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

IT’S NOT YET TIME TO PUT HYPOXIA TO BED

TO THE EDITOR: Wang et al. (4) argue that when explaining neurocognitive dysfunction in OSA, there has been insufficient attention given to hypercapnia, which may be more important than hypoxia. Although we agree with the former point, we believe that it may be premature to conclude the latter.

We agree with Wang and colleagues that the evidence for a relationship between hypoxia and cognition is equivocal. However, we would argue that many studies in this area may not have used the most appropriate measures of hypoxia or adequately accounted for potentially important interindividual differences that moderate cognitive effects.

Specifically, most studies describe the severity of hypoxia in terms of O2 nadir or time spent below a threshold level of saturation. Such measurements may not capture individual differences in depth and time spent in a hypoxic state nor the intermittent nature of hypoxia in OSA. It is possible that such indices of hypoxia (e.g., the Integrated Area of Desaturation) might demonstrate stronger associations with cognitive dysfunction.

Furthermore, there is mounting evidence that differences between individuals in factors such as disease duration, cognitive reserve, age (2, 3), and other comorbidities (1) can markedly influence the relationship between cognitive function and hypoxia by reducing or increasing vulnerability to cognitive impairment.

More investigation is warranted on the role of hypoxia in neurocognitive dysfunction in OSA. For the reasons stated in this Viewpoint, it’s not yet time to put hypoxia to bed.

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COMMENT ON VIEWPOINT: HYPERCAPNIA IS MORE IMPORTANT THAN HYPOXIA IN THE NEURO-OUTCOMES OF SLEEP-DISORDERED BREATHING

TO THE EDITOR: The author’s suggestion that hypercapnia is more important than hypoxia in the pathophysiology of neurocognitive deficits in OSA is based on evidence from their laboratory of slowed EEG in hypercapnic OSA patients and a treatment reversal correlation of EEG deficit and wake PCO2 (3). Although potentially important, the reported findings do not relate directly to OSA per se. Daytime hypercapnia is only present in the minority of OSA patients, because daytime ventilation is not compromised by OSA itself (4), a fact reflected in their referenced study where daytime hypercapnia was attributed to comorbid COPD and obesity hypoventilation syndrome (2). Additionally, studies showing little improvement in neurocognitive function in OSA patients after alleviation of nocturnal hypoxia is not evidence that those patients were hypercapnic post-treatment nor does it negate the role of hypoxia in inducing neurocognitive deficits (3). It implies rather that the damage may be irreversible, as supported by evidence of cell death in animal models (1).

Also important is the lack of distinction between the effects of sustained vs. intermittent gas exposures. Although intermittent hypercapnia may contribute to neurocognitive deficits because of acute changes in cerebral blood flow, pH, catecholamines, and neuronal excitability, compelling evidence for lasting effects is lacking. However, chronic intermittent hypoxia in animals induces spatial learning deficits and neuronal loss in the hippocampus and frontal cortex due to systemic oxidative stress, inflammation, neuronal apoptosis, and inhibition of brain-derived neurotrophic factor expression, which is essential for normal hippocampal long-term potentiation, a form of neural plasticity critical in learning and memory (1, 5).

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COMMENT ON VIEWPOINT: HYPERCAPNIA IS MORE IMPORTANT THAN HYPOXIA IN THE NEURO-OUTCOMES OF SLEEP-DISORDERED BREATHING

TO THE EDITOR: The authors have identified significant cross-correlation between changes in hypercapnia, EEG spectral activity, and daytime sleepiness. Also, hypercapnia and not hypoxia caused EEG slowing, suggesting a depression of cortical electrical activity (3). Hypercapnia, by altering the brain and intracellular pH may alter the functional sensitivity of the neurons and hence cortical electrical activity. Although, hypercapnia and hypoxia increase cerebral blood flow and O2 delivery to the tissues, the beneficial effects of hypercapnia on oxygen consumption of the brain (CMRO2) are marginal at best (2). However, tissue hypoxia in the presence of intracellular acidosis from hypercapnia may have additional metabolic effects on the neurons (1), worsening neuronal function and outcome.

