HHS Public Access

Author manuscript

Curr Opin Organ Transplant. Author manuscript; available in PMC 2019 May 21.

Published in final edited form as:

Curr Opin Organ Transplant. 2018 April ; 23(2): 151–161. doi:10.1097/MOT.0000000000000500.

The dawn of liver perfusion machines

Danielle Detelich and **James F. Markmann**

Division of Transplant Surgery, Massachusetts General Hospital, Boston, Massachusetts, USA

Abstract

Purpose of review—Despite high demand, a severe shortage of suitable allografts limits the use of liver transplantation for the treatment of end-stage liver disease. The transplant community is turning to the utilization of high-risk grafts to fill the void. This review summarizes the reemergence of ex-vivo machine perfusion for liver graft preservation, including results of recent clinical trials and its specific role for reconditioning DCD, steatotic and elderly grafts.

Recent findings—Several phase-1 clinical trials demonstrate the safety and feasibility of machine perfusion for liver graft preservation. Machine perfusion has several advantages compared with static cold storage and may provide superior transplantation outcomes, particularly for marginal grafts. Ongoing multicenter trials aim to confirm the results of preclinical and pilot studies and establish the clinical utility of ex-vivo liver machine perfusion.

Summary—Mounting evidence supports the benefits of machine perfusion for preservation of liver grafts. Thus, machine perfusion is a promising strategy to expand the donor pool by reconditioning and assessing viability of DCD, elderly and steatotic grafts during the preservation period. Additionally, machine perfusion will serve as a platform to facilitate graft intervention and modification to further optimize marginal grafts.

Keywords

clinical trials; liver transplantation; machine perfusion; marginal graft; static cold storage

INTRODUCTION

The concept of ex-vivo machine perfusion dates at least back to the Lindbergh Apparatus in the 1930s, establishing prolonged ex-vivo metabolic function in isolated organs [1,2]. Belzer *et al*. [3] first applied machine perfusion to human transplantation with the successful transplantation a kidney following 17 h of hypothermic machine perfusion (HMP); Starzl *et al*. [4] subsequently transplanted 7 HMP-preserved livers.

Correspondence to James F. Markmann, Division of Transplant Surgery, Massachusetts General Hospital, 55 Fruit Street, White 517, Boston, MA 02114, USA. Tel: +1 617 643 4533; jmarkmann@mgh.harvard.edu.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

The development of specialized preservation solutions in the 1980s allowed static cold storage (SCS) to emerge as the primary organ preservation modality, shelving the need for machine perfusion [5]. SCS was a simple, effective and transportable alternative to the cumbersome machine perfusion devices of the time. Organ preservation with SCS has been remarkably successful over the past 30 years, facilitating widespread application of liver transplantation as the only treatment for end-stage liver disease.

Global trends in liver disease combined with the success of liver transplantation have increased demand for transplantation, resulting in a shortage of suitable organs. One strategy to expand the donor pool is utilization of extended criteria donor (ECD) grafts, specifically donation after circulatory death (DCD), steatotic or elderly grafts. These marginal organs have increased susceptibility to ischemia reperfusion injury (IRI) and subsequent high risk of primary nonfunction (PNF), early allograft dysfunction (EAD) and biliary complications. These risks demand strict limitations on allowable ischemia time and minimization of other risk factors, precluding routine use of ECD grafts [6].

Utilizing ECD grafts depends on optimizing preservation conditions. Metabolic activity during SCS is substantially slowed, but does not cease completely. Oxygen debt results in deranged mitochondrial metabolism and accumulation of toxic metabolites. Paradoxically, oxygen inflow during reperfusion results in production of reactive oxygen species (ROS), widespread activation of inflammatory pathways and cell death, a process termed ischemia-reperfusion injury (IRI) [7–9]. The standard criteria donor (SCD) graft possesses sufficient physiologic reserve to overcome preservation-induced IRI, though this does not hold true for ECD grafts. Machine perfusion is reemerging as an alternative to SCS, with potential for superior preservation of marginal grafts.

