The IDEAL framework for machine perfusion in liver transplantation

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Standfirst

Liver transplantation is challenged by organ scarcity and ageing donors. Machine perfusion is a promising technique to enhance organ preservation and assessment, improving liver utilization and patient outcomes. Here, we discuss current practices in machine perfusion using the IDEAL framework and outline the steps needed to advance this technology clinically.

Machine perfusion of donor livers has made substantial progress, transitioning from preclinical studies towards standard of care in numerous hospitals worldwide. Various machine perfusion modalities are now in clinical use, with multiple devices developed, tested, and implemented for each approach. Conducting high-quality research in surgery has historically been challenging due to the nature of surgical innovation, which has often led to methodologically weaker approaches. Here, we outline current practices in liver machine perfusion using the IDEAL (Idea, Development, Exploration, Assessment, Long-term) framework, which provides a structured pathway for implementation, from early adoption to widespread clinical use.[1]

In situ abdominal normothermic regional perfusion (NRP) is used to recondition and assess donor livers following both controlled and uncontrolled donation after circulatory death (DCD). Initially introduced in Spain in 1989 for kidney grafts from uncontrolled DCD donors, a protocol for liver transplantation was first implemented by the Barcelona group in 2002.[2] Today, NRP is widely used for DCD organ recovery in numerous transplant centres across Italy, UK, France, Sweden, the Netherlands, and the United States. It has been associated with lower rates of post-transplant cholangiopathy and early allograft dysfunction compared to static cold preservation.[3] Additionally, NRP is often combined with *ex situ* perfusion modalities, particularly in uncontrolled or otherwise high-risk DCD donors. To date, abdominal NRP has been evaluated up to IDEAL stage 2b (observational studies), but no randomized controlled trials have been conducted **(Figure 1).**

Short-duration (1-2 h) hypothermic oxygenated machine perfusion (HOPE) of human donor livers has been shown to improve mitochondrial function and energy charge, thereby reducing oxidative injury and inflammation upon reperfusion during transplantation.[4] This concept was clinically introduced for DCD livers by Dutkowski and colleagues in 2012, and is typically used end-ischemic (at the end of the static cold preservation period) in the recipient hospital.[5] Since then, multiple IDEAL Stage 2 studies have been conducted, followed by six published randomized controlled trials (RCTs) demonstrating reduced liver-related post-transplant

complications and graft loss, and a decreased incidence of post-transplant cholangiopathy in DCD liver transplantation (IDEAL Stage 3) (Supplementary Table 1) Additionally, an international multicentre study comprising 1,202 perfused livers reported long-term (5-year) graft and patient survival outcomes, reaching IDEAL Stage 4.[6] A variant is prolonged HOPE, in which donor livers are perfused overnight to postpone transplantation until daytime, thereby avoiding night-time surgery. This approach has been evaluated up to IDEAL stage 2b **(Figure 1)**.[7]

Normothermic machine perfusion (NMP) preserves donor livers at physiological temperatures *ex situ*, enabling metabolic function assessment. Pioneered by Friend and colleagues, the first liver transplantation using NMP was performed in 2013.[8] This modality offers the potential to extend preservation time and evaluate high-risk donor livers. NMP can be applied in both *end-ischemic* and *continuous* (perfusion initiated at the donor hospital and continued for most of the preservation period) modes. Numerous IDEAL Stage 2 studies have been conducted for both approaches, and four randomized controlled trials, including a total of 801 patients, have been published (IDEAL Stage 3) **(Figure 1, Supplementary Table 1)** Although NMP is increasingly adopted in transplant centres worldwide in both continuous and end-ischemic protocols, international, multi-centre, real-world data sets on long-term clinical outcomes are still awaited. Extended duration (multi-day) liver perfusion is currently still in the research phase and provides a platform for *ex-situ* therapeutic interventions, with first-in-human studies exploring its clinical application (IDEAL Stage 0-1) **(Figure 1, Supplementary Table 1)**.[9]

Following the successful clinical implementation of NRP, HOPE and NMP, several research groups have explored combinations of perfusion modalities. For example, sequential *ex situ* HOPE, controlled oxygenated rewarming and NMP—designed to first restore mitochondrial function in the cold and subsequently assess viability at normothermia—enabled the safe transplantation of otherwise non-utilized, high-risk donor livers.[10,11] Similarly, combining *in situ* NRP with *ex situ* HOPE has shown favourable outcomes and has since been adopted as

standard of care in Italy.[12] To date, studies on combined modalities remain at IDEAL stage 2b, with IDEAL stage 3 trials still awaited **(Figure 1)**.

A key objective in clinical machine perfusion research is to advance all perfusion modalities to IDEAL stage 4. For NMP, for which a substantial number of procedures have been performed worldwide, long-term, multi-centre, real-world outcome data are highly anticipated. International collaboration (such as the establishment of an international liver machine perfusion registry, pursued by the European Society of Organ Transplantation) could provide invaluable insights to benefit liver transplant recipients.

