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Comparing the effect of hypercapnia and hypoxia on the electroencephalogram during wakefulness

David Wang [a,b,*], Brendon J. Yee [a,b,c], Keith K. Wong [a,b,c], Jong Won Kim [c,d], Derk-Jan Dijk [e], James Duffin [f,g], Ronald R. Grunstein [a,b,c]

[a] Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney, Australia
[b] Woolcock Institute of Medical Research, University of Sydney, Australia
[c] Centre for Integrated Research and Understanding of Sleep (CIRUS), University of Sydney, Australia
[d] School of Physics, University of Sydney, Australia
[e] Surrey Sleep Research Centre, University of Surrey, UK
[f] Department of Anaesthesia, University of Toronto, Canada
[g] Department of Physiology, University of Toronto, Canada

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HIGHLIGHTS

- Hypoxia has been considered as the key mechanism in daytime drowsiness and neurocognitive impairment in sleep-disordered breathing.
- We compared the effect of hypoxia and hypercapnia on EEG spectra during wakefulness using a rigorously controlled experimental method, and found that hypercapnia, but not hypoxia caused EEG slowing.
- These data imply that hypercapnia may be more mechanistically important in neurobiological impairments in sleep-disordered breathing patients.

ABSTRACT

Objective: Hypoxia has been postulated as a key mechanism for neurocognitive impairment in sleep-disordered breathing. However, the effect of hypoxia on the electroencephalogram (EEG) is not clear.
Methods: We examined quantitative EEG recordings from 20 normal volunteers under three 5-min ventilatory control protocols: progressive hypercapnia with iso-hyperoxia (pO_2 = 150 mmHg) (Protocol 1), progressive hypercapnia with iso-hypoxia (pO_2 = 50 mmHg) (Protocol 2), and progressive hypoxia with a CO_2 scrubber in the circuit (Protocol 3). Each protocol started with a 5-min session of breathing room air as baseline.
Results: In Protocol 1, compared to its baseline, iso-hyperoxia hypercapnia led to a lower Alpha% and higher Delta/Alpha (D/A) ratio. Similarly, in Protocol 2, the iso-hypoxia hypercapnia induced a higher Delta%, a lower Alpha% and higher D/A ratio. No difference was found in any EEG spectral band including the D/A ratio when Protocols 1 & 2 were compared. In Protocol 3, the Delta%, Alpha% and D/A ratio recorded during hypoxia were not significantly different from baseline.
Conclusions: We found that hypercapnia, but not hypoxia, may play a key role in slowing of the EEG in healthy humans.
Significance: Hypercapnia may be a greater influence than hypoxia on brain neuroelectrical activities.

1. Introduction

Sleep-disordered breathing (SDB) is a common cause of increased daytime sleepiness and neurocognitive impairment

* Corresponding author at: Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. Tel.: +61 2 9114 0446; fax: +61 2 9515 7196.
E-mail address: david.wang@sydney.edu.au (D. Wang).

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which may lead to a 2–3 times increased risk of motor vehicle and occupational accidents (Teran-Santos et al., 1999; Lindberg et al., 2001; Malhotra and White, 2002). Patients with SDB usually have a slower waking electroencephalogram (EEG) which correlates with increased daytime sleepiness and may be corrected by continuous positive airway pressure (CPAP) therapy (Morisson et al., 1998, 2001; D'Rozario et al., 2013). The underlying mechanism of SDB-related daytime drowsiness is unclear. It has been postulated that neurobiological impairments in obstructive sleep apnea (OSA) are a result of a combination of sleep fragmentation and hypoxia. However, the correlation between sleep disruptions measured by apnea and arousal frequency and daytime sleepiness is not robust (Cheshire et al., 1992; Kingshott et al., 1998). SDB is actually characterized by recurrent episodes of both hypoxia and hypercapnia (Dempsey et al., 2010). It has been claimed that it is the intermittent hypoxia that causes daytime sleepiness (Mediano et al., 2007; Dempsey et al., 2010; Canessa et al., 2011; Quan et al., 2011). However, supplemental O_2 therapy does not improve hypersomnolence in OSA patients despite improving oxygenation (Gold et al., 1986; Phillips et al., 1990; Lim et al., 2007). Similarly, there has been a lack of convincing evidence demonstrating that hypoxia alone significantly affects EEG leading to neurocognitive impairment (Kraaier et al., 1988; Van der Worp et al., 1991; Jernajczyk et al., 2006). Hypoxia protocols in previous studies usually lead to concomitant hyperventilation and hypocapnia which can independently affect EEG activity (Burykh, 2008). The potential importance of hypercapnia in sleep-disordered breathing has been neglected partially due to the lack of clinical equipment to reliably measure continuous changes in the arterial CO_2 pressure (pCO_2) during overnight sleep study.

