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Special Article

Past, Present, and Future of Dynamic Kidney and Liver Preservation and Resuscitation

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The increased demand for organs has led to the increased usage of "higher risk" kidney and liver grafts. These grafts from donation after circulatory death or expanded criteria donors are more susceptible to preservation injury and have a higher risk of unfavorable outcomes. Dynamic, instead of static, preservation could allow for organ optimization, offering a platform for viability assessment, active organ repair and resuscitation. *Ex situ* machine perfusion and *in situ* regional perfusion in the donor are emerging as potential tools to preserve and resuscitate vulnerable grafts. Preclinical findings have ignited clinical organ preservation research that investigates dynamic preservation, its various modes (continuous, preimplantation) and temperatures (hypo-, sub, or normothermic). This review outlines the current status of dynamic preservation of kidney and liver grafts and describes ongoing research and emerging clinical trials.

Abbreviations: AST, aspartate aminotransferase; c, continuous; CAD-MP, cardiac death–machine perfusion; COMPARE, cold oxygenated machine perfusion of aged renal grafts; CIT, cold ischemia time; COPE, Consortium for Organ Preservation in Europe; COR, controlled oxygenated rewarming; DBD, donation after brain death; DCD, donation after circulatory death; DCD III, controlled donation after circulatory death (circulatory arrest after withdrawal of treatment, Maastricht class III; DGF, delayed graft function; EAD, early allograft dysfunction; ECD, expanded criteria donor; GS, graft survival; HBD, heart-beating donor; HE, heat exchanger; HMP, hypothermic machine perfusion; HRP, hypothermic regional perfusion; MP, machine perfusion; N.A., not available; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; O_2, oxygen; pi, preimplantation; PNF, primary nonfunction; POMP, pulsatile oxygenated machine perfusion; RCT, randomized controlled trial; RP, regional perfusion; SCS, static cold storage; SMP, subnormothermic machine perfusion; SRP, subnormothermic regional perfusion

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Introduction

The shortage of suitable organs for transplantation has resulted in the increased use of "higher risk" grafts. Kidneys and livers from donation after circulatory death (DCD) or from expanded criteria donors (ECDs) after brain death are particularly susceptible to the harmful effects of warm and cold ischemia and reperfusion injury. Consequently, these organs have an increased probability of developing initial graft dysfunction (delayed graft function [DGF] in kidney, early allograft dysfunction [EAD] in liver), primary nonfunction (PNF), biliary complications and decreased long-term graft survival (1–5). Optimized organ-preservation strategies protecting these vulnerable grafts should allow organ viability assessment and resuscitation, reducing the unnecessary discard of organs. For this purpose, novel dynamic preservation strategies are being developed.

This overview outlines the current status of dynamic preservation of kidney and liver grafts and describes ongoing research and emerging clinical trials. These trials were identified by a thorough search of available online registry databases. Appendix S1 outlines the search strategy. Table S1 shows a nonexhaustive list of currently nonregistered trials identified through our network.

From Dynamic to Static Storage and Back

The concept of dynamic organ preservation was developed by Carrel and Lindbergh in the 1930s (6,7). Some

30 years later, after extensive work by pioneering groups led by Belzer (8–10) and Starzl (11–13), hypothermic dynamic preservation using plasma or blood-based solutions became a clinical reality. Dynamic preservation was the only way to preserve deceased organs until static cold storage (SCS) solutions became available (14–16). SCS offered a simple and effective way to preserve and transport organs and soon became the most commonly used storage method. Recently, with increasing use of higher risk grafts, there has been a resurgence of interest in dynamic preservation strategies. These strategies could offer optimized organ preservation and real-time graft viability assessment as well as a platform for delivery of conditioning agents to repair damaged organs, resulting in improved organ quality and utilization.