ADVANTAGES OF MACHINE PERFUSION

Although intricate in execution, the concept underlying machine perfusion is quite simple. Constant circulation supports endothelial function and washes out metabolic waste. Supplementation of oxygen, nutrients, metabolic substrates and other ‘additives’ allows the liver to maintain physiologic metabolic function, recover the energy deficit incurred during the procurement and early preservation period, and institute normal repair and regenerative pathways. In other words, machine perfusion is a platform for the graft to ‘live’ outside the body. machine perfusion has several advantages compared with SCS, including:

1. Prevents cold ischemia-related organ damage
2. ‘Reconditions’ marginal allografts
3. Allows viability assessment to detect poorly functioning organs before liver transplantation
4. Prolongs preservation period to improve organ utilization and surgical logistics
5. Serves as a platform for targeted therapeutic interventions

Machine perfusion is classified by perfusion temperature as normothermic (35–38 °C), hypothermic (4–10 °C) or subnormothermic (20–30 °C). The reader is directed to recent reviews for description of the key technical components [10,11].

NORMOTHERMIC MACHINE PERFUSION

Normothermic machine perfusion (NMP) aims to simulate a near-physiologic environment, which maintains normal metabolic function and avoids cold ischemic injury. Viability is assessed by measurement of hemodynamic performance (vascular flow and resistance), biochemical parameters and synthetic function [12,13]. NMP is technically challenging, requiring dual perfusion of the hepatic artery and portal vein, an oxygen carrier perfusate and nutritional supplementation to support the fully functional liver [14,15].

NMP is still investigational in the clinical setting. The Oxford group reported the first phase 1 clinical trial, demonstrating that NMP with the transportable OrganOx Metra device is safe and feasible in both donation after brain death (DBD) and DCD grafts [16■]. One minor technical issue was corrected during ground transport, however, no device failures occurred and all livers were successfully transplanted. Notably, the NMP cohort had a significantly lower peak in AST and lower incidence of EAD after transplantation compared with matched controls and no recipient developed ischemic cholangiopathy [16■]. This study also demonstrated viability assessment during NMP, via measurement of hemodynamics, metabolic and synthetic function during perfusion.

Two North American groups, Selzner *et al.* [17■] from Toronto and Bral *et al.* [18■] from Edmonton, have also completed phase 1 NMP trials using the OrganOx Metra. Both studies confirmed the safety and feasibility of NMP and produced comparable outcomes to SCS. Importantly, Bral *et al.* reported one instance where perfusion was aborted and the liver ultimately discarded because of an unrecognized operator error during cannulation, highlighting the technical complexity and specific training required for safe ex-vivo perfusion.

These pilot studies employed continuous NMP, where perfusion is initiated at the donor hospital and continued for the duration of preservation. In contrast, end-ischemic NMP occurs at the recipient hospital after a period of SCS [19■]. Watson *et al.* [20■] described a series of 12 declined livers treated with end-ischemic NMP. Viability was assessed by lactate clearance, glucose and liver enzyme concentrations, and ability to maintain pH. Although bile production is often suggested as a key marker of viability, the authors postulate that the quality of the bile, marked by alkaline pH, indicates functionality rather than the absolute quantity [20■]. See Table 1 for additional details of completed NMP trials.

Three multicenter, phase III randomized control trials (RCTs) comparing NMP to SCS are currently underway. The Consortium for Organ Preservation in Europe (COPE) conducted a seven-center European study. Compared with SCS, NMP-preserved livers had lower peak AST and reduced incidence of EAD post-liver transplantation. Although NMP improved early graft function in both DBD and DCD livers, the magnitude of effect was significantly greater in the DCD organs [21■■]. The published results, including long-term follow-up

data, will represent an important step in defining the clinical role of NMP in liver transplantation and are eagerly awaited [21■■]. See Table 2 for details of the additional ongoing RCTs and pilot trials.

HYPOTHERMIC MACHINE PERFUSION

Hypothermic machine perfusion (HMP) restores mitochondrial function, reducing ROS release and inflammatory cascade activation upon reperfusion [22]. HMP has also been shown to improve hepatobiliary secretory function and preserve endothelial function in discarded ECD livers [23,24].

