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SATURACIÓN NOCTURNA Y PERFILES DE RESPIRACIÓN PERIÓDICA A LO LARGO DEL TIEMPO EN JÓVENES SANOS A LA ALTURA

Nocturnal Oxygenation And Periodic Breathing Profiles Over Time In Healthy Acute High Altitude Sojourners

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DEDICATORIA

A nuestras familias, quienes estuvieron con nosotros en todo momento.

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DECLARACIÓN DEL AUTOR

El presente trabajo a presentar es original y se han seguido los lineamientos respectivos para respetar la ética en investigación y que el mismo será utilizado para obtener el título de médico-cirujano.

TABLA DE CONTENIDOS

RESUMEN

Objetivos

Evaluar los cambios agudos en la saturación nocturna durante el sueño, respiración periódica y síntomas de Mal de Montaña Agudo (MMA) en viajeros sanos a la altura.

Métodos

Se hicieron medidas de poligrafía nocturna en 10 sujetos por 5 noches consecutivas en altura y 2 noches antes y después (2761msnm). Se analizaron los perfiles de saturación nocturna con medidas continuas de saturación de la oxihemoglobina (SpO_2) durante el sueño, la severidad de apnea fue representada por el Índice de Apnea-Hipopnea (IAH). Se respondió el Lake Louise Score (LLS) para determinar MMA. Se empleó medidas repetidas de regresión logística para examinar las respuestas de las variables dependientes entre la altura y el nivel del mar. Se utilizó SpO_2 de la primera noche en altura para el análisis secundario basado en el promedio de saturación nocturna y logIAH.

Resultados

Comparado al nivel del mar, la SpO_2 promedio fue más baja ($p<0.0001$) y logIAH fue más alto en altura ($p<0.0001$). SpO_2 aumentó progresivamente ($p<0.001$) mientras que logIAH permaneció elevado ($p<0.978$). Los desaturadores profundos aumentaron su SpO_2 a lo largo de una semana de exposición a niveles observados en los desaturadores superficiales. Comparando los subgrupos con IAH bajo vs alto, estos últimos muestran una tendencia de mayor LLS (ΔLLS, 0.7 ± 0.3, $p=0.16$).

Conclusión

SpO_2 nocturna disminuyó agudamente en altura y mejoró en el tiempo, mientras que la respiración periódica permaneció elevada durante la semana de exposición. Esta última parece predecir elevación en LLS. Disturbios respiratorios del sueño en Altura podría predecir MMA y comprometer las funciones diurnas.

Keywords: High altitude, Sleep, Sleep Disordered Breathing

ABSTRACT

Study Objectives

Assess acute changes in nocturnal sleep oxygenation, sleep disordered breathing and symptoms of Acute Mountain Sickness (AMS) in healthy High Altitude (HA) sojourners.

Methods

Ten subjects born at Sea Level (SL) were enrolled and underwent nocturnal polygraphy for 5 consecutive nights at HA and 2 nights before and after HA (2761 m). Nocturnal oxygen profiles were characterized by the mean Oxyhaemoglobin Saturation (SpO_2) during sleep, and sleep apnea severity was represented by the Apnea-Hypopnea Index (AHI). Repeated measures linear regression was used to examine responses in outcome variables (SpO_2, logAHI and LLS) between HA and SL. Mean SpO_2 on night 1 at HA was used to stratify *post-hoc* analyses based on mean level of nocturnal desaturation and logAHI. Subjects completed the Lake-Louise Score (LLS) survey every day.

Results

Compared to SL, mean SpO_2 was lower at HA ($p<0.0001$) and logAHI was higher at HA ($p<0.0001$). SpO_2 increased progressively ($p<0.001$) while logAHI remained high at HA ($p<0.978$). Those with marked decreases in SpO_2 at HA initially exhibited progressive increases in SpO_2 over the week sojourn to levels observed in the mild desaturators. Compared to subgroups with low AHI those with high AHI showed a trend towards higher LLS (ΔLLS, 0.7 ± 0.3, $p=0.16$).

Conclusion

Nocturnal SpO_2 decreased acutely at HA exposure and increased over time, whereas AHI increased and remained elevated over a one-week sojourn. The latter tends to predict elevations in LLS, while mean nocturnal SpO_2 deteriorated acutely but improved over time. Nocturnal hypoxemia and SDB at HA could predict AMS and compromise daytime function.

Keywords: High altitude, Sleep, Sleep Disordered Breathing

SUMMARY

This study was conducted at sea level and at moderate altitude in young healthy subjects, rather than extreme altitude in professional hikers or mountaineers.

The severity and time course of HA acclimatization in Sleep Disordered Breathing (SDB) has not been well characterized. The major goal of the present study was to examine the magnitude of SDB upon acute exposure to HA and examine the extent at which the study subjects acclimatized at a moderate altitude. The relationship between SDB and the daytime function was also examined.