Features and Modalities of Dynamic Preservation

During dynamic preservation, recirculating perfusate (either acellular or blood-based) is continuously pumped through the organ vasculature. The perfusate can be nonoxygenated or oxygenated. A heat exchanger regulates temperature from hypothermia via subnormothermia to normothermia. Machine perfusion (MP) perfuses the organ *ex situ*, after it has been procured, cannulated and connected to a pump (Figure 1A). Continuous MP (from procurement to implantation) or preimplantation MP (after a period of SCS and just before transplantation) are most commonly used (Figure 2). Dynamic preservation can also begin before organ procurement by recirculating donor blood or a preservation solution *in situ,* after cannulation of the aorta/iliac arteries and vena cava/iliac veins (Figure 1B). The abdominal compartment is isolated from the thorax by a balloon in or a clamp on the descending thoracic aorta, preventing cardiac and cerebral perfusion. This technique is also called abdominal regional perfusion (RP).

Key elements determining dynamic preservation modalities are temperature (Figure 2) and perfusion settings.

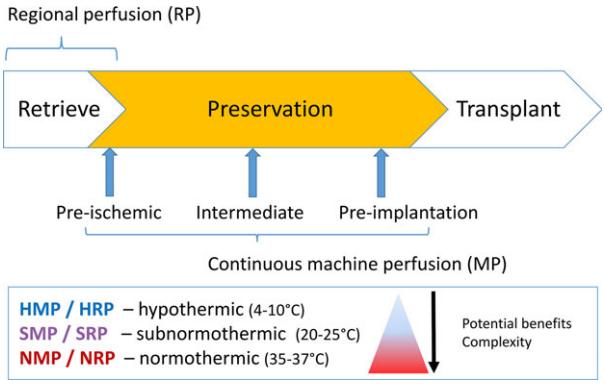

Figure 2: The different dynamic preservation strategies currently entering clinical practice with the different modalities of their use. HMP, hypothermic machine perfusion; HRP, hypothermic regional perfusion; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; SMP, subnormothermic machine perfusion; SRP, subnormothermic regional perfusion.

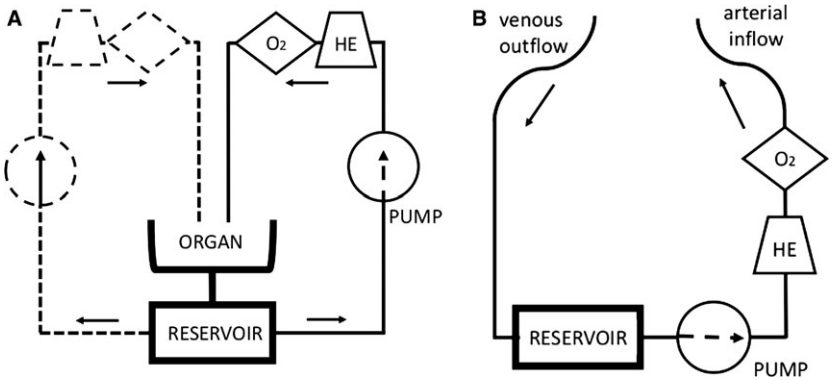

Figure 1: Classical buildup of an*ex vivo* (A) and *in vivo* (B) dynamic preservation circuit. Perfusate is pumped through the organ vasculature by a pump (usually a roller or centrifugal pump). Addition of a heat exchanger allows variation of the temperature, and an oxygenator can be added to the circuit to oxygenate the perfusate. In case of hypothermic dynamic preservation, the organ and reservoir are often topically cooled with ice without the need for a heat exchanger. During *ex vivo* machine perfusion (A), the organ sits in an organ chamber that is connected to a reservoir that drains the perfusate. In case of dynamic preservation of the liver, dual perfusion of the portal vein and hepatic artery can be established by separately cannulating these vessels. Often a second pump will drive the hepatic artery perfusion (circuit in dotted line) so that different pressure/flow settings can be used. During *in vivo* regional perfusion (B), the pump will drive the perfusate into the donor's arterial circulation, and the venous cannulation guarantees return of the perfusate. A heat exchanger and oxygenator can be added to the circuit. The arrows denote the direction of flow. HE, heat exchanger; O_2, oxygenator.

