels, a significantly shortened length of hospital stay, and an improved renal function.[33]

In 2012, Henry *et al.* researched molecular markers of IRI after HMP. Tissue samples for this study were obtained from patients who had completed the groups prospective cohort study (the Guarrera 2010 study, mentioned above). They compared grafts preserved with HMP with those preserved using SCS and used molecular techniques like reverse transcription polymerase chain reaction (RT-PCR), immunohistochemistry and electron microscopy to understand the expression of inflammatory cytokines, oxidation markers, and ultrastructural damage in the liver allograft. They found that HMP significantly reduced proinflammatory cytokine expression, relieved downstream activation of adhesion molecules and prevented ultrastructural damage to the liver compared with SCS controls.[34] However, they did note a rise in the pro-apoptotic markers such as cytochrome c and caspase 3 in the HMP group. The clinical significance of this finding remains unclear and further studies to validate the results of this trial are recommended.

The same group also conducted a case matched study in 2015 where 31 transplant recipients with HMP-preserved ECD "orphan" livers (initially rejected by UNOS) were compared with recipients transplanted with SCS-preserved livers. In this study, they defined ECD as (a) donor age >65 years; (b) hepatitis C virus (HCV) positive with 15% macrosteatosis; (c) >25% macrovesicular steatosis by biopsy; or (d) donor aspartate transaminase (AST) or alanine transaminase (ALT) >1000 IU/L at the time of organ offer. The HMP group was compared with a control group of 30 patients transplanted during the same time period, matched for donor and recipient age, MELD score, donor risk index, and CITs. Immediately prior to implantation, grafts in both groups were flushed with 1–1.5 L of Hextend solution (Hospira, Inc., Lake Forest, IL) via the portal vein. The surgical technique and perioperative care protocols were similar in both the groups, minimizing the risk of bias in the trial. They demonstrated a significantly lower biliary complication rate in the HMP group versus the SCS group (4 vs. 13, $P = 0.001$). Mean hospital stay ($\pm$ standard deviation) was also significantly shorter in the HMP group (13.64 ± 10.9 vs. 20.14 ± 11.12 days, $P = 0.001$).[35] They also observed a more rapid recovery of liver and renal markers to normal reference ranges in the HMP group. On analyzing the perfusion parameters, they also suggested

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that elevated portal pressure and high-effluent AST could be predictive of impending reperfusion injury. Ultimately, while the researchers concluded HMP facilitated the successful transplantation of "orphan" livers, this strategy did not confer any 1-year survival benefit over the SCS group.

Other researchers, however, have reported that HMP led to an increased hepatic vascular resistance and a lower threshold for shear stress–induced endothelial injury.[36,37] This was hypothesized to lead to an inadvertent inflammatory response by the Kupffer and Stellate cells, which lie in close proximity to the sinusoidal endothelial cells. The question arises if there is a role of measuring vascular resistance and flow as surrogate markers of viability in HMP as is common practice in kidney HMP. Trials designed to primarily look into this finding would provide valuable insight of viability assessment during HMP.

HYPOTHERMIC OXYGENATED MACHINE PERFUSION

Literature is divided on whether HMP alone ensures a sufficient supply of dissolved oxygen to the ischemic, energy-depleted allograft. On the one hand, it has been postulated that the dissolved oxygen in the perfusate under atmospheric pressure is sufficient in a metabolically dormant allograft. On the other hand, many researchers thought that the inherently impaired ECD grafts may require a higher oxygen supply to metabolize the accumulated succinate and regenerate ATP.[38] So, MP strategies such as the hypothermic oxygenated MP solely via the portal vein (HOPE) or dual portal vein and hepatic artery hypothermic oxygenated machine perfusion (DHOPE) came into clinical practice.[39,40] HOPE strategies aim to provide the marginal donor grafts with adequate oxygen to repay the incurred oxygen debt. It is usually performed in an end-ischemic setting, oxygenating, and "reconditioning" the liver after SCS preservation.

The molecular impact of oxygenating the perfusate was illustrated by comparing end-ischemic HOPE to SCS, and to non-oxygenized HMP in a porcine model. In this study, HOPE was able to prevent mitochondrial and nuclear injury, as well as Kupffer cell and endothelial activation.[41] Consistent with these results, other researchers also demonstrated hepato-protective effects of HOPE in various animal models.[28,42]

First human trials began in 2015 when Dutkowski *et al.* compared 25 HOPE treated transplants to 50 SCS-preserved controls (Table 4). In this trial, HOPE treated livers from Zurich (n = 25) were compared with SCS-preserved controls from Birmingham (n = 10) and Rotterdam (n = 40). Criteria for matching included donor WIT and key confounders summarized in the balance of risk (BAR) score (donor age, recipient age, MELD score, cold

Table 4 Summary of Relevant Hypothermic Oxygenated Machine Perfusion Trials.