INTRODUCTION

In an increasingly global society, millions of people are traveling to altitude for a variety of reasons. Most are acutely exposed to High Altitude (HA) for several days or weeks at a time, such as tourists, hikers, miners, transport drivers and office workers. The prevalence of AMS varies from 25-90% in the general population, depending on the rate of ascent and the altitude reached (1,2) with symptoms which vary from mild to life-threatening, requiring immediate descent. For many years scientists have tried to elucidate factors predisposing to AMS, although relatively little is known about the severity and time course for adaptation to high altitude.

In prior work, investigators have focused primarily on acclimatization to extreme altitude among highly fit individuals able to handle high levels of physical exertion. In general, HA lowers oxygen saturation during the daytime, while cardiac output and rate increase to compensate for the hypoxemia. As subjects acclimatize, heart rate and cardiac output fall, but do not reach sea level values (3,4). Most commonly, high-altitude illness is characterized

by a combination of symptoms including headache, gastrointestinal symptoms, fatigue and sleep disturbances (5). The latter can lead to impaired daytime functioning, which generally improves with acclimatization, but never reaches sea level values (6). It has been suggested that female hormones may stabilize the ventilatory control by increasing cerebral blood flow, making it easier for women to acclimatize compared to men (7). Susceptibility to AMS may be related to alteration in ventilatory drive, with studies demonstrating both increases and decreases in hypoxic/hypercapnic sensitivity (8),(9). Therefore, hypoxemia during wakefulness may predispose to AMS.

Sleep is associated to decreased ventilatory drive and worsening of nocturnal hypoxemia. Under isocapnic conditions, the hypoxic ventilatory response is blunted during all sleep stages compared with wakefulness, especially during rapid eye movement (REM) sleep (10). Hypoxemia is also known to destabilize breathing patterns during sleep, leading to intermittent desaturation, arousals from sleep and periodic breathing (11). In native highlanders, HA is independently associated with increase of prevalence and severity of SDB consisting of (1) sustained nocturnal hypoxemia without PB, (2) periodic obstructive or central sleep apnea (12). Nonetheless, the severity and time course of HA acclimatization in SDB has not been well characterized.

The major goal of the present study was to examine the magnitude of SDB upon acute exposure to HA and to examine the extent at which the study subjects acclimatized at a moderate altitude. We hypothesized that subjects would acclimatize progressively with increasing time at altitude (SDB and nocturnal mean SpO_2). We also explored whether SDB predicted symptoms of AMS. To minimize potential confounding factors, we have designed a time course study of Sleep Disordered Breathing parameters to compare differences within subjects between baseline SL and HA exposure over 9 days.

METHODS

Participants

A prospective descriptive study was conducted in 10 healthy young lowlanders. We enrolled medical students in a university hospital in Lima, Peru who agreed to participate in a cook stove mitigation project at HA (Ayacucho, Peru). Inclusion criteria included age >18 years, born and residing at SL, and no personal history of sleep disorders, pulmonary or cardiovascular disease. Ten participants met the inclusion and exclusion criteria, based on medical history and general physical exam conducted by the investigators. Informed consent was obtained for a protocol that was approved by the Universidad Peruana Cayetano Heredia institutional ethics review board in Lima, Peru (Project Code 100399, Date of approval: 01/06/2017).

Study setting and design

The present study, an observational transversal study, evaluated 10 healthy lowlanders aged 19-27 years before, during and after a 9-day journey from sea level 154m (Lima, Peru) to an altitude of 2761m (Ayacucho, Peru). The sea level site of the study was located in the household of each participant, in different districts of Lima (154m). Participants travelled to high altitude in Ayacucho, located at 2750 m by airplane in less than 2 hours. Participants were asked to follow the same daily routine, and eat a normo-caloric balanced diet. Participants were told not to take any prophylactic medication for high altitude illness, sleep aid, caffeine or alcohol.

Study procedures and protocols

Anthropometrics

Measurements of age, weight, height, neck, waist and hip circumference, and Mallampati score were performed by the same examiner. BMI and waist-to-hip ratio were calculated.

Questionnaires

Subjects completed the Lake Louise survey each day and the overall score was computed (5).

Sleep disordered breathing assessment

Participants underwent unattended nocturnal recordings of nasal airflow, thoracic excursion, and pulse oximetry (SpO_2) (ApneaLink Plus; ResMed, Ltd., San Diego, USA) for two nights at SL, followed by 9 nights at HA and two nights following descent to SL (Figure 1). Before their first night of study, participants attended a practice session with an instructional video demonstrating how to deploy the device. These devices were initialized by a single computer the morning before each nocturnal recording. Participants were instructed to wear and activate the devices at bedtime and to remove their devices after final awakening. A minimum of 3 hours of recording time was required for the recording to be included in the study. A total of 116 sleep recordings were obtained between SL and HA, of which 98 fulfilled the previously mentioned criteria.

Recordings were scored and reviewed at the Johns Hopkins Sleep Disorders Center. Sleep-wake state was estimated in 30-second epochs determined by duration of movement artifact in the recorded signals. More than half of the epoch was deemed as wakefulness, while less than half of the epoch was considered to be sleep.

