Clinical evidence summary

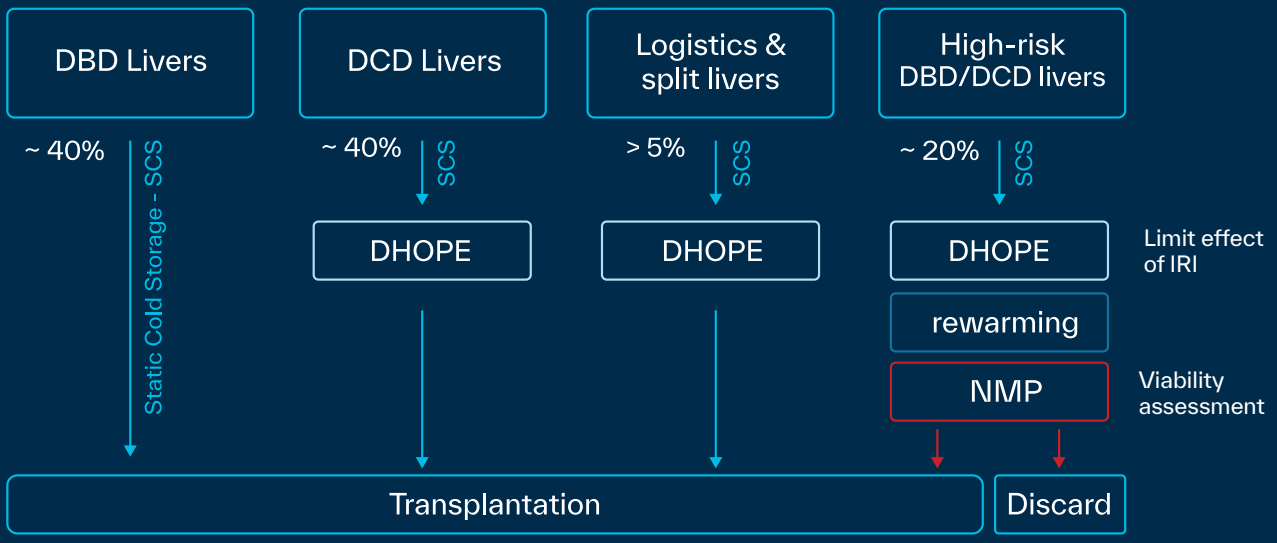
Liver Assist

XVIVO

In the past two decades, machine perfusion has emerged as a major advancement in liver transplantation. With each clinical study, we gain deeper insights into optimizing graft preservation and utilization for different donor livers.

Liver Assist, in the last decade, has played a pivotal role, offering clinicians a choice of protocols, whether cold, warm, sub-normothermic, or a combination. These protocols are complementary, not competitive, as they all serve different purpose from improving patient outcomes to increasing organ utilization.

For instance, University Medical Centre Groningen, has established a framework based on clinical data to guide the precise application of these protocols.



Schematic overview of liver machine perfusion protocols used at University Medical Centre Groningen[1]

Liver Assist's clinical application has been impressively documented in over 70 peer-reviewed publications. This clinical summary highlights its role in e.g., enhancing outcomes for transplant recipients, enabling the safe transplantation of marginal livers, and extending preservation times for logistical reasons.

Contents

1. van Leeuwen OB, Porte RJ. Ex situ machine preservation of donor livers for transplantation: HOPE for all? Br J Surg. 2021 Oct 23

Liver Assist

Unlock the power of flexibility

Liver Assist is a pressure controlled ex-vivo perfusion system for donor livers. With customizable settings, it offers the flexibility to choose from various protocols, including DHOPE, HOPE, COR, and NMP.

