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A pilot study of sleep, cognition, and respiration under four 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/m², exposed to nine hours 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 (FIO₂ 0.13), intermittent hypoxia was achieved by administering nasal nitrogen, alternating with brief (approximately five seconds) boluses of nasal oxygen. Pre and post exposure assessments included polysomnography, attention (20-minute Psychomotor Vigilance Test), working memory (10-minute 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.

Keywords

sleep; intermittent; hypoxia; cognition; altitude; working; memory

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

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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; 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 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.

METHODS

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/m². 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.

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 $9 \times 7 \times 6$ foot tent. Altitude was set and continuously monitored using a central controller with real-time output. Altitude and CO₂ levels within the tent were monitored continuously throughout the exposure. CO₂ 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 CO₂ levels. Independent verification of CO₂ levels was performed by an automatic CO₂ monitoring system (Realterm, Colorado Altitude Training, Colorado Springs, CO, USA), which yielded 0.4% mm Hg as an average value during the night (range 0.1 to 0.52%). Oxygen saturation was monitored continuously overnight.

Subjects were exposed to nine hours 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 FIO₂ at the altitude setting of 13,000 feet using an oxygen sensor (Crowcon, Gasman, 2002) showed FIO₂ to be 0.13 inside the tent system. At this FIO₂, steady state subject saturations while awake were 83–85%.

Induction of Intermittent Hypoxia

Intermittent hypoxia, which started on the first night at 13,000 feet, was achieved by administering a brief (approximately five seconds) bolus of nasal oxygen alternating with nitrogen, delivered via nasal prongs, every three minutes. 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 liters per minute, 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.”

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 three-second EEG alpha arousals (American Academy of Sleep Medicine arousals¹⁶) were scored.

Respiratory event scoring

Modified standard research criteria¹⁷ were used to score abnormal respiration during sleep. Obstructive apnea was scored when there was an absence of airflow for greater than 10 seconds 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 seconds 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 seconds, 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-second 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 of altitude-induced respiratory change, when 6 cycles or 2 continuous minutes of concordant waxing and waning flow and effort occurred. We relaxed the usual 10 minute duration requirement to capture shorter periods of periodic breathing, expressed as a percentage of total sleep time.

An intermittent oxygen desaturation index (ODI, dips per hour of sleep) was calculated using a 3% criterion for the pre-exposure study. The desaturation criterion required a 3% drop from the preceding 20-second stable baseline – a drop from 88% to 85% would be scored but not an 88% to 86% change. As global measures of nocturnal hypoxic exposure, the following were computed: total sleep time at less than 90% saturation and at less than 80% saturation. All scoring was done manually by the third author.

Neuropsychological and vigilance assessments

Subjects practiced the tests employed in the study until performance (reaction time, percentage correct) was stable, which usually took about 20 minutes for the working memory task and occurred after one practice run of the Psychomotor Vigilance Task (PVT).¹⁸ Further practice sessions were not permitted. Assessments were performed at baseline (prior to hypoxia exposure) and repeated at the end of the protocol. A research Multiple Sleep Latency Test¹⁹ (test is terminated after three epochs of stage I sleep or a single epoch of any other stage) was performed at baseline and at the end of the protocol. To minimize circadian effects on performance, vigilance and working memory testing was done between 8 A.M. and 10 A.M. in every case. An integrated assessment of subjective sleepiness and mood was assessed on a scale of 0 (very sleepy compared to usual state, depressed mood) to 10 (no change from usual state, normal mood state). This measure was obtained from the PVT device, immediately before and following the 20-minute PVT, and averaged.

The working memory assessment used a 10-minute verbal 2-back and 3-back task.¹⁵ One alphabet was presented to the subject every four seconds, with encouragement to respond as rapidly as possible while maintaining accuracy. Percent correct and mean response times were computed. Two 10-minute sets were presented consecutively with a one-minute break. This provided 300 responses per testing point for both the 2 and 3-back, and the mean value of all responses provided a single performance speed for tabulation and computation.

The Rey Auditory Verbal Learning Test (RAVLT)^{20, 21} was administered between the first and second naps before and after hypoxic exposure. One additional RAVLT test was administered after 2 weeks of hypoxia as an IRB-suggested safety measure.

