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Reply to Tasker, and to Lellouche and L'Her

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Contributions

- EP: Additional sensitivity analysis
- EP, DM, MS, SH: Writing of letter

Declarations

The views expressed are those of the authors and are not necessarily those of the NIHR, the NHS or the UK Department of Health and Social Care

Running Head

Hyperoxemia and outcome in critical care patients

Descriptor

6.4 Epidemiology, 13.04 Oxidants/Antioxidants

To the Editor:

Professor Tasker queries whether patients undergoing brainstem death testing could bias the association between exposure to hyperoxemia and mortality in our recent study (1). In our database, these patients represent a tiny fraction of patients evaluated. For the day 1, 3, 5 and 7 cohorts, there were only 33 (0.1%), 14 (0.1%), 9 (0.1%) and 6 (0.1%) patients, respectively in whom there was semantic labelling for death confirmed using neurological criteria. Owing to these low numbers, we did not attempt to stratify by this variable. This is likely to be a small underestimate of patients exposed to apnoea testing, as this label only refers to patients who met full criteria, rather than patients who underwent brainstem death testing itself. Though in the UK it is standard practice not to proceed with testing unless there is good evidence that it is likely to be positive. A sensitivity analysis however confirms that our original findings are robust even after exclusion of these patients.

We would respectfully disagree that the study implies an “all-or-nothing” effect. The Royston method for evaluating exposures with a spike-at-zero is designed to introduce a discontinuity in a continuous variable at zero. Both indicator and dose components must be considered simultaneously. By analogy to cigarette exposure, this would be akin to suggesting that smoking is associated with harm, but we are unclear whether smoking 20 cigarettes a day is worse than smoking 10. The statistical power to demonstrate the dose independent effect is much higher than the dose dependent effect.

Drs L’Her and Lellouche request summary distribution measures of PaO_2. Concerning the study variable of interest (i.e. “hyperoxemia dose”, samples with PaO_2 ≥13.3 kPa), the median was 15.8 kPa and the 5%, 25%, 75% and 95% centiles were 13.5, 14.3, 18.9 and 30.5 kPa, respectively. This is a right skewed distribution as one would expect after censoring

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values <13.3 kPa. Regardless, we would challenge their assertion that "If the range of PaO_2 values is too narrow, no dose-effect relationship could be made". The effect of interest was cumulative exposure so even minor deviations of the underlying PaO_2 would thus aggregate and become apparent over time. Notwithstanding this, there was good variability in the raw data that informed the creation of the "hyperoxemia dose" variable.

Our approach was clear in that we were trying to create an unambiguous definition of oxygen excess, rather than attempting to establish an optimal level for PaO_2. The Helmerhorst paper (2) cited did not, in our view, account for inherent confounding from treatment-physiology interactions; the optimal PaO_2 they reported should be viewed with a degree of healthy scepticism. We believe that questions over optimal PaO_2, and the importance of balancing this against prevention of significant hypoxemia, remain unanswered. While there is mounting evidence of the harm associated with excess oxygen exposure, there remains a lack of strong causal evidence. We would advocate for well powered, randomised controlled trials to help elucidate these important questions.

References

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2. Helmerhorst HJF, Arts DL, Schultz MJ, van der Voort PHJ, Abu-Hanna A, de Jonge E, et al. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care: Crit Care Med. 2017 Feb;45(2):187–95.