Author	Trial	Design	n	Machine	Key findings
Dutkowski *et al.*[40] in 2015	HOPE vs. SCS	Multicentric clinical trial Case-matched Analysis 1:2	25 vs. 50	Device: LiverAssist Perfusate: UW gluconate solution (KPS®-1)	Decreased peak ALT levels, cholangiopathy, biliary complications Increased 1-year graft survival.
Van Rijn *et al.*[39] in 2017	DHOPE vs. SCS	Nonrandomized trial Case-matched 1:2	10 vs. 20	Device: LiverAssist Perfusate: UW gluconate solution (Belzer MPS®) supplemented with Glutathione	Lower serum ALT, GGT, ALP, and bilirubin levels at day 30 in comparison with SCS controls
Schlegel *et al.*[43] in 2019	HOPE- (DCD) vs. SCS (DBD)	Prospective Case-matched 1:1	50 vs. 50	Device: LiverAssist Perfusate: UW gluconate solution (KPS®-1)	Similar overall graft survival despite extended donor warm ischemia times in HOPE group
Van Rijn *et al.*[45] in 2021	DHOPE vs. SCS	Multicenter, prospective, randomized controlled clinical trial	78 vs. 78	Device: LiverAssist Perfusate: UW gluconate solution (Belzer MPS®) supplemented with glutathione	Significant reduction of non-anastomotic biliary strictures, Postreperfusion syndrome, EAD
Czigany *et al.*[44] in 2021	HOPE vs. SCS (ECD-DBD)	Prospective randomized control trial	23 vs. 23	Device: LiverAssist Perfusate: UW gluconate solution (Belzer MPS®)	Decreased peak ALT levels, reduction in the 90-day complication rate, shorter ICU- and hospital stay

DCD, donation after circulatory death; DBD, donation after brain death; ECD, extended criteria donors; HOPE, hypothermic oxygenated machine perfusion; DHOPE, dual hypothermic oxygenated machine perfusion; SCS, static cold storage; UW, University of Wisconsin; ALT, alanine transaminase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; EAD, early allograft dysfunction; ICU, intensive care unit.
Listed perfusion devices: LiverAssist, Organ Assist, XVIVO, Groningen, the Netherlands.
Listed perfusate: Belzer-MPS; Preservations Solutions Inc., Elkhorn, WI, USA.
KPS-1, Organ Recovery Systems, Itasca, IL, USA.

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storage, re-transplantation, preoperative recipient life support). The researchers found that the HOPE-treated livers had a lower peak ALT release after reperfusion (1239 vs. 2065 U/L, $P = 0.02$). HOPE treated livers also had a lower incidence of EAD, as expressed by the International Normalized Ratio (INR) on day 1. Incidence of intrahepatic cholangiopathy (0% vs. 22%, $P = 0.015$), and biliary complications (20% vs. 46%, $P = 0.042$) were lower in the HOPE-treated group. Finally preservation with HOPE increased the 1-year graft survival (90% vs. 69%, $P = 0.035$). However, it is important to keep the following in mind while interpreting the results of this trial. The implantation technique differed among the two groups. The transplant procedure was performed by classic liver implantation technique in HOPE-treated livers, but by a cava preserving technique (piggyback) in SCS livers (Rotterdam and Birmingham). The immunosuppression protocols also varied in both groups with all patients in the HOPE groups receiving additional Basiliximab on day 0 and day 4 while only 40 of the 50 controls received the additional immunosuppression. All HOPE-treated DCD liver grafts were stored in Institute George Lopez-1 (IGL) solution until MP, whereas unperfused liver grafts were stored using UW solution. Finally, the cold storage time was generally shorter in the HOPE group compared with unperfused livers, because of in-house donors in all HOPE-treated cases. These factors may influence the results of the trial since the control group differed in many key variables compared with the perfused group.[40]

In a nonrandomized control matched trial, van Rijn and colleagues, matched each recipient of DHOPE-preserved graft to two matched controls who underwent liver transplantation preserved using SCS at the same center. The procurement and implantation techniques were standardized between both the groups and matching was based on recipient age (±5 years), donor warm ischemia time (±5 min), and MELD score (less than 22). Results demonstrated that DHOPE-preserved recipients had lower post-transplant serum ALT, γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), and bilirubin levels in comparison with SCS-preserved controls. They noted that none of the 10 DHOPE-preserved livers required re-transplantation for non-anastomotic biliary stricture (NAS), compared with 5 of 20 in the comparison group, although this result was not significant statistically ($P = 0.14$). They noted a significantly higher incidence of postoperative hypokalemia in the DHOPE group compared with the control (3 vs. 0, $P = 0.03$). This study was limited by their small sample size and the use of historical controls. The control group included transplants done 6 years before the study group. Advancements in surgical experience and technology would influence the outcomes of patients and therefore the results of this study.[39]

