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Reply to: "The importance of adequate oxygenation during hypothermic machine perfusion"

To the Editor:

We thank Brüggenwirth, de Meijer *et al.* for their interest in our work that obviously shakes up the idea, which is well established today, that HOPE is the future of organ preservation, particularly of liver grafts. Our objective was not to question this idea or the pre-eminence of the HOPE method over other conservation strategies.

We think that it would have been relevant to measure the oxygenation of the preservation solution, but we did not do it for 2 reasons: i) we assumed that the surface perfusion was sufficient to ensure pO_2 >100 mmHg, as was the case when the Belzer team[1] used this oxygenation method to show the superiority of machine perfusion over simple cold storage (SCS); ii) it was difficult to check the amount of dissolved oxygen with commercial measuring devices, as described in previous studies.[2] Indeed, these machines are calibrated to take measurements on blood samples and not on a crystalloid, and even less when this crystalloid contains a colloid. The manufacturer guidelines used to set up the monitor and oxygen optode sensors are not adequate in this context; further adaptation of the method is required to make the pO_2 measurement relevant.

We would also like to share the idea that contrary to what Brüggenwirth *et al.* appear to imply and to the best of our knowledge, nothing in the liver transplantation literature indicates that ATP synthesis is linearly correlated with the amount of oxygen dissolved in the perfusate. In a model of renal transplantation, no correlation has been found between ATP and pO_2 values obtained with hypothermic perfusion, SCS, and static cold hyperbaric oxygenation (106, 176, and 282 mmHg, respectively).[3] It has been shown that cellular respiration and subsequent cellular ATP levels remain independent of O_2 supply until the oxygen concentration falls below a critical value in the range of 3 to 5 mmHg.[4] This appears to be related to the fact that O_2 availability in the mitochondria limits the rate of ATP synthesis relative to its rate of utilization.[5] Since hypothermia drastically reduces cell metabolism, maintenance of a high ATP level may not be necessary. PO_2 would rather depend on the perfusion condition (solution viscosity, temperature, perfusion pathway) and flow rate.

In the title of our paper, we used the conditional tense to present SCS+M101 as an alternative to HOPE for liver graft preservation. We showed that SCS+M101 did better than SCS, but we also stated without ambiguity that the performance of livers preserved with SCS+M101 was not as good as that of livers preserved with HOPE. We carefully mentioned in our paper that the experimental perfusion machine that was used for our HOPE group was homemade, designed based on the machine used by the Belzer group.[1] As a consequence, we consider that the results we obtained with our HOPE treatment are perhaps not completely comparable to those obtained in the papers cited by de Meijer *et al.* using commercial perfusion machines such as the ECOPS device (OrganAssist®). Our results are more comparable to those obtained by Compagnon *et al.*,[5] for which the pO_2 during the perfusion period was 126 ± 15 mmHg in the hypothermic machine perfusion group.

We also defend the idea that the superiority of HOPE over SCS-M101 is less related to the availability of O_2 than to the continuous washing out of the sinusoids permitted by HOPE. We discussed the idea that this difference could be the result of the permanent organ flushing enabled by HOPE. This mechanical action actually prevents the accumulation of toxic compounds and cellular debris in the sinusoids, which represents a rarely advanced advantage of perfusion over static preservation.

Nevertheless, we still believe that SCS+M101 could be an alternative to HOPE among other strategies such as normothermic perfusion.[6,7] Indeed, the superiority of continuous infusion over SCS has been demonstrated for decades (even with the aid of surface oxygenation). However, it is still rarely used in clinical practice. There is a reason for this: the simplicity of SCS compared with the difficulty of handling and the cost of implementing HOPE. The advantage of adding M101 to a solution of SCS then takes on its full meaning when it is admitted that a lower metabolic performance than with HOPE can be compensated for by i) an immediate supply of oxygen (which only transportable machines would allow, but none are on the market today), and ii) great ease of use.

As the authors of this query remind us, HOPE allows measurements capable of judging the quality of the graft. We fully agree with this statement although the markers of interest in the perfusate or liver tissue still need to be validated. However, nothing prevents such an assessment in tissue samples or rinse effluent from grafts preserved by SCS.

An anticipated advantage of HOPE is the improved quality of so-called extended criteria grafts; we will start an

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experimental study in this context, using the same transplantation model in pigs, to investigate the benefit of SCS+M101 over SCS and to compare it with HOPE, which is still considered the gold standard. Following the advice of de Meijer *et al.*, we will aim to adapt existing solutions to measure the pO_2 in the perfusate.

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Authors' contributions
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Supplementary data
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