Effect of mild obstructive sleep apnea in mountaineers during the climb to Mount Aconcagua

ABSTRACT

Objective: to compare mountaineers with and without asymptomatic sleep apnea (OSA) before the ascent and to study high altitude-related sleep disorders, its interaction with metabolic, neuroendocrine and immunological components. Material and Methods: During an expedition to Mount Aconcagua, researchers assessed the respiratory polygraphy (RP), clinical condition and inflammatory parameters, and rhythm of cortisol secretion in mountaineers sleeping at different altitude camps. Results: 8 athletes (4 women), 36 years old (25-51) participated. Baseline and final BMI were; 23.6 (20.9-28.7) and 22.77 (20.9-27.7), respectively: p<0.01. 40 valid RP recordings were analyzed. At 746 m.a.s.l. (baseline), only 2 mountaineers presented mild asymptomatic OSA. The OSA group presented baseline apnea-hypopnea index (AHI) values between 5-15 events per hour, which evidence a mild respiratory sleep disorder with AHI increased by altitude depending of central apneas and hypopneas (p<0.05) as high altitude periodic breathing pattern but no increase in obstructive apneas (p<0.01). The circadian rhythm of cortisol was maintained in all cases in which they had not received treatment with dexamethasone and their values increased with the altitude reached. Increased systolic blood pressure was observed in the OSA group. Conclusion: In a context of hypobaric hypoxia, individuals with pre-existing asymptomatic OSA are prone to experiencing lower oxygen saturations and clinical deterioration. Keywords: Hypoxia; Altitude Sickness; Sleep Apnea Syndromes; Metabolic Syndrome.
INTRODUCTION

Mountaineering is increasingly attracting the interest of amateur people. High-altitude mountaineering takes place at > 2,500 Meter about sea level (m.a.s.l.), the altitude above which symptoms and complications derived from hypobaric hypoxia (HH) are more frequent. The initial altitude-induced response includes respiratory and cardiovascular changes that begin within minutes of exposure. At the same time, alterations in hyperventilation occur at rest and during acute physical exercise. Heart rate and respiratory rate increase similarly to cardiac output and minute ventilation, decreasing the partial pressure of carbon dioxide in arterial blood; however, these alterations are not enough to affect cellular oxygen consumption.

Several studies have shown that acute or chronic exposure at altitudes between 2000 and 5000 m.a.s.l. result in sympathetic-adrenal and immunological responses. Sleep respiratory disorders are a group of prevalent conditions that affect quality of life and shorten life expectancy. Patients with undetected obstructive sleep apnea (OSA), exposed to severe hypoxia may suffer a deterioration of their mental and physical capacity, which could affect their performance during mountaineering expeditions. Periodic breathing (PB) or Cheyne-Stokes respiration (CSR), at high altitudes was first described in 1898 by Mosso. At > 2,000 m.a.s.l., some individuals are prone to experiencing PB or CSR. At > 5,000 m.a.s.l., however, most people will experience these disorders. The severity of the disorder correlates with the respiratory response to hypoxia (Hh).

OSA is defined as a respiratory event index (REI) > 5 events/hour (ev/h). In general, patients with moderate (14.9 to 30 ev/h) or severe (> 30 ev/h) disease present symptoms and need treatment. Most asymptomatic patients with mild (5 to 14.9 ev/h) OSA ignore their condition. In high-altitude settings, simplified and self-administered diagnostic methods like respiratory polygraphy (RP) which measures heart rate, O2 saturation, nasal flow and thoracic effort (level III AASM) provide relevant information about physiological variables.

In engineering, a loop gain (LG) describes the stability of a feedback-loop system. LG measures RP signals to assess the behavior of the respiratory control system during PB. There are different specific mechanisms according to PB type. In general, however, a high LG and unstable breathing during sleep are observed. In relation to the decrease in CO2 and the state of hypoxia in altitude, it is a product of hypobaric hypoxia. The presence of hypoxia, ventilation is stimulated, so hypocapnia occurs, which is ultimately the pathophysiological axis of periodic breathing related high altitude.

HH generates tachypnea and polypnea due to hypoxia, with the consequent decrease in CO2, which increases the respiratory minute volume (hyperpnea), hypocapnic inhibits the respiratory center and leads to apnea, increasing as a consequence CO2 and worsening hypoxia, increasing as a consequence CO2 and making more expected hypoxia in an unstable system - through negative feedback (gain). The sleep apnea produces increase of CO2, increases the hypoxemia that stimulates the ventilatory minute volume producing a new phase of hyperpnea. These cycles are repeated and have been characterized as an abnormal breathing pattern with central apneas and hypopneas, which alternate with hyperventilation. If the loop gain (LG) is < 1, the response to the disturbance is so weak that the system will return to normal. High LG (> 1), however, promotes recurrent apnea because the response to the initial disturbance is over-compensated.