Hypothermic dynamic preservation aims to slow down cellular metabolism and counteract undesirable and detrimental effects of ischemia. It combines low temperature (4–10°C) with an acellular colloid-containing preservation solution using, in the majority of cases, the Na-gluconate/hydroxyethyl starch MP solution developed by Belzer et al (17). Some evidence shows that hypothermic dynamic preservation should be controlled by pressure and not flow, using low pressures to avoid pressure-related injury (18–20). Pulsatile renal artery perfusion (25–30 mmHg) is best for the kidney (20–26). The liver is perfused through the portal vein with a continuous flow that, in most circuits, is pressure-controlled (3–5 mmHg, sometimes achieved by gravity) and occasionally flow-controlled (19,27–33). It is not entirely clear whether portal perfusion alone is sufficient. Maintaining the peribiliary vascular plexus seems to be of vital importance for the prevention of ischemic-type biliary strictures (34). Because mainly the hepatic artery supplies this plexus, some authors have advocated dual perfusion (portal vein and hepatic artery) (34). However, it seems that cold portal vein perfusion allows perfusion of the intra- and extrabiliary vascular supply (35). To date, clinical trials have either used single pressure-controlled portal vein perfusion (30,32) or nonpulsatile flow-controlled dual perfusion (27,31).

Normothermic dynamic preservation (35–37°C) aims to restore normal cellular processes while facilitating viability assessment (36,37). Normothermic preservation mandates an oxygenated perfusate with an oxygen carrier (usually red blood cells). Compared with hypothermic conditions, under which the graft is essentially cold-stored in the event of pump failure, an organ in a normothermic system is vulnerable to warm ischemia should machine failure occur. Higher, near-physiological pressures are used for arterial perfusion of kidney (70–85 mmHg) (38–40) and liver (60–105 mmHg) (41–44). Pressure-controlled pumping of pig kidneys resulted in improved renal perfusion and better preserved structural integrity, whereas flow control caused diffuse and global glomerular destruction (40).

Subnormothermic dynamic preservation (20–25°C) aims to avoid cold-induced injury without increasing metabolism to a level at which intense oxygenation requires an oxygen carrier. Both acellular and cellular perfusates have been used (45–49). Pressure settings used for perfusion are set at 40 mmHg for kidney (49), 4–8 mmHg for portal vein and 25–70 mmHg for hepatic artery (46–48,50).

Controlled oxygenated rewarming (i.e. slowly rewarming an SCS organ to 20°C) aims to avoid abrupt temperature changes. A possibly underestimated side effect of quickly rewarming an organ from hypo- to normothermic or subnormothermic conditions may cause a "heat shock," leading to mitochondrial dysfunction (51).

Ex Situ Dynamic Preservation

Kidney

Nonoxygenated hypothermic MP: Nonoxygenated hypothermic MP (HMP) of the kidney, at low perfusion pressures (20–30 mmHg), has been shown to reduce DGF and may improve graft survival (52). The largest randomized controlled trial (RCT) comparing SCS with continuous HMP of deceased donor kidneys using the LifePort (Organ Recovery Systems, Itasca, IL) showed an overall reduced risk of DGF and a survival benefit, the latter most pronounced in ECD kidneys (21,24). This portable device uses conventional roller-pump technology to generate a pressure-controlled pulsatile flow. Continuous HMP of kidneys from DCD III (circulatory arrest after withdrawal of treatment) also resulted in a decreased risk of DGF, but no impact on graft survival could be demonstrated (22). A parallel trial, also using the LifePort, did not demonstrate a reduction in DGF for DCD III kidneys (23). The use of both continuous and preimplantation HMP in the latter may be a reason for the discrepancy between these trials. It has been suggested that relatively short periods of HMP (<4 h) following long periods of SCS in DCD kidneys has reduced or no benefit compared with continuous HMP (53). Although Watson and colleagues are comparing continuous and preimplantation HMP with SCS in two ongoing trials (Table 1), no RCTs are currently comparing continuous and preimplantation HMP directly.