Recording Analysis and Definitions

Arousals were defined by either of the following criteria: movement or swallowing artifacts in the flow or effort signal, or a decrease in the pulse photoplethysmography that was associated with a 10% increase in basal heart rate. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep, which were scored and classified in accordance with 2016 AASM recommended guidelines. Apneas were defined

as the absence of flow for ≥ 10 seconds and were further classified as obstructive, central, or mixed in accordance with standard criteria. Hypopneas were defined as a reduction in the nasal pressure signal by 30% that was accompanied by either a 3% desaturation or arousal. Hypopneas were also classified into obstructive, mixed and central types based on the presence or absence of inspiratory flow limitation, as previously described. (13)

Data analysis

All anthropometric, demographic and sleep study variables are presented as median (interquartile range) (Table 1). Our analyses were designed to test our primary hypotheses examining the effect of altitude and days at high altitude on nocturnal oxygenation (mean SpO_2), AHI (log-transformed AHI) and AMS symptoms (LLS). In *post-hoc* stratified analyses, dichotomous comparisons were based on whether nocturnal mean SpO_2 fell above or below the mean value for the entire group on night 1 at high altitude with those below the mean categorized as deep desaturators and those above considered to be mild desaturators. AHI was treated similarly with those characterized with low or high levels based on values below or above the median logAHI on first night at high altitude, respectively. Subjects were classified into two different phenotypes according to their respiratory response during sleep: Those with marked fluctuation on the SpO_2 channel and those with stable fluctuation. Nonparametric Mann-Whitney rank sum tests were used to compare parameters between groups with deep/mild nocturnal desaturators and low/high logAHI. Repeated measures linear regression (XTMixed, Stata, Inc.) was used to examine responses in outcome variables (SpO_2, logAHI) between HA and sea level, and over 9 consecutive nights at HA. Non-parametric comparisons of demographic/anthropometric predictors of these outcomes were performed in these subgroups. Analyses were conducted using STATA (version 14,1; UPCH, Lima, Peru). Significance was inferred for $p<0.05$.

RESULTS

Patient characteristics

Demographic and anthropometric characteristics are shown for the 10 subjects in Table 1 for the entire group and subgroups split by those with deep/mild desaturation and high/low AHI. All subjects were healthy lowlanders (4 males, 6 females) aged between 19-27 (median: 21, IQR: 20-24) years with a median BMI of 21.58 $kg.m^{-2}$ (IQR: 20.7-24.6). Six were Latino, three were Asian, and one was Caucasian. Anthropometric and demographic parameters did not differ significantly between AHI subgroups (high or low) or between nocturnal desaturation subgroups (deep and mild). Specifically, these groups did not differ significantly in the degree of adiposity (BMI), in measures of regional fat distribution (waist to hip ratio, and neck and waist circumferences), or in age. Compared to the mild desaturators, deep desaturators were predominantly male but did not differ in BMI or age ($p<0.524$).

Effect of Altitude and Acclimatization on Nocturnal Oxyhemoglobin Saturation Profile

Compared to SL, the mean SpO_2 for the entire group was significantly lower at HA ($p<0.0001$), but increased progressively over time ($p<0.001$) (Graph 1, left panel). Of note, marked variability in nocturnal SpO_2 profiles over time was observed among subjects (Graph 1, middle and right panel). Deep desaturators exhibited marked decreases in nocturnal mean SpO_2 initially, but SpO_2 rose progressively to levels observed in the mild desaturators over the period of exposure (Figure 2). Compared to the mild desaturators, deep desaturators were predominantly Asian (n=3) and male (only one male was part of the mild desaturators group), but did not differ in BMI or age ($p<NS$) (Table 1).

Effect of Altitude and Acclimatization on Sleep Disordered Breathing

SpO_2 tracings exhibited two different types of respiratory response despite the same mean nocturnal SpO_2; those with stable, constant nocturnal SpO_2 and those with marked fluctuation of SpO_2 due to periodic apneas and hypopneas (Figure 3).

AHI was significantly higher at HA compared to SL but did not change over time (Graph 2). It remained elevated at HA and did not decrease during the days of exposure, unlike mean nocturnal SpO_2, which exhibited improvement during HA (Graph 3). Of note, marked variability in logAHI was observed among subjects, which prompted a *post-hoc* analysis comparing those with low vs high logAHI. Both subgroups did not show significant difference changes in AHI during HA exposure; nor did they show any difference in mean nocturnal SpO_2 (Graph 4 and 5). Subjects with low AHI were predominantly female (M:F – 1:3) and did not differ in BMI or age (p=<NS) (Table 1).

Effect of Altitude and Acclimatization on Acute Mountain Sickness

We found no difference in LLS between SL and HA for the group as a whole. Nonetheless, LLS values rose during the first two days at HA but decreased over time. Comparing subgroups with high and low logAHI, we found that those with higher AHI showed a trend toward higher LLS (ΔLLS, 0.7±0.3, p=0.16), but did not differ in age, sex or BMI.

