BRIEF REPORT

Improving Sleep at Altitude: A Comparison of Therapies

George W. Rodway, PhD; Mark E. Edsell, MB, ChB, FRCA; Bob Wong, PhD; Jeremy S. Windsor, MB, ChB, for the Caudwell Xtreme Everest Research Group

From the University of Utah College of Nursing and School of Medicine, Salt Lake City, UT (Drs Rodway and Wong); The Centre for Altitude, Space and Extreme Environment Medicine (CASE), University College, London, UK (Drs Rodway, Edsell, and Windsor); and St George's Hospital, London, UK (Dr Edsell).

Objective.—This study aimed to compare 3 treatment modalities during sleep at an altitude of 5300 m to identify strategies for reducing the incidence of periodic breathing at high altitude.

Methods.—Fifteen trekkers, with identical ascent profiles and no signs or symptoms of altitude illness, served as subjects. All study participants arrived at 5300 m after a gradual ascent from 1300 m. On their second night at 5300 m, subjects were randomly assigned (with a computer-based random assignment procedure) to 1 of 4 different treatment groups: control ($n = 4$); 1 L/min O₂ via a demand system during sleep ($n = 3$); 1 L/min O₂/CO₂ mix (1.5% CO₂) via a demand system during sleep ($n = 4$); or 125 mg acetazolamide 30 minutes before bedtime ($n = 4$). Heart rate, respiration rate, blood oxygen saturation, tidal volume, minute volume, and apnea hypopnea index were measured.

Results.—Upon comparing the 4 groups, there were no statistically significant differences between the variables. One-way analysis of variance indicated a trend toward statistical significance for SaO₂ between groups ($F = 2.9$, $P = .08$), and Tukey Honestly Significant Difference (HSD) post hoc tests indicated a trend in the SaO₂ difference between the 1 L/min oxygen and control groups ($P = .07$). While 1-way analysis of variance suggested no difference for respiratory rate between groups ($F = 2.5$, $P = .1$), Tukey HSD indicated a trend in statistical difference of the respiratory rate between 1 L/min O₂ and 1 L/min O₂/CO₂ mixture ($P = .08$).

Conclusions.—These statistical trends found between control and treatment groups indicate that further study is warranted.

Key words: nocturnal periodic breathing, treatment, high altitude, hypoxia

Introduction

On ascending to altitude, unacclimatized lowlanders typically complain of poor sleep. This is often characterized by a difficulty in getting to sleep, a restless night punctuated with frequent awakenings, and a feeling of tiredness the next day.¹ In most cases, this is due to cycles of periodic breathing that occur as a result of the fall in the partial pressure of oxygen (PO₂) that is commonly seen on ascent to altitude.² By increasing PO₂ with supplemental oxygen, it is possible to reduce periodic breathing and, hence, improve the quality of sleep.^{1,3,4} Alternatively, it is also possible to treat this condition by addressing the hypocapnia and resulting respiratory alkalosis that typically precedes the apneic phase of periodic

breathing at altitude.⁵ This has been done successfully by either inhaling small quantities of carbon dioxide while asleep or taking a carbonic anhydrase inhibitor such as acetazolamide prior to going to bed.^{6,7} By triggering a metabolic acidosis, acetazolamide also counteracts the respiratory alkalosis seen during periodic breathing, and it is a safe and effective way of improving oxygenation.⁸

In this small study, our intention was to compare the effects of O₂, O₂/CO₂ mixture, and acetazolamide vs placebo on nocturnal oxygenation and ventilation at 5300 m. We wished to identify a practical strategy for reducing the incidence of nocturnal periodic breathing at high altitude.