By contrast, for NRP and combined perfusion modalities, RCTs (IDEAL Stage 3) remain a critical unmet need. Given the demonstrated superiority of HOPE and NMP over static cold preservation, conducting trials that compare NRP or combined modalities against static cold preservation alone would be ethically challenging in most countries. Instead, future trials could focus on comparing *in situ* NRP with *ex situ* DHOPE or NMP to further refine perfusion strategies in DCD liver transplantation. Subsequently, RCTs directly comparing different perfusion modalities should be initiated. One such trial is currently recruiting participants to compare end-ischemic HOPE and end-ischemic NMP (clinicaltrials.gov NCT04644744), with results eagerly awaited. Additionally, several observational studies have evaluated perfusion strategies, including comparisons between NRP and end-ischemic NMP. However, other IDEAL stage 3 trials have yet to be conducted, highlighting an urgent need for further comparative studies.

Unfortunately, many IDEAL stage 3 studies on machine perfusion have used varying endpoints, limiting the ability to progress towards stage 4. To date, there has been no consensus on the most appropriate endpoint for machine perfusion trials, despite the efforts of workgroups within the International Liver Transplantation Society to establish an internationally accepted standard. In addition to differences in endpoints, variability in perfusion

techniques poses another challenge. Both the perfusate components and the perfusion devices used in studies differ markedly. More research is required to systematically compare perfusion devices and different types of perfusate. Furthermore, many machine perfusion studies focus on assessing donor liver viability, but there is considerable variation in the criteria used for viability assessment across transplant centres worldwide.

In summary, over the past decade, machine perfusion has gradually become the standard of care for donor liver preservation in some transplant centres worldwide. However, broader adoption and implementation are influenced by resource availability and cost considerations, including perfusion devices, disposables, trained personnel, and reimbursement mechanisms where available, as well as by differing regulatory pathways across countries. Overcoming these hurdles will require international communication and collaboration to further advance the field of liver machine perfusion. The COPE 2 initiative, building on the original COPE consortium, is establishing a pan-European expert network to drive the next generation of clinical trials, ultimately improving patient outcomes and advancing liver transplantation.

References

1 McCulloch, P. *et al.* No surgical innovation without evaluation: the IDEAL recommendations. *Lancet* **374**, 1105-1112, doi:10.1016/S0140-6736(09)61116-8 (2009).

2 Fondevila, C. *et al.* Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. *Am J Transplant* **7**, 1849-1855, doi:10.1111/j.1600-6143.2007.01846.x (2007).

3 Hessheimer, A. J. *et al.* Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* **70**, 658-665, doi:10.1016/j.jhep.2018.12.013 (2019).

4 Schlegel, A. *et al.* Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. *EBioMedicine* **60**, 103014, doi:10.1016/j.ebiom.2020.103014 (2020).

5 Guarrera, J. V. *et al.* Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant* **10**, 372-381, doi:10.1111/j.1600-6143.2009.02932.x (2010).

6 Eden, J. *et al.* Long-term outcomes after hypothermic oxygenated machine perfusion and transplantation of 1,202 donor livers in a real-world setting (HOPE-REAL study). *J Hepatol*, doi:10.1016/j.jhep.2024.06.035 (2024).

7 Bruggenwirth, I. M. A. *et al.* Prolonged hypothermic machine perfusion enables daytime liver transplantation - an IDEAL stage 2 prospective clinical trial. *EClinicalMedicine* **68**, 102411, doi:10.1016/j.eclinm.2023.102411 (2024).

8 Ravikumar, R. *et al.* Liver Transplantation After Ex Vivo Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial. *Am J Transplant* **16**, 1779-1787, doi:10.1111/ajt.13708 (2016).

9 Clavien, P. A. *et al.* Transplantation of a human liver following 3 days of ex situ normothermic preservation. *Nat Biotechnol* **40**, 1610-1616, doi:10.1038/s41587-022-01354-7 (2022).

10 van Leeuwen, O. B. *et al.* Transplantation of High-risk Donor Livers After Ex Situ Resuscitation and Assessment Using Combined Hypo- and Normothermic Machine Perfusion: A Prospective Clinical Trial. *Ann Surg* **270**, 906-914, doi:10.1097/SLA.0000000000003540 (2019).

11 van Leeuwen, O. B., Lantinga, V.A., Lascaris, B. et al. 'Back-to-base' combined hypothermic and normothermic machine perfusion of human donor livers. Nat Protoc (2025). https://doi.org/10.1038/s41596-024-01130-8.

12 Ghinolfi, D. *et al.* Sequential Use of Normothermic Regional and Ex Situ Machine Perfusion in Donation After Circulatory Death Liver Transplant. *Liver Transpl* **27**, 385-402, doi:10.1002/lt.25899 (2021).

