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Published in:
JHEP reports : innovation in hepatology

DOI:
[10.1016/j.jhepr.2020.100194](https://doi.org/10.1016/j.jhepr.2020.100194)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Brüggenwirth, I. M. A., van Leeuwen, O. B., Müller, M., Dutkowski, P., Monbaliu, D., Martins, P. N., Porte, R. J., & de Meijer, V. E. (2021). The importance of adequate oxygenation during hypothermic machine perfusion. *JHEP reports : innovation in hepatology*, 3(1), [100194].
<https://doi.org/10.1016/j.jhepr.2020.100194>

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The importance of adequate oxygenation during hypothermic machine perfusion



To the Editor:

We read with interest the recent article by Alix *et al.* describing the effect of M101 (a marine worm hemoglobin) added to the static cold storage (SCS) solution for liver preservation.¹ In this study, the authors compared SCS+M101 to SCS alone and to hypothermic oxygenated machine perfusion (HOPE). The authors claim that adding the oxygen carrier M101 to SCS could be an alternative to HOPE for liver graft preservation. Although the authors should be commended for investigating an innovative approach to prevent ATP depletion during graft preservation, there are several important methodological issues to address.

First, we disagree with the author's definition of HOPE and believe that this control group is flawed. The authors state that, during HOPE, a continuous oxygen flow was delivered to the surface of the preservation solution. However, this approach is substantially different from the previously described (and currently clinically used) method of HOPE, where a membrane oxygenator in the machine perfusion circuit allows for active oxygenation of the preservation solution to achieve partial oxygen pressures (pO₂) of (at least) 70 kPa (500 mmHg).^{2,3} Delivering oxygen only to the surface of the preservation solution is unlikely to achieve an adequate pO₂. Unfortunately, there is no information on the oxygen content in the perfusate.

Secondly, the different oxygenation strategy may account for the decreasing ATP levels during machine perfusion, which is a very unlikely phenomenon during HOPE if the preservation solution is adequately oxygenated. In fact, several groups have previously shown increased ATP levels at the end of both single and dual HOPE, in experimental and clinical studies (Table 1).^{2,4-10} The observed decrease in ATP levels during machine perfusion

supports our hypothesis that the HOPE methodology applied by the authors does not achieve adequate perfusate pO₂ levels. Adequate oxygenation under hypothermic conditions remains the key strategy to decrease reperfusion injury, as mitochondria are reprogrammed by cold oxygenation, leading to metabolism of accumulated succinate and NADH with significant increases in ATP levels within just 1–2 hours of HOPE.¹¹

Third, in the results presented by the authors, mitochondrial activity and post-transplantation injury markers are similar between livers preserved with SCS supplemented with M101 vs. HOPE. However, we postulate that by using HOPE with an adequate pO₂ of the preservation solution, mitochondrial function would have been substantially improved. Notably, high (100%) oxygen delivery best preserves functional and structural liver integrity compared to low (20%) oxygen delivery.¹² In addition, machine perfusion in the absence of oxygen is not able to prevent reperfusion injury and triggers hepatocyte death.^{12,13}

Fourth, the effect of M101 supplementation in SCS solutions should be further tested in experimental models, such as animal models or preclinical research models using severely injured grafts, *e.g.* in livers exposed to extended donor warm ischemia, or in severely steatotic livers.

Fifth, we believe there are several other benefits of HOPE, such as the ability to assess liver viability or extend preservation time, which are currently unlikely to be achieved by SCS.

Taken together, we believe that it is currently overstated that M101 supplemented to the SCS solution could be an alternative to HOPE for liver graft preservation. Based on the results presented, supplementation of M101 to the SCS solution seems better than SCS alone, but this requires more research. Additionally, this method still does not achieve the results that can be obtained with HOPE.

Table 1. Studies using HOPE for donor liver preservation with measurement of ATP.

Reference	Protocol	Fold ATP increase
Brüggenwirth <i>et al.</i> (2020) ⁵	20-hour dual HOPE of discarded human livers	5
Van Rijn <i>et al.</i> (2017) ²	2-hour dual HOPE of human livers	11
Westerkamp <i>et al.</i> (2016) ⁶	2-hour dual HOPE of discarded human livers	15
Monbaliu <i>et al.</i> (2012) ⁷	24-hour dual HOPE of discarded human livers	2
Stegeman <i>et al.</i> (2009) ⁸	90-minute HOPE of rat livers	6
Vekemans <i>et al.</i> (2007) ⁹	24-hour HOPE of porcine livers	1
Dutkowski <i>et al.</i> (2006) ¹⁰	1-hour HOPE of rat livers	1

ATP, adenosine triphosphate; HOPE, hypothermic oxygenated machine perfusion.

Keywords: Liver preservation; Liver transplantation; ATP; Hypothermic oxygenated machine perfusion.

Received 17 August 2020; received in revised form 29 September 2020; accepted 5 October 2020; Available online 9 October 2020

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

Authors' contributions

IB, RP, VM wrote the manuscript in consultation with OL, MM, PD, DM and PM. All authors critically revised the final manuscript and approved the submitted version.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2020.100194>.

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Author names in bold designate shared co-first authorship

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