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CORRESPONDENCE

In reply: Hyperoxia-induced brain ischemia: the Strawman comes up short

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To the Editor,

We appreciate Dr. Moon's interest and critique[1] of our recent correspondence to the *Journal*.[2] Dr. Moon suggests that the cerebral blood flow (CBF) effects of intraoperative hyperoxia are unlikely to contribute to postoperative delirium (POD). This assertion is based on previous studies, summarized by Johnson *et al*.,[3] which show that hyperoxia is associated with an increase in cerebral oxygenation despite the associated decrease in CBF. As he notes, our correspondence did not focus on hyperoxia in isolation but identified a potentially worrisome synergism between hyperoxia and hypocapnia in decreasing CBF. Furthermore, significant regional heterogeneity was apparent, with both expected and inverse blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI) responses observed.[4] Although Johnston *et al*.,[3] present literature indicating an increase in jugular venous oxygen tensions with hyperoxia, this is a global measure of cerebral oxygenation with no nuance regionally. Also, as highlighted in their review, there were studies using single microregional electrodes inserted into the cerebral cortex that showed an increase in regional tissue oxygenation with increases in arterial oxygen (O_2) tension. But, they caution that the response to increasing arterial partial pressure of oxygen (PO_2) is damped. Other studies in Johnson's review, using multiple surface electrodes, reported increasing heterogeneity of brain oxygenation with increasing inspired oxygen, findings more consistent with ours. Heterogeneity is presumed to be related to regional vasoconstriction in some areas and shunting in others. In support of this finding is our observation that with increasing end-tidal (ET) O_2 there are regional differences in cerebral oxygenation/flow with BOLD imaging (see Fig. 3 in Reference[4]). In fact, there are regions of decreased BOLD (a marker for increased regional cerebral venous hemoglobin desaturation) with increasing ET O_2—so called "blue" brain. Our prior Strawman correspondence[5] highlighted similar alterations in ET CO_2, where inverse or "blue" brain responsiveness was felt to be a biomarker of cerebral tissue in patients at risk for POD. Importantly, the contention that a decrease in global CBF with hyperoxia is not associated with cerebral hypoxia does not agree with the results of Macey *et al*.[6] Using similar MRI methodologies, they show areas of altered regional BOLD responsiveness to increasing PO_2. These areas of altered BOLD response, in large part, vanish with inhalation of increasing concentrations of the potent cerebral vasodilator, CO_2, increasing the BOLD signal and thus increasing the regional cerebral venous oxygenation. Thus, by using these MRI approaches, with tight control of ET gases, we have shown regional decreases in CBF or BOLD signal with hyperoxia with a resolution of up to 150,000 voxels.[4] As such, areas of regional risk with hyperoxia may well exist, even in the presence of globally increased jugular venous O_2 tensions,

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especially in older patients with underlying cerebral pathology at greater likelihood of POD.

End-tidal O_2 tensions are often higher than need be for safe conduct of anesthesia and we have previously reported that the mean CO_2 delta during routine anesthesia was 13 mmHg using high fidelity data capture.[7] Intracranial steal ("blue" brain) can occur with alterations as small as 5 mmHg in ET CO_2 in patients with CBF compromise. We cannot comment on the concepts raised about glucose delivery as we did not examine this, but concur with Dr. Moon's assessment.

On the basis of these preliminary findings, we advocate for tighter control of ET O_2 and CO_2 for management of patients at risk of POD, but agree with Dr. Moon that the ideas advanced require outcome data. For this reason, we are conducting a pilot study (NCT02126215) to investigate the feasibility and safety of tighter control of ET gases during anesthesia. In this regard, we agree with Dr. Moon that the Strawman, as originally articulated[5] needs further investigation. It remains to be seen if he comes up short or stands on his own.

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