Methods

Subjects: Fifteen healthy trekkers (12 male, 3 female; age range 25–55, mean age 38.1), with identical ascent profiles and no signs or symptoms of altitude illness

Corresponding author: George W. Rodway, PhD, University of Utah College of Nursing and School of Medicine, 10 South 2000 East, Salt Lake City, UT 84112 (e-mail: gwr@u.utah.edu).

during daytime waking hours, served as subjects. Study participants had no history of chronic cardiopulmonary disease, no known history of obstructive sleep apnea, and were not taking any prescription medications (including medications for altitude illness or sleep) during the trek prior to this study. We obtained approval for this study from the University College London Committee on the Ethics of Non-NHS (National Health Service) Human Research. All participants gave written informed consent. All study participants arrived at Mount Everest 5300 m Base Camp after a gradual 13-day ascent from Kathmandu, Nepal. On their second night at 5300 m, subjects were randomly assigned (with a computer-based random assignment procedure) to 1 of 4 different treatment groups: control ($n = 4$); 1 L/min O_2 via a demand system during sleep ($n = 3$); 1 L/min O_2/CO_2 mix (1.5% CO_2 ; remainder of gas mixture 98.5% O_2) via a demand system during sleep ($n = 4$); or 125 mg acetazolamide 30 minutes before bedtime ($n = 4$). The relatively small percentage (1.5%) of CO_2 added to the O_2/CO_2 mixture was based primarily on ethics board considerations. In addition, acetazolamide 125 mg at bedtime is a widely accepted dosing regimen for nocturnal periodic breathing prophylaxis,⁸ even though the half-life of acetazolamide is variously reported as being between 3 to 9 hours and 10 to 15 hours. Heart rate (HR), respiration rate (RR), blood oxygen saturation (SpO_2), tidal volume (V_t), minute volume ($\dot{V}_E$), and apnea hypopnea index (AHI) were measured. Apnea hypopnea index values are typically categorized as mild (5–15), moderate (15–30), and severe sleep apnea (over 30). Variables were measured continuously during sleep with a Vivometrics Lifeshirt (Ventura, CA, USA). The mean duration of nocturnal monitoring for the 15 subjects was 494 minutes (range 433–566 minutes).

Independent variables: Participants randomized to the O_2 or O_2/CO_2 treatment arm of the study received 16.7 mL of gas per breath (volume coinciding with a flow rate of 1 L/min) from the 3-L cylinder during sleep. The cylinder was pressurized to 300 bar and, therefore, contained approximately 900 L of gas. The O_2/CO_2 treatment group received 1.5% CO_2 in the gas mixture specially prepared by adding CO_2 to designated oxygen cylinders. The acetazolamide treatment group received acetazolamide 125 mg at bedtime.

Equipment: Participants received supplemental oxygen or the O_2/CO_2 mixture through a nasal demand breathing system (PD 110, Summit Oxygen, UK).

This system consisted of a nasal cannula attached to a battery-operated pulse dose meter and released oxygen into the nasal cavity when a fall in pressure was sensed along the nasal cannula. A dial on the regulator controlled the volume of oxygen delivered by each pulse.

Throughout the study, the participants slept in a comfortable well-ventilated 2-man tent. The nasal demand system and oxygen cylinders are manufactured and tested to UK safety specifications. The accuracy of the pulse dose was confirmed by manufacturer's tests prior to departure and following the return of the system to the UK.

The LifeShirt system is an ambulatory, multi-sensor, continuous monitoring system for collecting, analyzing, and reporting physiologic data. The LifeShirt is able to collect continuous physiologic data throughout the study night via various sensors, including basic pulmonary function via respiratory inductive plethysmography (RIP) bands, electrical activity of the myocardium via a 3-lead echocardiogram, and arterial oxygen saturation via pulse oximetry.

The sensor array of the LifeShirt System is embedded in a sleeveless undergarment made of Lycra material that fits snugly and can be worn comfortably for extended periods. RIP sensors for monitoring a variety of pulmonary signals are embedded in this shirt. This ensures their correct and durable placement and allows multichannel recording. The RIP sensors consist of a sinusoidal arrangement of electrical wires that are excited through an extremely low current, electrical oscillator circuit. One sensor was sewn into the shirt at the level of the rib cage (fourth intercostal space) and one at the level of the abdomen (umbilicus). From these signals, a variety of calibrated respiratory pattern measures are extracted, such as minute ventilation, tidal volume, and respiratory rate. Additionally, apneas and hypopneas (identification and classification) can be automatically detected. An onboard personal digital assistant continuously encrypts and stores the patient's physiologic data on a compact flash memory card. VivoLogic, a proprietary personal computer-based software, decrypts and processes recorded data and provides viewing and reporting features.