- O_2 Oxygenated
- Temperature controlled perfusion 12°C - 37°C
- 24h Up to 24H cold perfusion to support logistics
- Pressure controlled pulsatile (60 bpm) and continuous perfusion
- Functional viability assessment during NMP (bile and perfusate analysis)

DHOPE – Dual Hypothermic Oxygenated Perfusion | HOPE – Hypothermic Oxygenated Perfusion | NMP – Normothermic Machine Perfusion | COR – Controlled Oxygenated Rewarming | SCS – Static Cold Storage | DCD – Donation after Circulatory Death | DBD – Donation after Brain Death | ECD – Extended Criteria Donor | RCT – Randomized Controlled Trial | EAD – Early Allograft Dysfunction | PRS – Post Reperfusion Syndrome | PNF – Primary Non Function | HAT – Hepatic Artery Thrombosis | NAS – Non-anastomotic Biliary Strictures | CIT – Cold Ischemic Time | RR – Risk Ratio | OR – Odds Ratio | CCI – Comprehensive Complication Index® | ICU – Intensive Care Unit | IPTW – Inverse Probability of Treatment Weighting | DRI – Donor Risk Index | MEAF – Model For Early Allograft Function | ALT - Alanine Transaminase

XVIVO

Improved outcome

Hypothermic oxygenated machine perfusion (HMP) refers to perfusing a donor liver with an oxygenated acellular machine perfusion solution at temperatures of 12°C or below. HMP can be performed through dual perfusion (DHOPE), where both the portal vein and hepatic artery are perfused simultaneously. The hepatic artery is known to be vital for oxygenating the delicate bile ducts, and dual perfusion ensures flow through both major vessels.

Alternatively, HMP can be carried out solely through portal vein perfusion, often referred to as HOPE, which eliminates the need for cannulation of the hepatic artery. HOPE and DHOPE are shown to promote mitochondrial resuscitation which in turn mitigates the primary driver of ischemia-reperfusion injury, a common complication for liver transplant recipients. Liver Assist can perform both HOPE and DHOPE. Below is a selection of studies conducted using the device along with their outcomes.

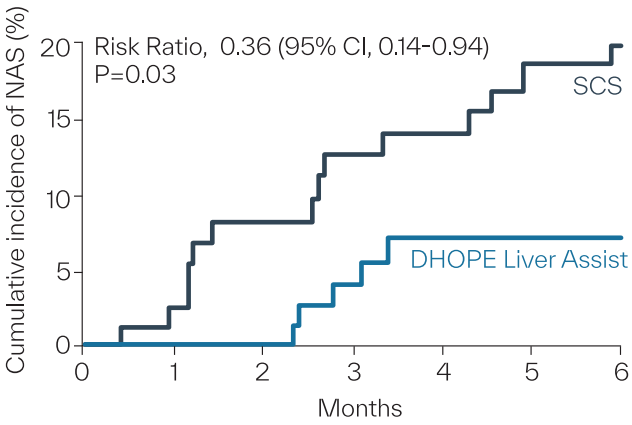
DHOPE in DCD

Hypothermic machine perfusion in liver transplantation – A randomized trial

van Rijn R, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S, Erdmann JI, Gilbo N, de Haas RJ, Heaton N, van Hoek B, Huurman VAL, Jochmans I, van Leeuwen OB, de Meijer VE, Monbaliu D, Polak WG, Slangen JJG, Troisi RI, Vanlander A, de Jonge J, Porte RJ.

N Engl J Med / 2021 / doi: 10.1056/NEJMoa2031532

This multicentre, randomized controlled trial (RCT), published in the New England Journal of Medicine, studied the effect of dual hypothermic oxygenated perfusion (DHOPE) on the incidence of non-anastomotic biliary strictures (NAS) following transplantation of livers donated after circulatory death (DCD). Patients were randomly assigned (1:1 ratio) to receive a liver preserved either with static cold storage (SCS; n=78) alone, or with SCS followed by a period of DHOPE (n=78) using Liver Assist prior to transplantation. The study demonstrates that end-ischemic DHOPE reduces the risk of developing NAS by 64% (RR 0.36, p=0.03) and led to significant reductions in early allograft dysfunction (EAD; RR 0.61) and post-reperfusion syndrome (PRS; RR 0.43) compared to SCS alone.