The protocol had a clause for continued cognitive testing for 4 weeks if there were adverse changes (30% worsening from baseline for individual subjects) following exposure, but this was not activated as this threshold was not reached by any subject.

Statistical methods

To calculate sample size, we used the number of lapses on the PVT (reaction times > 500 milliseconds) as the primary variable of interest. Lapses are a sensitive biomarker of increased homeostatic sleep drive in the context of conditions causing excessive sleepiness, including sleep deprivation or sleep fragmentation, and are quite rare in rested individuals on the 10-minute PVT. Our own experience using the 20-minute version has shown a mean lapse frequency of 5–8 in healthy subjects. Our sample size was powered (0.9) to detect a change in mean lapse frequency of 5 ± 2 at baseline to 10 ± 4 after exposure.

Means and standard deviations were computed for polysomnographic and cognitive variables. Paired t-tests were used to assess the effects of exposure on sleep and cognition. Repeated measures Analysis of Variance was used to assess the impact of hypoxia on the Rey Auditory Verbal Learning test, as three time points were obtained. The Wilcoxon rank sum test was used to assess pre and post-exposure effects on performance, sleep and respiration, as the data were not normally distributed. STATA SE8 (StataCorp, College Station, Texas, USA) was used for analysis.

RESULTS

Sleep quality during sleep hypoxia

No statistically significant changes from baseline were observed regarding different sleep variables, including total sleep time, sleep efficiency, percentage of total sleep time in various sleep stages, REM latency, arousal index, or periodic leg movement index (Table 1). Apparent mean reductions in total sleep time or increases in the arousal index and stage I sleep did not reach statistical significance.

Sleep hypoxia

The model successfully induced nocturnal hypoxia, as summarized in Table 2. Determined by the experimental protocol, the induced ODI was 19.2 / hours of sleep, from a baseline of 0.2 / hours of sleep. Re-oxygenation always reached or exceeded 90%, with $78 \pm 8\%$ of boluses resulting in an oxygen saturation that exceeded 95%. The mean SaO₂ nadir was reduced from $95.3 \pm 2.1\%$ pre-exposure to $82.1 \pm 6\%$ at end-exposure ($p < 0.001$). Subjects spent $44.8 \pm 28.3\%$ of total sleep time at a SaO₂ below 90%, which was statistically significant compared to pre-exposure ($p = 0.006$). Subjects spent $0.04 \pm 0.08\%$ of total sleep time below a SaO₂ of 80%, which was not statistically significant in comparison to the pre-exposure SaO₂ nadir. Medically significant cardiac arrhythmias (atrial flutter or fibrillation, ventricular tachycardia) were not induced in any of the subjects.

Respiration during sleep hypoxia

As summarized in Table 2, hypoxia exposure was associated with the induction of specific patterns of sleep-disordered breathing. The number of central apneas induced by the oxygen bolus was 15.3 ± 4.6 , about half the total number of central apneas. Episodes of respiratory instability and periodic breathing occurring immediately after following the oxygen bolus was more prominent in NREM sleep (Figures 1–3).

Sleepiness and cognitive performance

There were no significant differences from baseline across the period of exposure in any of the following variables: 1) subjective sleepiness; 2) two and 3-back mean reaction times (accuracy was > 95% in all instances), slowest 10% reaction times, and fastest 10% reaction times; and 3) the following measures of the Psychomotor Vigilance Test: mean reaction times, 10% slowest reaction times, false starts, or lapses (Table 3).

The mean sleep latency was unchanged: 9.1 ± 3.1 minutes pre-exposure, and 9.7 ± 2.8 minutes post-exposure (paired t-test p : 0.5). The RVT showed no adverse effects of hypoxia on verbal learning and encoding (Table 4).

DISCUSSION

This pilot study is the first that describes the effects of subacute intermittent nocturnal hypoxia on alertness and cognition in healthy human volunteers. Our major findings were that 1) multiple nights of intermittent nocturnal hypoxia can be safely and effectively induced in humans; 2) the exposure provokes a spectrum of respiratory abnormalities; 3) sleep quality was relatively well-maintained under intermittent hypoxia; 4) the exposed subjects showed no significant deficits in subjective or objective alertness, objective vigilance, verbal learning, or working memory. These results are limited by the small sample size, and that on a background of hypoxia, episodic reversal was achieved by brief boluses of oxygen, somewhat the inverse of sleep apnea.