We recently reported increased Slow Wave Sleep (SWS) in 97 patients with respiratory failure with associated high awake arterial CO_2 measurements. Awake pCO_2 measured from arterial blood gas (ABG) sampling in those patients was the best predictor for the increased SWS, while hypoxia related parameters were not related (Wang et al., 2011). Some uncontrolled studies suggest that hypercapnia may cause slowing of the EEG in a dose-dependent manner (Woodbury and Karler, 1960; Matakas et al., 1978; Forslid et al., 1986; Kalkman et al., 1991; Bloch-Salisbury et al., 2000; Halpern et al., 2003; Thesen et al., 2012) and impaired mental and psychomotor function (Hesser et al., 1978; Sayers et al., 1987; Henning et al., 1990; Fothergill et al., 1991). Our recent intervention study demonstrated a significant cross-correlation between a reduced wake pCO_2, a faster sleep EEG (reduced Delta/Alpha ratio) and reduced daytime sleepiness during positive airway pressure treatment in hypercapnic SDB patients (Wang et al., in press). Multiple regression analyses showed that the degree of change in hypercapnia but not hypoxia was the only significant predictor of both the Delta/Alpha ratio and daytime sleepiness (Wang et al., in press). In order to directly compare the generic effect of hypoxia and hypercapnia on EEG, the present study used an experimental design that carefully controlled for the mix of inspired oxygen and carbon dioxide while monitoring EEG activity during wakefulness. Delta/Alpha ratio was the primary outcome of interest.

2. Methods

This experiment was conducted at the clinical sleep laboratory of the Royal Prince Alfred Hospital (RPAH), a major teaching hospital of the University of Sydney. The study protocol was approved by Sydney South West Area Health Service (SSWAHS) Ethics Review Committee (Protocol Number: X11-0325). All participants provided written informed consent. The Australian & New Zealand Clinical Trial Registry number is ACTRN12612000454875.

2.1. Subjects and procedure

The twenty normal volunteers were medical students and staff members from Sydney Medical School/RPAH. They did not have sleep apnea or other medical complaints. All subjects fasted for 3 h prior to the tests. While connected to a two-channel EEG system (C3–A2, C4–A1; Alice 5 diagnostic sleep system, Respironics, USA), they were tested for their ventilatory response to hypercapnia and hypoxia under three standard protocols using a fully computerized testing system (Rebuck and Campbell, 1974; Duffin, 2011). The three rebreathing protocols included testing the EEG responses to (1) hypercapnia plus sustained hyperoxia (Protocol 1) (Duffin, 2011), (2) the combined effect of hypercapnia plus sustained hypoxia (Protocol 2) (Duffin, 2011), and (3) hypoxia with mild hypocapnia induced via a CO_2 scrubber (Protocol 3) (Rebuck and Campbell, 1974). Each of the three protocols started with a 5-min session of breathing room air through a mouth piece connected to the full apparatus. Protocol 1 consisted of a 5-min rebreathing session, measuring the EEG response to hypercapnia with pO_2 held constant at 150 mmHg (hyperoxia). Protocol 2 also included a 5-min rebreathing session, measuring the EEG response to hypercapnia and hypoxia with pO_2 held constant at 50 mmHg (hypoxia). To achieve a stable control of pO_2 for these two protocols, our computer system continuously analyzed O_2 consumption over the previous 3 breaths during the test and used a prediction model to determine how much O_2 to supply to the circuit. Protocol 3 also involved with ~5-min session of rebreathing but with a CO_2 scrubber in the circuit. A 30 min resting break was taken between each protocol. The EEG data were later synchronized with data from the ventilatory response computer. An oximeter was connected to both the ventilatory response computer and the polysomnography (PSG) computer and the oximeter output was recorded simultaneously during each testing session. This channel was also used as a marker for synchronization of the two computers.

2.2. EEG spectral analyses

All EEG recordings were converted to European Data Format (EDF) for the spectral analyses. We analyzed each EEG segment corresponding to each breath cycle because we measured end-tidal pCO_2 breath by breath. To minimize blinking artifact in the EEG we encouraged all subjects to keep their eyes open and stare at a relaxing picture on the wall during each testing session. In addition, we minimized behavioral variability by using subjects as their own control (comparing between sessions). All EEG sampling rates were >200 Hz. The bandpass was between 0.3 and 93 Hz. A standard Fast Fourier Transform (FFT) with a rectangular weighting window was performed twice: first, to the largest power of 2 data points smaller than the total number of data points, selected from the beginning of the segment, and second, to the same number of data points selected from the end. This double FFT method weights middle data points. Delta, theta, alpha and beta bands were defined as the frequency ranges 0.5–4.5 (delta), 4.5–8 (theta), 8–12 (alpha), 12–32 (beta) Hz, respectively. The EEGs were then further examined by an automatic algorithm which excluded EEG segments showing excessive delta power using a standard two sigma rule (i.e., median + 2 standard deviations). For our statistical analyses, we focused primarily on the EEG recorded at C3/A2. However, when the C3/A2 channel was contaminated with many artifacts, we used C4/A1 as an alternative channel. Individual spectral band power and total summed power between 0.5 and 32 Hz were calculated. Spectral band% was calculated as individual band power/total summed power between 0.5 and 32 Hz × 100. Delta/Alpha (D/A) ratio was calculated as delta power/alpha power.