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Original Article

Effect of added dead space on sleep disordered breathing at high altitude

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ABSTRACT

Objective: Sleep disordered breathing with central apnea or hypopnea frequently occurs at high altitude and is thought to be caused by a decrease in blood CO_2 level. The aim of this study was to assess the effects of added respiratory dead space on sleep disordered breathing.
Methods: Full polysomnographies were performed on 12 unacclimatized swiss mountaineers (11 males, 1 female, mean age 39 ± 12 y.o.) in Leh, Ladakh (3500 m). In random order, half of the night was spent with a 500 ml increase in dead space through a custom designed full face mask and the other half without it.
Results: Baseline data revealed two clearly distinct groups: one with severe sleep disordered breathing ($n = 5$, AHI > 30) and the other with moderate to no disordered breathing ($n = 7$, AHI < 30). DS markedly improved breathing in the first group (baseline vs DS): apnea hypopnea index (AHI) 70.3 ± 25.8 vs 29.4 ± 6.9 ($p = 0.013$), oxygen desaturation index (ODI): 72.9 ± 24.1/h vs 42.5 ± 14.4 ($p = 0.031$), whereas it had no significant effect in the second group or in the total population. Respiratory events were almost exclusively central apnea or hypopnea. Microarousal index, sleep efficiency, and sleep architecture remained unchanged with DS. A minor increase in mean $PtcCO_2$ ($n = 3$) was observed with DS.
Conclusion: A 500 ml increase in dead space through a fitted mask may improve nocturnal breathing in mountaineers with severe altitude-induced sleep disordered breathing.

1. Introduction

Sleep disordered breathing (SDB) with central apnea or hypopnea frequently occurs at high altitude [1,2]. This condition is often associated with sudden arousals from sleep and a sense of suffocation, which alters sleep quality and daytime performance [3,4]. Different therapies such as oxygen, acetazolamide [5], and theophylline [6] have been proposed to treat altitude-induced SDB; however, none are commonly used by mountaineers due to side effects or inconvenience. At high altitude, hypoxia increases chemoreceptor sensitivity (controller gain) and induces hyperventilation with a decrease in $PaCO_2$ levels. When $PaCO_2$ drops below a certain level called the "apnea threshold," breathing stops until $PaCO_2$ builds up and stimulates breathing again. In hypobaric hypoxic conditions (hypobaric chamber), administration of CO_2 at constant SaO2 yielding an increase in $PaCO_2$ of 1–2 mm Hg stabilizes nocturnal breathing and eliminates hypoxia-induced SDB [7]. These results emphasize the critical role of CO_2 on central SDB pathophysiology, but CO_2 administration at high altitude is not feasible under field conditions. Added dead space through a non-vented mask has been shown to increase $PaCO_2$ and was successfully used to treat Cheyne-Stokes breathing and idiopathic central apnea, both of which share some common pathophysiological features with altitude-induced SDB [8–10]. We hypothesized that a dead space mask would be a safe and practical treatment to treat this condition. The aim of this study was to test the feasibility and the physiological effects of added respiratory dead space on altitude-induced SDB in mountaineers after rapid ascent to 3500 m.

2. Methods

2.1. Subjects

The study was conducted in Leh, Ladakh (India) at 3500 m above sea level. Twelve unacclimatized healthy Swiss mountaineers

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(Mean age: 39 ± 12 years [range 20–56 y.o.], BMI 25.3 ± 2.3 kg/m^2, 1 female) taking part in a mountain expedition were studied within the first 96 h after their arrival in Leh. They had no known medical problems, had not spent time above 2000 m during the month preceding the study, and had refrained from any alcohol, caffeine, or respiratory stimulants during the 24 h before the sleep study. Exclusion criteria were <18 or >70 years of age, chronic illness, medication use, or known obstructive sleep apnea. All participants gave informed consent and the protocol was approved by the Lausanne University Ethics Committee.

Added respiratory dead space (DS) was applied during sleep using a full face non-vented mask with an open plastic (PET) bottle connected to the mask outlet. The total volume of the DS (mask + PET bottle) was 500 ml (Fig. 1).

