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COMMENTARY

# Ischemia-free liver transplantation. Is this the right answer to overpass organ shortage and post-liver transplant complications?

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Liver transplantation (LT) results dramatically improved over the past years; nevertheless, the number of patients awaiting LT far exceeds the available grafts and waiting list mortality remains high. The use of so-called "extended criteria" donors (ECD) is proposed to improve the availability of donor allografts and reduce waiting list mortality [1]. Most ECD livers share the common denominator of being more vulnerable to ischemia-reperfusion injury (IRI) in comparison to standard grafts, hence carrying an increased risk of post-LT early allograft dysfunction (EAD), primary non-function and ischemic cholangiopathy [1, 2].

In the last years, ex-situ machine perfusion (MP) was introduced in clinical practice to minimize the duration of static cold storage (SCS), protect organs from the detrimental effects of IRI, facilitate repair/regeneration of ECD grafts, expand donor pool, and improve graft survival after LT [1]. Beneficial mechanisms of MP have been demonstrated for both hypothermic and normothermic machine perfusion (NMP) in preclinical and clinical studies [1, 2, 3, 4].

In this non-randomized study [5], 38 liver grafts were transplanted using an ischemia-free liver transplantation (IFLT) technique and compared to 130 conventional LT. IFLT is a surgical procedure enabling continuous oxygenated blood supply to the liver of brain-dead donors during procurement, preservation, and implantation using NMP. IFLT group showed a reduced EAD rate (5•3 vs 50•0%, p<0•001), decreased AST, ALT and bilirubin peak within 7 days (365 vs 1445 IU/L, p<0•001; 155 vs 694 IU/L, p<0•001; 2•34 vs 5•10 mg/dl, p<0•001), reduced ICU stay (1•48 vs 1•81 days, p=0•006), but comparable biliary complications rate (10•5 vs 18•5%, p=0•326) and one-year graft and patient survival (89•5 vs 81•5%, p=0•326; 92•1 vs 82•3%, p=0•142). These results were confirmed in a subgroup analysis considering ECD donor livers as defined by the presence of at least one of the following: donor age>60 years, serum sodium level>165 mmol/L, biopsy-proven macro-vesicular steatosis>30%, donor AST/ALT>1,000 IU/L, total bilirubin>3 mg/dL, cold ischemia time≥12 hours.

This work has the potential to change clinical practice and the paradigms of donor selection. This first-in-human clinical trial is the proof-of-concept that avoiding IRI is safe and technically feasible. Authors successfully combined surgical skills with the newest technological tools. Nevertheless, the study shows limitations that restrict the relevance of the reported findings: questionable endpoints selection, inappropriate study population, and lack of randomization.

Even if several clinical trials evaluating the efficacy of machine perfusion (MP) in LT used EAD as primary end-point [6], Olthoff's criteria [7] are often used for their simplicity rather than sensitivity, as other scores proved to be more accurate in predicting post-LT graft loss [8, 9]. EAD, as defined by Olthoff, is highly dependent on transaminases levels. Still their correlation with a poor outcome has never been confirmed in the context of MP technology [10]. Primary endpoint should better be conventional "hard" endpoints such as graft loss, patient death or clinically relevant complications (e.g., ischemic cholangiopathy) until a validated biomarker able to predict clinical outcomes is identified [6].

The choice of considering young donors with low donor risk index, might have concealed the clinical relevance of IFLT. Although all grafts may benefit from the absence of IRI, IFLT should be tested in pre-defined ECD such as DCD, older or severely steatotic grafts, to magnify its potential efficacy. Lastly, as there is no accepted definition of ECD and the decision to use or not a graft is often based on a subjective evaluation rather than objective viability criteria,

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randomization is crucial because it can minimize the biases commonly involved in liver graft selection and allocation [10].

Moreover, even if IFLT constantly provides blood flows and oxygenation, the in-situ extensive hilar dissection and cannulation and the complex manipulation have the potential to cause vasospasm and tissue hypoperfusion. Perfusate oxygenation and metabolic parameters, vascular flows and pressures should be constantly monitored during the whole process to guarantee an ischemia-free and not only a reperfusion-free procedure.

SCS remains the standard, however, IFLT has the potential to become the new standard for organ procurement and preservation only if the risen costs, logistic complexity and extra time and personnel requirements are objectively justified by increased available grafts or decreased post-LT complications.

The evaluation of IFLT potentiality cannot be restricted to clinical practice only, as it might be a terrific boost for scientific research, promoting a deep integration among basic science, health care researchers and industry. The adoption of IFLT in everyday clinical practice requires a further improvement of NMP technology: simplification of machine setup, implementation of an automated system for perfusate biochemical parameters evaluation and correction, perfusion extension avoiding the accumulation of catabolic products, improvement of safety during transportation, as the transplant community often showed to prefer a reassuring simplification rather than a complex optimization (e.g., back-to-base approach). Without the detrimental effect of IRI, graft ex-situ perfusion will require a redefinition of viability parameters and will become an optimal platform for therapeutics delivery, thus maximizing patient safety and promoting a further improvement of organ quality.

IFLT is a promising approach to mitigate the problem of organ shortage and post-LT complications. Its future relies on the capacity of the transplant community to show “hard” clinical advantages, integrate the competences of all stakeholders to simplify and optimize MP technology and ultimately, provide a positive cost-effectiveness analysis.

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DG: designed and wrote the commentary
WJ: designed and critically reviewed the commentary
PNM: designed and critically reviewed the commentary

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## Declaration of Competing Interest

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