It is possible that the length of HMP and its protective effect may be different for different kidney types. Recent large registry analyses (>90 000 kidneys) have shown that in standard criteria kidneys, HMP reduces the risk of DGF compared with SCS, regardless of very short or very long cold ischemia time (CIT) (54). In the same study, the risk of DGF was reduced for ECD kidneys with CIT >6 h only and for DCD kidneys with CIT 6–24 h only (54). An effect of shorter pumping times for ECD and DCD may have been missed because of lower numbers in the analyses; however, if this is not the case, then the result suggests that these kidneys need to be pumped for at least 6 h to benefit from HMP. Nevertheless, because CIT is a well-established predictor of DGF (3), a balance between minimizing CIT and any potential benefits of HMP is required. To date, there is a lack of evidence that HMP allows longer duration of CIT. It seems that just a few hours of HMP, as long as the total CIT is not extended, can have a positive impact on early graft function compared with SCS. In addition, published studies have reported no robust tools for viability assessment during HMP. Although previous studies have shown that increased vascular resistance and high perfusate injury marker concentrations are risk factors for DGF, they are not accurate enough to predict long-term outcomes or to justify kidney discard (55,56). The

Table 1: Overview of ongoing or planned clinical trials in kidney preservation based on a search of online clinical trial registries (see Appendix S1)

Donor type	Preservation	End point	Design	Start	Status	Registration	Acronym	Lead
DBD	piHMP versus SCS	DGF	RCT	08/2005	Analyzing	ISRCTN35082773	HBD Pump	Cambridge, U.K., C. Watson
DBD	c/piHMP versus SCS in normothermic and hypothermic DBD	DGF	RCT	11/2015	Not yet recruiting	NCT02525510	N.A.	San Francisco, CA, D. Malinoski, C. Niemann
DBD ≥50 years	HMP	6-mo GFR	Observational, case control	06/2016	Recruiting	NCT02055950	PREDICTION	Italy, P. Cravedi
ECD	piHMP	3-mo GS	Open, nonrandomized	10/2011	Recruiting	DRKS00000121	N.A.	Essen, Germany, A. Paul, A. Gallinat
ECD	piHMP with O_2 versus SCS	1 year GS	RCT	05/2014	Recruiting	ISRCTN63852508	COPE-POMP	COPE, A Paul, T. Minor, P. Kocabayoglu, R. Ploeg
ECD	c/piHMP versus SCS	DGF	RCT	04/2010	Recruiting	NCT01170910	IMPULSION	Lyon, France, L. Badet
DCD III	cHMP versus SCS	DGF	RCT	04/2011	Recruiting	ISRCTN50082383	CAD-MP	Cambridge, U.K., C. Watson, D. Summers
DCD III aged ≥50 years	cHMP with O_2 versus cHMP	1-year GS	RCT	01/2014	Recruiting	ISRCTN32967929	COPE-COMPARE	COPE, J. Pirenne, I. Jochmans, R. Ploeg
Deceased	HMP versus HMP with eternacept	DGF, 12-mo GS	RCT	04/2011	Recruiting	NCT01731457	N.A.	Poland, P. Domagala, A. Kwiatkowski

c, continuous; CAD-MP, cardiac death–machine perfusion; COMPARE, cold oxygenated machine perfusion of aged renal grafts; COPE, Consortium for Organ Preservation in Europe; DBD, donation after brain death; DCD III, donation after circulatory death (circulatory arrest after withdrawal of treatment); DGF; delayed graft function; ECD, expanded criteria donor; GS, graft survival; HBD, heart-beating donor; HMP, hypothermic machine perfusion; IMPULSION, Pulsatile Perfusion Preservation in Kidney Transplantation From Expanded Criteria Donors; N.A., not available; O_2, oxygen; pi, preimplantation; POMP, pulsatile oxygenated machine perfusion; PREDICTION, Pulsed Perfusion for Marginal Kidneys; RCT, randomized controlled trial; SCS, static cold storage.

development of novel biomarker identification platforms, such as proteomics and metabolomics, may allow better assessment.