2.2. Sleep studies

Overnight sleep recordings were performed in individual hotel rooms using portable Titanium acquisition systems (Embla Systems, Broomfield, CO). Two electrooculogram electrodes (EOG; one to each outer cantus) and four EEG electrodes (F1,F2 O1 and O2) were applied to the scalp using the International 10–20 System [11], and two surface electromyogram (EMG) electrodes were placed over submental muscles. EEG and EOG electrodes were referenced to the linked earlobes (A1 + A2). Chest and abdominal movements, nasal air pressure (to assess nasal airflow), and body position were also simultaneously recorded. Oxyhemoglobin saturation was recorded using a Nonin pulse oximeter (Nonin Medical, Inc., Plymouth, MN) using a sampling frequency of 10 Hz. When DS was applied, ventilation was monitored with a pneumotachograph coupled to a differential pressure transducer (Embla Systems, Broomfield, CO). Transcutaneous CO_2 ($PtcCO_2$) was also continuously recorded with a transcutaneous capnooxymeter (Radiometer, Basel, Switzerland). Only six randomly selected individuals had $PtcCO_2$ recordings since we had only two capnooxymeters.

2.3. Protocol

Each subject had a single night recording within the first 96 h after rapid ascent to Leh (3500 m). In random order, half of the night was spent without (baseline), and the other half with, DS. The randomization was performed by tossing a coin before the night study to determine if DS would be applied during the first or the second part of the night.

2.4. Data analysis

Data were visually analyzed using Somnologica software version 5.1 (Embla Systems, Broomfield, CO). An experienced investigator (DA) performed the EEG analysis for the whole night. Sleep stages and arousals were scored according to standard criteria [12] with modified respiratory channel tags to prevent the scorer from knowing the condition of the recording (DS or baseline). An apnea was defined as a $\geqslant$90% reduction in airflow signal amplitude for a minimum of 10 s. A hypopnea was defined as a $\geqslant$50% reduction in airflow signal amplitude for more than 10 s associated with $\geqslant$3% oxygen desaturation or an arousal (AASM 2007 alternative criteria) [13].

2.5. Statistical analysis

Paired *t*-tests were used to compare sleep and respiratory parameters between conditions (baseline vs DS). The minimal sample size required to have 80% power to detect a 5 ± 5 events/h difference in AHI with an alpha of 5% was 10 subjects, but we chose to include 12 subjects in case there were technical problems with the recordings.

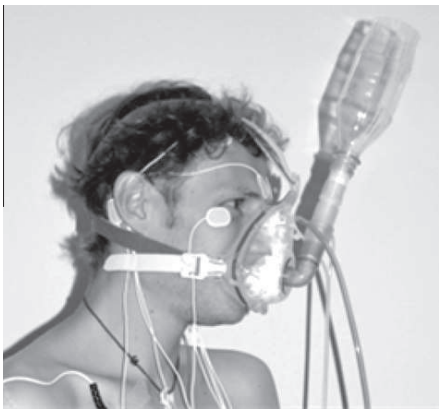

Fig. 1. Illustration of the dead space mask consisting of a non-vented full face mask connected to a PET bottle (total volume 500 ml).

3. Results

Analysis of the baseline data revealed a wide variety of SDB severity ranging from 0 to 99.6 events per hour (Table 1). Baseline AHI was not significantly different when recorded in the first part vs second part of the night: 1st part ($N = 7$) AHI 45.1 ± 27.4 vs 2nd part ($N = 5$) AHI 41.4 ± 32.7 $p = 0.66$. Five subjects had severe SDB (defined as an AHI > 30 events/hour), five had mild/moderate SDB (AHI 5–30/hr), and two had no SDB (AHI < 5/h). In the group as a whole and in subjects with no to moderate OSA ($n = 7$), dead space induced no significant changes in breathing parameters. In subjects with severe SDB ($n = 5$), DS markedly improved nocturnal breathing, with AHI decreasing from 70.3 ± 25.9/h (baseline) to 29.4 ± 6.3/h (DS) ($p = 0.013$) (Fig. 2) and ODI from 72.9 ± 24.1/h to 42.5 ± 14.4/h ($p = 0.031$). The proportion of the night spent in REM sleep (with DS) was 15.7% in responders vs 10.2% in non responders ($p = 0.39$). A recording sample of a good responder (subject #3) is displayed on Fig. 3. Mean oxygen saturation remained unchanged from 85.8 ± 2.7% to 86.1 ± 2.1% with DS ($p = 0.88$). Respiratory events were almost exclusively central apnea or hypopnea, except for one subject with mild obstructive sleep apnea at baseline.