Schlegel *et al.* published long-term outcomes (5 years) of HOPE treated transplants in 2019. They compared 50 HOPE-treated human livers transplanted from DCD donors at the University Hospital in Zurich to an untreated DCD cohort (n = 50) from the liver unit at Queen Elizabeth Hospital Birmingham. Matching was done to correct potential confounders like cold ischemia time, recipient age, and MELD score. The overall donor–recipient risk expressed by the UK DCD risk score was significantly higher in the HOPE group (median of 9 score points vs. 3 points, $P < 0.0001$) because of a longer WIT and donor age (upper limit of DCD donation in Switzerland being 90 years). Despite the higher risk score, they found that HOPE-treated liver transplants achieved similar overall graft survival. The number of NAS was more than twice in untreated DCD livers compared with HOPE-treated livers. Overall, seven grafts were lost in the untreated DCD liver group by ischemic cholangiopathy or PNF compared with none in the HOPE group ($P = 0.0125$). On a subgroup analysis with tumor-related graft failure excluded, the 5-year graft survival was 94% for HOPE-treated DCD liver transplants versus 78% in controls ($P = 0.024$). However, since 70% of the transplant recipients in the HOPE group had hepatocellular carcinoma, excluding tumor-related graft failure potentially skews the results. There were differences in the perioperative protocols between the two centers, which need to be considered. While DCD livers were procured by the super rapid cannulation technique at both centers, additional *in situ* perfusion of the portal/mesenteric vein was performed at Birmingham. The cold flush at the UK center was done with UW solution, whereas a IGL-1 solution was used at Zurich. The immunosuppression protocols also differed between the two centers. These may constitute a bias and limit the clinical significance of the results of this trial.[43]

Results of a prospective, multicenter, randomized controlled trial, conducted by Czigany *et al.* wherein 46 patients undergoing transplantation using ECD (DBD) from four centers were randomly assigned to HOPE (n = 23) or SCS (n = 23), were published in 2021. They demonstrated a 47% decrease in peak serum ALT levels in the HOPE group. To correct for an assumed washout effect of MP, they also considered relative changes of peak serum ALT instead of absolute values. They observed a significant reduction in the 90-day complication rate, a significantly shorter ICU- and hospital-stay in HOPE-preserved livers compared with the SCS controls. The authors of this trial used standardized protocols for perioperative care and immunosuppression protocols across all participating centers. The surgical technique however was not standardized and the participating centers used differing techniques as per their local protocols.[44]

In another recent prospective, metacentric, controlled trial, the authors randomly assigned DCD livers to preservation using either DHOPE (MP group) or SCS (control group). The trial was conducted in six liver transplantation centers in Europe. Randomization took place immediately

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after a donor liver had been deemed to be suitable and both the patients and the organ procurement team were blinded to the trial group allotment. The primary endpoint in this trial was the incidence of symptomatic NAS at 6 months after transplantation. Criteria for diagnosis of NAS were prespecified and all patients underwent a routine magnetic resonance cholangiography (MRC) at 6 months posttransplant. The imaging was reviewed independently by two radiologists who were unaware of the group allotment to minimize the bias. A total of 160 patients were enrolled, of whom 78 received a machine-perfused liver and 78 received a liver after SCS. They observed a significant reduction of symptomatic NAS in the machine-perfused group compared with the control group (6% vs. 18%; $P = 0.03$). However, it is worth mentioning that the incidence of asymptomatic NAS diagnosed at the 6-month MRC imaging was higher in the MP group (55% vs. 39%). Seven livers of the MP group were diagnosed with severe NAS on MRC imaging versus three livers in the control group. This difference may manifest as clinically significant NAS over a longer follow-up period. They also reported a 15% reduction in postreperfusion syndrome in the recipients of a machine-perfused liver (risk ratio, 0.43; 95% CI, 0.20 to 0.91). EAD occurred in 26% of the machine-perfused livers, as opposed to 40% of control livers (risk ratio, 0.61; 95% CI, 0.39 to 0.96). There were ultimately no relevant differences between the two groups in the use of renal-replacement therapy, in the durations of ICU or hospital stay, or in graft and patient survival at 1 year.[45]

