Editorial Commentary

Continuous normothermic machine perfusion of donor livers in the United States: the challenging road from the trial-world into the real-world

Otto B. van Leeuwen[1]^, Philipp Dutkowski[2]^, Diethard Monbaliu[3]^, Vincent E. de Meijer[1]^

[1]Department of Surgery, UMCG Comprehensive Transplant Center, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands; [2]Department of Visceral Surgery, University Hospital Basel, Basel, Switzerland; [3]Department of Abdominal Transplant Surgery, University Hospitals Leuven, Leuven, Belgium

Correspondence to: Vincent E. de Meijer, MD, PhD. Department of Surgery, UMCG Comprehensive Transplant Center, University of Groningen and University Medical Center Groningen, PO Box 30.001, 9700RB Groningen, The Netherlands. Email: v.e.de.meijer@umcg.nl.

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Over the past decade, various liver machine perfusion techniques have been clinically implemented worldwide (*Figure 1*). Currently, there are two main *ex situ* liver perfusion techniques: hypothermic oxygenated perfusion and normothermic oxygenated perfusion. In the United States (U.S.), hypothermic machine perfusion was initially pioneered by James Guerrera. Meanwhile, clinical practice has largely shifted towards normothermic machine perfusion (NMP) (1). This shift is due to U.S. Food and Drug Administration (FDA) approval of normothermic devices and recent groundbreaking randomized controlled trials (RCTs) (*Table 1*). Recently, Chapman *et al.* published another multicenter RCT comparing static cold storage (SCS) with continuous NMP (cNMP) for donor liver preservation (NCT02775162) (2). Notably, in all but one NMP trial, cNMP was utilized from the donor hospital, during organ transport, through to the recipient hospital. This contrasts with 'back to base' or 'end-ischemic' NMP (eNMP), where NMP is initiated at the recipient hospital after initial SCS preservation.

In the current study, 383 donor livers were randomized across 14 U.S. liver transplant centers to either cNMP (n=192) or SCS (n=191) between October 2016 and February 2020, with 266 livers (69%) ultimately transplanted. The primary endpoint was early allograft dysfunction (EAD) as defined by the Olthoff criteria (3), with no significant difference found between cNMP (20.6%) and SCS (23.7%). The authors suggest that the inclusion of lower-risk donors (median donor risk index of 1.6) may have influenced the results. Accordingly, a *post-hoc* analysis revealed a lower EAD rate for higher-risk donor livers in the cNMP group. Secondary outcomes, including 1-year patient survival (92.5% *vs.* 96.6%) and graft survival (97.0% *vs.* 97.7%), however, were similar between the groups. The incidence of serious adverse events was also comparable (95 in cNMP *vs.* 93 in SCS after 1 year), though 14 device malfunctions were reported, none leading to graft loss.

While this study adds valuable data to the rapidly evolving field of liver machine perfusion, several aspects merit further consideration. It is somewhat surprising that the current trial, unlike the European COPE Trial, despite having a similar design, size, and endpoints, reports

^ ORCID: Otto B. van Leeuwen, 0000-0002-8600-0479; Philipp Dutkowski, 0000-0002-3016-604X; Diethard Monbaliu, 0000-0002-0506-1609; Vincent E. de Meijer, 0000-0002-7900-5917.