Overall, the DS mask did not significantly alter sleep quality, with the microarousal index remaining unchanged (Baseline vs DS: 22.3 ± 12.7/h vs 26.2 ± 15.9/h; $p = 0.48$). There was a non-significant decrease in sleep efficiency: 90.2 ± 8.6% vs 84.1 ± 13.7% ($p = 0.28$). The sleep efficiency and microarousal index variations (baseline vs DS) were not different between responders and non-responders ($p = 0.66$ and 0.62, respectively). Analysis of sleep stages showed no significant difference between baseline and DS: stage NREM 1: 8.3 ± 4.5% vs 11.6 ± 11.5% ($p = 0.34$), NREM 2: 39.7 ± 12.9% vs 44.3 ± 14.9% ($p = 0.49$), NREM 3: 25.2 ± 14.3% vs 16.1 ± 12.6% ($p = 0.14$), NREM 4: 0% vs 0%, and REM: 15.8 ± 10.7% vs 11 ± 9.4% ($p = 0.23$). Due to calibration problems, we could obtain valid $PtcCO_2$ data only on 3/6 subjects. In all three subjects a slight increase in mean $PtcCO_2$ was observed with DS: 33.6 ± 1.8 mm Hg at baseline vs 35.0 ± 2.62 mm Hg with DS ($p = 0.13$).

4. Discussion

To the best of our knowledge this is the first study assessing the physiological effects of additional dead space on altitude-induced

Table 1
Main polysomnography results for all subjects.

Subjects	AHI		ODI		Mean Sao2		Sleep effic.		Microarousals	
	BL	DS	BL	DS	BL	DS	BL	DS	BL	DS
1*	99.6	41.2	98.5	67.5	86.6	85.3	98.6	58	28	28.2
2*	80.8	28.3	92.3	35.2	83.1	88.6	85	93.8	47.3	3.7
3*	77	24.2	77	32.8	83	83.7	87.7	67.3	31.2	23
4*	63.7	28.7	54.5	42.1	88	88	81.5	78.6	42.7	59.5
5*	30.2	24.5	42.4	35	88.7	85.1	88.7	98	21.7	21.2
6	21	64.8	22.8	75.6	86.1	88.7	96.7	77.2	23.1	49.8
7	11.3	16.7	16.8	14.7	86.5	87.2	84.0	95.9	13.4	11.8
8	8.7	5.9	7.4	9.5	80.6	80.6	71.3	95.3	9.9	20.2
9	7.5	6.4	10.8	8.4	90.7	89.8	98.8	96.5	14	21.1
10	6.5	15.1	10.7	25.4	85.7	84.6	97.6	88.9	13	19.2
11	5.1	12.5	7.8	12	90.7	90	97.4	91.6	11.3	17.2
12	0	40.8	13.3	43	85.5	82.4	94.7	68.7	11.6	39.2
All subjects										
Mean	34.3	25.8	37.9	33.4	86.3	86.2	90.2	84.2	22.3	26.2
Sd	35.7	16.9	34.4	21.7	3.1	3.0	8.6	13.7	12.7	15.9
p	0.40		0.60		0.88		0.28		0.48	
Subgroup with severe SDB										
Mean*	70.3	29.4	72.9	42.5	85.8	86.1	88.3	79.1	34.2	27.1
Sd*	25.9	6.3	24.1	14.4	2.7	2.1	6.4	17.0	10.6	20.3
*p**	0.01		0.03		0.87		0.39		0.52	

The subjects with a * subgroup with severe SDB defined as an AHI > 30/h. A separate analysis * with mean, SD, and *P* value (paired *t*-test) was performed for this subgroup. AHI = Apnea-hypopnea index. ODI = 3% oxygen desaturation index. SaO2 = Oxygen saturation level. Sleep effic. = Sleep efficiency. BL = Baseline. DS = Dead Space.

