HYPERCAPNIA IS MORE IMPORTANT THAN HYPOXIA IN THE NEURO-OUTCOMES OF SLEEP-DISORDERED BREATHING

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Running head: CO₂ is more important than O₂ in SDB neuro-outcomes

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Obstructive sleep apnea (OSA) results in awake neurocognitive impairment with societal implications (22). However, the relevant pathophysiological mechanism(s) for this impairment are unclear impacting on disease monitoring and targeted treatment (1, 17). Among a number of candidate factors, hypoxemia and sleep fragmentation are generally recognized as two key underlying mechanisms (1, 4), with hypoxemia having the strongest evidence base (7, 17). However, recent large clinical trials failed to find a strong link between nocturnal hypoxia and neurobehavioral impairment. In the landmark APPLES study, the severity of O₂ desaturation explained only < 2% of the variance of neurocognitive performance improvement in 1204 OSA patients, and arousal index was not a significant predictor (17). In the recent LATINO study with the largest sample size of 8059, apnea hypopnea index (AHI) with 3% desaturation were very weakly associated with neurocognitive functions after controlled for confounders (β ranged from 0.003 to 0.005) (18). In a multicenter European study, 1649 OSA patients with excessive daytime sleepiness (EDS) and 1233 OSA patients without EDS had only 1% of difference in SpO₂ nadir, no difference in mean SpO₂, and similar arousal index (37/h vs 33/h) (20). In human experimental studies, neurocognitive function was measured in 11 healthy subjects at ground level and simulated altitude of 13,000 feet. Two weeks of nocturnal continuous hypoxia at altitude did not induce subjective sleepiness or impair objective vigilance and working memory (24). In addition, the effect of 4 weeks nocturnal intermittent hypoxia on attention, working memory, Multiple Sleep Latency Test, and the Rey Auditory Verbal Learning Test was measured in 8 healthy subjects and again no effect was detected (29). Moreover, if hypoxemia is the dominant factor for neurocognitive impairment, then EDS should improve with supplemental O₂ therapy. However, studies have not found that supplemental O₂ improves daytime hypersomnolence in OSA patients despite improving oxygenation (13, 16).

Interestingly, while OSA usually comes with repetitive episodes of both hypoxia and hypercapnia, only the effect of hypoxia has been more intensively studied. A simple test is by entering key words of “Sleep Apnea
and Hypoxia” in PUBMED, returns 2866 publications; In contrast, there are only 867 publications with the key words of “Sleep Apnea and Hypercapnia”. It is therefore not surprising that hypercapnia has not been considered as a major factor in OSA related neurocognitive impairment in any major review in this field (1, 5, 12).

In this context, we conducted a series of clinical and experimental studies to evaluate the effect of hypoxia and hypercapnia on EEG activation and neurobehavioral performance. Firstly, we demonstrated that 97 hypercapnic sleep-disordered breathing (SDB) patients have a significantly high degree of EEG slowing which was best predicted by increased wake PCO₂ measured by arterial blood gases. Hypoxia related parameters were not significant predictors (26). In the second interventional study, we demonstrated a significant cross-correlation between a reduced wake PCO₂, a faster sleep EEG and reduced daytime sleepiness with CPAP/BiPAP treatment in 55 hypercapnic SDB patients (27). Multiple regression analysis showed the degree of change in hypercapnia to be the only significant predictor for both daytime sleepiness and EEG activation (Delta/Alpha ratio) measures (27). In the third experimental study, we separately compared the effect of hypoxia and hypercapnia on quantitative EEG on 19 healthy men, and found a positive linear correlation between the increasing hypercapnia and the slowing in EEG, while hypoxia did not show such an effect (28). (Figure 1) In the fourth study, using a RCT crossover design comparing the effects of modafinil or placebo, we demonstrated significant correlations between our quantitative EEG activation measures and key neurocognitive performance in OSA patients (25).

Despite limited research, evidence from these studies support our notion that hypercapnia may slow brain neural activity and cause neurobehavioral impairment. In a brain imaging study, breathing 5% CO₂ significantly reduced all functional connectivity MRI indices in 14 healthy volunteers, and resulted in a suppression of cerebral metabolic rate of oxygen (CMRO₂) which was proportional to the end-tidal CO₂.
change (30). Another study found that 5% CO₂ attenuated evoked and spontaneous magnetoencephalogram (MEG) spectral activity and decreased early sensory components in both auditory and visual modalities as well as cognitive components related to memory and language in 7 healthy volunteers (23). In undersea diver-related experimental studies, a dose-response relationship between higher CO₂ tensions and impaired cognitive and psychomotor performance were found (9, 10). In addition, a number of animal studies have demonstrated that hypercapnia, acute or chronic, led to slowing in EEG in eels (2), rats (8), rabbits (14), dogs (21), and monkeys (31).