HMP is the least complex machine perfusion system. Perfusion can be performed via the portal vein alone or as dual perfusion. Active oxygenation has shown benefit in DCD and steatotic livers, but is not a strict requirement [25,26■,27■,28,29]. In current practice, most centers will employ dual perfusion, active oxygenation (HOPE), or both (DHOPE; see Table 3 for details of completed HMP pilot studies). This versatility is facilitated by the minimal metabolic demands of the liver under hypothermic conditions. Additionally, HMP treatment is typically end-ischemic, avoiding need for device transportation or additional personnel/equipment. However, a distinct disadvantage of the near-dormant metabolism is the inability to perform meaningful viability assessment.

The largest HMP clinical trial, including 50 DCD grafts, has recently reported preliminary results including 5-year follow-up analysis. HMP-perfused grafts achieved superior outcomes compared with nonperfused DCD grafts and comparable outcomes to DBD grafts [26■]. Multicenter RCTs are currently underway evaluating HMP compared with SCS for extended DBD and DCD grafts [30] (see Table 4).

SUBNORMOTHERMIC MACHINE PERFUSION

Subnormothermic machine perfusion (SMP) serves as a compromise between warm and cold perfusion. Although an oxygen carrier may be utilized, liver metabolism is sufficiently reduced such that adequate oxygenation can be achieved via diffusion alone into a crystalloid-based perfusate. Additionally, SMP-preserved livers retain partial functional capacity, demonstrated by bile production and lactate clearance during perfusion. To date, the experience in SMP has been limited to animal transplantation and discarded human liver perfusion models [31–34].

CONTROLLED OXYGENATED REWARMING

Controlled oxygenated rewarming (COR) is the most recent machine perfusion iteration, in which machine perfusion is initiated at hypothermic temperatures and gradually increased to subnormothermia [35]. COR avoids heat shock injury caused by abrupt temperature shifts. The slow increase in metabolism and functional restitution prepares the graft for additional reconditioning during SMP or prior to normothermic reperfusion [36]. COR with a normothermic final temperature (COR35) was recently compared with subnormothermic COR (COR20) in a rat liver model [37]. The COR groups demonstrated similar therapeutic

benefit, however, the COR35 livers had more reliable bile production, which may enable reliable viability assessment [37].

COR has recently been applied clinically, with the successful transplantation of six DBD grafts accepted under 'rescue allocation' criteria [38■]. The COR group demonstrated lower peak AST and INR compared with controls with 100% patient and graft survival at 6 months. The same group is currently conducting a pilot trial (CORAL Trial) comparing COR to SCS (see Tables 3 and 4).

MACHINE PERFUSION OF MARGINAL ORGANS

The ex-vivo machine perfusion environment is unique in that the organ is both functional and isolated. Machine perfusion converts the preservation period from a race against the clock into an opportunity to apply targeted graft-improving interventions without systemic effect in the donor or recipient. In this regard, warm perfusion is ideal for manipulation of the functional liver. This concept will be discussed as it relates to DCD, steatotic and elderly grafts.

Donation after circulatory death/ischemia reperfusion injury

Of the 7500 liver transplants performed in the United States in 2016, only 6% were DCD [AOPO.org]. Of recovered DCD livers, 29% were discarded, compared with 6% of recovered DBD livers [AOPO.org]. Although striking, this still underestimates the discrepancy considering recovery is often not attempted in DCD donors. Improving utilization of DCD livers is clearly an important strategy to increase the donor pool.

As mentioned, IRI underlies EAD and PNF in marginal organs. The obligatory warm ischemia of DCD recovery preconditions the liver, and especially cholangiocytes, for severe injury during SCS and reperfusion [15]. The biliary consequence is ischemic cholangiopathy, occurring in 20–40% of DCD grafts, compared with 5% in DBD grafts [39]. This complication carries high morbidity and mortality, routinely requiring multiple invasive procedures and up to 50% require retransplantation [10].