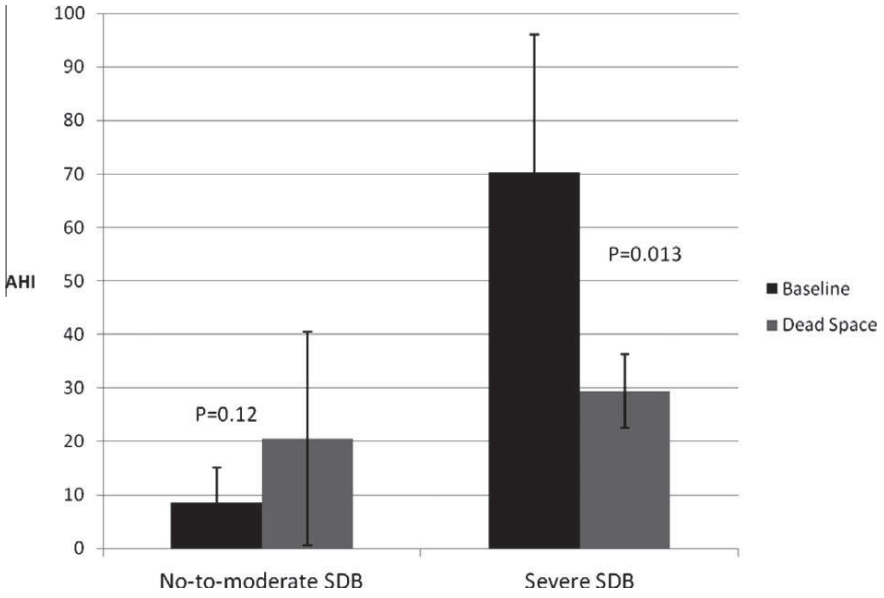

Fig. 2. Effect of added dead space on apnea-hypopnea index (AHI) in subjects with severe and mild-to-no sleep apnea.

SDB. We found that a 500 ml added respiratory dead space improved nocturnal breathing at high altitude in mountaineers with severe altitude-induced SDB, whereas it had no detectable effect in those with no-to-moderate disordered breathing. Previous studies performed at sea level showed a positive effect of DS on Cheyne-Stokes breathing in patients with heart failure and on idiopathic central apnea, which share some common pathophysiological features with altitude-induced SDB [8–10]. Kayat reported a reduction in AHI from 43/h to 9/h with a 600 ml DS in heart failure patients, while Xie and Szollosi found, respectively, a decrease in AHI from 60.1 to 7.1 /h (DS 700 ml) and from 30 to 15.9/h (DS 500 ml) in idiopathic central apnea patients. The AHI reduction we found at high altitude in subjects with severe SDB is consistent with Szollosi's results in Cheyne-Stokes breathing and idiopathic central sleep apnea, but is less pronounced than Kayat's and Xie's findings. This may be due in part to the smaller increase in DS that was used in our study and Szollosi's studies (500 ml vs 600–700 ml).

The slight increase in $PtcCO_2$ we observed with the DS mask is difficult to interpret (valid measurements only in three subjects), but we can hypothesize that DS stabilized nocturnal breathing by increasing the "CO_2 reserve" and preventing the CO_2 level from dropping below the apnea threshold. Such a minor (1–2 mm Hg) increase in CO_2 level has been reported to significantly improve central breathing disorders in conditions such as positive pressure-associated ventilator control instability [14]. This condition, which can occur in patients treated with CPAP, shares common