Our model is a reasonable approximation of clinical sleep-disordered breathing, as exposure is intermittent, associated with re-oxygenation, and occurs only during the sleep period. Sleep respiration at altitude is typically characterized by periodic breathing, dominant in NREM sleep.^{22, 23, 24} Besides the expected periodic breathing, we also saw central apneas induced by the oxygen bolus and respiratory instability immediately following the oxygen bolus. Central apneas following return to normoxia or hyperoxia have been described under a variety of relatively brief experimental conditions.^{25, 26–28} Hypoxia can increase the sleep CO₂ apneic threshold and hyperoxia can lower it.²⁹ A combination of hypocapnia and hyperoxia has previously been demonstrated to produce central apnea during NREM sleep.^{25, 30, 31} Cortical activity plays a role in maintaining respiratory rhythm,³² but in our model instability occurred even without cortical arousals. As we did not measure end-tidal CO₂ or O₂, the exact genesis of the changes noted is not known.

Our results were surprising as there is ample supportive evidence that hypoxia may be directly linked to cognitive dysfunction, such as chronic obstructive lung disease,³³ and altitude exposure.¹⁴ Hypoxia has direct effects on sleep in rodents, including increased wake and stage I sleep, associated with reduced delta power and decreased REM sleep.^{34, 35} Veasey and colleagues exposed mice to intermittent hypoxia during the lights-on period daily for eight weeks and demonstrated reduced sleep latency, oxidative injury in wake-promoting regions of the brain, and increased sensitivity to sleep deprivation.² Murine models of sleep intermittent hypoxia have demonstrated executive dysfunction, excessive sleepiness, oxidative injury to basal forebrain structures, and brainstem motor neurons.^{2, 36–38} Prior models of intermittent hypoxia also demonstrate executive and learning dysfunction and hippocampal injury.^{9, 12, 39} Results using brain morphometric techniques in humans are mixed,^{40, 41} with both extensive and limited hippocampal signal reductions in hypoxic sleep-disordered breathing. In addition, healthy volunteers may be more resistant to the adverse effects of intermittent hypoxia and sleep fragmentation on cognition than patients with sleep apnea. The duration of exposure remains important, as we evaluated 4 weeks vs. years of exposure that occur in sleep apnea patients.

Our model has several important limitations. The pattern of hypoxia and re-oxygenation does not exactly mimic that seen in sleep apnea, where the background is typically not hypoxic. The piezo effort bands are less accurate in estimating respiratory effort than respiratory inductance plethysmography or esophageal manometry. The expense and degree of labor of the experiment at the pilot stage did not allow for a perfect design – randomized, sham arm, control arm of placebo intermittent hypoxia, counterbalanced design, retesting several weeks after hypoxia, and control for learning and habituation effects. The sample size is small, but powered to detect moderate changes in vigilance. The tests used may not have been sensitive enough, but we did use field standards shown to be sensitive to increases in sleep drive and sleep debt. Subjective assessments of sleepiness and mood following sleep deprivation are progressively inaccurate over time even if performance is deteriorating, but the complete absence of subjective change argues against this explanation. The Psychomotor Vigilance Test used has been shown in numerous publications to be sensitive to the effects of excessive sleepiness.¹⁸ We have used the 2-back working memory task to assess the effects of single night sleep deprivation and auditory sleep fragmentation, and cognitive function in sleep apnea and narcolepsy, with a consistent demonstration of slowing of performance.⁴² The Multiple Sleep Latency Test¹⁹ is a standardized objective test of sleepiness. The Rey verbal learning test is sensitive to hippocampal function. It is thus unlikely that a major component of sleepiness-induced brain function was not sampled by our methods. More subtle effects, however, cannot be excluded. The average age of our subjects is less than the majority of patients with sleep apnea, and younger individuals may be more tolerant to intermittent nocturnal hypoxia or simply have greater reserve to adapt. Our subjects, who continued their usual daytime jobs during the experimental period, were not monitored during the day but were instructed not to nap (and verified on return to the GCRC). While this design may result in imperfect control of the experimental environment, it is a more real-life condition.