Oxygenated HMP: Oxygenation during HMP appears to be beneficial. Several preclinical studies have shown that cellular metabolism is slower but not at a standstill, and respiration continues during HMP, resulting in oxidative stress (57,58). Recent comparative porcine studies have demonstrated that, particularly in DCD, oxygenated continuous HMP improves early kidney graft function (59–61). In donation after brain death (DBD) settings, it seems that a short period of oxygenated preimplantation HMP could be sufficient to improve creatinine clearance compared with SCS, possibly as effective as continuous oxygenated HMP (62,63). The ideal oxygen tension, providing balance between benefit of oxygen and risk of increased production of oxygen free-radical species, remains unknown (60,64).

The effect of oxygenated HMP is being investigated in two RCTs initiated by the Consortium on Organ Preservation in Europe (COPE) (Table 1) using the Kidney Assist (Organ Assist, Groningen, the Netherlands). The Kidney Assist oxygenates the preservation solution and uses a centrifugal pump to generate a pressure-controlled pulsatile flow. COPE-COMPARE randomizes one kidney from DCD III donors aged ≥50 years to oxygenated continuous HMP and the other to nonoxygenated continuous HMP. The trial is powered to demonstrate a difference in glomerular filtration rate at 1 year after transplantation, with DGF and graft survival as secondary end points (Appendix S2). In COPE-POMP, powered to demonstrate a difference in 1-year graft survival, ECD kidneys are randomized on arrival at the recipient center to a minimum of 2-h preimplantation oxygenated HMP versus continued SCS (Appendix S3).

Normothermic MP: A short period of normothermic MP (NMP) immediately prior to implantation has been found to improve kidney graft function, to replenish ATP and to reduce injury in a number of large animal models (36). A pilot clinical study compared 18 ECD kidneys that received 1 h of preimplantation blood-based NMP with 47 matched SCS controls. Remarkably low DGF rates were seen with preimplantation NMP (5.6% vs. 36.2%) (38). Currently, there are no registered ongoing RCTs comparing preimplantation NMP with SCS. In contrast to HMP, kidney function can be evaluated during NMP by assessing macroscopic appearance of blood perfusion, renal blood flow and urine output (65,66), but proof of concept of transplanting kidneys that were discarded and subsequently resuscitated by preimplantation NMP has not yet been reported. Developing and validating tools assessing graft quality, predictive of transplant outcome, are needed to aid decision making on whether to use or discard.

Subnormothermic MP and controlled oxygenated rewarming: Continuous subnormothermic MP (SMP) of DCD porcine kidneys has demonstrated improved creatinine clearance and preservation of structural integrity compared with continuous oxygenated HMP and SCS (49). In a pig reperfusion model, 3 h of controlled oxygenated rewarming (COR) following 18 h SCS enhanced creatinine clearance compared with continuous or preimplantation HMP (51). Clinical use of SMP or COR in kidney transplantation has not yet been reported.

Liver

Hypothermic MP: Experimental evidence shows that livers can be preserved by low-pressure oxygenated HMP (or hypothermic oxygenated perfusion) using either continuous or preimplantation perfusion (33). Oxygenated HMP reduces ischemia–reperfusion injury and protects against biliary injury in preclinical models; however, no evidence yet shows that HMP can extend liver preservation times (29,67). HMP of discarded human livers confirmed the feasibility and safety of the technique (28,68–70). The Columbia University group was the first to report the transplantation of 20 DBD livers preserved by preimplantation HMP compared with matched SCS controls (27). Preimplantation HMP provided safe preservation in this pilot study, with low EAD rates (5% vs. 25% of SCS livers). Guarrera et al recently reported on transplanting "orphan" livers—refused for transplantation by numerous centers—after preimplantation HMP and achieving reduced EAD rates, fewer biliary complications and shorter hospital stay compared with matched SCS controls (31).