Recent evidence shows that machine perfusion reconditions DCD allografts, effectively reversing the deleterious effects of ischemia. However, machine perfusion alone may not be sufficient for all grafts. Addition of targeted interventions during perfusion has been suggested to augment the protective effect against IRI. Various targeted anti-inflammatory, antioxidant, antiapoptosis and vasoactive pharmaceuticals have been added to storage solutions with the goal of modulating IRI, however, the experience in ex-vivo perfusion is limited [40–43].

Goldaracena *et al.* assessed the effect of an anti-inflammatory cocktail (prostaglandin E1, acetylcysteine, sevoflurane and carbon monoxide) and decreased circuit temperature (33 °C) in a porcine transplantation model. Compared with controls perfused at 37°C or SCS, livers receiving anti-inflammatory treatment had reduced markers of inflammation, improved endothelial function and improved graft function [44■].

Defatting

Consequent to the increasing incidence of fatty liver disease, 40–60% of donor allografts have fatty infiltration [45]. The limit of acceptable donor steatosis has yet to be established. Grafts with mild macrosteatosis (<30%) are generally considered safe for transplantation; however, moderately (30–60%) or severely (>60%) macrosteatotic grafts are often declined because of increased risk of EAD, PNF and acute rejection postliver transplantation [45–50]. Steatosis exacerbates IRI secondary to increased ROS generation, pro-inflammatory immune system activation, impaired mitochondrial ATP production and microcirculatory dysfunction, resulting in hepatocyte necrosis and graft failure upon reperfusion [46,47].

NMP and SMP have been investigated as alternative preservation methods of steatotic livers in animal models [51,52]. Okamura *et al.* evaluated the effect of SMP on severely steatotic rat livers. SMP-preserved livers exhibited maintained microvascular integrity and sustained mitochondrial function, resulting in higher energy charge compared with cold-stored organs [53].

Kron *et al.* [54■] evaluated end-ischemic HOPE of severely steatotic livers in a rat transplantation model. HOPE reduced inflammatory injury and subsequent fibrosis postliver transplantation, an effect that was dependent on oxygenation. However, HOPE had no impact on the amount of steatosis in the graft. The authors then analyzed the effect of HOPE in six steatotic human livers from their clinical trial, including five DCD. All livers demonstrated adequate early function as well as lower peak postliver transplantation ALT, decreased incidence of PNF (0 versus 25%), shorter ICU stay and improved 1-year patient survival (100 versus 42%) compared with SCS controls, a promising proof-of-concept for HOPE in fatty livers [54■].

Perfusion defatting seeks to augment the protective effect of perfusion by adding a pharmacologic ‘defatting cocktail,’ stimulating lipid metabolism [55]. Such treatment has been shown to significantly reduce lipid droplet burden, increase ATP production and lessen oxidative stress in cultured hepatatocytes [46]. Use of a defatting cocktail reduced intracellular lipid content by 50% during 3h of NMP in steatotic rat livers [56]. Efficacy of defatting cocktails may require normothermia, as similar effect was not seen under subnormothermic conditions [55].

Clinical experience of defatting is scarce. Banan *et al.* [57■] administered a defatting cocktail to two steatotic livers in an ex-vivo perfusion model, demonstrating a 10% reduction in one liver, although neither steatotic liver displayed increased markers of IRI. Considering that steatosis resolves quickly postliver transplantation, overcoming the initial risk of PNF/EAD may be key to improving viability and long-term survival [58,59].

Elderly

The functional capacity and physiologic reserve of the liver undergo normal decline with age, marked by volume loss, decreased blood flow, impaired regenerative capacity and atherosclerotic changes in the arterial vasculature [60]. Elderly donors also have more medical comorbidities. Concordantly, advanced donor age has been identified as an independent risk factor for EAD, graft loss and reduced recipient survival after liver

transplantation, particularly in HCV-positive recipients [60,61]. Despite the aging general population, use of elderly grafts is limited. With careful donor and recipient selection, some centers have found success with septuagenarian or even octogenarian donors [62,63]. These results suggest that age may be a confounder and coexisting risk factors are at least partially responsible for the observed poor function [64].