In conclusion, we report the absence of significant subjective or objective sleepiness, or objective vigilance and working memory impairment, following 4 weeks of nocturnal intermittent hypoxia in healthy adult volunteers, using a model of episodic reoxygenation in a controlled hypoxic environment. Technical improvements in the model, such as longer periods of normoxia, and tracking / control of CO₂ to minimize periodic breathing, and a sham / placebo controlled design may yield more precise assessments of the effects of sleep hypoxia on human cognitive function.

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Figure 1. Effects of Intermittent Hypoxia on NREM sleep respiration

Snapshot(480 seconds) from a polysomnogram under intermittent hypoxia demonstrates the following: 1) oxygen bolus-induced central apnea on the left side of the figure; and 2) post-bolus central apnea and respiratory instability (right side). Note the rapid rise in saturation with each bolus of nasal oxygen and slower reduction. Heart rate demonstrates expected fluctuations with sleep-respiration. Conventional sleep stage is III, NREM. There are no arousals associated with the respiratory abnormality. Thus, respiratory and sleep quality effects are relatively dissociated. The signals from top are: EEG: C3-A2 referential recording, EOG: electrooculogram, EMG: submental electromyogram, FLOW: airflow (nasal cannula-pressure transducer system), ABD: abdominal effort (piezo bands), Sa: finger oximetry and HR: heart rate.

Figure 2. Effects of Intermittent Hypoxia on REM sleep respiration

Snapshot (480 seconds) from a polysomnogram under intermittent hypoxia demonstrates the following: 1) relative hyperoxia-induced central apnea on the left side of the figure; and 2) post-hyperoxic central apnea respiratory instability is not induced. Note the rapid rise in saturation with each bolus of nasal oxygen. Heart rate demonstrates expected fluctuations commonly seen in REM sleep, independent of respiration. There are no arousals associated with the respiratory abnormality. Thus, respiratory and sleep quality effects are relatively dissociated. The signals from top are: EEG: C3-A2 referential recording, EOG: electrooculogram, EMG: submental electromyogram, FLOW: airflow (nasal cannula-pressure transducer system), ABD: abdominal effort (piezo bands), Sa: finger oximetry and HR: heart rate.

Figure 3. Dissociation of sleep and respiratory effect of intermittent hypoxia

Snapshot (180 seconds) from a polysomnogram under intermittent hypoxia demonstrates a central apnea without arousal. There is mild respiratory instability in the minute following the central apnea. The signals from top are: EEG: C3-A2 referential recording, EOG: electrooculogram, EMG: submental electromyogram, FLOW: airflow (nasal cannula-pressure transducer system), ABD: abdominal effort (piezo bands), Sa: finger oximetry and HR: heart rate.

Table 1

Polysomnography under intermittent hypoxia

Variable	Pre-exposure	End-exposure	Wilcoxon ranksum test (p)
TST (hours)	421.4 ± 51.8	389.3 ± 66	0.3
SE (%)	87.9 ± 10.4	84.1 ± 12.5	0.6
Stage I (% TST)	9 ± 3.8	16.4 ± 12.2	0.2
Stage II (% TST)	48 ± 6.7	43.5 ± 14.2	0.4
Stage III (% TST)	10.2 ± 4.4	8.9 ± 5.4	0.6
Stage IV (% TST)	6.2 ± 5.7	5.7 ± 5.7	0.8
REMS (% TST)	26.6 ± 3	25.4 ± 4.9	0.8
REML (minutes)	100.4 ± 63.6	101.3 ± 56.9	0.9
Arl (/ hour sleep)	16.3 ± 9.9	30.7 ± 19.6	0.1
PLMI (/ hour sleep)	5.4 ± 13.8	0.2 ± 0.4	0.3

TST: total sleep time

SE: sleep efficiency

REMS: rapid eye movement sleep

REML: REM sleep latency

Arl: arousal index

PLMI: periodic leg movement index

There are no statistically significant differences in all conventional sleep measures before and at the end of the 4-week intermittent hypoxia exposure period. Although total sleep time appear to be reduced by a mean of 30 minutes, and the mean arousal index and stage I sleep is apparently increased, inter-individual variability is high and the results do not reach statistical significance.