From a mathematical point of view, LG is the response to a disturbance and can be calculated as follows: \( LG = \frac{2\pi}{(2\pi DR - \sin(2\pi DR))} \). Theoretically, LG is inversely proportional to lung volume and duty ratio (DR).

Mathematical models have shown that fluctuating patterns and apnea thresholds (measured through RP) increase LG and result in lower DR. DR is used to measure LG. DR defined as the respiratory cycle length divided by the periodic breathing cycle length (Hyperpnea/Hyperpnea + Apnea). This relationship is explained in the supplement to Sand et al. work.

Patients with sleep apnea face a higher risk for O2 desaturation during the night. It is uncertain whether unstable sleeping patterns at high altitude are caused by PB or frequent wakeups, but in both cases there is O2 desaturation, which may adversely affect mountaineers’ performance.

Exercise performed under hypoxic conditions at high altitude represents an additional stress condition in relation to the exercise performed at sea level, even when its intensity can by relative. The increase in altitude or the degree of hypoxia is a primary factor that influences the level of variation in physiological and biochemical parameters that can modulate the immune response mediated by exercise.

The primary objective of this work was to evaluate the differences in respiratory polygraphy of andinist with a basally elevated REI without symptoms compared with mountaineers with normal REI (less than 4.9) during the ascent to Mount Aconcagua and the secondary objectives were: to evaluate the differences in inflammatory parameters and metabolic of both groups and the response to exercise and cardiovascular stress (BNP/blood pressure ratio).

MATERIAL AND METHODS

Design

This is a prospective and descriptive study on healthy mountaineers doctors during an ascent to Mount Aconcagua in a 19-day expedition in January 2016 (Figure 1). The expedition and study were part of a research conducted during a course on Mountain Medicine for the evaluation of respiratory disturbances at high altitude. Inclusion criteria: the doctors of the course who agreed to have respiratory polygraphs at different heights. Those doctors who did not believe they could perform polygraphs at all heights were excluded. A retrospective analysis was performed according to the PR after the expedition, separating the participants into two groups according to the measurements of REI at the beginning of the study (before the ascent). OSA group (with pathological
Effect of mild obstructive sleep apnea in mountaineers

REI and 2. non-OSA group (REI < 5 ev/h). All participants voluntarily signed the corresponding informed consent form.

Respiratory Polygraphy

Portable level III devices (American Academy of Sleep Medicine - AASM) Apnea Link Plus (ResMed, Sydney, Australia) were used. They included nasal pressure cannula, respiratory effort band, and oximetry (average signal time < 1 second) with a finger sensor (XPod, Nonin, USA). Respiratory polygraphy tests were self-administered9,10. All study participants were trained in the use of polygraphs before the ascent9,18. Recordings were edited and analyzed manually (sequential manual scoring) at a posterior stage using Apnea Link® 9.0. Only recordings with a total recording time (TRT) > 4 hours of good-quality signal were considered valid. Events were edited manually by pulmonologists trained in the use of current AASM standards7. Apneas were defined as a > 90% drop in airflow and hypopneas as a > 50% drop in airflow associated with a ≥ 3% drop in O2 saturation for ≥ 10 seconds5.

REI was defined as the number of respiratory events (apneas + hypopneas) observed during TRT (ev/h). Patients were classified either as normal (REI < 5 ev/h), mild (REI between 6 and 14.9 ev/h), moderate (REI between 15 and 29.9 ev/h) and severe (REI > 30 ev/h).

Oxygen desaturation index (ODI) was also calculated using TRT (ev/h) and the desaturation time for each threshold (90-85% and 80%) was measured in minutes and as a percentage of valid TRT. Lowest saturation values were also recorded. ODI was defined as a 3% desaturation with regard to the immediately preceding baseline value and according to the same categories defined for REI (mild, moderate and severe)9.

Periodic Breathing at High Altitude

High-altitude Periodic Breathing (HAPB) was defined as 2 hours of TRT with the typical polypnea/apnea7 or crescendo-decreasendo pattern15-19. Cycle length was measured from the start of an apnea event to the next or from peak-to-peak in diamond-shaped patterns. At least 20 measurements were recorded in pages with good-quality signal and findings were averaged out (in seconds). Finally, the hyperventilation/apnea phase (or hypoventilation, if applicable) was calculated. (Hyperpnea/Hyperpnea + apnea) was the formula used for DR13-15.