Supplementary information

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Fig. 1 | The current IDEAL framework for machine perfusion in liver transplantation. Landmark studies noted for each perfusion modality at its most advanced stage in the IDEAL (Idea, Development, Exploration, Assessment, Long-term) framework. Large observational studies support the use of in situ normothermic regional perfusion (NRP) as an effective approach to limiting initial warm ischemic injury in donation after circulatory death (IDEAL Stage 2b). Six published randomized trials, along with long-term real-world data, demonstrate that hypothermic oxygenated machine perfusion (HOPE) effectively reduces ischemia-reperfusion injury and improves recipient outcomes (IDEAL Stages 3 and 4). Four randomized trials also support the use of normothermic machine perfusion (NMP) as an effective method for liver preservation during transport and/or for end-ischemic assessment at the recipient hospital (IDEAL Stages 2b and 3). NRP, prolonged HOPE (HOPE-PRO), and combined modalities must progress to Stage 3 before advancing to Stage 4. See Supplementary Table 1 for study details and key information on available IDEAL Stage 3 randomized trials.

Supplementary Table 1 | Selected landmark trials in machine perfusion for liver transplantation

Author, year	Study design	Donor type	Primary outcome
Hypothermic oxygenated machine perfusion (HOPE)			
van Rijn et al, 2021[1]	RCT	DCD	End-ischemic HOPE significantly decreased non-anastomotic biliary strictures, compared to SCS
Czigany et al, 2021[2]	RCT	DBD	End-ischemic HOPE significantly reduced EAD, compared to SCS
Ravaioli et al, 2022[3]	RCT	DBD	End-ischemic HOPE significantly reduced EAD, compared to SCS
Schlegel et al, 2023[4]	RCT	DBD	End-ischemic HOPE did not improve occurrence of Clavien ≥III complications, compared to SCS
Grat et al, 2023[5]	RCT	DBD	End-ischemic HOPE did not improve occurrence of EAD, compared to SCS
Panayotova et al, 2024[6]	RCT	DBD and DCD	Portable HMP-O2 showed noninferiority for EAD compared to SCS
Normothermic machine perfusion (NMP)			
Nasralla et al, 2018[7]	RCT	DBD and DCD	Continuous NMP significantly reduced EAD, compared to SCS
Ghinolfi et al, 2019[8]	RCT	DBD	End-ischemic NMP did not improve 6-month graft or patient survival, compared to SCS
Markmann et al, 2022[9]	RCT	DBD and DCD	Continuous NMP significantly reduced EAD, compared to SCS
Chapman et al, 2023[10]	RCT	DBD and DCD	Continuous NMP did not reduce EAD, compared to SCS
Guo et al, 2023[11]	RCT	DBD	Ischemia-free NMP significantly reduced EAD compared to SCS

RCT, randomized controlled trial; DCD, donation after circulatory death; DBD, donation after brain death; HOPE, hypothermic oxygenated machine perfusion; SCS, static cold storage; EAD, early allograft dysfunction; HMP-O2, hypothermic machine perfusion with pre-oxygenated preservation solution; NMP, normothermic machine perfusion.

Supplementary Information references:

1. van Rijn, R. *et al.* Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. *N Engl J Med* **384**, 1391-1401 (2021).
2. Czigany, Z. *et al.* Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death: Results From a Multicenter Randomized Controlled Trial (HOPE ECD-DBD). *Ann Surg* **274**, 705-712, (2021).
3. Ravaioli, M. *et al.* Hypothermic oxygenated perfusion in extended criteria donor liver transplantation-A randomized clinical trial. *Am J Transplant* **22**, 2401-2408 (2022).
4. Schlegel, A. *et al.* A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. *J Hepatol* **78**, 783-793 (2023).
5. Grat, M. *et al.* Routine End-ischemic Hypothermic Oxygenated Machine Perfusion in Liver Transplantation From Donors After Brain Death: A Randomized Controlled Trial. *Ann Surg* **278**, 662-668 (2023).
6. Panayotova, G. G. *et al.* Portable hypothermic oxygenated machine perfusion for organ preservation in liver transplantation: A randomized, open-label, clinical trial. *Hepatology* **79**, 1033-1047 (2024).
7. Nasralla, D. *et al.* A randomized trial of normothermic preservation in liver transplantation. *Nature* **557**, 50-56 (2018).
8. Ghinolfi, D. *et al.* Pilot, Open, Randomized, Prospective Trial for Normothermic Machine Perfusion Evaluation in Liver Transplantation From Older Donors. *Liver Transpl* **25**, 436-449 (2019).
9. Markmann, J. F. *et al.* Impact of Portable Normothermic Blood-Based Machine Perfusion on Outcomes of Liver Transplant: The OCS Liver PROTECT Randomized Clinical Trial. *JAMA Surg* **157** (2022).

10. Chapman, W. C. *et al.* Normothermic Machine Perfusion of Donor Livers for Transplantation in the United States: A Randomized Controlled Trial. *Ann Surg* **278**, e912-e921 (2023).
11. Guo, Z. *et al.* A randomized-controlled trial of ischemia-free liver transplantation for end-stage liver disease. *J Hepatol* **79**, 394-402 (2023).