DISCUSSION

The major goal of our study was to examine the effect of acute exposure to moderate altitude and acclimatization on SDB. Our results showed that mean nocturnal saturation decreased sharply upon ascent to HA, but increased progressively over time, whereas AHI maintained elevated at HA and did not wane over time. Moreover, SpO_2 tracings exhibited two different types of respiratory response, despite similar mean nocturnal SpO_2 levels, those with stable nocturnal SpO_2 and those with marked fluctuation of SpO_2 due to PB. LLS score rose during the first two days at HA and decreased over time. The most common symptom was headache, followed by fatigue.

In stratified analyses, we found that mild desaturators had worse AHI than deep desaturators, and that mean nocturnal SpO_2 did not differ between subjects with high and low logAHI. Our study found that even though mean nocturnal SpO_2 improved over time at HA, AHI remained stable. During HA exposure it is possible that participants: (1) desaturated repeatedly at sleep onset or (2) defended nocturnal saturation by hyperventilating, leading to recurrent arousals and PB. Of note, these findings may represent part of a continuum spectrum of HA acclimatization response, and may also have major implications on the role of PB with daytime symptoms or may indicate that sleep parameters do not tend to acclimatize during acute exposure to HA.

Extending the current HA literature, most investigators conducted sleep studies at extreme altitude exceeding the 4000m and focused primarily on expert mountaineers or athletes (14,15). Very few conducted studies like ours at only moderate elevations, or else worked in simulated altitude chambers with either hypobaric or normobaric hypoxia (16–19). Furthermore, several previous research studies focused primarily on the first and last night at the designated altitude, or conducted sleep studies during a sojourn across different altitudes (14,15,20–24). In contrast, our study was held at a moderate altitude (2800m), which is more typically encountered by travelers, and young healthy non-physically active subjects were recruited. Moreover, our study recorded each night of exposure to the same altitude throughout the whole study to visualize more closely the acclimatization process.

Subgroup analysis: Marked variability among subjects in respiratory responses during sleep, as well as in nocturnal SpO_2, was observed. Some subjects exhibited substantial elevations in AHI, which prompted a comparison of those with low vs. high AHI. Our study also used the mean nocturnal SpO_2 on first night at HA to classify subjects into deep and mild desaturators. Deep desaturators exhibited sharp decreases in nocturnal mean SpO_2 initially, but SpO_2 rose progressively to levels observed in the mild desaturators over the exposure

period. Even though both groups reported similar levels of mean nocturnal SpO_2, the process to how they reached that final value is what we consider interesting to discuss. Deep desaturators seemed able to tolerate nocturnal hypoxemia, while the mild desaturators did not, which could explain why they had greater AHI values compared to the former group. This leads to a big dilemma during sleep at HA, where the body has to choose between sleeping at the expense of catching a breath or breathing at the expense of sleep quality. Existing literature suggests that renal reactivity at HA is crucial for good acclimatization. Zouboules et al. found that renal compensatory metabolic acidosis begins from the first day and it plateaus at the fifth day of exposure (25). By that time, peripheral chemoreceptors also increased their sensitivity due to persistence of alkalosis (26). According to our results, both groups reached a plateau level of mean nocturnal SpO_2 by the fifth to seventh day of exposure, supporting the previous idea. At last, our findings on SpO_2 are very emphatic, which means that at least half of the population who are exposed acutely to HA may experience nocturnal hypoxemia, which may lead to impaired daytime symptoms according to some literature (27–29); and we might also dare to suggest that PB, since it remained stable throughout our study, might not influence on AMS symptoms.

Exposure to HA disturbs sleep and respiratory physiology, especially during the first days of exposure to moderate altitude. PB is the most frequent respiratory event associated with HA exposure, which appears above 2000m and is associated with disturbance of sleep architecture characterized by a superficial sleep with less deep stages and frequent arousals. There are two mechanisms involved in PB: hypoxic and hypercapnic ventilatory response. Initially, due to hypobaric hypoxia, the body hyperventilates and eliminates CO_2, leading to low CO_2 arterial concentration below the respiratory center threshold, thus producing apnea. At this point, the concentration of CO_2 rises quickly, and the hypercapnic ventilatory response takes place, leading to compensating polypnea (20,30,31), this cycle is known as PB. Due to the sleep fragmentation, PB may lead to poor quality of sleep (32,33) and, theoretically, more daytime symptoms, therefore AMS. This would also support the

argument that PB is not a good adaptive response to HA (33–35). However, whether PB affects or not on daytime symptoms is still controversial (9). According to our results, PB was not a determinant factor for development of AMS and neither was associated with lower mean nocturnal SpO_2 levels.