Whether DHOPE has benefits over HOPE has not been studied in humans.[29] While it was postulated that DHOPE would better mimic the physiological conditions of the liver and be particularly beneficial for the bile ducts and cholangiocytes, a randomized trial using experimental animal protocols found no significant differences in endothelial cell function and injury between the groups. They did find significantly reduced lactate dehydrogenase (LDH) levels in DHOPE perfused livers, but the clinical impact of this finding is uncertain.[29]

Viability Testing in HOPE

There are emerging data on viability testing of the allograft during HOPE prior to implantation. In 2019, Muller and colleagues performed a detailed perfusate analysis in 54 HOPE-perfused livers at their centre.[46] They included both DBD and DCD livers, which were subjected to end-ischemic HOPE for a minimum of one hour. They used 3 L of highly oxygenated UW solution (MPS-Belzer) as perfusate, which was not exchanged during the entirety of the perfusion. They measured various metabolites like glucose, lactate, ALT, flavin mononucleotide (FMN), nicotine adenine dinucleotide (NAD), and others in the perfusate of these livers and correlated them to posttransplant arterial lactate clearance, INR, factor V, liver transaminases, hospital stay, and postoperative complications. They found a strong correlation of FMN release with coagulation factors and peak transaminases after transplant. They also found perfusate FMN correlated with hospital stay and importantly with cumulative complications after transplant, in contrast to other perfusate metabolites. The researchers also gave a physiologic explanation of this finding. Under physiologic conditions, FMN is very tightly bound to complex I of the ETC. When the respiratory chain is halted, it dissociates from complex I and is easily detectable in acellular machine perfusates.[47] They hypothesized that FMN release serves as surrogate marker for impaired cellular energy production, as high FMN release also correlated with ATP-breakdown in ischemic livers.[27,46]

This study suggests that assessment of liver graft quality is feasible during HOPE and further studies to validate these results in other perfused liver cohorts are awaited.

SUB-NORMOTHERMIC MACHINE PERFUSION

As the experience with HMP yielded favorable results, researchers investigated SNMP protocols (20–25 °C) to assume an intermediate role between HMP and NMP. They hypothesized a benefit to the allograft from a lower metabolic demand at sub-physiological temperature, while still maintaining sufficient metabolism for viability testing and for preservation of graft function.[48] As discussed below, NMP protocols have great logistic challenges and SNMP strategies aim to alleviate some of those, while achieving a compromise between cold and warm perfusion. To date, most of the research has been focused on animal models of liver transplant or on discarded human livers and we await further randomized trials using this strategy.[48–51]

NORMOTHERMIC MACHINE PERFUSION

While SCS and HMP strategies aim to slow down liver metabolism to preserve allograft viability, NMP techniques aim at maintaining the liver in a state of near physiological metabolism and synthetic liver function. In theory, this technique shows promise to further reduce preservation injury, and provide optimal conditions for increased pretransplant viability. It also allows for ex-vivo assessment of organ viability and integrity, and may potentially provide researchers an avenue for therapeutic interventions during ex vivo perfusion.[9] On the flip side, NMP poses significant logistic challenges as the machines are bulky and unsuitable for easy transport. Failure of perfusion during transportation may jeopardize the graft without immediate conversion to SCS. The need for trained percussionists and requirement of blood based perfusate also increase the overall cost of the technique. These factors have hindered widespread utilization of NMP.

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Viability Testing in Normothermic Machine Perfusion

Early research in NMP focused on optimizing allograft selection and allocation via graft viability testing. In 2013, the first series of successful NMP in human livers was reported by Op den Dries and colleagues.[52] They studied the markers of hepatic function to assess the viability of four discarded human livers preserved with NMP. Their technique consisted of pressure and temperature controlled pulsatile perfusion of the hepatic artery and continuous portal perfusion for 6 h. Levels of ALT, GGT and potassium concentrations remained stable in the perfusate and they noted a decrease in the lactate levels. The bile production was also preserved throughout the ex vivo NMP. They concluded NMP was feasible and also allowed for assessment of graft viability before transplantation.