Analysis: Data are reported as means with 95% CI. Statistical significance was established at $P \leq .05$ *a priori*. Statistical Package for the Social Sciences (version 16.0; SPSS Inc, Chicago, IL) was used for analysis. Dependent variables (HR, RR, SpO_2 , V_t , $\dot{V}_E$, and AHI) were analyzed via a 1-way analysis of variance. Treatment group was used as the independent variable for the analyses of variance, and the mean values from the night's sleep of each subject were the inputs for the analyses. Tukey HSD was used for post hoc multiple comparison testing in order to determine at which treatment levels the means actually differed.

Results

In the 4 groups enrolled into this study, there were no differences in HR, RR, SpO_2 , V_t , $\dot{V}_E$, and AHI when

Table 1. Mean (95% CI). *P* values represent differences between groups from 1-way analysis of variance

	Treatment Groups				<i>P</i> value	<i>F</i> value
	Acetazolamide	O ₂	O ₂ /CO ₂	Control		
<i>n</i>	4	3	4	4		
HR	66.2 (58.6–73.8)	65.0 (35.9–94.1)	76.0 (62.7–89.3)	75.0 (53.8–96.2)	0.3	1.2
RR	19.4 (18.5–20.3)	17.1 (11.9–22.3)	22.2 (15.5–29.0)	19.2 (17.2–21.1)	0.1	2.5
SaO ₂	68.3 (55.8–80.8)	81.4 (61.0–101.8)	72.9 (52.5–93.3)	57.5 (36.4–78.6)	0.08	2.9
Vt (mL)	878.2 (622.8–1133.6)	699.9 (638.3–761.4)	623.0 (354.8–890.2)	746.0 (435.7–1055.4)	0.2	1.8
$\dot{V}_E$ (L/m ⁻¹)	17.0 (12.5–21.5)	11.9 (7.6–16.3)	14.0 (6.0–22.0)	14.3 (8.0–20.7)	0.39	1.1
AHI	45.7 (7.0–84.3)	20.0 (–23.8–63.7)	19.6 (–11.0–50.1)	50.1 (–4.6–104.7)	0.59	0.68

HR, heart rate; RR, respiration rate; SaO₂, blood oxygen saturation; Vt, tidal volume; $\dot{V}_E$, minute volume; AHI, apnea hypopnea index.

compared to each other or the control group. Means with 95% CI for each of the 4 groups are listed in Table 1, and Figure 1 shows the raw data (VT, AHI, $\dot{V}_E$, and SaO₂) for each group. One-way analysis of variance indicated a trend toward statistical significance for SaO₂ between groups ($F = 2.9$, $P = .08$), but this analysis yielded no other results approaching statistical significance (HR, $F = 1.2$, $P = .3$; RR, $F = 2.5$, $P = .1$; Vt, $F = 1.8$, $P = .2$; $\dot{V}_E$, $F = 1.1$, $P = .39$; and AHI, $F = 0.7$, $P = .6$). More specifically, Tukey HSD post hoc tests indicated a statistical trend in the SaO₂ difference between the O₂ and control groups ($P = .07$) as well as in the RR difference between the O₂ and O₂/CO₂ groups ($P = .08$).

Discussion

This study emphasizes the extraordinary effect that a low PO₂ has upon physiological parameters during sleep at altitude. At Mount Everest Base Camp (5300 m), the mean arterial oxygen saturation (SaO₂) of 4 unmedicated, healthy participants (who were free of any symptoms of altitude illness) was 57.5% and their AHI was 50.1 episodes per hour. Thus, it seems clear that extraordinary physiological stress can take place during sleep in an environment that holds just one half of the PO₂ present at sea level. Although we were unable to find differences between the 4 groups in our study—perhaps due to the small sample size of each group—mean arterial oxygen saturations (SaO₂) were higher in all 3 treatment groups compared to the control. Despite the lack of measured differences in RR, HR, Vt, $\dot{V}_E$ and AHI, our results were consistent with physiological patterns that we had anticipated: 1) those using supplemental oxygen had the highest SaO₂ and the lowest HR, RR and $\dot{V}_E$; and 2) those using acetazolamide and the O₂/CO₂ mix had the highest RR and $\dot{V}_E$.

