

REPLY: IS HEPATOCYTE NECROSIS A GOOD MARKER OF DONOR LIVER VIABILITY DURING MACHINE PERFUSION?

We thank Professor Neil and coauthors for reading our work and for their numerous contributions to the field, in particular the Viability Testing and Transplantation of Marginal Livers (VITTAL) trial.⁽¹⁾ This is a critical area of investigation, and the authors bring up points worthy of further discussion. We have the following responses.

The authors state we use “hepatocyte necrosis as the basis of determining a liver is non-viable.” To clarify, we evaluated the Suzuki score, of which hepatocyte necrosis comprises one third of the points. In this score, equal weight is also given to the assessment of congestion and sinusoidal dilation and of vacuolar degeneration in the specimen. We agree, however, that relying on histology without transplantation is a limitation in our experimental design.

There is a distinction to note in the first point detailing successful transplantation of two donation after brain death (DBD) livers with a high degree of necrosis⁽²⁾; from the report, it appears the degree of necrosis on biopsy was similar before and after perfusion. In our study, we observed livers with progressive histologic injury score throughout perfusion. Thus, these two situations are not totally analogous. In our opinion, progressive necrosis during normothermic machine perfusion (NMP) is more concerning for nonviability and should preclude transplant.

Regarding the VITTAL data,⁽¹⁾ it appears there was minimal necrosis overall in the DBD subgroups, suggesting that necrosis is not a major driver of graft dysfunction in the DBD setting. It would be interesting to know, however, if there were pre-NMP biopsies that could be compared with the biopsies taken during NMP. Again, we would hypothesize the magnitude of change in histology is likely more important than a single measurement.

In the subgroup analysis provided of the donation after circulatory death (DCD) livers from the VITTAL trial,⁽¹⁾ nonviable livers (as defined by their criteria) had a significantly higher median hepatocyte necrosis compared to viable livers (median 20% vs. 1%). This finding suggests that in the DCD setting

there is likely an association between histologic tissue injury and organ viability, consistent with our study.


Lastly, the authors disagree with our conclusion that perfusate lactate clearance does not discriminate between viable and nonviable livers during NMP. In general, we agree lactate is likely the best marker available and that a high lactate level is an ominous sign. However, the true negative predictive value of lactate in the determination of viability is unknown. In the VITTAL trial, the negative predictive value was 100%, given that there were no instances of primary nonfunction (PNF). However, there are examples in the literature of livers that cleared lactate during NMP but went on to develop PNF,⁽³⁾ suggesting that there are cases where these criteria will fail.

Given the low overall rate of PNF following NMP, we suggest future work should focus on predictors of ischemic cholangiopathy. We believe the VITTAL data also support this concept, given that 18% of the livers meeting viability criteria ultimately developed severe ischemic cholangiopathy requiring retransplantation. Unfortunately, this is difficult to study in the preclinical setting, and we must continue to draw conclusions in an observational manner using clinical cases.

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[Correction added on 7-Oct-2021, after first online publication: The full title of the article has been added in this version.]

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Potential conflict of interest: Dr. Hartwig consults for Intuitive, Paragonix, and Biomedinnovations. The other authors have nothing to report.