Machine perfusion serves two primary roles in the elderly. First is neutralizing the impact of other risk factors that predispose to IRI and subsequent dysfunction (such as prolonged CIT or steatosis). Secondly, viability assessment confirms the functionality and helps predict the effect of comorbid factors on transplant outcomes. Pezzati *et al.* [65] report a case of an octogenarian graft with severe atherosclerosis and poor initial flush that was reconditioned and assessed with NMP prior to successful transplantation. If machine perfusion can limit the CIT, mitigate steatosis and recondition the DCD graft, then a much larger pool of elderly donors would be acceptable for transplantation.

FUTURE DIRECTIONS

Ex-vivo organ perfusion technology is rapidly advancing. Progression from the experimental to the clinical realm has demonstrated early success, particularly for marginal livers. Attention is now turning toward employing the perfusion system as a platform for concurrent graft modification. Intervention during the ex-vivo period is highly advantageous to alter the liver phenotype prior to transplantation whereas avoiding systemic effects in the donor or recipient. We briefly introduced emerging therapies to reduce IRI and defat steatotic grafts, however, this just scratches the surface of conceivable interventions. Additional targets, such as antiviral medication for viral hepatitis, immune modulation for tolerance induction and gene therapy are under exploration [66,67]. Novel drug delivery systems, such as nanoparticles, aim to augment therapeutic efficacy with precise control of drug delivery and release and may prove to be a key component of machine perfusion graft intervention [68]. Machine perfusion has also been utilized during radical ex-vivo hepatic surgery, such as during autotransplantation for end-stage alveolar echinococcosis or resection of large tumors with critical invasion of the retrohepatic vena cava [69,70]. Continued research will solidify the use of machine perfusion as a tool for graft intervention in transplantation as well as facilitate treatment of hepatic disease in the nontransplantation setting.

CONCLUSION

The ever-increasing demand for liver transplantation has put suitable liver allografts at a premium and the use of marginal grafts represents a practical method for increasing the donor pool. Use of these grafts is dependent on the ability to recondition the graft and assess its viability. Recent clinical trials demonstrate that machine perfusion is capable of fulfilling both requirements. Continued investigation is necessary to determine optimal perfusion conditions, establish indications for machine perfusion and set guidelines for institutional implementation prior to becoming standard practice. Regardless, a new day in transplantation has arrived and the future of ex-vivo machine perfusion is bright.

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KEY POINTS

- A severe shortage of liver allografts suitable for transplantation exists globally.
- Utilization of marginal grafts (such as DCD, steatotic and elderly) is a strategy to expand the donor pool.
- Machine perfusion has multiple theoretical advantages compared with SCS for preservation of marginal grafts and may facilitate their use in liver transplantation.
- Clinical trials demonstrate safety of machine perfusion and confirm improved outcomes compared with SCS.
- Ongoing and future research will further expand the role of machine perfusion as a platform for graft intervention.

Table 1.

Recent normothermic machine perfusion clinical trials

Author	Region	Study design	*N*	Donation type	Device	Perfusate	Timing	Perfusion duration (hours)	Aim	Outcome
Ravikumar *et al.* [16■]	Oxford, UK	Pilot	20	Four DCD Sixteen DBD	OrganOx Metra	pRBC with Gelofusine	Continuous	9.3 median	Feasibility and safety of NMP	NMP is safe and feasible. Less EAD and lower postop transaminases in NMP cohort. Magnitude of benefit larger in DCD livers
Selzner *et al.* [17■]	Toronto, Canada	Pilot	10	Two DCD Eight DBD	OrganOx Metra	pRBC with Steen Solution	Continuous	8 median (5.7–9.7)	Feasibility and safety of NMP using Steen Solution	NMP with Steen solution is feasible and safe. NMP resulted in reduced AST/ ALT on postop days 1–3
Bral *et al.* [18■]	Edmonton, Canada	Pilot	10; 30 matched controls	Four DCD Six DBD	OrganOx Metra	pRBC with Gelofusine	Continuous	11.5 median (3.3–22.5)	Feasibility and safety of NMP	Nine of ten livers perfused and transplanted. One perfusion aborted because of operator error. Post-liver transplantation AST, bilirubin, early allograft dysfunction INR and lactate similar between groups. Significantly longer median ICU and hospital stay in NMP group. No ischemic cholangiopathy in NMP grafts at 6 months follow-up.
Mergental *et al.* [19■]	Birmingham, UK	Pilot Study	6 (declined)	Four DCD Two DBD	Liver Assist (n=5); OrganOx Metra (n=1)	pRBC with 5% Albumin	End-ischemic	5.1–9.4	Evaluate potential utility of discarded organs following	Implemented viability criteria: lactate clearance, bile production, flow rates. Five of six discarded