The initial clinical experience of preimplantation HMP of eight DCD livers by the University of Zürich group, showing feasibility of the technique with no evidence of ischemic cholangiopathy at 8 mo after transplant despite extended DCD criteria (30), was recently expanded. Dutkowski et al transplanted 25 DCD livers after preimplantation oxygenated HMP and compared them with a matched cohort of 50 SCS DCD livers; the pumped livers showed a reduced rate of intrahepatic cholangiopathy at 1-year follow-up and improved 1-year graft survival versus SCS livers (32). Further studies comparing preimplantation HMP with SCS have been announced (Table 2), some using single portal vein perfusion and others targeting dual perfusion. The Columbia system relies on dual flow-controlled perfusion with low pressures and continuous flow over portal vein and hepatic artery, whereas the Zürich team applies pressure-controlled portal vein perfusion with continuous flow. The Zürich group has used both the ECOPS and the Liver Assist device for this purpose (Organ Assist, Groningen, the Netherlands). No trials are exploring continuous HMP; however, Guarrera et al suggest that prolonged SCS prior to HMP

Table 2: Overview of ongoing or planned clinical trials in liver preservation based on a search of online clinical trial registries (see Appendix S1)

Donor type	Preservation	End point	Design	Start	Status	Registration	Acronym	Lead
DBD	piHMP with O_2 versus SCS	Postoperative complications (Clavien-Dindo class 3–4)	RCT	09/2011	Recruiting	NCT01317342	HOPE	Zürich, Switzerland, P. Dutkowski
DCD	piHMP with O_2	6-mo GS	Pilot	04/2014	Completed	NTR4493	Dual HOPE	Groningen, the Netherlands, R. Porte
DCD	piHMP with O_2 versus SCS	IBS on 6-mo MRCP	RCT	10/2015	Recruiting	NCT02584283	Dual HOPE	Groningen, the Netherlands, R. Porte
DBD + DCD III	cNMP	30-day GS	Historic control	10/2012	Completed	ISRCTN14355416	N.A.	London, U.K., N. Heaton
DBD + DCD III	cNMP versus SCS	Peak AST	RCT	04/2014	Recruiting	ISRCTN39731134	COPE-WP2	COPE, P. Friend, D. Nasralla, R. Ploeg
Deceased	NMP	EAD	Matched controls	07/2015	Recruiting	NCT02515708	N.A.	Cleveland, OH, C. Quintini
Deceased	NMP	Safety	Pilot	06/2015	Recruiting imminent	NCT02449694	REVIVE	Leeds, U.K., M. Attia
Deceased	NMP versus SCS	EAD serious adverse events	RCT	09/2015	Recruiting imminent	NCT02522871	OCS Liver PROTECT Trial	N.A.

AST, aspartate aminotransferase; c, continuous; COPE, Consortium for Organ Preservation in Europe; DBD, donation after brain death; DCD, donation after circulatory death; DCD III, donation after circulatory death (circulatory arrest after withdrawal of treatment); EAD, early allograft dysfunction; GS, graft survival; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated perfusion; IBS, ischemic-type biliary strictures; N.A., not available; NMP, normothermic machine perfusion; MRCP, magnetic resonance cholangiopancreatography; pi, OCS, organ care system; preimplantation; RCT, PROTECT, TransMedics (OCS) Liver Trial: Preserving and Assessing Donor Livers for Transplantation; randomized controlled trial; REVIVE, Trial of the TransMedics Organ Care System™ Liver For Preserving and Assessing Donor Livers for Transplantation; SCS, static cold storage; WP2, work package 2.

may negatively affect outcomes, and thus they encourage the development of a portable device.

Adequate perfusate oxygenation seems necessary to protect the liver against ischemia–reperfusion injury (71), although the ideal oxygen tension is unknown. Findings are inconsistent, and a balance between beneficial effects of oxygen and production of radical oxygen species is likely to be important (71,72). There is also debate about whether active oxygenation (e.g. by an oxygenator, or bubbling oxygen through the perfusate) is needed in the hypothermic setting; Guarrera et al report perfusate oxygen tensions >120 mmHg in an open system without active oxygenation (27).

Viability assessment during HMP is largely unexplored. Bile is not produced during HMP, and although perfusate transaminases might correlate with graft injury, data from large clinical trials are needed to determine the value of HMP as a tool to predict outcome (27,28,73,74).