"The cumulative number of treatments for non-anastomotic biliary strictures was lower by a factor of almost 4 after machine perfusion, as compared with control." Van Rijn et al, 2021

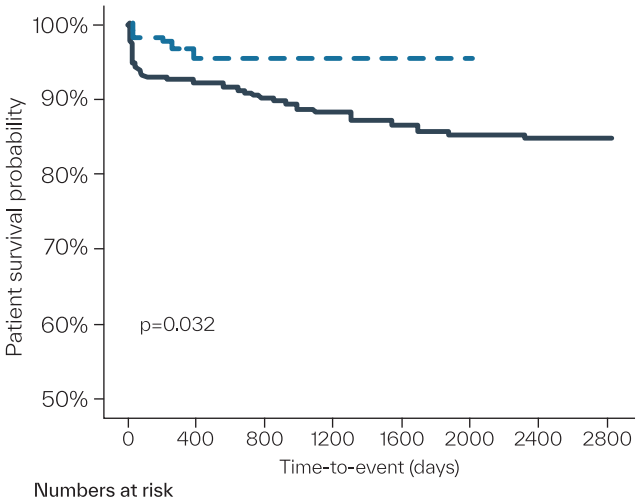
Outcome of liver transplantation with grafts from brain-dead donors treated with dual hypothermic oxygenated machine perfusion, with particular reference to elderly donors

Patrono D, Cussa D, Sciannameo V, Montanari E, Panconesi R, Berchialla P, Lepore M, Gambella A, Rizza G, Catalano G, Mirabella S, Tandoi F, Lupo F, Balagna R, Salizzoni M, Romagnoli R.

Am J Transplant / 2022 / doi: 10.1111/ajt.16996

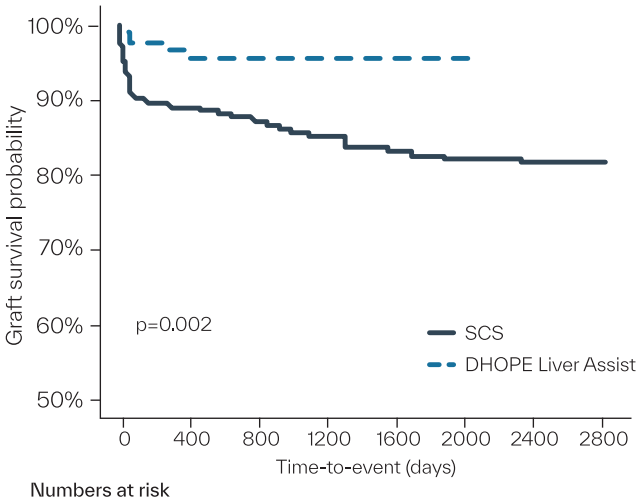
In this single-center, retrospective cohort study, the effect of end-ischemic DHOPE on extended criteria DBD-grafts (ECD-DBD) was assessed. Inverse probability of treatment weighting (IPTW) was used to overcome selection bias and allow comparison of outcomes in DHOPE-treated grafts (n=121) with grafts preserved by SCS (n=723). The study demonstrated that end-ischemic DHOPE using Liver Assist was associated with a significant reduction of early allograft failure (OR 0.24, p=0.024), fewer severe post-operative complications (Clavien-Dindo grade ≥3; OR 0.57, p=0.046) and lower cumulative morbidity at discharge (CCI: –7.20 points, p=0.003). DHOPE was also associated with improved patient and graft survival (p=0.032; p=0.002). The authors conclude that these findings prompt a wider adoption of this preservation technique in clinical practice, especially when grafts from elderly donors are used.

> "/.../ a simple intervention applied at the end of cold preservation improves graft survival and post-transplant course"
>
> Patrono et al, 2022



Numbers at risk
IPTW-adjusted patient survival (whole cohort)

SCS	723	633	517	425	310	195	104	9
DHOPE Liver Assist	121	90	51	23	4	1	0	0



Numbers at risk
IPTW-adjusted graft survival (whole cohort)

SCS	723	618	501	411	304	191	102	9
D-HOPE Liver Assist	121	90	51	23	4	1	0	0

DHOPE in DBD

Routine end-ischemic hypothermic oxygenated machine perfusion in liver transplantation from donors after brain death: A randomized controlled trial.

Grat M, Morawski M, Zhylko A, Rykowski P,Krasnodebski M, Wyporski A, Borkowski J, Lewandowski Z, Kobryn K, Stankiewicz R, Stypulkowski J, Holowko W, Patkowski W, Mielczarek-Puta M, Struga M, Szczepankiewicz B, Gornicka B, Krawczyk M.