Clinical evaluation

When reaching the predicted levels after ensuring correct hydration and rest, blood pressure, heart rate and respiratory rate was measured.

Acute Mountain Sickness (AMS): was assessed using the Lake Louise scoring system20 (mild disease = > 3 score; moderate disease = 4-6 score; and severe disease = > 7 score), physical examination, and a self-administered evaluation. The protocol implemented was as follows: in mild AMS cases, examination was repeated after 2 hours and subjects received non-steroidal anti-inflammatory drugs (NSAID); in moderate AMS cases, subjects were instructed to interrupt the ascent and received NSAID's (acetazolamide or IM corticosteroids after 2 hours); and in severe AMS cases, subjects were instructed to descend to receive treatment for potential cerebral and/or pulmonary edema20. Sleepiness was assessed using Epworth sleepiness scale (ESS)21.

Laboratory measurements

The circadian phase was evaluated through salivary cortisol25, taking the samples immediately before going to sleep and waking up on the same days and altitude where the respiratory polygraphy was performed. Cortisol was always taken when getting up after breakfast and at bedtime25. Both situations on the mountain depend on the operation scheduled each day.

The samples were preserved until processing by enzyme immunoassay with electrochemiluminescent development (Roche®).

In the blood samples we evaluated: red blood cell count, hematocrit, hemoglobin, granulocytes, lymphocytes and platelets (automated counter: Wiener® Counter®), D-dimer (Elisa with fluorometric development of Biomerieux®), urea, creatinine, uric acid, LDH, CPK, PCR, (chemical autoanalyzer and reagents Roche®); IL6, troponin, myoglobin and NT-proBNP with (enzyme immunoassay autoanalyzer with electrochemiluminescent development and reagents Roche®).

The serum samples were fractionated at the extraction site and transported immediately refrigerated to the laboratory in the city of Mendoza where they were frozen until processing.

Statistical Analysis

Outcomes are presented as mean value, standard error, range or percentage. Chi-square, Kruskal-Wallis, and Dunn’s multiple-comparison tests were used (statistical significance = p<0.05).

RESULTS

4 women and 4 men took part in this study. Their mean age was 36 years (range; 25-51). A total of 43 polygraphy records were performed. 39 valid recordings (> 240 minutes) were analyzed (Table 1). Two mountaineers presented mildly elevated REI values with no symptoms (ESS < 10) with an REI of 11 and 13 ev/h, respectively (OSA group). They were compared to those with an REI of < 4.9 ev/h (control group, non-OSA
The relationship between lowest saturation values (RP-recorded) and different camp altitudes was analyzed: OSA; Y = -0.0052x +96.731 r²= 0.77 vs. non-OSA group; Y = -0.056x + 84.288 r²= 0.77 p<0.01 (Figure 2D).

Participants with high altitude PB presented significant differences in DR between groups p<0.01 (Figure 3).

The REI values increase with the high altitude and at the expense of the central apneas and with this the oxygenation parameters, the ODI and the lower saturation are worse in the OSA group (Table 2).

Table 1. Total number of studies by high-altitude according to the OSA and non-OSA group, and the total number of episodes of high-altitude periodic breathing of both groups.

| Altitude (masl) | Study number | Study with OSA | Study with Non-OSA | Study with PB |
|----------------|--------------|----------------|-------------------|--------------|
| Mendoza        | 746          | 2              | 4                 | 0            |
| Penitentes     | 2581         | 1              | 2                 | 1            |
| Las Cuevas     | 3200         | 2              | 6                 | 3            |
| Confluencia    | 3300         | 2              | 6                 | 2            |
| Plaza de Mulas | 4300         | 2              | 6                 | 7            |
| Plaza Canadá   | 4900         | 2              | 1                 | 3            |
| Nido de Cóndores | 5380      | 1              | 2                 | 3            |

REI increased with altitude also with the characteristics of periodic breathing: non-OSA group; Y=0.0029x - 4.081 r² 0.51 vs. OSA group; Y=0.0169x - 9.193; r² 0.44, p<0.01 (Figure 2A) with more central apneas (Figure 2B), and hypopneas in the OSA group, p<1.5. About obstructive apneas, no statistically significant differences were observed between both groups.

Oxygenation evaluated by the desaturation index per hour of night recording show more increment in the ODI in the OSA group < 0.05 (Figure 2C) and T < 80% was the only indicator that presented a correlation with height: r²: 0.85 (IC: 0.71-0.93) p<0.01.

