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Original Article

A pilot study of sleep, cognition, and respiration under 4 weeks of intermittent nocturnal hypoxia in adult humans ☆

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ABSTRACT

Study objectives: A pilot study to examine the effects of intermittent nocturnal hypoxia on sleep, respiration and cognition in healthy adult humans.
Methods: Participants were eight healthy, non-smoking subjects (four male, four female), mean age of 26.4 ± 5.2 years, and BMI 22.3 ± 2.6 kg/m^2, exposed to 9 h of intermittent hypoxia between the hours of 10 P.M. and 7 A.M. for 28 consecutive nights. At a simulated altitude of 13,000 feet (FIO_2 0.13), intermittent hypoxia was achieved by administering nasal nitrogen, alternating with brief (approximately 5 s) boluses of nasal oxygen. Pre- and post-exposure assessments included polysomnography, attention (20-min Psychomotor Vigilance Test), working memory (10-min verbal 2 and 3-back), Multiple Sleep Latency Test, and the Rey Auditory Verbal Learning Test. Obstructive and non-obstructive respiratory events were scored.
Results: Overall sleep quality showed worsening trends but no statistically significant change following exposure. There was no difference after hypoxia in sleepiness, encoding, attention or working memory. Hyperoxic central apneas and post-hyperoxic respiratory instability were noted as special features of disturbed respiratory control induced by intermittent nocturnal hypoxia.
Conclusions: In this model, exposure to nocturnal intermittent hypoxia for 4 weeks caused no significant deficits in subjective or objective alertness, vigilance, or working memory.

1. Introduction

Multiple mechanisms are thought to contribute to sleepiness in patients with sleep-disordered breathing. These include sleep fragmentation [1], hypoxia [2], partial chronic sleep deprivation from sleep time lost due to arousals [3], cytokine dysregulation [4], obesity-associated biology [5,6], and interactions with individual adaptations [7]. However, treated patients often experience residual daytime sleepiness [8]. Possible mechanisms for incomplete recovery include (1) treatment failure – suboptimal use of positive airway pressure therapy, in terms of inadequate duration or consistency of use, or insufficient treatment pressure; (2) other causes of hypersomnia, including chronic partial sleep deprivation, circadian phase delay, comorbid depression or Attention Deficit Hyperactivity Disorder; and (3) permanent injury due to chronic hypoxia [2]. This final reason is particularly worrisome, as there are no treatments available to reverse injury or enhance recovery, and could be especially detrimental to the developing brain [9].

Data on the direct effects of pure nocturnal hypoxia on wake cognition in humans are not available. In those with sleep-disordered breathing, sleep fragmentation frequently coexists with nocturnal hypoxia, and those with more severe degrees of hypoxia may have greater sleep fragmentation [10]. In those with chronic obstructive lung disease and severe nocturnal desaturations, the REM-dominant nature of these oxyhemoglobin desaturations confines the majority of the hypoxic burden to a relatively short portion of the sleep period, but fragmentation of REM sleep may occur [11]. Living at altitude exposes individuals to continuous hypoxia, but this model is not entirely relevant to clinical sleep medicine since most patients in the sleep clinic do not have daytime hypoxia. Thus, there is a need for an experimental model of pure nocturnal hypoxia in humans, ideally one that has flexibility in the duration of exposure. Such a model may then complement animal models of intermittent hypoxia [9,12], which have shown clear evidence of executive function deficits, neuronal injury, and residual hypersomnolence.

Experimental hypoxia in a controlled, simulated high-altitude environment has been used for several years to study cognitive

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and hemodynamic effects of extreme altitude exposures [13,14]. Despite extensive study of the effects of continuous hypoxia on sleep at altitude, the effect of nocturnal intermittent hypoxia, a closer approximate of sleep-disordered breathing, has not been studied in healthy volunteers. We recently completed an assessment of sleep, sleep respiration, and cognition in healthy subjects exposed to a simulated altitude of 13,000 feet for 14 consecutive nights and were surprised to find no decrement in vigilance (Psychomotor Vigilance Test) or verbal working memory as assessed by a 2-back task [15]. The current study was undertaken to examine the effects of intermittent nocturnal hypoxia on sleep, respiration, and cognition to further the understanding of sleep-only intermittent hypoxia in adult humans.

2. Methods

2.1. Study subjects

Eight healthy, non-smoking subjects (four male, four female) completed the study. All women began exposure during the week following menses and all tested negative for pregnancy by a urinary β-HCG test. The subjects had a mean age of 26.4 ± 5.2 years and BMI of 22.3 ± 2.6 kg/m^2. All subjects underwent a routine history and physical examination to exclude cardiopulmonary or neurological disease prior to giving written informed consent. Screening procedures included a detailed sleep history and specific inquiry regarding prior exposure to altitude. The subjects were selected to not have prior altitude exposure (greater than 2 weeks above 5000 feet in the previous three months), delayed or advanced habitual sleep times (outside of 10–11 P.M. to 6–7 A.M.), unrefreshing sleep, habitual loud snoring, daytime napping, restless legs, anxiety or depression (by past or current diagnosis or treatment), past or current drug abuse, alcohol dependence or binge drinking, tobacco smoking, or active medical conditions such as diabetes and hypertension. Subjects were required to taper and discontinue all caffeine use for the week prior to study entry, agree not to use caffeine or alcohol, take naps or use over-the-counter substances during the course of the protocol; this was verbally confirmed daily. They were allowed to continue their regular day job outside the General Clinical Research Center (GCRC) and returned for sleep and hypoxia exposure. Subjects were thus at sea level during the day.