Functional markers such as bile production and composition, lactate clearance and liver enzymes in the perfusate were identified surrogate markers of graft performance after transplantation.[53–56] The 2017 "Viability testing and transplantation of marginal livers" (VITTAL) trial was a nonrandomized, prospective, single-arm trial, which used the following criteria to assess graft viability post NMP in discarded human livers:

1. lactate clearance to <2.5 mmol/L or
2. bile production and 2 of the following 3 criteria:
   a. pH-homeostasis > 7.3,
   b. Stable pressure/flow dynamics of the graft (i.e., hepatic artery flow >150 ml/min, portal vein flow >500 ml/min)
   c. Homogenous graft perfusion with soft parenchymal consistency

71% (n = 22 out of 31) of the included livers met these viability criteria in this trial and these allografts had a 100% 90-day survival.[57,58]

In 2018, Watson *et al.* published their findings on viability assessment of allografts during ex vivo NMP. They reported that liver viability during NMP could be assessed using a combination of lactate clearance, transaminase release, glucose metabolism, and maintenance of acid–base balance. They also observed that livers which could not produce bile with a pH of >7.4 developed postoperative cholangiopathy. Livers which achieved a biliary pH of >7.5 had minimal stromal necrosis of the major intrahepatic ducts on histological examination, while livers that had a bile pH < 7.5, had moderate or severe stromal necrosis.[59]

Matton and colleagues also published similar findings in 2019 after studying 23 human donor livers after 6 h of end-ischemic NMP to determine biomarkers of graft viability. They found a biliary bicarbonate levels (>18 mmol/L), biliary pH (>7.48), biliary glucose (<16 mmol/L), a bile/perfusate glucose ratio (<0.67) and a biliary LDH levels (<3.7 U/L) to be accurate biomarkers of reduced posttransplantation biliary complications.[60] Further research to standardize the viability criteria are on the horizon.

Relevant Clinical Trials of Normothermic Machine Perfusion

In 2016, in a phase 1, nonrandomized, prospective trial by Ravikumar *et al.*, the outcomes of the recipients of 20 consecutive NMP donor livers were compared with those of 40 matched control patients who received SCS-preserved donor livers (Table 5). They used the OrganOx Metra® (OrganOx Limited, Oxford, UK) liver perfusion device which maintained the perfusate at normal temperature, and within physiological ranges for pO_2, pCO_2, pH, and at physiological pressures in the liver. They reported a similar 30-day graft survival rate and significant decrease in peak AST levels in the NMP-preserved livers compared with the controls.[61] While this study was going on in Europe, Selzner and colleagues published the first North American results of NMP using the same OrganOx Metra® NMP device. They compared the outcomes of 10 NMP-preserved liver transplants to a matched historical control group of 30 grafts using SCS as the preservation technique. They reported consistent findings and concluded that liver preservation with NMP was safe and produced results comparable with SCS.[62]

In 2017, a preliminary report from the Canadian National Transplant Research Project however reported significantly prolonged intensive care and hospital stays after NMP. They also highlighted safety and logistic concerns after a technical failure in vessel cannulation led to a graft discard.[63] To mitigate some of the logistic challenges with NMP, the same group conducted a study with the aim to determine whether an alternative, more practical approach including SCS while transport followed by NMP would compromise beneficial outcomes of continuous NMP. They reported no difference in graft function, incidence of complications, or graft and patient survival despite significantly prolonged mean CIT (6 vs. 3.2 h; $P = 0.001$) in the allografts, which were transported using the SCS technique.[64]

Results of a large, international, metacentric, randomized clinical trial comparing NMP with SCS for liver transplant were published in 2018. Conducted by the Consortium for Organ Preservation in Europe (COPE), this study compared outcomes between 121 NMP-preserved and 101 SCS-preserved allografts. The authors reported a 50% lower level of graft injury, as measured by raised AST levels, in NMP-preserved livers compared with conventional SCS-preserved allografts. To minimize the hypothetical AST "wash-out" effect in the NMP-treated organs, the authors measured the first posttransplantation

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Table 5 Summary of Relevant Normothermic Machine Perfusion Trials.

Author	Trial	Design	n	Machine	Key findings
Ravikumar *et al.*[61] in 2016	NMP vs. SCS	Nonrandomized clinical trial Case-matched analysis 1:2	20 vs. 40	Device: OrganOx Metra® Perfusate: Gelofusine®	Similar 30-d graft and patient survival Feasibility of NMP
Selzner *et al.*[62] in 2016	NMP vs. SCS	Pilot study Case-matched 1:3	10 vs. 30	Device: OrganOx Metra® Perfusate: albumin-based Steen solution, pRBC	Similar 30-d graft and patient survival Feasibility of NMP
Nasralla *et al.*[65] in 2018	NMP vs. SCS	Multicenter, Randomized controlled trial Case-matched 1:2 with declined livers	120 vs. 101	Device: OrganOx Metra® Perfusate: Gelofusine®, pRBC	50% lower level of graft injury Lower EAD Lower graft discard
Quintini *et al.*[66] in 2022	NMP in declined livers	Nonrandomized clinical trial	21	Device: Proprietary	Able to salvage and successfully transplant 15 of 21 livers
Markmann *et al.*[68] in 2022	NMP vs. SCS	Prospective, randomized control trail	153 vs. 147	Device: Transmedics ® Organ Care Systems™ Perfusate: albumin-based Steen solution, pRBC	Reduced EAD, IRI Higher salvage of DCD allografts