Ann Surg / 2023 / doi: 10.1097/SLA.0000000000006055

In this randomized controlled trial (RCT), assessing the effect of end-ischemic DHOPE in DBD liver transplantation, livers donated after brain death were allocated (3:1) to either static cold storage (SCS, n=78) or SCS followed by at least 2 hours of DHOPE using Liver Assist (n=26). While no statistically significant differences in early (up to 90-days) post-operative outcomes were seen following transplantation of low-risk DBD livers, DHOPE in DBD-livers with a donor risk index (DRI) above 1.7 was associated with significantly better early graft function (MEAF score: 4.92 vs 6.31, p=0.037), lower overall morbidity (CCI: 4.35 vs 22.60, p=0.05) and improved patient survival (100% vs 84.6%).

"/.../ HOPE exerts beneficial effects on early LT outcomes from high-risk DBDs." Grat et al 2023

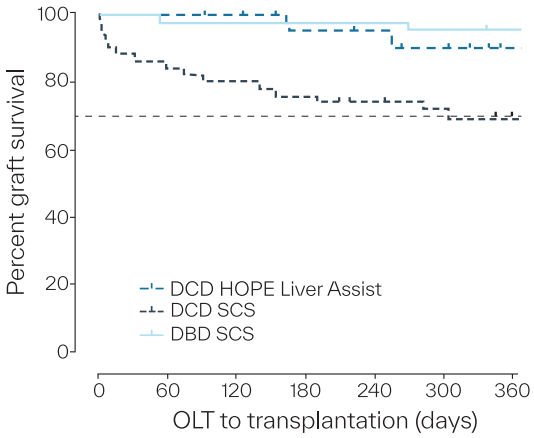
HOPE in DCD

First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: An international-matched case analysis.

Dutkowski P, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, DeOliveira ML, Kron P, Clavien PA.

Ann Surg / 2015 / doi: 10.1097/sla.0000000000001473

Published in 2015, Dutkowski et al present the results of the first comparative study on the impact of Hypothermic Oxygenated Perfusion (HOPE) using Liver Assist* in DCD liver transplantation. 25 HOPE-treated DCD livers were compared to a matched cohort of 50 DCD livers preserved with SCS. The study shows that, compared to SCS, end-ischemic HOPE of DCD-livers improves early allograft function (EAD: 20% vs 44%, p=0.046), reduces graft injury in terms of intrahepatic cholangiopathy (0% vs 22%, p=0.015), biliary complications (20% vs 46%, p=0.042), and improves 1-year graft survival (90% vs 69%, p=0.035). In addition, HOPE-treated DCD livers achieved similar results as matched DBD livers (n=50) in all investigated endpoints. The authors conclude that the study provides strong evidence that applying HOPE protects extended DCD livers from initial reperfusion injury leading to better graft function and the prevention of intrahepatic biliary complications.



Patients at Risk:

DCD HOPE	25	25	23	21	20	18	14
DCD SCS	50	44	41	39	35	33	30
DBD SCS	50	49	49	49	49	48	47

*The device used was ECOPS – an early version of Liver Assist.

"HOPE may therefore offer optimization of liver grafts before implantation by a simple and practical perfusion technique with a high impact on enlarging the donor pool." Dutkowski et al 2015

