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Commentaries on Viewpoint: Hypercapnia is more important than hypoxia in the neuro-outcomes of sleep-disordered breathing

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## Last Word on Viewpoint: Hypercapnia is more important than hypoxia in the neuro-outcomes of sleep-disordered breathing

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TO THE EDITOR: We agree with Olaithe and colleagues (see Ref. 4) that we should never “put hypoxia to bed.” The reason is simple: in clinical sleep-disordered breathing (SDB) scenarios, there are inseparable combinations of repetitive hypoxia and hypercapnia or hypocapnia (ventilatory overshoot mechanisms) events. We believe that any SDB neuro-outcomes should consider a combination effect rather than blame hypoxia alone, given the evidence we presented. Assuming that measurement challenges applicable to large studies are overcome, novel interactive hypoxia/hypercapnia indices may better explain the individual vulnerability to SDB neuro-impairment.

Deacon and Malhotra (1) questioned that our major evidence for the relationship between hypercapnia and neurocognitive deficit was based on hypercapnic SDB patients (3) and most of the OSA patients do not have daytime hypercapnia. We note a lack of reliable and cost-effective widely applicable tools to precisely measure  $P_{CO_2}$  continuously in ordinary OSA patients overnight. We studied hypercapnic SDB patients, which allowed us to use the gold standard ABG  $P_{CO_2}$  measurement during wake and there is a wide spectrum of change in  $P_{CO_2}$  after treatment, which makes it possible to correlate with EEG activation change (3). Importantly, to minimize this limitation, we conducted a clinical experiment on normal volunteers to examine the generic effect of hypercapnia and hypoxia (comparable to levels seen in OSA) on EEG activation (5). Again we found significant correlation between hypercapnia and slowing in EEG, whereas a similar effect was not found with hypoxia alone (Fig. 1 in Viewpoint) (5). This finding is also supported by human brain imaging studies, undersea diver experiments, and a number of animal studies (see Viewpoint, Ref. 4). We agree that most of the OSA patients do not have daytime hypercapnia; they do not have daytime hypoxemia either and that does not exclude hypoxia as a mechanism for SDB related neuro-impairment. More work with less bias to hypoxia is required.

Supplemental  $O_2$  does not generally improve SDB neuro-impairment despite improving overnight oxygen saturation; both Deacon and Malhotra and Zuo and Chuang (see Ref. 1) suggest that may be due to irreversible oxidative stress-asso-

ciated neuronal injuries. This is a complex area. Compliant CPAP therapy can generally improve SDB-related neurobehavioral impairment (2). We reflect that the difference between CPAP and  $O_2$  supplement therapy is that CPAP is more likely to improve hypoxia, hypercapnia, and sleep fragmentation, whereas  $O_2$  supplementation only improves hypoxia.

Other comments are generally supportive to our Viewpoint and provided more in-depth exploration of the complex mechanism between hypoxia-hypercapnia interaction and neural pathophysiology and raised more thought-provoking questions. In research studies, it is important to check 1) is the hypoxia model actually testing the mixed effect of hypoxia and hypercapnia/hypocapnia? 2) is the hypoxia level comparable to OSA level, particularly for animal studies?

The effect of hypercapnia has been long ignored and significantly understudied and it is the time to think beyond hypoxia. Hypercapnia, particularly the interaction between hypoxia and hypercapnia/hypocapnia should be the next frontier of research in SDB neuro-outcomes. Measurement is a key requirement and presents opportunities for cost-effective technological development.

### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

### AUTHOR CONTRIBUTIONS

D.W., R.J.T., and R.R.G. conception and design of research; D.W. drafted manuscript; D.W., R.J.T., B.J.Y., and R.R.G. edited and revised manuscript; D.W., R.J.T., B.J.Y., and R.R.G. approved final version of manuscript.

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