Normothermic MP: NMP simulates *in vivo* conditions and requires dual perfusion through the hepatic artery and portal vein at physiological conditions. It is thought to enable organ viability assessment (75,76), to reduce PNF, to improve early graft function, and to reduce ischemic cholangiopathy by improved perfusion and preservation of the peribiliary vascular plexus and peribiliary glands (37,41,42).

After numerous preclinical studies showing the benefit of continuous NMP, a phase I study in the United Kingdom showed that prolonged continuous NMP with the portable Metra device (OrganOx, Oxford, UK) is feasible and safe (77). Twenty livers, of which 10 had high-risk profiles, were successfully transplanted with 6-mo survival similar to that of 40 matched controls. Currently, a large phase III RCT is comparing continuous NMP using the Metra device with SCS within COPE (Table 2, Appendix S4). The primary outcome is peak aspartate aminotransferase in the first 7 days after transplant (as a risk factor for graft survival), and the trial will also assess organ discard rates, PNF, EAD, ischemic cholangiopathy on magnetic resonance cholangiopancreatography at 6 mo, and graft and patient survival. Two trials with a different NMP liver device (OCS Liver) developed by TransMedics (Andover, MA) have been initiated (Table 2); one is a safety study and the other is an RCT with EAD as the primary outcome. Another RCT comparing NMP with SCS is running in Cleveland, Ohio, using a homemade circuit and targeting EAD as the primary end point (Table 2).

The first case report using preimplantation NMP of a human liver followed by successful transplantation has been published recently (44). Another case report describes an orphan liver liver successfully transplanted

after assessment by preimplantation NMP, with the decision to transplant made on the basis of normalization of lactate (<2 mmol/L) and bile production by the graft (78). These two parameters are judged as important markers, although additional research in large trials is needed to confirm this. Animal studies in DCD settings have suggested that continuous NMP is superior to preimplantation reconditioning with NMP (37); however, if preimplantation NMP were to prove noninferior to continuous NMP, this may offer logistical benefits for a certain category of donor livers, and viability assessment might still be possible (75,78).

SMP and controlled oxygenated rewarming: Animal survival, liver function and bile duct preservation have been shown to be better after SMP than SCS in rat and pig models (45,48,79–82). Although SMP has not been used clinically, discarded livers can be supported by SMP with adequate flow rates, bile production and various biochemical parameters as potential surrogates for organ viability with histological analysis revealing no additional injury due to SMP (46,47).

Slowly rewarming the liver during COR to 20°C over 3 h by pumping the hepatic artery and portal vein has been shown to improve tissue energetics and histological appearance in a pig model (50). The first clinical COR application of six high-risk orphan DBD livers showed feasibility of COR, with good function at 3 months compared with historical SCS controls (83).

In Situ Dynamic Preservation or Abdominal RP

RP of abdominal organs in DCD donors applies extracorporeal membrane oxygenation to deliver oxygen after a period of warm ischemia. Hypothermic RP (HRP) reduces metabolic activity and requirements, whereas normothermic RP (NRP) may support the restoration of cellular processes by the constant supply of oxygen and substrates in a near-physiological way (84).

HRP in DCD has shown overall good kidney graft survival (>85%), but PNF could not be avoided and high rates of DGF (up to 75%) have been reported (84). The largest reported series of 320 kidney transplants from DCD I and II (failed resuscitation outside or inside the hospital) shows 87% 1-year graft survival (85). HRP (at 4–10°C) of livers has not been reported. NRP in DCD III has also shown good kidney graft survival with lower DGF rates (between 8% and 42%) (84,86).

NRP of DCD II and III livers has shown a wide range of graft survival rates (43–91%) but acceptable patient survival (71–91%), although incidence of PNF and ischemic cholangiopathy is higher than in recipients of DBD livers (84).