Several limitations should be considered when reviewing our results. First, our inferences are based on a small sample of healthy young adults, therefore limiting the generalizability of the study. However, most of the studies done at high altitude use small groups of study (15,29,35), mainly due to the complexity of the study design and costs. We also imposed a strict daily schedule on our participants throughout the study in order to reduce the potential confounds of random factors that can perturb our measurements. Confounding by comorbid conditions was also minimized by studying young healthy individuals. Second, we recognized that our nocturnal recording devices did not provide a definitive assessment of sleep-wake stage since we used a respiratory polygraph (ApneaLink, ResMed Inc.). Nonetheless, we excluded epochs with obvious movement artifacts as wakefulness from our estimates of sleep apnea severity (AHI) in an effort to capture the severity of the nocturnal exposure to periodic breathing at altitude. Third, we also lacked objective measurements of CO_2 in order to determine the extent of acclimatization and quantify variability in the renal response to HA among the subjects throughout the study.

As well as in obstructive sleep apnea and chronic pulmonary disease have different phenotypes according to the heterogeneity of clinical presentation or molecular-genetic features, this study highlights the potential existence of two phenotypes depending on the respiratory response, both of them reaching the same value of SpO_2 over the period of exposure but not reaching SL values, and that AHI does not show a marked variation acutely (36,37). The underlying mechanisms of these responses are not clear, neither the magnitude of their influence on AMS development. Different factors, such as age, sex, genetics, may influence on the kind of response a person exhibits at HA. Of note, sleep is

considered a vulnerable state, with an even greater load of physiologic stress at HA. Thousands of short-time workers and tourists may experience this acute acclimatization effects every time they ascend to HA, and at least half of the persons who travel to altitude would experience significant decrease on nocturnal SpO_2 which could affect their daytime performance (since we believe that deep desaturators would rather sleep than breathe well). Further research must be done in this topic to elucidate if there is a proper adaptive response throughout their continuous exposure and long term repercussions on our physiology.

CONCLUSION

As expected, nocturnal oxygenation deteriorated at HA acutely at HA exposure but improved progressively over a week's exposure, particularly in the men. Deep desaturators nocturnal SpO_2 decreased sharply at acute exposure to HA and rose progressively over time. AHI increased at HA acutely, remained elevated over a week's exposure, and predicted elevations in LLS, but did not experience acclimatization. AHI and nocturnal hypoxemia may be mutually exclusive HA phenotypes with specific end-organ manifestations of AMS, and both could compromise daytime function markedly in miners, transport workers, athletes and tourists.

ABBREVIATIONS

AMS : Acute Mountain Sickness

SDB : Sleep Disordered Breathing

PB : Periodic Breathing

HA : High Altitude

SL : Sea Level

SpO_2 : Oxyhaemoglobin Saturation

AHI : Apnea-Hypopnea Index

BMI : Body Mass Index

LLS : Lake-Louise Score

REM : Rapid Eye Movement

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APPENDIX

Figure 1: Timeline of study

	Entire group	Nocturnal Desaturation		p-value	Apnea Hypopnea Index		p-value
		Deep	Mild		Low	High	
Number of Subjects	*10*	*5*	*5*		*4*	*6*	
Sex	*4 Males, 6 Females*	*3 Males, 2 Females*	*1 Male, 4 Female*	*0.22*	*1 Males, 3 Females*	*3 Males, 3 Females*	*0.10*
Age (years)	*21 (20-24)*	*21 (20-21)*	*22 (20-24)*	*0.75*	*24 (21-25)*	*22 (20-23)*	*0.38*
Anthropometrics							
Height (meters)	*1.66 (1.60-1.78)*	*1.64 (1.60-1.67)*	*1.78 (1.60-1.78)*	*0.29*	*1.64 (1590-1.77)*	*1.87(1.6-1.1.78)*	*0.91*
Weight (kilograms)	*60.0 (57.0-75.0)*	*57.0 (57.0-62.0)*	*75.0 (58.0-78.0)*	*0.17*	*57.5 (55.0-66.5)*	*65.05(57.0-78.0)*	*0.45*
Body Mass Index (kg/m2)	*21.58 (20.70-24.60)*	*21.19 (20.44-21.71)*	*23.23 (21.45-24.62)*	*0.35*	*21.08 (20.57-23.34)*	*23.16 (21.19-26.20)*	*0.29*
Neck circumference (centimetres)	*32.5 (30.5-38.0)*	*32.0 (30.0-32.0)*	*38.0 (35.0-39.0)*	*0.05*	*32.75 (30.25-36.50)*	*32.5 (32.0-39.0)*	*0.69*
Mallampati Score	*2 (1-3)*	*2 (1-2)*	*3 (2-3)*	*0.45*	*2 (1-3)*	*2 (2-3)*	*0.66*
Waist circumference (centimetres)	*80.5 (70-86)*	*71.0 (70-82)*	*84.0 (79-91)*	*0.21*	*75.0 (70.5-81.5)*	*84.0 (70-91)*	*0.45*
Hip circumference (centimetres)	*89 (84-94)*	*84 (79-89)*	*94 (89-95)*	*0.06*	*87.5 (82.5-92)*	*90 (84-94)*	*0.68*
Waist/Hip Ratio	*0.90 (0.87-0.97)*	*0.90 (0.87-0.90)*	*0.97 (0.89-0.98)*	*0.35*	*0.89 (0.81-0.94)*	*0.93 (0.87-0.97)*	*0.52*
Mean sleep saturation %							
Sea level	*96 (95-96)*	*95 (95-96)*	*96 (95-96)*	*0.15*	*95.93 (95.21-96.33)*	*95.57 (94.86-95.81)*	*0.15*
High altitude	*89 (88-90)*	*88 (86-89)*	*90 (89-91)*	*0.0001*	*88.48 (87.21-90.27)*	*88.75 (87.42-90.14)*	*0.69*
Apnea hypopnea index events.h-1							
Sea level	*1.34 (0.72-3.13*	*0.85 (0.65-1.3)*	*2.4 (1.1-3.5)*	*0.0275*	*0.6 (0.4-1.5)*	*1.25 (0.5-2.0)*	*0.0912*
High altitude	*10.65 (6.88-16.56)*	*4.7 (2.8-8.4)*	*10.2 (5.5-15.4)*	*0.003*	*2.05 (1.5-3.4)*	*9.9 (4.6-16.1)*	*0.00001*

