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Letter in response to the comments of Ravi Yadav and James Kumar

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To the Editor,

We thank Yadav and Kumar for their thoughtful response to our article, "A Comparative Analysis of the Effect of Norepinephrine and Dobutamine on Hepatic Blood Flow." We appreciate their insightful comments and the opportunity to further clarify the rationale, scope, and methodological considerations underlying our study, as well as to expand on the interpretation of our findings.

We acknowledge that Yadav and Kumar provide an accurate assessment of the limitations of our study[1]. As with any clinical investigation, our study has inherent limitations, which we have recognized and discussed in the original manuscript. We welcome the opportunity to further elaborate on these aspects and place our findings in their appropriate clinical context.

First, we fully agree that our study should not be interpreted as a randomized comparison between norepinephrine (NOR) and dobutamine (DOBU)[2]. As explicitly described in the Methods and reiterated in the Discussion, our analysis was based on two prospectively conducted observational studies that were subsequently pooled after ethical approval for secondary comparative analysis. We deliberately acknowledged that this design introduces the possibility of selection bias and residual confounding and that causal inferences cannot be drawn. Rather than demonstrating superiority of one vasoactive agent over another, our intention was to compare two clinically relevant physiological strategies under standardized intraoperative conditions using direct measurements of hepatic blood flow – a methodology that remains exceptionally rare in humans[3].

Regarding baseline differences and potential confounding, we agree that baseline mean arterial pressure, heart rate, remifentanil administration, and the exclusion of sinus tachycardia in the DOBU cohort deserve consideration. These differences were transparently reported in Table I and discussed as study limitations. Importantly, however, all patients underwent identical perioperative management according to the institutional pancreatic surgery protocol, including standardized anesthesia, goal-directed hemodynamic therapy, fluid management, and timing of measurements following hemodynamic stabilization. Although residual confounding cannot be excluded, the standardized intraoperative protocol substantially reduced variability unrelated to the vasoactive interventions.

The role of somatostatin (SST) merits particular attention, as it is widely used as a portal inflow modulator and, as such, has the potential to influence portal venous flow (PVF)[4]. We intentionally addressed this issue because previous work from our group demonstrated that SST reduces PVF. In the present study, somatostatin was administered in both cohorts according to surgical indication, with comparable exposure between groups, thereby reducing – although not eliminating – the potential for systematic confounding. We therefore explicitly identified SST as a potential effect modifier and acknowledged that future randomized studies should stratify patients according to SST administration to better account for its influence on portal venous flow.

The comments regarding statistical methodology are appreciated. Our analyses were exploratory and hypothesis-generating rather than confirmatory. Linear mixed-effects models were selected because they appropriately account for repeated within-subject measurements and interindividual variability while maximizing statistical efficiency in relatively small physiological datasets. Normality assumptions were evaluated using histograms and Q-Q plots before model fitting. We acknowledge that no formal multiplicity adjustment was applied and that this may increase the risk of type I error. However, the primary objective was not to establish multiple independent hypotheses but rather to characterize the integrated physiological response of systemic and hepatic hemodynamics to two vasoactive strategies. We agree that larger prospective studies with prespecified statistical plans are warranted.

The authors also question our use of the phrase that DOBU exerted a "greater effect" than NOR. We respectfully emphasize that this wording refers to the magnitude of the observed physiological changes within the statistical model rather than implying clinical superiority. Throughout the Discussion, we consistently caution against extrapolating these physiological findings to patient outcomes. Specifically, we state that improved hepatic blood flow (HBF) should not be interpreted as evidence of improved postoperative liver function or overall clinical benefit, and that further

studies evaluating patient-centered outcomes are required before any therapeutic recommendations can be made. We therefore fully agree that physiological endpoints should not automatically be equated with clinically meaningful outcomes.

Nevertheless, our findings provide important mechanistic insight into the relationship between systemic hemodynamics and organ perfusion. The study demonstrates that changes in macrohemodynamic variables are accompanied by corresponding changes in hepatic perfusion, although the effects differ between vasoactive agents. NOR improved systemic hemodynamic parameters, consistent with its established hemodynamic profile, but this was associated with a reduction in total HBF. In contrast, DOBU increased total HBF, primarily through an increase in PVF, while hepatic arterial flow (HAF) decreased, most likely reflecting activation of the hepatic arterial buffer response. These observations should therefore be interpreted as physiological effects that improve our understanding of the differential hemodynamic actions of these agents, rather than as evidence that one treatment is clinically superior to the other[5].

Concerning postoperative outcomes, we entirely concur with the correspondents. Our study was designed as a physiological investigation and was neither powered nor intended to evaluate postoperative liver dysfunction, complications, or survival. This limitation was explicitly acknowledged, and we proposed prospective randomized trials incorporating both physiological measurements and clinically relevant postoperative endpoints as the logical next step.

Finally, we appreciate the observation regarding the apparent discrepancy in the DOBU sample size. The text correctly states that sixteen patients were included in the DOBU cohort. The value "n = 14" reported in Table I is indeed a typographical error that escaped the proofreading process and should read "n = 16." We are grateful that this inconsistency was identified and welcome the opportunity to correct it through an erratum. We also agree that more detailed reporting of measurement reproducibility and adherence to reporting guidelines such as STROBE would further improve transparency in future studies.

In conclusion, we appreciate the constructive comments and agree that our findings should be interpreted within the context of their observational design. Nevertheless, we believe that the principal strength of the study lies in the direct intraoperative measurement of PVF and HAF using transit-time flowmetry under carefully standardized conditions. These data provide novel physiological insight into the differential hepatic effects of two commonly used vasoactive agents and generate clinically relevant hypotheses that now warrant evaluation in adequately powered randomized controlled trials incorporating postoperative liver function and patient-centered outcomes.

Sincerely,

The Authors

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