Table 2

Respiration during intermittent hypoxia

Variable	Pre-exposure	End-exposure	Wilcoxon ranksum test (P)
CAI (/ hour sleep)	0.9 ± 0.6	30.1 ± 29.5	0.04
OAI (/ hour sleep)	1.4 ± 3.2	0.2 ± 0.3	0.3
HI (/ hour sleep)	4.6 ± 4.9	12.3 ± 11.4	0.05
HFLI (/ hour sleep)	4.3 ± 4.9	11.5 ± 11	0.05
RDI (/ hour sleep)	6.8 ± 7.7	42.6 ± 36.2	0.02
Minimum nocturnal oxygen saturation	95.3 ± 2.1	82.1 ± 6	> 0.001
Periodic breathing time (% total sleep time)	0	36.7 ± 12.2	> 0.001
% TST < Sa90	0	44.8 ± 28.3	0.006
% TST < Sa80	0	0.04 ± 0.08	0.2

CAI: Central apnea index

OAI: Obstructive apnea index

HI: Hypopnea index

HFLI: Hypopneas with flow-limitation

RDI: respiratory disturbance index

TST: total sleep time

There is a marked increased in central apneas under intermittent hypoxia. Note that the majority of hypopneas induced by intermittent hypoxia have associated flow-limitation in the nasal cannula-pressure transducer trace.

Table 3

Attention and memory after intermittent hypoxia

Variable	Pre-exposure (mean $\pm$ SD)	End-exposure (mean $\pm$ SD)	Wilcoxon ranksum test (P)
PVT Mean RT	355 $\pm$ 75	334 $\pm$ 84	0.4
PVT 10% Slowest RT	640 $\pm$ 276	550 $\pm$ 207	0.3
Lapses (RT > 500 milliseconds)	7.1 $\pm$ 5.9	7.4 $\pm$ 8.6	0.6
False starts	1.3 $\pm$ 1.1	1.4 $\pm$ 1.3	0.4
2-back mean RT	709 $\pm$ 385	602 $\pm$ 362	0.2
2-back 10% fastest responses	502 $\pm$ 220	526 $\pm$ 178	0.3
2-back 10% slowest responses	1278 $\pm$ 332	1347 $\pm$ 317	0.3
3-back mean RT	874 $\pm$ 530	716 $\pm$ 498	0.2
3-back 10% fastest responses	587 $\pm$ 257	596 $\pm$ 218	0.2
3-back 10% slowest responses	1487 $\pm$ 373	1532 $\pm$ 289	0.3
Multiple Sleep Latency Test	9.12 $\pm$ 3.1	9.74 $\pm$ 2.8	0.5

PVT: Psychomotor Vigilance Test

Attention and working memory performance are unchanged after 4-weeks of hypoxia exposure.

Table 4

Effects of hypoxia on the Rey Auditory Verbal Learning Test (RAVLT)

RVLT Measure	Pre - IH	14 nights IH	28 nights IH	Significance F(2,21), p
Encoding	7.8 ± 1.3	9 ± 1.5	8.5 ± 2.7	0.84, 0.45
Learning	59.3 ± 9	58.5 ± 9.5	60.3 ± 12.6	0.06, 0.95
Proactive Interference	8.9 ± 3.4	10.4 ± 3.2	13.6 ± 2.6	5.04, 0.02
Retroactive Interference	13.6 ± 2.9	13.6 ± 2.8	14.1 ± 1	0.12, 0.89
20-minute delay recall	12.9 ± 4.2	13 ± 2.9	12.6 ± 4	0.02, 0.98
Recognition - Hit	14.1 ± 1.4	14.1 ± 1.4	13.8 ± 1.8	0.16, 0.85
Recognition – Correct Rejections	14.8 ± 0.5	14.6 ± 0.7	14.9 ± 0.4	0.42, 0.66
Recognition - Miss	0.9 ± 1.4	0.9 ± 1.4	1.25 ± 1.8	0.16, 0.85
Recognition – False alarms	0.3 ± 0.5	0.4 ± 0.7	0.1 ± 0.4	0.42, 0.66

The RAVLT is essentially unchanged by 4-weeks of intermittent sleep hypoxia. The only statistically significant result is an *improved* performance on the proactive interference task. The data in this table are total scores of recalled items in the RAVLT.