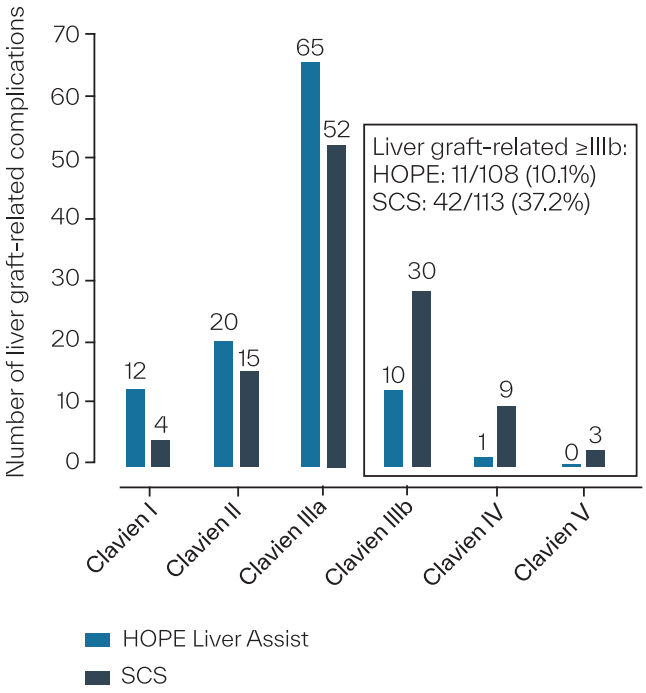
HOPE in DBD

A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation

Schlegel A, Mueller M, Muller X, Eden J, Panconesi R, von Felten S, Steigmiller K, Sousa Da Silva RX, de Rougemont O, Mabrut JY, Lesurtel M, Cerisuelo MC, Heaton N, Allard MA, Adam R, Monbaliu D, Jochmans I, Haring MPD, Porte RJ, Parente A, Muiesan P, Kron P, Attia M, Kollmann D, Berlakovich G, Rogiers X, Petterson K, Kranich AL, Amberg S, Müllhaupt B, Clavien PA and Dutkowski P.

J Hepatol / 2023 / doi: 10.1016/j.jhep.2022.12.030

In this multicenter randomized controlled trial, studying the effect of hypothermic oxygenated perfusion (HOPE) on post-transplant morbidity, livers donated after brain death (DBD) were randomly assigned (1:1 ratio) to either SCS alone (n=85), or SCS followed by 1-2 hours of hypothermic oxygenated perfusion (HOPE, n=85) prior to transplantation. The study shows that while the overall number of reported complications were similar between groups, recipients of HOPE-treated livers experienced a 41% reduction in severe (Clavien-Dindo≥IIIb) complications (6.6% vs 12.0%; RR: 0.59) overall, and a 74% reduction of liver graft-related severe complications (10.1% vs 37.2%; RR: 0.27). Also, no graft failures due to liver-related complications occurred in the HOPE group, while 6 liver-related graft failures occurred in the control group (p=0.004).



"As it is a simple and quick perfusion technique, it [HOPE] can be applied easily after organ transport during recipient hepatectomy" Schlegel et al 2023

Viability assessment

Normothermic machine perfusion (NMP) involves perfusing the liver through both the hepatic artery and portal vein with blood based oxygenated solution, medications, and nutrients at 37°C. This technique is intended to restore graft function following SCS, enabling the assessment of high-risk livers under nearly physiological conditions.

To help alleviate potential injuries caused by rapid rewarming following SCS, a controlled rewarming step, COR, may be applied. During this step, the liver is gradually rewarmed until it reaches 37°C.

The flexibility of Liver Assist allows operation of both NMP and COR. Below is a selection of studies conducted using the device along with their outcomes.

NMP

Observations on the ex situ perfusion of livers for transplantation.

Watson CJ, Kosmoliaptsis V, Pley C, Randle L, Fear C, Crick K, Gimson AE, Allison M, Upponi S, Brais R, Jochmans I, Butler AJ.

Am J Transplant / 2018 / doi: 10.1111/ajt.14687

In this observational study, the biochemistry and perfusion characteristics of 47 high-risk and initially rejected livers were studied using normothermic machine perfusion (NMP), resulting in 22 transplantations. By using readily available measurements that could be analyzed during NMP using the Liver Assist, the authors identified specific variables associated with successful transplantation. They found that by using a combination of transaminase release, glucose metabolism, lactate clearance, and maintenance of acid-base balance, the viability of a donor liver can be assessed prior to transplantation, and that evaluation of bile pH may offer a valuable insight into bile duct integrity and the risk of post-transplant ischemic cholangiopathy.