Curr Opin Organ Transplant. Author manuscript; available in PMC 2019 May 21.

Author	Region	Study design	*N*	Donation type	Device	Perfusate	Timing	Perfusion duration (hours)	Aim	Outcome
									viability assessment during NMP	grafts deemed viable during NMP and successfully transplanted.
Watson *et al.* [20■]	Cambridge, UK	Pilot Study	12 (declined), 24 matched controls	Nine DCD Three DBD	Liver Assist	pRBC with succinylated gelatin or Steen	End-ischemic	4.7 median (2–8.8)	NMP efficacy for rejected grafts	Postreperfusion syndrome and vasoplegia can be minimized by avoiding hyperoxia during NMP

DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; NMP, normothermic machine perfusion; RCT, randomized control trials.

Table 2.

Ongoing normothermic machine perfusion clinical trials

Author	Registration	Region	Study design; status	Estimated *N*	Donation type	Device	Timing	Aim	Outcome
COPE Consortium (Nasralla *et al.* [21■■])	ISRCTN39731134	Multinational Europe (seven centers)	Phase III RCT; completed	Enrolled: 272 (137 NMP 135 SCS) Transplants: 222 (121 NMP 101 SCS)	Enrolled: 78 DCD 194 DBD Transplants: 53 DCD 167 DBD	OrganOx Metra	Continuous	NMP versus SCS	Preliminary results: lower post-liver transplantation mean peak AST and reduced incidence of EAD in NMP group. Magnitude of effect significantly greater in DCD livers
Liver PROTECT Trial	NCT02522871	Multicenter USA	Pivotal RCT; recruiting	300	SCD/ECD	Transmedics OCS Liver System	Continuous	NMP versus SCS	
WP01 Trial	NCT02775162	Multicenter USA	Phase III RCT; recruiting	266	SCD/ECD	OrganOx Metra	Continuous	NMP versus SCS	
VITTAL Trial	NCT02740608	Birmingham, UK	Pilot; recruiting	22	ECD grafts declined by all UK centers	OrganOx Metra	End-ischemic	Validate viability assessment criteria; identify proportion of transplantable grafts from rejected organ pool	
Post SCS Normothermic Machine Liver Perfusion	NCT03176433	Oxford, UK	Phase I/II; recruiting	30	SCD/ECD	OrganOx metra	End-ischemic	Safety and feasibility of end-ischemic NMP	
Pilot Study to Assess Safety and Feasibility of NMP in Human liver transplantation	NCT02515708	Cleveland, Ohio, USA	Pilot; recruiting	25	SCD/ECD	Custom	Continuous	Safety and feasibility	
Normothermic Liver Preservation Trial	NCT03089840	Alberta, Canada	Phase I/II; recruiting	50	SCD/ECD	OrganOx metra	Continuous or end-ischemic	Safety and feasibility	
Using Ex-vivo NMP with Organox Metra to Store Human Livers for Transplantation	NCT02478151	Toronto, Canada	Phase I; recruiting	40	SCD/ECD	OrganOx metra	Continuous	Safety and feasibility	
CEFEMA Trial	NCT02940600	Pisa, Italy	Pilot; recruiting	30	DBD, older than 70 years	Liver Assist	Not specified	NMP versus SCS of elderly donors	

DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; NMP, normothermic machine perfusion.

Table 3.