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Patients with obstructive sleep apnea (OSA) have multiple risk factors for stroke, which increase with OSA severity (4). The vasoreactivity of cerebral arterioles may be altered in the presence of chronic or fluctuating hypercapnia in these patients, exposing them to further ischemic insults during hypoxic episodes. Hypercapnia and hypoxia may represent a continuum of pathophysiological events in the brain in patients with OSA; however, our understanding of the role of hypercapnia in OSA is limited by the lack of a continuous CO2 monitoring device or a noninvasive biomarker of CO2 measurement that can correlate PaCO2 with oxygenation measured by oximeter. This would help in teasing out the components of hypercapnia and hypoxia that are metabolically linked, in understanding their relative contributions to neuro-impairment in OSA. Last, clinical trials focusing on hypercapnia may help in developing interventions to decrease neurocognitive impairment in OSA.

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OXIDATIVE STRESS-INDUCED NEUROLOGICAL IMPAIRMENT IN OSA

TO THE EDITOR: Hypoxia and hypercapnia are two common outcomes associated with obstructive sleep apnea (OSA). However, research focusing on hypoxia in OSA is more prevalent than hypercapnia (4). Wang et al. (4) indicated that hypercapnia-related OSA neurological impairment is largely overlooked. In their view, hypercapnia may potentially outweigh the effect of hypoxia, and thus is primarily responsible for the neurobehavioral abnormalities observed in OSA individuals.

The pathophysiology of OSA involves the complex interaction between hypoxia and hypercapnia. As a result of obstructive breathing, patients with OSA often experience chronic intermittent hypoxia and chronic hypercapnia, which both can contribute to the elevation of systemic oxidative stress, leading to impaired neuroplasticity and cognitive dysfunction (2, 3, 5). Particularly, redox imbalance and diminished antioxidant capacity have been observed in the presence of OSA-related hypoxia (3). In addition, neurons are prompted to generate excessive reactive oxygen and nitrogen species under hypercapnia acidosis via CO2/HCO3 buffering system (1). Common comorbidities of OSA including smoking and obesity also further exacerbate oxidative stress in OSA (3).

As mentioned by Wang et al. (4), improving oxygenation via O2 supplementation in OSA patients does not alleviate neurocognitive impairment. This is likely attributed to the sustained oxidative stress and the irreversible oxidative-associated neuronal injuries. Thus future studies could emphasize the potential effects of hypoxia and hypercapnia on the resultant oxidative damage to advance our knowledge of the mechanisms underlying OSA neural pathophysiology.

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COMMENT ON VIEWPOINT: HYPERCAPNIA IS MORE IMPORTANT THAN HYPOXIA IN THE NEURO-OUTCOMES OF SLEEP-DISORDERED BREATHING

TO THE EDITOR: In their thought-provoking article, Drs. Wang, Thomas, Yee, and Grunstein (1) suggest that hypercapnia may play a significant role in alterations of neurologic function. However, the article raises a number of thorny issues, which are not so easily resolved. To begin, our current tools for assessing neurologic function are rudimentary, making it difficult to interpret the findings in a broader context. Likewise, the short-term changes in EEG activity may be observed with hypercapnia but the functional implications are unclear. On a different note are the neurological changes associated with hypercapnia also related to the cardiovascular and endocrine alterations that occur with sleep-disordered breathing? More broadly, are there additional factors that play a larger role than hypoxia in determining neurologic outcomes, such as sleep architecture, fragmentation, or the severity and length of oxygen desaturation?

I agree with the authors that the study of hypercapnia in patients with sleep-disordered breathing is severely limited by the lack of a tool for the rapid and accurate measurement of carbon dioxide values. As the authors note, many scholars have used hypoxia as a proxy for hypercapnia, but such a metric is insufficient. For example, in pulmonary hypertension associated with untreated obstructive sleep apnea, the observed hypoxia may be a result of sleep-disordered breathing and pulmonary hypertension and not necessarily a reflection of hypercapnia. Until a device for the real-time, noninvasive measurement of carbon dioxide is developed, investigators should take care not to overinterpret hypoxia as a marker for hypercapnia.

REFERENCE


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