> “Liver viability during normothermic perfusion can be assessed using a combination of transaminase release, glucose metabolism, lactate clearance, and maintenance of acid-base balance.” Watson CJ, 2018

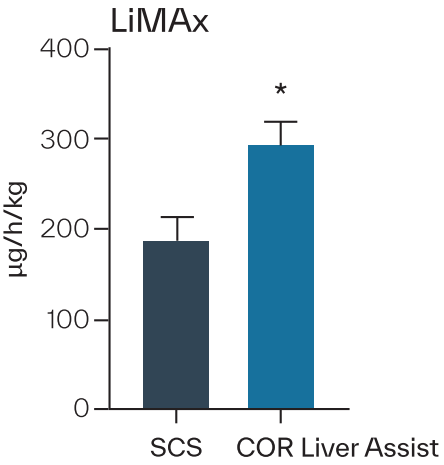
COR

Controlled oxygenated rewarming as novel end-ischemic therapy for cold stored liver grafts. A randomized controlled trial.

Minor T, von Horn C, Zlatev H, Saner F, Grawe M, Lüer B, Huessler EM, Kuklik N, Paul A.

Clin Transl Sci / 2022 / doi: 10.1111/cts.13409

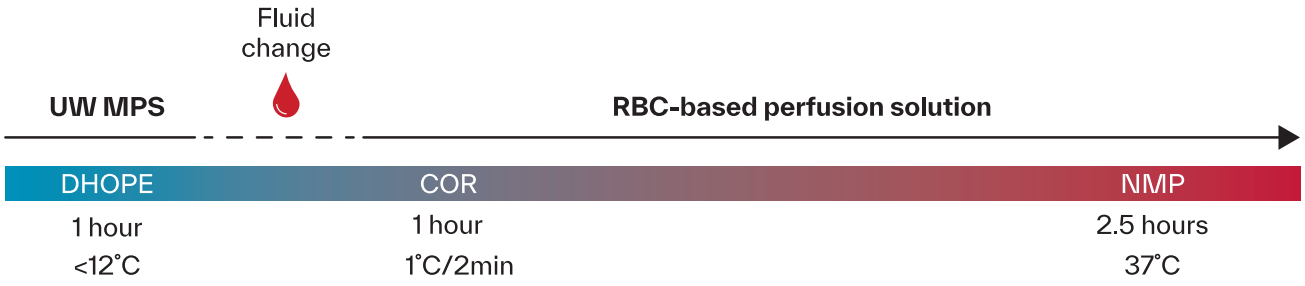
In a single center, randomized controlled trial, extended criteria livers donated after brain death (ECD-DBD) were assigned to either conventional static cold storage (SCS, n=20) or to SCS followed by 90 min controlled oxygenated rewarming (COR, n=20) using Liver Assist. Perfusion teperature was initially maintained at 8°C and then gradually increased to 20°C during 1 hour. Liver function test (LiMAx) revealed that recipients of COR-treated livers had significantly better early graft function as compared to traditionally preserved livers (p=0.006). Also, fewer severe (Clavien-Dindo ≥IIIb) complications were reported in the COR-group (8 vs 15). The authors conclude that rewarming/reperfusion injury of liver grafts can be safely and effectively mitigated by controlling of the rewarming kinetics prior to blood reperfusion.



Resuscitation and assessment

One of the more sophisticated protocols is DHOPE-COR-NMP which combines the best of two worlds in sequence. End-ischemic DHOPE has shown to protect against ischemia-reperfusion injury of the liver parenchyma and the bile ducts. While end-ischemic NMP allows for viability assessment, it doesn't seem to provide the same level of protection against ischemia-reperfusion injury. This sequential protocol where 1-hour DHOPE is followed by a perfusion fluid exchange and then 1 hour rewarming before NMP is applied for 2-3 hours, could help increase utilization of high-risk donor livers[1]. Due to the flexibility of Liver Assist, the device can operate the DHOPE-COR-NMP protocol.

1. van Leeuwen OB, Porte RJ. Ex situ machine preservation of donor livers for transplantation: HOPE for all? Br J Surg. 2021 Oct 23



DHOPE – COR - NMP

Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers

van Leeuwen OB, Bodewes SB, Lantinga VA, Haring MPD, Thorne AM, Brüggenwirth IMA, van den Berg AP, de Boer MT, de Kleine RHJ, Lascaris B, Nijsten MWN, Reyntjens KMEM, de Meijer VE, Porte RJ.