Data are presented as n or median (interquartile range). Mean sleep saturation: peripheral capillary oxyhaemoglobin saturation.

Table 1: Demographic, anthropometrics and sleep disordered breathing parameters

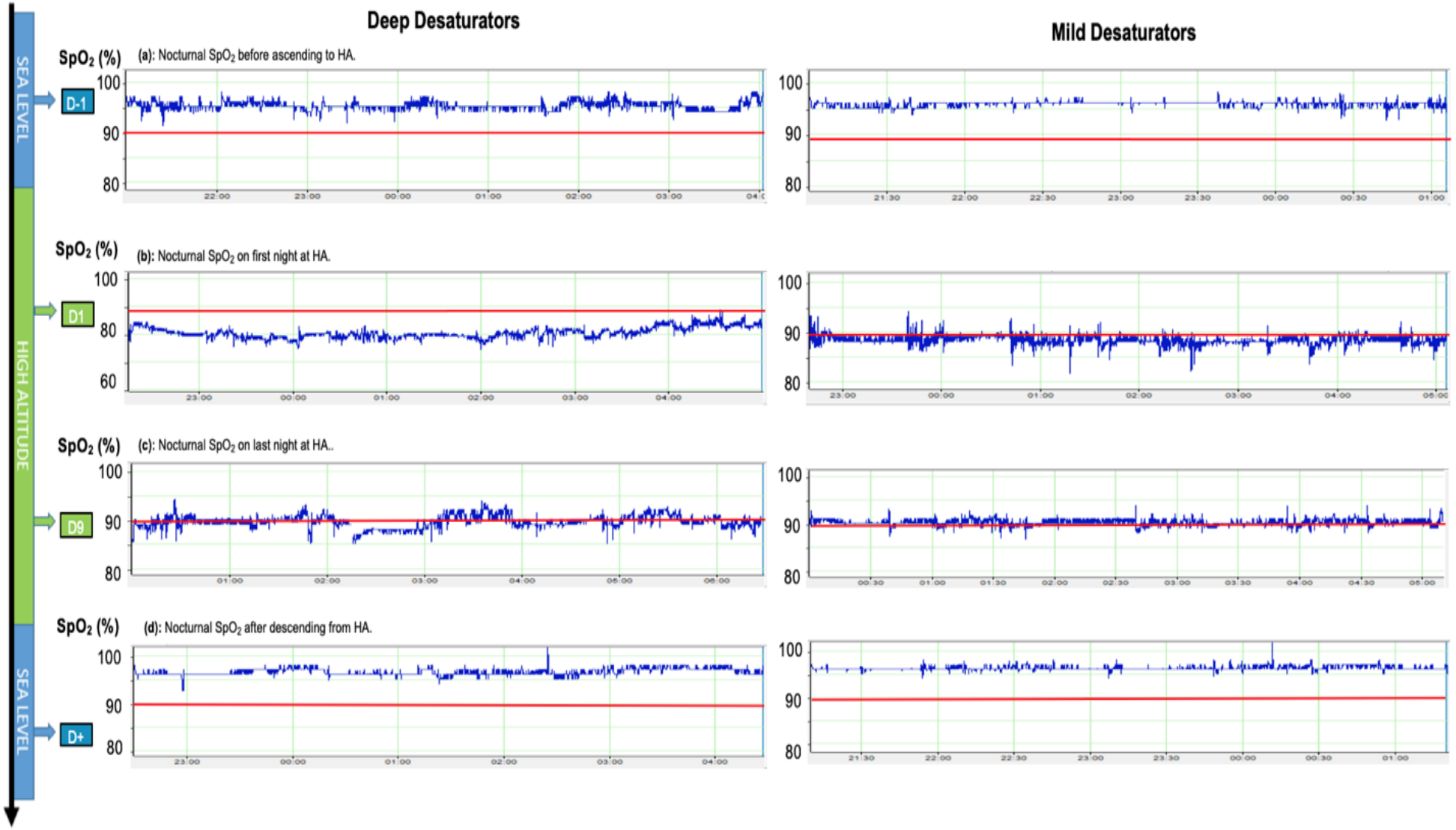
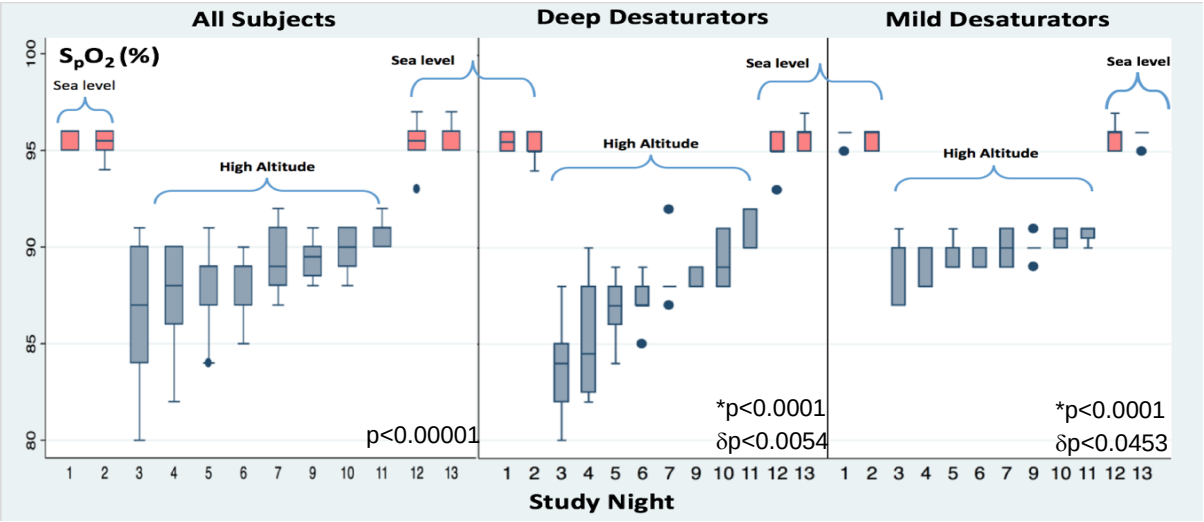