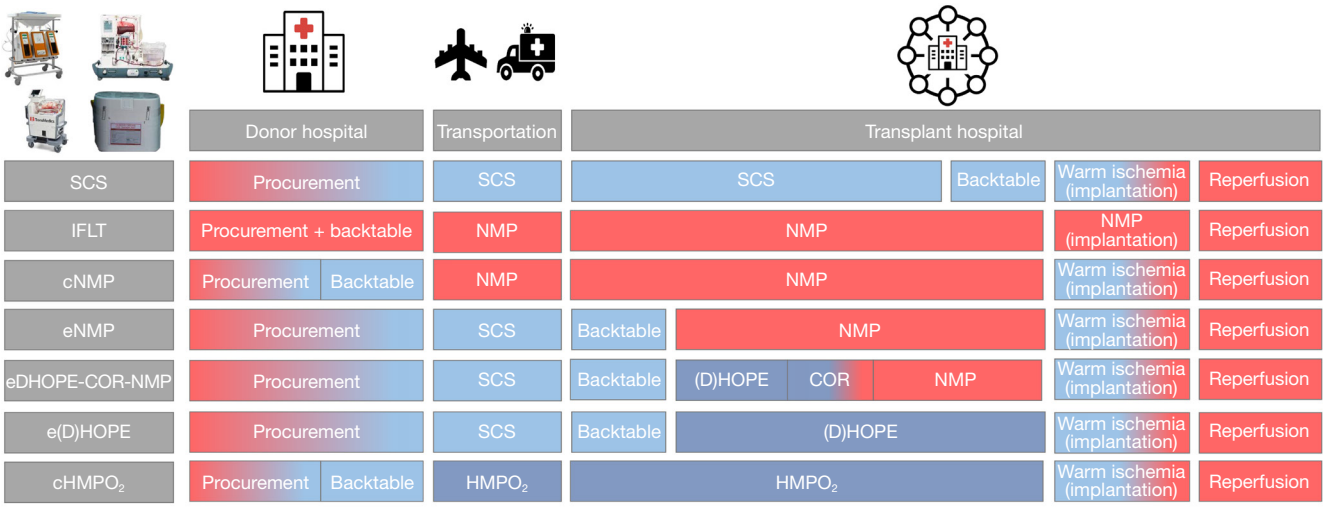

Figure 1 Overview of various machine perfusion techniques currently used in clinical practice. cNMP, continuous normothermic machine perfusion; e(D)HOPE, end-ischemic (dual) hypothermic oxygenated machine perfusion; eDHOPE-COR-NMP, sequential end-ischemic dual hypothermic oxygenated machine perfusion-controlled oxygenated rewarming-normothermic machine perfusion; NMP, normothermic machine perfusion; eNMP, end-ischemic normothermic machine perfusion; $cHMPO_2$, continuous hypothermic machine perfusion with pre-oxygenation; IFLT, ischemia-free liver transplantation; SCS, static cold storage.

different outcomes (*Table 1*) (4). The choice of EAD as the primary endpoint, though accepted at the time the study was conducted, raises concerns today, as acknowledged by the authors. EAD, a composite endpoint primarily dependent on immediate and peak postoperative transaminases, was developed during the SCS era and has not been validated in NMP cohorts (5). Although the study was initiated in 2016, the 2021 International Liver Transplantation Society Consensus Guidelines now recommend against using EAD as a clinically relevant endpoint for RCTs (6).

Additionally, the study's secondary endpoints, including 1-year patient and graft survival, were comparable between groups, with low event rates observed in both. Using graft or patient survival as an endpoint in RCTs typically requires a very large study cohort due to the already high survival rates in the U.S. population studied. Future NMP trials should focus on higher-risk donors and recipients to better detect potential differences in survival outcomes.

Since the trial was designed to assess superiority of cNMP over SCS in reducing EAD, randomization should theoretically have been performed after final organ acceptance (i.e., following graft assessment by the transplant surgeon). Randomization before final acceptance of the graft may introduce selection bias. Although this approach is logistically challenging for cNMP, where perfusion begins at the donor hospital, it is reassuring that an equal number of livers were excluded from each study arm (56/192 for cNMP versus 60/191 for SCS). However, this finding is somewhat counterintuitive, as cNMP could theoretically improve organ utilization by allowing viability assessment during perfusion. Notably, and unlike the European COPE Trial, which reported a 20% increase in utilization after cNMP, this study did not demonstrate such an advantage (4). Only 3 out of 56 excluded livers randomized to cNMP were not utilized after transport. The additional role of viability assessment during cNMP in the trial was therefore marginal, even though the 'eye of the surgeon' is notoriously poor at predicting graft viability. In fact, 40 (21%) and 50 (25%) livers randomized to cNMP and SCS, respectively, were deemed unsuitable for retrieval and were never procured. Including these high-risk livers in future NMP trials could offer a more accurate assessment of the true impact of viability assessment on organ utilization.

cNMP, unlike 'back-to-base' eNMP, requires significant nationwide logistical adjustments. Donor surgeons must be proficient in arterial reconstruction and perfusion device management. The introduction of the TransMedics OCS® perfusion service in the U.S. addresses these challenges by providing the device, perfusion solution, disposables, and transport, along with ensuring donor surgeons who are experienced in liver procurement, vascular reconstruction, and cannulation. However, these services, offered in various

Table 1 Overview of the randomized controlled trials performed on normothermic machine perfusion of donor livers