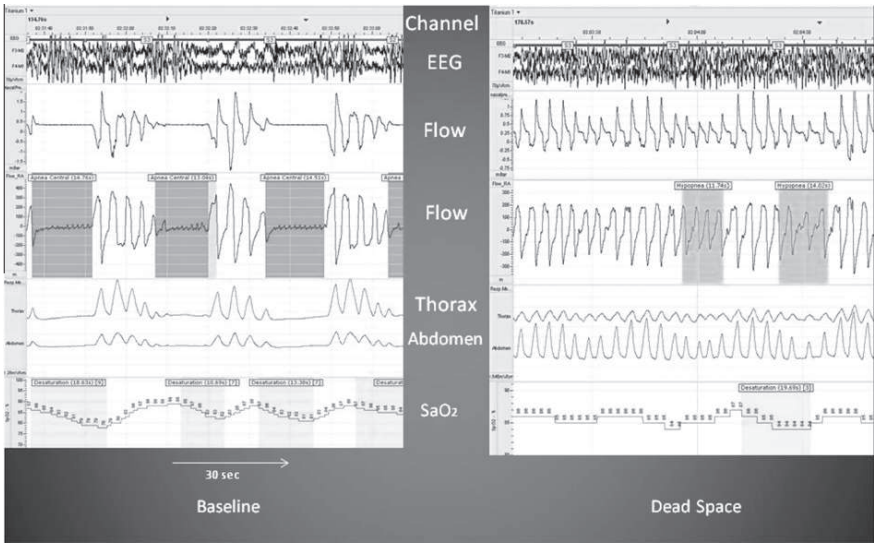

Fig. 3. Example of PSG recording with and without dead space in a participant with severe altitude-induced sleep breathing disorder.

features with altitude induced SDB, since it is also suspected to be due to an underlying alteration in chemoreceptor sensitivity. The slightly lower absolute CO_2 values we found compared to Berssenbrugge et al. [7] may be due, at least in part, to a difference in the measurement technique: we measured transcutaneous pCO_2 ($PtcCO_2$) while Berssenbrugge and colleagues measured arterial CO_2 level ($PaCO_2$). A modest underestimation of $PaCO_2$ by the $PtcCO_2$ monitor we used was reported in a previous study [15].

We were surprised by the wide range of sleep disordered breathing severity we found in our subjects, with AHI ranging from 0 to 99.6 events per hour. This effect does not seem to be due to a "time of the night" artifact since the "baseline" AHI was not significantly different when recorded in the first or in the second part of the night. This suggests that important differences exist in individuals' susceptibilities to altitude-induced SDB, which may be due to differences in hypoxia-induced increase in chemoreceptor sensitivity among individuals. Considering that SDB severity increases in parallel with increasing altitude, as shown by Bloch et al. [2], it is possible that if we conducted the same experiment at higher altitude a greater proportion of the participants would have developed severe SDB and shown a positive response to the DS mask.

With the DS mask, sleep quality was not significantly affected; there were no significant alterations in sleep efficiency, microarousal index, or percentage of slow wave sleep. Among subjects with severe altitude-induced SDB who showed a significant decrease in AHI we expected to observe an increase in sleep quality, but this was not the case. This may be due to the inspiratory resistance of the CPAP mask we used. Some of our subjects felt that the small increase in inspiratory effort secondary to the resistance of the mask was uncomfortable for them. This increase in respiratory resistance may also be responsible for the increase in AHI we observed in some subjects with no to moderate SDB at baseline. We suspect that a more comfortable mask with a larger outlet and lower inspiratory resistance could yield a greater improvement not only in AHI, but also in sleep structure and sleep efficiency.

There are a few limitations to this study. First, this study was not initially powered for subgroups analysis since we did not expect to find such a difference in baseline AHI among our subjects. However, the difference in AHI with vs without DS in the severe SDB group was so important that it yielded significance despite the small size of this subgroup. Second, DS was applied only during half of the night (split-night protocol) in each subject, which prevents us from speculating on the effect of DS during a full night and over the long-term. These are thus only preliminary data that will need to be confirmed in a study involving a larger sample of subjects. Finally, we did not plan a washout period (without DS) when the subjects had DS during the first night period but, considering the mild increase in $PtcCO_2$ we found with DS ($\sim$1–2 mm Hg) and the rapid return of CO_2 to baseline after DS removal, we do not believe that the application of the DS mask during the first part of the night influenced the breathing pattern during the second part of the night. Moreover the effect of DS (delta AHI) was not different when DS was applied during the first or second part of the night ($p = 0.87$).

In conclusion, these data suggest that DS may improve nocturnal breathing in individuals with severe altitude-induced sleep disordered breathing. This may be an affordable and viable treatment option for mountaineers or for high-altitude populations suffering from altitude-induced sleep disordered breathing.

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Conflict of interest

R.H. is a recipient of grants from Lausanne University and the Lancardis Foundation. A.W. has participated in speaking engagements and has consulted for Respironics.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2012.02.012.

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