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French Editorial from the ACHBPT

Comment on "*Hypothermic machine perfusion in liver transplantation—a randomized trial*"

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We read with great interest the article by van Rijn *et al.* published in March 2021, in *The New England Journal of Medicine* (1). In this multicenter, randomized controlled trial, the authors investigated the efficacy of dual hypothermic oxygenated perfusion (D-HOPE) versus static cold storage (SCS) in grafts from donors after cardiac death (DCD) to decrease the rate of non-anastomotic biliary stenosis (NAS) within the first 6 post-transplant months. One hundred and seventy-eight patients were included and the outcome of 78 D-HOPE-grafts were compared with 78 SCS-grafts. The rates of NAS were 6% and 18% in the D-HOPE group and the SCS group, respectively (HR =0.36; 95% CI: 0.14–0.94; P=0.03). The incidence of reperfusion syndrome and early allograft dysfunction (EAD) defined according to the Olthoff criteria, were secondary endpoints and were significantly lower in the D-HOPE group. The authors should be commended for conducting the first randomized controlled trial evaluating D-HOPE and we found it relevant that the authors directly investigated DCD grafts since they represent an increasing source of donors.

There is no doubt that the oxygenated preservation technique will play an increasing role in preserving grafts retrieved from extended criteria donors. Based on this trial, D-HOPE has taken a place in the range of techniques for the preservation of grafts with extended criteria. Indeed, Guarrera *et al.* reported that oxygenated perfusion through the portal vein reduced hepatocyte suffering in expanded criteria grafts (2). More recently, Nasralla *et al.* (3) showed the benefit of normothermic oxygen perfusion (NOPE) in the preservation of liver grafts and in this study, a subgroup analysis showed the benefit of NOPE in preserving ECD grafts.

However, in this outstanding publication, two ideas should be discussed regarding the primary endpoint and the procurement procedure in DCD. To our knowledge, this is the first study to define NAS with precision. Indeed, post-transplant biliary complications can have multiple causes but NAS is directly linked to prolonged ischemia of the bile ducts and should not be related to anastomotic stenosis due to technical reasons or hepatic artery stenosis or thrombosis. In this trial, the need to meet five clinical, radiological and biological criteria avoids the risk of overestimating the rate of NAS. We found, however, that the rate of NAS that enabled calculation of the H1 hypothesis (29% in CSC livers) was overestimated. As a matter of fact, the final rate of NAS in the SCS arm was only 18%.

In France, the rate of NAS in DCD is only 6% (4)! This low percentage is related to the conditions in which the DCD are managed. As shown in *Figure 1*, 5 minutes after asystole, the femoral artery and vein are cannulated and extracorporeal membrane oxygenation (ECMO) is initiated. This *in situ* normothermic regional perfusion (NRP) restores blood supply to the abdominal organs after death using extracorporeal circulation for a limited period before organ recovery. More specifically, it participates in restoring physiologic oxygenation of the biliary tree. Using this technique, Watson *et al.* (5) recently reported the results

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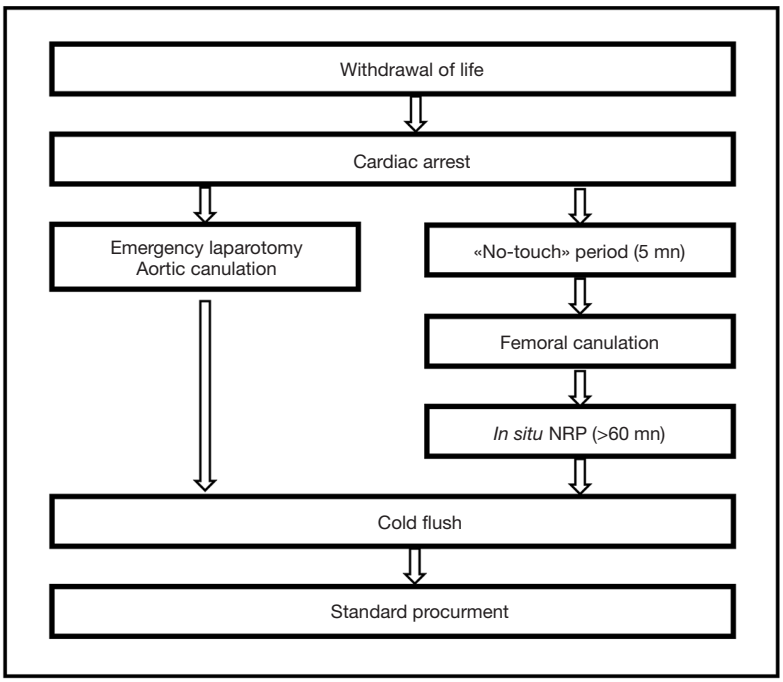

Figure 1 Diagram of the procedural steps in the procurement of DCD donors. The left side shows the procedure performed in the trial and the right side shows the procedure performed in France. DCD, donors after cardiac death; NRP, normothermic regional perfusion.

of a series 43 livers retrieved from DCD + NRP. None of the recovered livers developed cholangiopathy compared with a 27% total incidence of cholangiopathy in non-NRP livers (P<0.0001). Moreover, patient and graft survival was improved in the DCD-NRP group. In 2020, Muller *et al.* (4) performed an international multicenter retrospective study comparing the outcome of livers retrieved from DCD without NRP and preserved with HOPE (portal only, DCD + HOPE) with livers retrieved from DCD + NRP + SCS. The rate of NAS in the DCD + HOPE group was 8.6%, i.e., close to the 6% reported by van Rijn *et al.* whereas it was 4% in the DCD + NRP + SCS group (1).

This trial is a great contribution to countries that apply the super rapid procurement technique to DCD. Indeed, this dynamic preservation method is expected to close the gap with transplantation from brain-dead donors and increase the pool of functional grafts. However, even if the authors rightly point out the simplicity and safety of D-HOPE as an argument for its widespread use, we believe that HOPE or even NOPE could provide equivalent results.

In conclusion, this work is a major milestone in the quest for optimal liver graft preservation. Given that it is a multicenter study of good methodological quality, its results should be considered reliable. Several other trials are expected to be completed in the near future to reinforce the value of organ perfusion in transplantation. A next step could be a prospective randomized three-arm study comparing HOPE, D-HOPE and NOPE as methods to reduce the risks of NAS in DCD.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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