Figure 2: Compressed nocturnal SpO2 recordings in a deep desaturator subject. **(a)** shows nocturnal SpO2 before ascending to HA, **(b)** on first night at HA, **(c)** on last night at HA and **(d)** after descending from HA. Red line indicates a value of SpO2 of 90%.



Graph 1: Nocturnal oxygenation profiles in study time course. (*) Significance between mean nocturnal SpO2 between deep and mild desaturators at HA. (δ) Significance between first and last nocturnal SpO2 at HA in the same group.

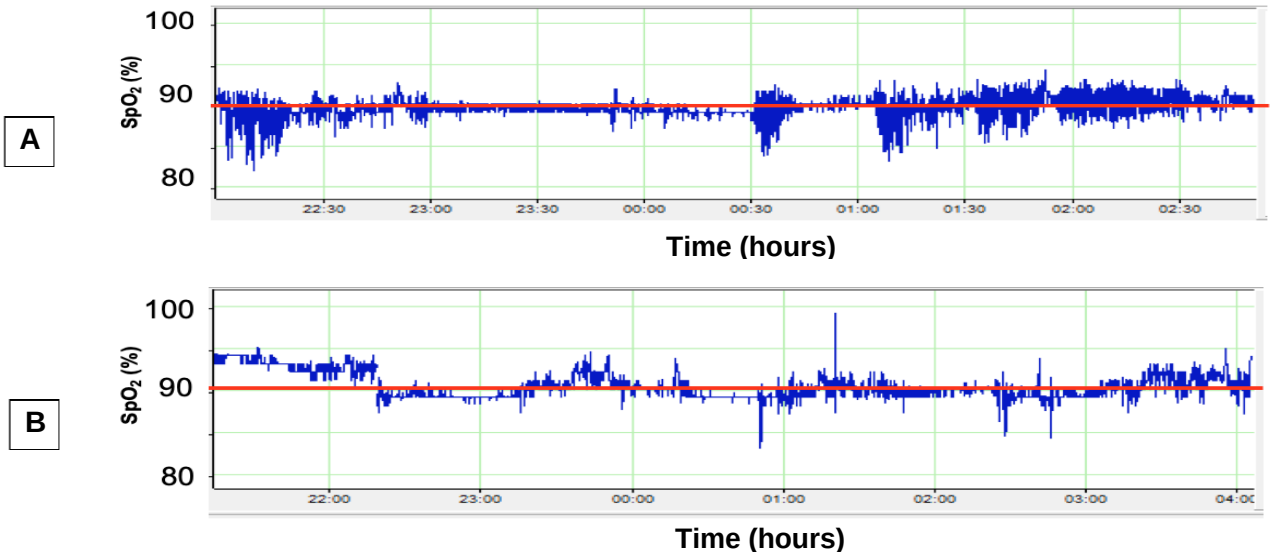
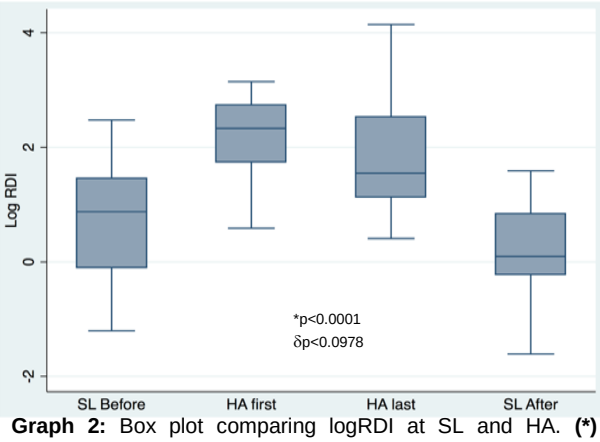
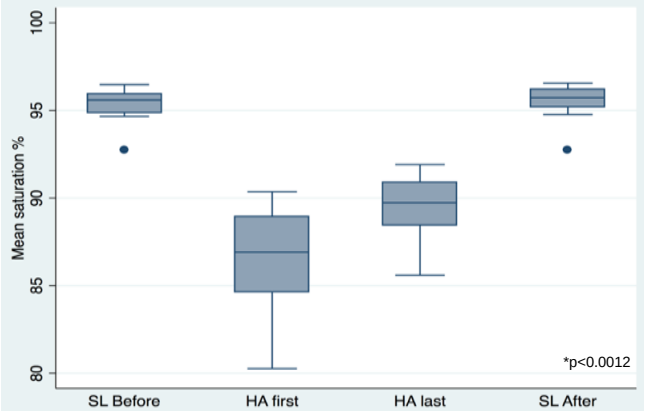


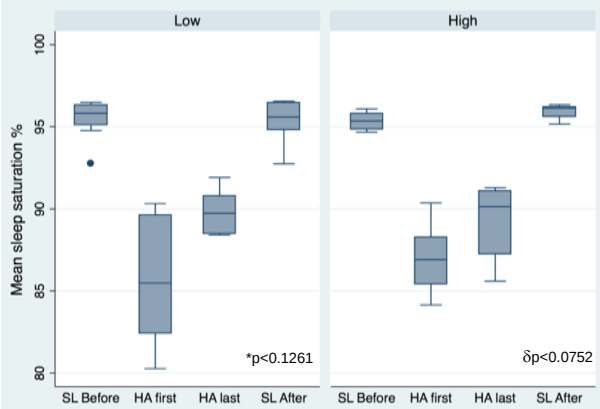
Figure 3: Phenotypes of respiratory responses at HA. **(A)** The top trace shows a subject with marked fluctuation of SpO2. **(B)** The bottom trace shows a subject with constant SpO2 during the night. Red line shows mean SpO2.