NMP, normothermic machine perfusion; SCS, static cold storage; EAD, early allograft dysfunction; IRI, ischemia reperfusion injury; DCD, donation after circulatory death.
Listed perfusion devices: OrganOx Metra® OrganOx Limited, Oxford, UK.
Transmedics ®Organ Care Systems™, TransMedics, Inc., Andover, MA, USA.
Listed perfusate: Gelofusine®, B. Braun, Melsungen, AG, Germany.

value between 12 and 24 h after reperfusion. They also reported on a lower incidence of EAD and a lower rate of discarded livers in the NMP group (only 12% of accepted livers were rejected at the recipient center in contrast to 24% in the SCS group). Three livers in the perfused group had to be discarded due to poor hepatic/portal flow during NMP. While the authors reported on lower peak AST levels in the NMP group, there was no difference in the graft survival and the 1-year patient survival rate (>95% in both groups). The researchers did report one case of graft discard due to malfunction of the pinch valve in the NMP machine. The researchers were able to reduce the period of cold ischemia by 3.7 times in the NMP group (2.1 h vs. 7.8 h) compared with the SCS group which may explain the results of this trial.[31,65]

A recent study by Quintini *et al.* highlighted the role of NMP in bridging the organ shortage in liver transplants. They enrolled 21 human livers which were declined for transplantation in their study. All the allografts were subjected to NMP via a proprietary device without technical issues. Out of these 21 discarded livers, 15 (71.5%) allografts met the author viability criteria at the end of NMP which were ultimately transplanted successfully. This group used liberalized viability criteria like lowest perfusate lactate level of <4.5 mmol/L (versus 2.5 mmol/L) among others for the allograft to be considered for transplant. The successful posttransplant functioning of these livers preserved with NMP led Quintini and colleagues to conclude that current viability criteria could be expanded.[66] Since this trial was a single institutional study with a small sample size, further multicentric studies are awaited to validate the liberal viability criteria used by this group.

Overcoming the Logistic Challenges of Normothermic Machine Perfusion

The logistics of continuous NMP can be challenging. Clinical adoption of NMP may be facilitated by simplifying logistics and reducing costs. With this aim in mind, Ceresa *et al.* looked into the feasibility and safety of post-SCS normothermic machine perfusion (pSCS-NMP) in liver transplantation. In this multicenter prospective study, they studied 31 patients who underwent transplant using donor grafts subjected to pSCS-NMP.

They reported a 30-day graft survival rate of 94% and a 1 year survival rate of 84%.[67] As mentioned above, Bral *et al.* so conducted a similar study wherein the allografts were transported via the SCS technique and were subjected to pre-implantation NMP for reconditioning. They reported consistent results and concluded that the pSCS-NMP approach was safe, did not compromise the overall benefit of NMP, and offered a practical alternative to portable normothermic ex situ machine transport.[64]

Sometimes referred to as a "Liver-in-a-Box," the Organ Care System™-Liver (Transmedics® Organ Care Systems™, TransMedics, Inc., Andover, MA, USA) is a portable NMP solution to preserve allografts. A multicenter, randomized clinical trial was conducted between 2016 and 2019 at 20 US liver transplant programs to evaluate the outcomes for 300 recipients of livers preserved

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using either the OCS™ system (n = 153) or SCS (n = 147). The authors reported a significant decrease in EAD in the NMP group (18% vs. 31%; P = 0.01). The MP-preserved livers also had a significant reduction in histopathologic evidence of IRI (6% vs. 13%; P = 0.004). Use of NMP also allowed for a significantly higher use of DCD livers. Finally, the NMP group was also associated with significant reduction in incidence of ischemic biliary complications at 6 months (1.3% vs. 8.5%; P = 0.02) and 12 months (2.6% vs. 9.9%; P = 0.02) after transplant. Similar to the COPE trial, this trial was also able to shorten the CIT of the MP allograft significantly (175.4 min vs. 338.8 min using SCS). Despite the initial improvement in graft function, the 1-year graft survival rates were comparable between both the groups in the OCS trial.[68]

Both multicentric, randomized clinical trials comparing NMP with SCS ultimately failed to demonstrate a survival benefit by using the NMP technique. In a 2020 meta-analysis of all the clinical trials comparing MP-preserved allografts (NMP or HMP) with SCS-preserved livers, Jia and colleagues noted that HMP but not NMP was found to significantly protect grafts from total biliary complications and ischemic cholangiopathy (P < 0.05). None of the MP strategies offered any 1-year survival (graft and patient) advantage.[69] These results combined with the additional cost and logistic challenges, need for blood products, and trained personnel for NMP strategies should raise the question of the cost effectiveness of this technique. We eagerly await further randomized trials evaluating MP protocols to SCS and trials comparing HOPE/HMP with NMP strategies to confirm MP's superiority and its optimum application.

