CORRESPONDENCE

Strawman redux: management of end-tidal gases in patients at risk of perioperative neurocognitive disorder

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To the Editor,

In a previous published commentary in the *Journal*¹ entitled “Anesthesia and postoperative delirium: the agent is a strawman—the problem is CO₂”, we proposed that the conduct of anesthesia and, in particular, end-tidal (ET) carbon dioxide (CO₂) management may be an important contributor to cognitive dysfunction after surgery, now termed perioperative neurocognitive disorder (POND).² Subsequent work by our group and others has confirmed an association between intraoperative hypocapnia and one of the sub-categories of POND—postoperative delirium (POD).^{3,4} Not considered in these publications was the potential influence of the other ET respiratory gases, specifically O₂ or potential synergistic interactions between ET CO₂ and ET O₂ as additional contributing factors to the development of POD, although periods of both hypocapnia and hyperoxia are commonly observed during mechanical ventilation in the course of most routine anesthetics.

We have recently examined the combined effects of hyperoxia and hypocapnia on cerebral blood flow (CBF).⁵ Using pseudo-continuous arterial spin labelling, we have identified marked, dynamic changes in CBF during tightly

controlled changes in ET CO₂ and ET O₂ that are observed commonly during anesthesia. That study also showed the independent effect of hyperoxia at normocapnic values on regional decreases in CBF. Additionally, a synergistic decrement in CBF is described with combined hyperoxia and hypocapnia. Further analysis of these data in Figure (A–C) shows the change in CBF in a single subject under different test conditions. These conditions were (A) baseline (normoxia/normocapnia) and (B) spontaneous hyperventilation to lower the ET CO₂ to 5 mmHg below baseline in the presence of hyperoxia (ET O₂ = 400 mmHg). The difference map (image 2 – image 1) is presented in (C) and decreasing CBF is represented as a colour change from blue to purple. A marked global decrement with combined hyperoxia and hypocapnia is evident with regional grey matter flow frequently decreasing by approximately 50%. As such changes in ET respiratory gases are routinely observed during the course of standard anesthetic care, the magnitude of the resultant changes in CBF may be considered a potential contributory factor to POD. Control of end-tidal gases may be important, but a multicentre retrospective analysis of over 300,000 non-cardiac surgical patients suggests clinicians have not reached consensus on appropriate goals.⁶ After controlling for patient and procedural factors, the median ET CO₂ was consistently less than 40 mmHg with large inter-hospital and inter-provider variability.

We believe that these preliminary findings raise an important issue regarding research on delineating the mechanisms of POD. With access to breath-to-breath monitoring of ET respiratory gases, anesthesiologists are uniquely positioned to comprehensively examine these potential intraoperative drivers of POD. Such high-fidelity data should be incorporated and controlled for in studies

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Figure (A–C) Images from a healthy, awake subject comparing the CBF at baseline, i.e., normocapnia/normoxia (A). (B) The same patient after being instructed to spontaneously hyperventilate, decreasing the ETCO_2 to 5 mmHg below the baseline value while breathing O_2 to increase ETO_2 to 400 mmHg. A marked decrement in CBF is evident globally. In image C, the difference map (image

2–image 1) is shown indicating the regional decrease in CBF throughout the entire brain. See reference 5 for details of the methodology. Cerebral blood flow is shown as $\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. The number to the left and below each image is the distance above or below the anterior commissure–posterior commissure (AC–PC) line for that axial slice. CBF = cerebral blood flow.

examining the association of any anesthetic agent with POD. Future clinical research should conceivably better leverage these data streams of ET vapour, O_2 and CO_2 , blood pressure, pharmacologic blood concentration modelling of intravenous anesthetic agents, and serial blood gases and hemoglobin. A comprehensive understanding of contributing factors may allow the development of more effective preventative strategies.

We believe that clinical practice may benefit from an appraisal of how carbon dioxide elimination and oxygen delivery affect CBF and their potential influence on postoperative cerebral health including POND. In this light, we have registered a pilot study at www.clinicaltrials.gov (NCT04406350) to investigate the feasibility and safety of such an approach.

Disclosures None.

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