Mechanisms of Injury and Repair During MP

It is not known how dynamic preservation exerts its beneficial effects, but perfusion likely helps maintain a healthy endothelium and replenish ATP, and it might even alter the organ's immunogenicity (87,88). Increased nitric oxide–dependent vasodilation and improved cortical microcirculation at reperfusion regulated through improved endothelial nitric oxide synthase phosphorylation has been demonstrated in HMP-preserved DCD porcine kidneys (89). Moreover, a degree of vascular shear stress, which plays a critical role in normal vascular function, is maintained by the pulsatile flow of HMP, which could have an anti-inflammatory effect through the activation of flow-dependent genes (26,90).

Oxygenation during HMP has been shown to restore ATP content in kidney (61) and liver (33). In the liver, oxygenated preimplantation HMP reversibly suppresses mitochondrial oxidative metabolism after SCS, decreasing the mitochondrial release of reactive oxygen species on reperfusion with several-fold deactivation of numerous intracellular and extracellular pathways, including the host inflammatory response (19,88,91). Little is known about the working mechanisms of SMP and NMP besides the attempt to maintain a physiological environment. For blood-based perfusion, there is evidence that the absence of leukocytes and platelets limits the inflammatory response and reduces apoptosis (36). A comparison of preimplantation HMP with preimplantation NMP of rat DCD livers that were SCS for 4 h showed improved survival of both techniques compared with continued SCS after 30 min of donor warm ischemia time; however, when donor warm ischemia time was 60 min, preimplantation HMP resulted in improved survival (92).

Multiplatform -omics studies and combination with computational biology will allow the use of an integrated approach to identify new pathways of injury and repair during organ preservation (93). This will also ease identification of ways to improve dynamic preservation through development of targeted interventions.

How to Move Forward?

Dynamic preservation has the potential to improve (abdominal) organ preservation; however, many questions remain unanswered today. Dynamic preservation techniques should be not only compared but also evaluated in light of other optimization strategies such as donor hypothermia (94). Furthermore, it has become clear that organs with different baseline risk will benefit from different preservation methods, and graft-tailored conditioning should be the focus of future research. The use of dynamic preservation to resuscitate grafts, not only by restoring oxygen and nutrient flow but also by actively targeting repair, is currently

underexplored. Nevertheless, the addition of specific drug, gene or cell therapy to an isolated organ and not to a patient is very attractive and has the potential to increase the number of transplantable organs.

Much like organ donor intervention trials (95), organ preservation trials pose many regulatory, legal, ethical and logistical challenges including those unique to organ preservation trials. At which stage and from whom should consent for research be sought, as intended recipients may change following the preservation phase (e.g. due to a positive crossmatch or recipient nontransplantability)? How should reoffering of these organs occur when randomization and treatment of the organ has perhaps already started and the inevitable pressure of time remains? If discarded organs seem to perform well during organ preservation, should they then be reoffered and how should this be done? To facilitate organ preservation research, a debate between regulatory authorities and the transplant community is needed. In addition, the financial climate and device costs make it challenging to run investigator-driven trials independent of industry. Nevertheless, the search for optimized graft-tailored preservation and repair is crucial and as important as management of acute rejection in the early days of transplantation. It deserves to be tackled with high priority and the same urgency.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Nonexhaustive list of planned or ongoing clinical trials investigating dynamic preservation of kidney or liver that were not registered in an online clinical trial registry at the time of writing this manuscript.

Appendix S1: Search strategy of online clinical trial registries.

Appendix S2: The trial protocol of the Consortium for Organ Preservation in Europe COMPARE trial comparing continuous oxygenated hypothermic machine perfusion with continuous nonoxygenated machine perfusion in kidneys aged >50 years donated after circulatory death (Maastricht type III donors).

Appendix S3: The trial protocol of the Consortium for Organ Preservation in Europe POMP trial comparing oxygenated preimplantation hypothermic machine perfusion with static cold storage in kidneys from expanded criteria donors.

Appendix S4: The trial protocol of the Consortium for Organ Preservation in Europe normothermic machine perfusion (NMP) liver trial comparing continuous NMP with static cold storage of liver grafts.

Appendix S5: Overview of the collection of samples from the clinical trials in the Consortium for Organ Preservation in Europe.