CONTROLLED OXYGENATED REWARMING

Another recently described MP strategy is controlled oxygenated rewarming (COR). As our understanding of transplant physiology continues to grow, researchers have moved from cold towards warm perfusion strategies. However, in all the above mentioned techniques, a brief period of cold ischemia is inevitable. There is growing evidence that an abrupt temperature shift from hypothermic to normothermic perfusion may trigger mitochondrial dysfunction.[70] COR serves as a transition between cold storage and warm reperfusion with the aim to minimize organ damage. While the concept was proven in animal models, it was first in 2016, at Hoyer *et al.* applied the concept of COR to 6 cold stored human livers and concluded that the technique was safe and feasible.[71]

More recently, van Leeuwen *et al.* evaluated a sequential hypothermic-controlled rewarming-NMP strategy to resuscitate and assessed the viability of initially declined donor livers. They implemented a DHOPE-COR-NMP strategy in 16 livers from donors after circulatory death which were rejected nation-wide for regular transplantation. Of the 16 livers, 11 met the group's graft viability criteria and were successfully implanted. The authors reported a 20% increase in utilization of DCD livers at their centre.[72]

THERAPEUTIC STRATEGIES DURING EX VIVO MACHINE PERFUSION

Liver preservation using NMP is an evolving field with numerous research being focused on MP therapeutics to recondition the liver prior to transplant. This represents an exciting new frontier in liver transplants. The field of MP therapeutics in liver transplant is focused on defatting cocktails, vasodilators, anti-inflammatory agents, mesenchymal stem cell therapy, and gene therapy to optimize the graft during ex vivo NMP.[30,73–84]

Steatotic livers are associated with a higher rate of EAD, therefore, accounting for a large proportion of organ rejection. Therefore, several researchers have examined the possibility using defatting cocktails to recondition steatotic livers prior to transplant. In 2019, Boteon *et al.* infused PPARα (Peroxisome proliferator-activated receptor) ligands combined with other pharmacological modulators of lipid metabolism (defatting cocktail) to achieve decreased lipid content of human livers within 6 h. This was accompanied by a successful functional recovery and decreased expression of markers of reperfusion injury.[85]

Since liver sinusoidal endothelial cells, compared with hepatocytes, are more prone to injury during cold storage, researchers have also examined the use of prostaglandin E1 (PGE1) to improve the microcirculation.[74] Hara *et al.* first used PGE1 in a rodent model and observed that treated rodent livers had significantly improved bile production, in addition to decreased levels of liver injury markers.[80] Echeverri and colleagues studied the effects of adding BQ123 (an endothelin receptor agonist) and verapamil (a calcium channel blocker) to the perfusate in a porcine transplantation model. Consistent to other studies, they demonstrated an improved hepatic arterial flow and lower hepatocyte injury markers during NMP.[74]

The usage of gene modulation agents, such as antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) is especially exciting. In 2017, Goldaracena *et al.* demonstrated the use of ASO to silence miRNA-122, which is a necessary factor for HCV replication. They were able to induce HCV resistance in a porcine model.[73]

In 2020, researchers from Queen Elizabeth Hospital, Birmingham experimented with infusion of multi-potent adult progenitor cells into the right hepatic artery of six discarded allografts during NMP during perfusion. They observed a trans-endothelial migration of these stem cells with subsequent secretion of anti-inflammatory and immunomodulatory agents.[86]

Protection of mitochondria is crucial to prevent IRI. As discussed above, accumulation of succinate is a metabolic

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marker of ischemia and is responsible for mitochondrial ROS production during reperfusion. Pharmacological strategies targeted towards decreasing succinate accumulation is sufficient to ameliorate ischemia-reperfusion injury in murine models of heart attack and stroke.[19] NMP protocols holds great potential to effectively restore mitochondrial function and avoid redox stress-induced IRI.

