

## Response to Letter “Risk Factors for Acute Kidney Injury after Cardiopulmonary Bypass” by Rik H.J. Hendrix et al.

To the Editor,

In response to the letter by Hendrix et al. (1), the authors raise some important points about debating the causality of low oxygen delivery ( $DO_2$ ) on acute kidney injury (AKI) during cardiopulmonary bypass (CPB), and we thank them for their comments. First, it is important to highlight the difference between causality vs. association in observational research. In areas where information from randomized controlled trials (RCTs) is unavailable, observational studies may generate hypotheses and conclusions can be drawn. However, observational studies can only establish that significant associations exist between the variables of interest and a particular outcome. Observational studies cannot determine whether associations identified represent causal relationships (2). Therefore, the associations identified in our study are hypotheses generating and support the development of RCTs to evaluate the effect of alterations to practice based on oxygen delivery interventions.

Because AKI is multifactorial, it is likely that factors other than  $DO_2$  levels during CPB alone played a role in the etiology of AKI in our study. As Hendrix et al. point out, there were some statistically significant differences in possible contributing factors to AKI when comparing patients based on their exposure to  $DO_2$  above (area under the curve [AUC] $+$ ) or below (AUC $-$ ), a critical threshold. To avoid overfitting of the multivariate model, we limited the adjustment of preoperative factors by inclusion of the Euroscore II, which allowed for inclusion of a single metric representative of composite risk factors. This includes factors that were different between groups: age, diabetes, and chronic pulmonary disease. In our study population, cerebrovascular disease and hypertension were not univariate predictors of AKI, and, therefore, adjustment for these factors in the multivariate model should not change the result. Therefore, although it may be reasonable to speculate that the influence of these preoperative factors may have had an impact on the relative incidence of AKI between groups in our study, we maintain that the independent influence of  $DO_2$  has been demonstrated.

Having lower average CPB flow in the AUC $-$  group can be attributed to the inclusion of cardiac index in the calculation of  $DO_2$ . The speculation that both groups may have experienced increases in creatinine because of their average intraoperative mean blood pressures being lower than the optimal level reported by Hori et al. (3) is interesting; however, it is unlikely because these differences were not statistically or clinically significantly different [AUC $-$ : 62 {58–66} mmHg; AUC $+$ : 64 {60–68} mmHg, Hori et al:  $71 \pm 10.3$  mmHg]. Therefore, we respectively disagree with Hendrix et al. that in our study, that difference in AKI risk factors between groups ameliorates the influence of  $DO_2$  in this study.

Hendrix et al. (1) raise an important issue regarding reporting of studies regarding  $DO_2$  and CPB that we wish to support and that such studies should include metabolic measures such as oxygen consumption or serum lactate as an indicator of systemic oxygen delivery adequacy.

Finally, we thank Hendrix et al. (1) for their interest in our work and commitment to challenging the science that forms the basis of our profession. We hope that large observational studies may be published in the future to enable us to build an understanding of the impact of oxygen delivery and consumption on AKI while we await the results of prospective randomized studies.

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### REFERENCES

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