Editorial Commentary

Does ischemia-free machine perfusion lead to early allograft dysfunction (EAD) free liver transplantation?

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Normothermic machine perfusion (NMP) is an innovative technique used in solid organ transplantation that involves perfusing the organ with specialized solution or leukocyte depleted red blood cells at near-normal body temperature aiming at mimicking physiological conditions, and providing optimal conditions for organ preservation which leads to reduced risk of ischemia reperfusion injury (IRI) when compared to the standard static cold storage (SCS) (1). One of the key advantages of NMP is its ability to assess the quality of the organ in real-time and assessment of the organ performance prior to transplantation. By continuously monitoring parameters such as blood flow, oxygen consumption, and lactate production, clinicians can evaluate the viability of the organ and make more informed decisions about its suitability for transplantation. This real-time assessment can help reduce the risk of transplanting organs that may not function optimally or have a higher likelihood of complications post-transplant. Additionally, NMP may expand the pool of donor organs by allowing for the use of organs that may have been deemed marginal or unsuitable for transplantation using traditional methods (1,2). There are currently at least 4 NMP systems that have been in use in liver transplantation (LT) around the world and studies have demonstrated almost 50% reduction in liver discard rate and IRI with NMP compared to SCS (3,4). Overall, NMP represents a significant advancement in the field of liver and other solid organ transplantation, offering improved preservation, assessment, and utilization of donor organs.

In the *Journal of Hepatology*, Guo and colleagues report on the results of 65 adult LT recipients who received a primary donation after brain death (DBD) LT and who were randomized to either conventional SCS or to ischemia-free LT (IFLT) using the NMP Liver Assist device (5). Although NMP has increasingly been adopted by transplant centers worldwide as a method for organ preservation and assessment, the authors of the current study have taken NMP one step further with the development of IFLT.

The primary outcome measure of the study was early allograft dysfunction (EAD) using the Olthoff criteria (6). EAD has previously been validated as a predictor of inferior patient and graft survival, prolonged hospitalization and higher rates of biliary complications post-LT (7). EAD has also been associated with higher rates of post-transplant acute kidney injury (AKI) and end-stage renal disease (ESRD) in those with normal kidney function at time of LT and failure of renal recovery in those who had pre-LT renal dysfunction and later on developed EAD post-LT (8,9). A previous study demonstrated comparable patient and graft survivals between LT recipients with normal

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kidney function at LT who later developed EAD and those with pre-LT renal dysfunction who did not have EAD which means that EAD modifies the known negative impact of pre-LT renal dysfunction on post-LT outcomes (10). While multiple donor, recipient and peri-operative factors are associated with EAD, prolonged cold ischemia time, donation after circulatory death (DCD) LT, donor steatosis and intraoperative events are the major determinants of post-LT development. In the present randomised controlled trial (RCT), IFLT was associated with 18% absolute risk rection [95% confidence interval (CI): −30% to −1%, P=0.004] in EAD rates. In addition, post-reperfusion syndrome (PRS), unstable hemodynamics, median lactate level 1 h after reperfusion and median intensive care unit (ICU) stay were all lower in the IFLT group.

The rate of non-anastomotic biliary stricture at 1 year from LT was unusually high in the SCS group at 36%, which is almost double the published rate of non-anastomotic biliary stricture in DBD LT (11). This is much higher than would be expected from a cohort of DBD donors with a mean donor risk index (DRI) of 1.4. The authors do not specify what criteria were used to define a non-anastomotic stricture and it is possible that lack of a standard definition could account for the high rates. Previous classification systems for non-anastomotic biliary strictures have been described in the DCD setting and likely should be used for trials in the future to ensure consistency (12).

Although the authors demonstrated that the overall rates of multiple donor and recipient related factors that are known to be associated with EAD were comparable between groups, peri-operative events including operative time, blood transfusion requirement and rates of return to operating room (OR) were not included in the analysis and therefore it is unknown how these factors would have impacted the results.

In the present study all the livers were procured and transplanted at the same center. In most countries including the United States, the donor and the recipient are not co-located to the same hospital. The lack of co-location represents a major barrier to more broadspread adoption of the IFLT technique. Centralization of donor recoveries through the Donor Care Unit (DCU) model has been advocated by the National Academies of Sciences Engineering and Medicine (NASEM), and it is possible that co-location may become more common in the future, particularly given the increased utilization of advance perfusion techniques in organ procurement (13,14). Given the technically and logistically demands of IFLT, it is likely that co-location of the donor and the recipient would be a requirement which might limit the generalized use of this NMP technique on a large scale.