The possibility of repairing these poor-quality livers sufficiently to enable transplantation requires their preserving for several days. Most of the current approaches for NMP have been used only for a relatively short period of time (median perfusion time of 9 h). This is not sufficient time to allow for ex-vivo therapeutics. So, Eshmuminov and colleagues sought to develop an ultra-long perfusion system with the aim to preserve 10 discarded human livers for 7 days. Their perfusion system consisted of a dual vascular supply with high pressure, oxygen-rich arterial blood entering through the hepatic artery and low-pressure, oxygen-reduced blood entering via the portal vein. To mimic the physiological uptake of nutrients and the enterohepatic circulation of bile, they injected parenteral nutrition and ursodeoxycholic acid into the portal vein line of their perfusion machine. They also incorporated an integrated dialysis unit for removal of metabolic waste products from the blood. Their proprietary algorithm automatically adjusted the dialysate flow, and controlled hematocrit in the perfusate. Automated insulin and glucagon administration was used to maintain physiological blood glucose levels. Finally, balloons to mimic diaphragm oscillations were also integrated into the system to produce continuous movement of the liver. With this new perfusion system, the researchers were able to maintain viability of six out of ten human livers up to 7 days of ex-vivo perfusion without the need for additional blood products or perfusate exchange.[87,88]

The novel platform for long-term NMP and ex vivo therapeutics of human livers has the potential to be one of the most significant breakthroughs in transplant surgery of recent decades, enabling organ repair on the pump and it provides an exciting new direction for the world of liver transplants.

Over the last decade, there has been significant progress in the field of allograft preservation techniques. Despite this increased interest in the field of MP, and many clinical trials demonstrating favorable outcomes, only a minority of liver transplant centers worldwide currently own a liver MP device for use them outside of clinical trials (Table 6). A re-evaluation of some logistical aspects of organ allocation may be required to achieve wider adoption of MP techniques.

HOPE and NMP methods are promising approaches to optimize the marginal liver allografts. Both allow for viability testing of the allografts, which may prove important in predicting the quality and safety of the organ for transplantation. Ultimately these strategies may improve the outcomes of ECD liver transplants. Ex-vivo therapeutics provides a tremendous potential to further salvage the fragile allografts and increase the donor pool.

Table 6 Commercially Available Machine Perfusion Devices.[a]

Name	Protocol supported	Portal vein flow	Hepatic artery flow	Temperature range
Liver Assist[44]	HOPE, DHOPE, NMP, COR	Continuous, (pressure controlled) 8 mmHg	Pulsatile at 60 bpm, (pressure controlled) 60 mmHg	12–37 °C
PerLife® PerLiver®	HOPE, DHOPE, NMP, COR	Continuous, (pressure controlled)	Pulsatile, (pressure controlled)	4–37 °C
OrganOx Metra ®[61,89]	NMP	Continuous (flow monitored)	Continuous, (pressure controlled) 60–75 mmHg	37 °C
Transmedics ® Organ Care Systems™[68]	NMP	Continuous (pressure controlled) Mean pressure 5 mmHg	Pulsatile (pressure controlled) Mean pressure 70 mmHg	37 °C
VitaSmart™ Perfusion System	HOPE, DHOPE	Continuous (pressure controlled) <5 mmHg	–	4–12 °C
LifePort® Liver Transporter[89]	HMP	Continuous (pressure controlled) <3 mmHg	Continuous (pressure controlled) <3 mmHg	4–8 °C

HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; DHOPE, dual hypothermic oxygenated machine perfusion; SNMP, sub-normothermic machine perfusion; NMP, normothermic machine perfusion; COR, controlled oxygenated rewarming.
Listed perfusion devices: LiverAssist, Organ Assist, XVIVO, Groningen, the Netherlands; PerLife® PerLiver®, Aferetica, Bologna, Italy.
OrganOx Metra® OrganOx Limited, Oxford, UK.
Transmedics® Organ Care Systems™, TransMedics, Inc., Andover, MA, USA.
VitaSmart™ Perfusion System, Bridge to Life, Northbrook, IL, USA.
LifePort® Liver Transporter, Organ Recovery Systems®, Itasca, IL, USA.
[a]The data in this table are populated from various studies, which have used them. The respective studies are referenced for the readers' perusal.

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The field of liver transplants has overcome many daunting and unforeseen challenges over the past 50 years, MP may help us progress to the next level in the near future.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

A.B, and R.M conceptualized the study and also wrote the main manuscript text.

N.B, P.R, P.A, M.N, and M.S performed the review of literature and helped with the final draft of the manuscript.

All authors performed a critical review of the manuscript and approved the final version.

CONFLICTS OF INTEREST

The authors have none to declare.

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