Recent hypothermic machine perfusion and controlled oxygenated rewarming clinical trials

Author	Center	Study design	*N*; controls	Donor	Device	Perfusion route	Perfusate	Oxygen	Perfusion duration (h)	Aim	Findings
Guarrera *et al.* [28]	Columbia, New York	Pilot	20; 20 matched controls	DBD	Medtronic Portable Bypass System (PBS)	Dual	Vasosol	No	4.3 mean (3–7)	Safety and feasibility of HMP	HMP is safe and may improve graft function. HMP-preserved grafts demonstrated attenuated markers of liver injury post-liver transplantation
Dutkowski *et al.* [25]	Zurich, Switzerland	Pilot	25; 50 matched DCD controls and 50 SCS DBD controls	DCD	Liver Assist	PV only	UW MPS	Yes	1.9 median (1–2)	Compare SCS to HOPE for DCD liver. Additional comparison to cold-stored standard DBD grafts.	HOPE-treated livers showed reduced incidence of EAD, PNF and ischemic cholangiopathy compared with unperfused DCD grafts. Graft function, complication rate and graft survival comparable to DBD controls.
Guarrera *et al.* [29]	Columbia, New York	Pilot	31; 30 matched controls	ECD	Medtronic PBS	Dual	Vasosol	No	3.8 mean (3–7)	Safety of HMP for ‘orphan’ livers	HMP-preserved livers had reduced rate of EAD, less biliary complications and shorter mean hospital stay.
Van Rijn *et al.* [27■]	Groningen, Netherlands	Pilot	10; 20 matched controls	DCD	Liver Assist	Dual	UW MPS	Yes	2.1 median (2.1–2.3)	Safety and feasibility	DHOPE reduces IRI and restores ATP levels. DHOPE also reduced incidence of EAD and

Author	Center	Study design	*N*; controls	Donor	Device	Perfusion route	Perfusate	Oxygen	Perfusion duration (h)	Aim	Findings
											ischemic cholangiopathy
Hoyer *et al.* [38■]	Essen, Germany	Pilot	6; 106 historical controls	DBD (rescue allocation)	Liver Assist	Dual	Custodiol-N	Yes	1.5	Safety and feasibility	COR resulted in 50% reduction of peak transaminases post-liver transplantation with 100% graft and patient survival after 6 months. Perfusate glucose correlated with postop graft function

DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; COR, controlled oxygenated rewarming.

Table 4.

Upcoming hypothermic machine perfusion with controlled oxygenated rewarming clinical trials

Author	Registration	Center	Study design	*N*	Donor	Device	Perfusion route	Perfusate	Oxygen	Aim	Findings
Schlegel *et al.* [26■]		Zurich, Switzerland	Long-term follow-up report of pilot study	50; 50 matched controls and 50 DBD controls	DCD	Liver Assist	PV only	UW MPS	Yes	Long-term outcomes of HOPE versus SCS for DCD grafts. Comparison with standard DBD grafts	Preliminary report: HOPE perfused DCD grafts achieved similar outcomes to DBD grafts in terms of 5-year graft survival and ischemic cholangiopathy and superior to unperfused DCD livers
HOPE-ECD-DBD [30	NCT03124641	Multicenter Europe; Zurich group	Phase II RCT	46; recruiting	Extended criteria DBD	Liver Assist	PV only	UW MPS	Yes	HOPE versus SCS	
DHOPE-DCD	NCT02584283	Multicenter Europe; Netherlands group	Phase III RCT	156; recruiting	DCD	Liver Assist	Dual	UW MPS	Yes	Incidence of NAS following DHOPE versus SCS	
HOPE of Human Liver Grafts	NCT01317342	Zurich	Phase II RCT	70; recruiting	SCD/ECD	Liver Assist	PV only	IGL-1	Yes	Compare HOPE to SCS	
CORAL Trial	ISRCTN15686690	Essen, Germay	Pilot RCT	20; no longer recruiting	ECD	Liver Assist	Dual	UW MPS	Yes	Effect of COR versus SCS on IRI. Assess viability criteria	

DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; NMP, normothermic machine perfusion; PV, portal vein; RCT, randomized control trials.