This protocol was reviewed and approved by the Institutional Review Board (IRB) at the Beth Israel Deaconess Medical Center, Boston, Massachusetts. The informed consent detailed the possible cognitive consequences of hypoxia and altitude exposure and the unknown risks associated with the type of experimental hypoxia exposure.

2.2. Hypoxic exposure

The hypoxic exposure was achieved using a commercially available normobaric altitude tent (Colorado Altitude Training, Colorado Springs, CO, USA). Subjects slept in a standard hospital bed inside the 9 × 7 × 6 foot tent. Altitude was set and continuously monitored using a central controller with real-time output. Altitude and CO_2 levels within the tent were monitored continuously throughout the exposure. CO_2 was removed using soda-phosphate crystals with a fan-driven system within the tent to allow continuous passage of tent gas across the system and maintenance of stable CO_2 levels. Independent verification of CO_2 levels was performed by an automatic CO_2 monitoring system (Real-term, Colorado Altitude Training, Colorado Springs, CO, USA), which yielded 0.4% mm Hg as an average value during the night (range 0.1–0.52%). Oxygen saturation was monitored continuously overnight.

Subjects were exposed to 9 h of intermittent nocturnal hypoxia between the hours of 10 P.M. and 7 A.M. for 28 consecutive nights. Subjects underwent acclimatization to the hypoxic exposure with graded increases in simulated altitude over three nights. Simulated altitude levels started at sea level, followed by one night at 7700 feet, one night at 10,000 feet, and then exposure to a simulated altitude of 13,000 feet for 28 consecutive nights. Exposure was considered to begin (night #1) on the first night at 13,000 feet. Independent evaluation of the FIO_2 at the altitude setting of 13,000 feet using an oxygen sensor (Crowcon, Gasman, 2002) showed FIO_2 to be 0.13 inside the tent system. At this FIO_2, steady state subject saturations while wake were 83–85%.

2.3. Induction of intermittent hypoxia

Intermittent hypoxia, which started on the first night at 13,000 feet, was achieved by administering a brief (approximately 5 s) bolus of nasal oxygen alternating with nitrogen, delivered via nasal prongs, every 3 min. These boluses were delivered during both sleep and wakefulness, during the time in bed. Alternation of gasses was obtained using a pressure-powered, custom made valve device, which allowed control over duration of total cycle time and fractions of inspiration and expiration times. The flow rate of oxygen when "on" was 2–6 L/min, adjusted for the individual subject to obtain re-oxygenation with a target of 95%. The subject experienced continuous flow at the nares, thus eliminating any possible "switching effect."

2.4. Polysomnography

Two nights of tent acclimatization was provided to all subjects. Standard polysomnography using an Embla system (Embla, Denver, CO, USA) included recording the electroencephalogram, electrooculogram, chin and anterior tibialis electromyogram, airflow with an oronasal thermistor and nasal cannula pressure-transducer system, thoracic and abdominal effort with piezo effort bands, electrocardiogram, and finger oximetry at baseline. The recording was done at two time points, at baseline and on the last night of exposure. Standard stages (rapid eye movements [REM] and stage I–IV non-REM [NREM] sleep) and 3-s EEG alpha arousals (American Academy of Sleep Medicine arousals [16]) were scored.

2.5. Respiratory event scoring

Modified standard research criteria [17] were used to score abnormal respiration during sleep. Obstructive apnea was scored when there was an absence of airflow for greater than 10 s on the nasal cannula and thermistor with continued respiratory effort. Central apnea was scored when there was an absence of airflow on the nasal cannula and thermistor for greater than 10 s with no evidence of respiratory effort. Hypopneas with flow-limitation were identified when there was a sequence of progressive flow-limited breaths, the entire abnormality lasting at least 10 s, which terminated in an abrupt sinusoidal recovery breath. Hypopneas without flow-limitation were identified when there was no progressive flow-limitation but a clearly evident (approximately 30%) reduction in airflow and respiratory effort followed by a recovery in amplitude of both signals. Hypopneas were thus scored in the following circumstances: when there was an associated 3% oxygen desaturation, a 3-s American Academy of Sleep Medicine electroencephalogram alpha/beta arousal, and progressive flow-limitation or a major (30–50%) reduction in signal amplitude followed by sinusoidal recovery breath. Periodic breathing time expressed as a percent of total sleep time was scored separately as a measure