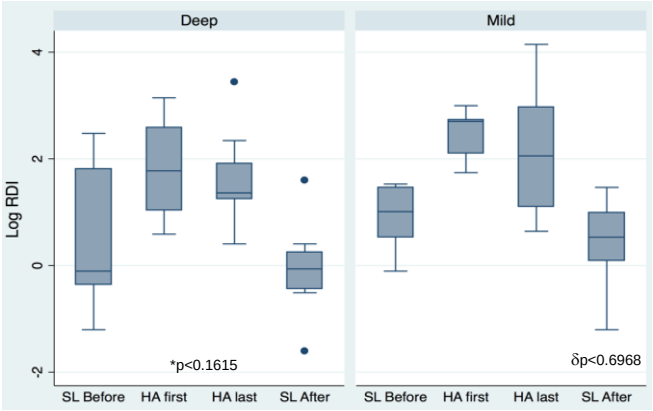
Graph 2: Box plot comparing logRDI at SL and HA. **(*)** logRDI between SL and HA. **(δ)** logRDI between HA first and last.



Graph 3: Box plot comparing mean sleep SpO2 at SL and HA. **(*)** Mean saturation between HA first and last.



Graph 4: Box plot comparing mean sleep saturation vs days of study by low and high RDI. **(*)** Mean Sleep Saturation between HA first and last in low logAHI group. **(δ)** Mean Sleep Saturation between HA first and last in high logAHI.



Graph 5: logAHI vs day of study by deep and mild desaturators. **(*)** LogRDI between SL and HA in deep desaturators subgroup. **(δ)** LogRDI between SL and HA in mild desaturators subgroup