Hypoxia has been considered as a key determinant of neurocognitive dysfunction in OSA, but this is mainly based on studies that have not adequately controlled for CO₂ (hypercapnia and/or hypocapnia) (7). Relevant problems are two-fold: 1) On one hand, we can often see that clinical SDB studies find a weak correlation between hypoxia and neurocognitive dysfunction and conclude that hypoxia maybe the key mechanism, while hypercapnia was not being measured, e.g. (17). In those studies, impairment may well be due to a mixed effect of hypercapnia and hypoxia, and hypercapnia may play an even more important role based on the above discussions. Specifically, we speculate that hypoxia may have an additive effect in addition to the EEG slowing effect of hypercapnia. As shown in Figure 1, the EEG activation response slope of hypercapnia with hypoxia (Slope B) is steeper than hypercapnia with hyperoxia (Slope A), while hypoxia by itself (Slope C) did not change EEG activation; 2) On the other hand, we can often see experimental studies using a hypoxia model which involved hyperventilation but did not control for hypocapnia, e.g. (11). Hypocapnia caused by hyperventilation is known to have a potent effect in slowing EEG and causing vasoconstriction and a reduction of cerebral blood flow (CBF) (15). In those studies, the altered neurobehavioral performance is more likely due to a mixed effect of hypocapnia and hypoxia. The interaction between hypocapnia, hypoxia, CBF and brain electrical activity is very complex and not well understood (6, 15). We certainly agree that extreme hypoxia by itself may lead to neurocognitive dysfunction.
impairment. However, the vast majority of the OSA population has relatively mild hypoxia but an unknown degree of hypercapnia.

A common argument for not measuring CO₂ in an OSA study is the lack of a fast response yet accurate CO₂ continuous monitoring device which can be simply used like an oximeter. Therefore, oxygenation measures are often clinically used as a surrogate for CO₂ measures. However, the two measurements can be divergent. For example, a recent study measured transcutaneous PCO₂ (PtcCO₂) (TCM4, Denmark) during different subtypes of SDB and surprisingly found that PtcCO₂ was the highest during flow limitation/simple snoring (112%), compared with steady breathing during sleep (108.4%), OSA (105.8%), hypopnea (105.4%), central/mixed apnea (102.0%) and wakefulness (100%) (19). Similarly, another study performed home sleep apnea tests as well as PtcCO₂ (SenTec) and SpO₂ measurements on 91 spinal cord injury patients. Nocturnal hypercapnia was presented in 28% and oxygen desaturation in 18.3% of patients. However, among the 15 (18.3%) patients with oxygen desaturation, only 5 of them had nocturnal hypercapnia. These patients had mild-moderate OSA and no central apnea (3).

In summary, although preliminary, current evidence raises the possibility that hypercapnia is mechanistically more important than hypoxia in SDB related neuro-impairment. We would like to highlight the necessity of CO₂ measurement in clinical sleep studies and encourage the development of an affordable and accurate CO₂ monitoring method for this purpose. Many clinical implications/research questions can be generated from our discussions. Most obvious one would be searching for a CO₂ related biomarker which could best account for the perplexing large inter-individual variability in SDB related neuro-outcomes. It could be individual measures of awake/sleep PCO₂, or ventilatory response to CO₂, or CO₂ response threshold, or brain MRI markers response to CO₂. Other research questions could be if there is any differential neuro-outcome from sustained hypercapnia (such as OHS) and the fluctuating hypercapnia
as seen in OSA, and if the high loop gain/ventilatory overshoot/periodic breathing seen in some patients
with SDB could serve as a protective mechanism in preventing hypercapnia and neurocognitive impairment?
A better understanding of these topics may improve the design of future clinical trials and provide targeted
solutions for the relevant clinical management.
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Figure 1. Conceptual graph of quantitative EEG activation (measured by Delta/Alpha ratio) response to 3 models of rebreathing hypercapnia and hypoxia. The 3 slopes were adopted from our experimental data in 19 normal subjects (Ref (28), Figure 2, with full technical details described)

Slope A: Response to rebreathing hypercapnia with PO₂ held constant at 150mmHg (hyperoxia)
Slope B: Response to rebreathing hypercapnia with PO₂ held constant at 50mmHg (hypoxia)
Slope C: Response to rebreathing hypoxia with CO₂ controlled by a scrubber (PCO₂ ≈ 35 mmHg)

Slope A = 0.471, Slope B = 0.756.

Interpretation: Slope A shows that while PO₂ is held constant, EEG linearly slows down with rebreathing (linearly increased) hypercapnia. Slope B is steeper than Slope A, suggesting a potential additive effect of hypoxia on top of hypercapnia in slowing EEG. Slope C shows that without hypercapnia, rebreathing hypoxia by itself does not change EEG activation.
FIGURE 1.