Study, year, registration No.	Perfusion type	No. of centers	Countries	Study period	Donor type: No. of inclusions	No. of transplantations	Device	Main endpoints
Nasralla *et al.*, 2018, ISRCTN 39731134	cNMP	6	United Kingdom, Belgium, Spain, Germany	06/2014–03/2016	DBD: 167; DCD: 55	cNMP group: 121; SCS group: 101	Metra, Organox	Peak AST reduction 49% (P<0.001) EAD: after cNMP: 10.1%; after SCS: 29.9%; P<0.01
Ghinolfi *et al.*, 2019, NCT02940600	eNMP	1	Italy	10/2016–04/2018	ECD-DBD: 20	eNMP group: 10; SCS group: 10	LiverAssist, XVIVO	Graft survival 6 months: after eNMP: 90%; after SCS: 90%; P=1.00
Markmann *et al.*, 2022, NCT02522871	cNMP	20	Unites States	01/2016–10/2019	DBD: 254; DCD: 39	cNMP group: 151; SCS group: 142	Organ Care System Liver, TransMedics	EAD: after cNMP: 18%; after SCS: 31%; P=0.01
Chapman *et al.*, 2023, NCT02775162	cNMP	14	Unites States	10/2016–02/2020	DBD: 128; DCD: 38	cNMP group: 136; SCS group: 130	Metra, Organox	EAD: after cNMP: 20.6%; after SCS: 23.7%; P=0.275

cNMP, continuous normothermic machine perfusion; eNMP, end-ischemic normothermic machine perfusion; DBD, donation after brain death; DCD, donation after circulatory death; ECD, extended criteria donor; SCS, static cold storage; AST, aspartate aminotransferase; EAD, early allograft dysfunction.

packages, further contribute to the already high medical costs, raising questions about the cost-effectiveness of cNMP. Although health economic implications were part of the study protocol, the current publication only reports on intensive care and hospital length of stay. In contrast, following the European COPE Trial, there has been a shift away from cNMP in the United Kingdom, with subsequent studies showing little difference in efficacy between cNMP and 'back-to-base' eNMP. Authors rightfully acknowledge this, and it will be interesting to see whether cNMP will withstand the test of time in the U.S., unlike in the United Kingdom.

These discrepancies between RCT settings and real-world clinical practice are crucial. RCTs often involve selective inclusion criteria, resulting in more favorable donor and recipient profiles than those typically seen in clinical practice. For instance, only 1% of participants in the current trial underwent retransplantation, and combined transplants, pediatric transplants, and patients with acute liver failure were excluded per protocol. To truly evaluate the benefiots of NMP in high-risk donor-recipient combinations, moving from IDEAL (Idea, Development, Exploration, Assessment and Long-term follow-up) stage 3 RCTs to IDEAL stage 4 real-world evidence is eagerly awaited (7).

The necessity of conducting this expensive and logistically complex multicenter RCT in the U.S., despite the existence of similar European RCT data funded by the same medical device company (OrganOx, Inc.), is somewhat questionable. The primary rationale appears to be regulatory, as noted in the publication (page e914): "*The study protocol was approved by the FDA to support a class III medical device PMA review*." The FDA's requirement for a new RCT in the U.S. population before allowing class III medical devices for market entry, despite available high-quality European data, raises concerns about resource allocation and imposes an unnecessary burden on clinicians, investigators, and device companies. The study report, published in November 2023, came nearly three years after the last patient inclusion (February 2020), while the FDA granted premarket approval of the OrganOx metra system in December 2021 (8). Given that the trial failed to demonstrate superiority of cNMP over SCS or improve organ utilization, the necessity of conducting this trial solely for FDA approval remains debatable.

When comparing primary outcomes across published RCTs in the field of liver NMP, which have mainly focused on short-term endpoints (*Table 1*), there is an emerging need to shift research towards more clinically relevant, long-term outcomes (2,6,9,10). Long-term, multi-center, real-world data on outcomes after cNMP and other NMP methods are eagerly anticipated. The development of an international liver machine perfusion registry, currently being pursued by the European Society of Organ Transplantation and the

European Liver Transplant Registry, could offer invaluable benefits to liver transplant recipients. However, this effort will require significant global collaboration.

In conclusion, the authors deserve commendation for this study and significant contributions to the field. As the landscape of liver preservation continues to evolve, it will be exciting to observe further advancements on both sides of the Atlantic in the coming years. Only time will tell whether cNMP will become a lasting practice in the U.S. and when the field will embrace the benefits of cold perfusion (11-15), eventually "Warming up to Cold Perfusion" in the U.S. as well (16).

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Footnote

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