Am J Transplant / 2022 / doi: 10.1111/ajt.17022

In this prespective, observational study, the effect of sequential hypothermic and normothermic machine perfusion was assessed. Briefly, after SCS, 54 initially discarded, high-risk (median DRI: 2.84) donor livers were placed on the Liver Assist for 1 hour of 'resuscitation' using DHOPE. After DHOPE, the temperature of the perfusion solution* was gradually increased (+1°C/2min) until reaching 37°C, whereby hepatobiliary viability was assessed during the initial 2.5h of NMP. After DHOPE-NMP, 34 livers (63%) met the predefined viability criteria and were subsequently transplanted. With a 1-year patient and graft survival of 100% and 94%, respectively, no incidence of primary non function (PNF) or hepatic artery thrombosis (HAT) and only one patient (3%) developing non-anastomotic biliary strictures (NAS), this study demonstrates that seqential use of DHOPE and NMP using Liver Assist enables safe selection of initially rejected high-risk livers with excellent results, providing an effective tool to increase the number of suitable donor organs for transplantation.

> "/.../ [DHOPE-NMP] provides an effective tool to increase the number of suitable donor organs for transplantation."
>
> van Leeuwen et al 2022

* For details regarding exact protocol and perfusion solutions used, see van Leeuwen et al 2022.

HOPE + DHOPE-COR-NMP

Reducing cold ischemia time by donor liver “back-table” preparation under continuous oxygenated machine perfusion of the portal vein.

Lantinga V A, Buis CI, Porte RJ, de Meijer VE, van Leeuwen OB.

Clin Transplanti / 2022 / doi: 10.1111/ctr.14762

Back-table preparation of a donor liver prior to machine perfusion can be time-consuming and thus add to the overall cold ischemic time (CIT). In this prospective, observational cohort study, the authors assessed if CIT could be reduced by performing part of the back-table procedure under continuous, single-sided perfusion through the port vein (HOPE). A total of 10 initially declined livers were included in the study, and compared to 60 regular back-table DHOPE-NMP livers. With a utilization rate of 90%, the study shows that CIT can be reduced by at least 1 hour if a donor liver is prepared ‘on the pump’ (median CIT: 214 vs 279, p<0.01). The authors state that based on these results, they have now introduced back-table preparation under continuous HOPE as standard of care.

“/.../ performing the back-table preparation under continuous HOPE has been introduced as standard of care in our transplant center.” Lantinga et al 2022

List of Publications

Systematic reviews and meta-analyses

Boteon, Y.L., et al., Impact of machine perfusion of the liver on post-transplant biliary complications: A systematic review. World J Transplant, 2018. 8(6): p. 220-231.*

Ghinolfi, D., et al., Machine Perfusions in Liver Transplantation: The Evidence-Based Position Paper of the Italian Society of Organ and Tissue Transplantation. Liver Transpl, 2020. 26(10): p. 1298-1315.*

Jia, J., et al., A Systematic Review and Meta-Analysis of Machine Perfusion vs. Static Cold Storage of Liver Allografts on Liver Transplantation Outcomes: The Future Direction of Graft Preservation. Frontiers in Medicine, 2020. 7.*

Lai, Q., et al., Use of machine perfusion in livers showing steatosis prior to transplantation: a systematic review. Updates Surg, 2020. 72(3): p. 595-604.*

Liew, B., et al., Liver transplant outcomes after ex vivo machine perfusion: a meta-analysis. Br J Surg, 2021. 108(12): p. 1409-1416.*

Michelotto, J., et al., Ex vivo machine perfusion: current applications and future directions in liver transplantation. Langenbecks Arch Surg, 2021. 406(1): p. 39-54.*

Parente, A., et al., Machine perfusion techniques for liver transplantation - A meta-analysis of the first seven randomized controlled trials. J Hepatol, 2023.*

Ramírez-Del Val, A., et al., Does machine perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation? - A systematic review of the literature, meta-analysis and expert panel recommendations. Clin Transplant, 2022: p. e14638.*