As we continue to adopt machine perfusion techniques, the issue surrounding costs and resource utilization will continue to be raised. NMP will increase the acquisition costs of a liver and therefore it is important to view any increased "costs" through the lens of a value-based system. The value with NMP will be its ability to reduce post-LT complications such as EAD, AKI and biliary complications, all of which increase the expense of a LT. NMP has also been shown to increase organ utilization, particularly when dealing with "marginal" liver grafts (15). Transplant centers will ultimately have to demonstrate that they are getting patients transplanted faster and with better outcomes. The choice of young donors with lower DRI such as in the present study likely do not represent the livers that would show the greatest benefit from an ischemia free approach. These livers typically have excellent outcomes with conventional cold storage. It would likely be easier to justify the increased cost and resource consumption of IFLT in the setting of more "marginal" liver grafts. IFLT is also more technically and logistically challenging than standard recovery and placement of the liver on NMP after a short period of cold ischemia, as is more commonly done. Given the exceptional results with NMP alone, it is possible that there may be limited incremental benefit to IFLT over NMP except in the most "marginal" donor liver cases (4).

In conclusion, the authors should be congratulated on this study and all the work they have done to develop IFLT. Continued research and refinement of NMP techniques hold the potential to further enhance transplant outcomes and address the ongoing challenges of organ shortage in transplantation. Perhaps ischemia-free machine perfusion will one day lead to EAD-free LT.

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Footnote

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References

1. López-Martínez S, Simón C, Santamaria X. Normothermic Machine Perfusion Systems: Where Do We Go From Here? Transplantation 2024;108:22-44.
2. Lindemann J, Yu J, Doyle MM. Normothermic machine perfusion for liver transplantation: current state and future directions. Curr Opin Organ Transplant 2024;29:186-94.
3. Nasralla D, Coussios CC, Mergental H, et al. A randomized trial of normothermic preservation in liver transplantation. Nature 2018;557:50-6.
4. Markmann JF, Vagefi PA, MacConmara MP. Normothermic Machine Perfusion Increases Donor Liver Use. JAMA Surg 2022;157:742-3.
5. Guo Z, Zhao Q, Jia Z, et al. A randomized-controlled trial of ischemia-free liver transplantation for end-stage liver disease. J Hepatol 2023;79:394-402.
6. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943-9.
7. Lee DD, Croome KP, Shalev JA, et al. Early allograft dysfunction after liver transplantation: an intermediate outcome measure for targeted improvements. Ann Hepatol 2016;15:53-60.
8. Wadei HM, Lee DD, Croome KP, et al. Early Allograft Dysfunction Is Associated With Higher Risk of Renal Nonrecovery After Liver Transplantation. Transplant Direct 2018;4:e352.
9. Wadei HM, Lee DD, Croome KP, et al. Early Allograft Dysfunction After Liver Transplantation Is Associated With Short- and Long-Term Kidney Function Impairment. Am J Transplant 2016;16:850-9.
10. Wadei HM, Keaveny AP, Taner CB, et al. Post-Liver Transplant Early Allograft Dysfunction Modifies the Effect of Pre-Liver Transplant Renal Dysfunction on Post-Liver Transplant Survival. Liver Transpl 2021;27:1291-301.
11. Meier RPH, Kelly Y, Braun H, et al. Comparison of Biliary Complications Rates After Brain Death, Donation After Circulatory Death, and Living-Donor Liver Transplantation: A Single-Center Cohort Study. Transpl Int 2022;35:10855.
12. Croome KP, Mathur AK, Aqel B, et al. Classification of Distinct Patterns of Ischemic Cholangiopathy Following DCD Liver Transplantation: Distinct Clinical Courses and Long-term Outcomes From a Multicenter Cohort. Transplantation 2022;106:1206-14.
13. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on Health Sciences Policy; Committee on A Fairer and More Equitable, Cost-Effective, and Transparent System of Donor Organ Procurement, Allocation, and Distribution, Hackmann M, English RA, Kizer KW, eds. Realizing the Promise of Equity in the Organ Transplantation System. Washington (DC): National Academies Press (US); February 25, 2022.
14. Croome KP. Should advanced perfusion be the standard of care for donation after circulatory death liver transplant? Am J Transplant 2024;24:1127-31.
15. van Leeuwen OB, de Vries Y, Fujiyoshi M, 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 2019;270:906-14.

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