These results demonstrate the wide range of interindividual cardiopulmonary responses to sleep at high alti-

tude. Perhaps the most prominent finding is that the subjects taking O₂ had the highest percent SaO₂ results (81.4 ± 4.7), yet the lowest $\dot{V}_E$ (11.9 ± 1.0). The mean AHI results for the O₂ and O₂/CO₂ groups, $20 (\pm 10.2)$ and $19.6 (\pm 9.6)$ respectively, were virtually identical values. These results should nevertheless be viewed and interpreted with the understanding that over 100 years ago, respiratory physiologists discovered that very small changes in PCO₂ were sufficient enough to dramatically alter ventilation. Haldane and Priestley⁹ showed that an increase in alveolar PCO₂ of about 1.4 mm Hg was sufficient to double the alveolar ventilation at rest in healthy humans. Expanding on this work, Douglas and Haldane showed that hypocapnia caused by hyperventilation with an oxygen-enriched gas produced apneas, but not periodicity, in the apnea pattern.¹⁰ This indicated that the development of hypoxia during nocturnal central apneas at high altitude was important in the subsequent Cheyne-Stokes-like periodicity.

More recently, this finding was supported by a study conducted during the landmark American Medical Research Expedition to Mount Everest in 1981, when Lahiri and colleagues showed that carbon dioxide inhalation (without supplementary oxygen) eliminated central apneas during sleep at high altitude, but not the respiratory oscillations.¹¹ In agreement with our results, Lahiri and coworkers¹¹ also showed an increase in RR and a decrease in maximal Vt with carbon dioxide inhalation. Taken together, such background knowledge provides strong support for O₂/CO₂ mixtures (rather than O₂ or CO₂ alone) as an aid to sleep-breathing problems at high altitude. However, the results from our study could be interpreted to suggest that the extra work of the heart and lungs when using this particular O₂/CO₂ mixture (compared to O₂ alone) is of no physiological advantage. Additionally, when considering the use of supplemental gas delivered from a metal tank vs pharmaceuticals in pill form, it must be kept in mind that the weight of the

Figure 1. Raw data plotted for blood oxygen saturation (SaO_2), tidal volume (V_t), minute volume ($\dot{V}_E$), and apnea hypopnea index (AHI). (Treatment: 1 = acetazolamide, 2 = O_2 , 3 = O_2/CO_2 , and 4 = control).

former may in some cases be a factor in its effective utilization. This is especially true in circumstances such as alpinism or high altitude trekking where every kilogram must be scrutinized.

Although certain trends are visible from our results, a number of study limitations are present. The small number of subjects in each arm of the study, the relatively large variation in subject response, the limited number of physiological parameters measured, and the relatively low doses of gas and acetazolamide may have led to our inability to identify differences between our groups. While a larger sample size may have resulted in a smaller CI within each group, the use of a higher dose of acetazolamide or supplemental gas may have resulted in a greater increase in oxygenation and significant changes in the other physiological variables we measured. It should also be noted that our results are not necessarily in line with other reports as reviewed in Weil² that suggest a 125 mg dose of acetazolamide is effective at reducing nocturnal periodic breathing at high altitude. We were intrigued by these findings and, while we have no definitive explanation for this, it is possible that the respiratory and metabolic acclimatization gained from a gradual 13-day ascent to 5300 m prior to the study (during the night of day 14) may have influenced the subject's response to acetazolamide. In addition, sleep staging was not measured, since the equipment needed to record EEG activity was not available and no subjective data on participant perception of sleep quality was collected.

