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Letter by Russell et al. Regarding Article, "Association Between Early Hyperoxia Exposure After Resuscitation from Cardiac Arrest and Neurological Disability: A Prospective Multi-Center Protocol-Directed Cohort Study"

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To the Editor:

We applaud Roberts et al. on their study[1] of the association between hyperoxia exposure and mortality and neurological function in cardiac arrest patients. Although similar findings have been reported[2, 3] this analysis considerably strengthens the case for hyperoxia-mediated harm in the post-cardiac arrest setting. In contrast to many such studies, it included a prospective data collection design with protocolized arterial blood gas (ABG) measurements allowing for calculation of time-weighted average of PaO_2. However, we feel that the data published in this manuscript is too limited to firmly support two of the authors' conclusions.

The statement by the authors that the "increased risk of poor neurological function appears to begin at 300mmHg" is misleading. In reality, this analysis shows that >300mmHg was the lowest *cutoff associated* with a *statistically significant* risk of poor neurological function. While this may sound like a small difference, it is significant. Because the hyperoxic tail is included in all the cutoffs analyzed, the numerical trend is toward harm in them all. In fact, Figure 3 suggests that perhaps there may be a threshold effect at ~250mmHg (as the mean point estimate shifts rightward beginning at this point), but use of this threshold does not show a statistically significant risk. It is premature to conclude, on the basis of these data, that harm from hyperoxia "begins" at any particular point, because this finding is limited by the statistical power of the analysis. In the absence of randomized trials (for which there may never be sufficient equipoise) the causal nature of this association is uncertain; on the other hand it remains unknown whether there is really a "safe" range of supraphysiologic arterial oxygen tension at all, a question which may vary between patient populations[4, 5]. To mitigate or affirm these concerns, would the authors be able to report point-estimates of risk

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in the subset of patients that fell in a hyperoxic range below the 300mmHg threshold (perhaps 200–299mmHg)?

We also disagree with the conclusion that providers must frequently measure ABG PaO_2 levels to reliably exclude hyperoxia. This assertion is based upon the poor correlation observed (r=0.23) between SaO_2 and PaO_2. Hemoglobin saturation and PaO_2 are not measured on the same scale, and indeed, the maximum SaO_2 of adult human hemoglobin corresponds, assuming normal homeostatic conditions, to less than 1/6 the maximum PaO_2 that can be achieved. The absence of a numerical correlation between these two different values is therefore clinically and scientifically meaningless, merely describing the already known sigmoidal, not linear, oxyhemoglobin dissociation curve. Supplemental Figures 1 and 3 appear to show that significant hyperoxia in the presence of a saturation below the high 90s was rare; it seems likely to us that these rare exceptions were patients with poor plethysmographic waveforms, which a bedside provider would readily recognize as an indication to proceed with ABG analysis. Therefore, with the use of clinical judgment, the SpO_2 can still often be used to rule out hyperoxia, avoiding unnecessary phlebotomy and resultant harms.

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