Yang, X., et al., Effectiveness of machine perfusion in liver transplantation: A meta-analysis of randomized controlled trials. Journal of Liver Transplantation, 2023. 12: p. 100176.*

Zhang, Y., et al., Hypothermic machine perfusion reduces the incidences of early allograft dysfunction and biliary complications and improves 1-year graft survival after human liver transplantation: A meta-analysis. Medicine (Baltimore), 2019. 98(23): p. e16033.*

*Publication includes other devices in addition to the XVIVO Liver Assist

Brüggenwirth, I.M.A., et al., Prolonged preservation by hypothermic machine perfusion facilitates logistics in liver transplantation: a European observational cohort study. Am J Transplant, 2022.*

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Chen, M., et al., Application of ischaemia-free liver transplantation improves prognosis of patients with steatotic donor livers - a retrospective study. Transpl Int, 2021. 34(7): p. 1261-1270.

Chen, Z., et al., Transplantation of Extended Criteria Donor Livers Following Continuous Normothermic Machine Perfusion Without Recooling. Transplantation, 2022. 106(6): p. 1193-1200.

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, 2021. 274(5): p. 705-712.

De Carlis, R., et al., Hypothermic Machine Perfusion of Liver Grafts Can Safely Extend Cold Ischemia for Up to 20 Hours in Cases of Necessity. Transplantation, 2017. 101(7): p. e223-e224.*

De Carlis, R., et al., Successful donation after cardiac death liver transplants with prolonged warm ischemia time using normothermic regional perfusion. Liver Transpl, 2017. 23(2): p. 166-173.

De Carlis, R., et al., How to Preserve Liver Grafts From Circulatory Death With Long Warm Ischemia? A Retrospective Italian Cohort Study With Normothermic Regional Perfusion and Hypothermic Oxygenated Perfusion. Transplantation, 2021. 105(11): p. 2385-2396.

de Jong, I.E.M., et al., Restoration of Bile Duct Injury of Donor Livers During Ex Situ Normothermic Machine Perfusion. Transplantation, 2023.

de Vries, Y., et al., Pretransplant sequential hypo- and normothermic machine perfusion of suboptimal livers donated after circulatory death using a hemoglobin-based oxygen carrier perfusion solution. Am J Transplant, 2019. 19(4): p. 1202-1211.

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Ghinolfi, D., et al., Sequential Use of Normothermic Regional and Ex Situ Machine Perfusion in Donation After Circulatory Death Liver Transplant. Liver Transpl, 2021. 27(3): p. 385-402.

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Ghinolfi, D., et al., Liver transplantation with uncontrolled versus controlled DCD donors using normothermic regional perfusion and ex-situ machine perfusion. Liver Transpl, 2023.*

Ghinolfi, D., et al., Pilot, Open, Randomized, Prospective Trial for Normothermic Machine Perfusion Evaluation in Liver Transplantation From Older Donors. Liver Transpl, 2019. 25(3): p. 436-449.

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Guo, Z., et al., Abrogation of graft ischemia-reperfusion injury in ischemia-free liver transplantation. Clin Transl Med, 2022. 12(4): p. e546.

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Horné, F., et al., Hypothermic Oxygenated Machine Perfusion (HOPE) Prior to Liver Transplantation Mitigates Post-Reperfusion Syndrome and Perioperative Electrolyte Shifts. J Clin Med, 2022. 11(24).

Hoyer, D.P., et al., Long-term Outcomes After Controlled Oxygenated Rewarming of Human Livers Before Transplantation. Transplant Direct, 2020. 6(4): p. e542.

Lantinga, V.A., et al., Reducing cold ischemia time by donor liver "back-table" preparation under continuous oxygenated machine perfusion of the portal vein. Clin Transplant, 2022. 36(8): p. e14762. See Page 11.

Lau, N.S., et al., Long-term normothermic perfusion of human livers for longer than 12 days. Artif Organs, 2022. 46(12): p. 2504-2510.

Maroni, L., et al., Normothermic with or without hypothermic oxygenated perfusion for DCD before liver transplantation: European multicentric experience. Clin Transplant, 2021. 35(11): p. e14448.

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*Publication includes other devices in addition to the XVIVO Liver Assist

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