It should also be noted that the well-known phenomenon of night-to-night respiratory variability may have produced somewhat different results if these studies had been repeated with the same subjects on multiple consecutive nights. For instance, in studies examining multiple study nights in the same subjects for comparison, there is evidence of broad interstudy variation in the percentage of subjects having discordant findings in AHI between study nights—for example, from 43% to 8%.^{12,13} Therefore, the case has been made that a negative first-night study is insufficient to exclude the diagnosis of sleep apnea in patients with clinical markers of this disease because of the potential for night-to-night variability.^{14,15} As such, the results of our single study night may have been somewhat different if it had been repeated on a second night. In line with the repeated-measures “ideal” for a study such as this, the investigation would have been strengthened if all subjects had acted as their own control on a preceding or subsequent study night.

To summarize, in this small pilot study we were unable to identify differences between those in our control and treatment groups. However, larger studies using similar or higher doses of acetazolamide, O_2 , and O_2/CO_2 mixtures may, in the future, be able to identify key differences between these treatments at high altitude. In

addition, we can confidently report that the novel equipment used to deliver supplemental gas and measure cardio-respiratory parameters in this study are well suited to the remote high altitude environment.

Acknowledgments

The research was funded from a variety of sources, none of which are public. The entrepreneur John Caudwell, whose name the expedition carries, donated £500,000 specifically to support the research. BOC Medical, now part of the Linde Group, generously supported the research early on and continues to do so. Eli-Lilly Critical Care, Smiths Medical, Deltex Medical, The London Clinic (a private hospital), and Rolex have also donated money to support the research and logistics. All monies were given as unrestricted grants. Specific research grants were awarded by the Association of Anaesthetists of Great Britain and Ireland, the Halley Stuart Foundation, and the UK Intensive Care Foundation. The CXE volunteers who trekked to Mount Everest Base Camp also kindly donated to support the research.

References

1. West JB. Commuting to high altitude: Value of oxygen enrichment of room air. *High Alt Med Biol.* 2002;3: 223–235.
2. Weil JV. Sleep at high altitude. *High Alt Med Biol.* 2004; 5:180–189.
3. Luks AM, van Melick H, Batarse RR, Grant I, West JB. Room oxygen enrichment improves sleep and subsequent day-time performance at high altitude. *Respir Physiol.* 1998;113:247–258.
4. Windsor JS, Rodway GW. Supplemental oxygen and sleep at altitude. *High Alt Med Biol.* 2006;7:307–311.
5. Wickramasinghe H, Anholm JD. Sleep and breathing at high altitude. *Sleep Breath.* 1999;3:89–102.
6. Anholm JD, Powles AC, Downey R III. Operation Everest II: Arterial oxygen saturation and sleep at extreme simulated altitude. *Am Rev Respir Dis.* 1992;145:817–826.
7. Berssenbrugge A, Dempsey JA, Iber C, Skatrud J, Wilson P. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. *J Physiol.* 1983;343:507–524.
8. Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PS, ed. *Wilderness Medicine*, 4th ed. Saint Louis, MO: Mosby; 2001:2–43.
9. Haldane JS, Priestley JG. The regulation of lung-ventilation. *J Physiol.* 1905;32:225–266.
10. Douglas C, Haldane JS. The causes of periodic or Cheyne-Stokes breathing. *J Physiol.* 1909;38:401–419.
11. Lahiri S, Maret K, Sherpa MG. Dependence of high altitude sleep apnea on ventilatory sensitivity to hypoxia. *Respir Physiol.* 1983;52:281–301.
12. Mosko SS, Dickel MJ, Ashurst J. Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly. *Sleep.* 1988;11:340–348.
13. Mendelson WB. Use of the sleep laboratory in suspected sleep apnea syndrome: is one night enough? *Cleve Clin J Med.* 1994;61:299–303.
14. Le Bon O, Hoffmann G, Tecco J, et al. Mild to moderate sleep respiratory events: one negative night may not be enough. *Chest.* 2000;118:353–359.
15. Meyer TJ, Eveloff SE, Kline LR, Millman RP. One negative polysomnogram does not exclude obstructive sleep apnea. *Chest.* 1993;103:756–760.