The circadian rhythm of salivary cortisol was maintained in all cases: mean morning cortisol: 0.90ng/ml; mean night cortisol: 0.40ng/ml p<0.001; in which the participants did not receive injectable or oral corticosteroids and the morning values increased with the altitude reached up to 3300 m.a.s.l. (0.844ng/ml at 765 masl; 0.867ng/ml at 3200 masl and, 1.211ng/ml at 3300masl) regardless of the effort made and weather conditions.

Finally, we observed an increase in the values of systolic blood pressure recorded as they progressed in altitude, being higher in the OSA group (p<0.01). OSA mountaineers did not reach the summit and had to take corticosteroids due to the severity of AMS (Lake Louise score > 5). In the control group, 3 participants took acetazolamide and corticosteroids, but presented no differences in O₂ saturation or REI, as compared to other participants in the same group, who did not need to take drugs.

Figure 2. Respiratory events increase with high-altitude: A. The respiratory event index (REI) with high-altitude periodic breathing; B. The REI itself; C. Oxygenation deteriorates by increasing both the ODI; D. The fall in Sat. Always in greater magnitude in mountaineers with previous OSA.
Effect of mild obstructive sleep apnea in mountaineers

Figure 3. As it is exposed to the high-altitude, the mountaineers begin to present high-altitude periodic breathing and the Duty Ratio can be measured, it is observed that it occurs to a greater extent in the mountaineers with OSA (gray square) than in the no-OSA group (black rhombus) where it occurs in fewer episodes and does not show much deterioration, it is closer to the unit.

Table 2. \( n = \) number of studies carried out according to high-altitude. According to the Altitude, the number of comparative studies between OSA and no-OSA can be seen. \( \bar{x} = \) mean of the value found. From left to right, the REI, the central apneas, the ODI and the lowest saturation. Note that the events under study are at the expense of central apneas and are accompanied by a greater deterioration of oxygenation, clearly worse in the OSA group. A stability of the episodes at the heights of 3300 and 4300 is evidenced by acclimatization.

| Altitude | OSA | No OSA | OSA | No OSA | OSA | No OSA | OSA | No OSA |
|----------|-----|--------|-----|--------|-----|--------|-----|--------|
| 746      |     |        | 2   | 12     | 4   | 0,26   | 2   | 10,25  |
| 2581     | 1   | 51     | 2   | 2,5    | 1   | 187    | 2   | 51     |
| 3200     | 2   | 44,9   | 6   | 3,1    | 2   | 161    | 6   | 44     |
| 3300     | 2   | 26,5   | 6   | 4,05   | 2   | 42     | 6   | 27,8   |
| 4300     | 2   | 32,4   | 6   | 8,63   | 2   | 37     | 6   | 26,2   |
| 4900     | 2   | 103,5  | 1   | 14     | 2   | 204    | 1   | 98     |
| 5380     | 1   | 92     | 2   | 16     | 1   | 193    | 2   | 98     |

\( \bar{x} = \) mean of the value found

Table 3. The increase in hemoglobin, urea, uric acid and creatinine in the OSA group after the expedition, although not significant, hemoconcentration evidence. The NT-pro-BNP increases further in the OSA group after the expedition. DD almost doubles and the inflammation measured by IL-6, although not significant increases in both groups. The differences may not be significant due to the low number of participants. The concentration of urea, creatinine and, uric acid, together with a higher BMI value in the OSA Group, shows the association of this pathology with the metabolic syndrome. \( \bar{x} = \) mean of the value found.

| P        | OSA before | no OSA before | OSA after | no OSA after | p   |
|----------|------------|---------------|-----------|--------------|-----|
|         | \( \bar{x} \) | Min Max       | \( \bar{x} \) | Min Max       |     |
| ns      | 7,25       | 7,2-7,3       | 6,9       | 4,9-8,6      | WBC 103/ul 10 | 9,1-10,9 | 9,5       | 7,2-12,2 | ns |
|         | 15         | 15-15         | 14,5      | 13,4-16,4    | hb g% 18  | 17,5-18,5 | 15,5      | 14,5-16,0 | 0,1 |
|         | 353        | 353-353       | 347       | 250-443      | RBC 10 3 ul 353 | 353-353 | 347       | 250-443 | ns |
|         | 165,67     | 115-216       | 233       | 112-352      | DD pg/ml 446,5 | 241-647 | 398       | 275-519 | ns |
|         | 5,39       | 1,4-9,38      | 1,4       | 1,4-14       | IL6 pg/ml 18,3 | 12,2-24,5 | 58,1      | 2,9-327 | ns |
| <0,01   | 1,15       | 1,1-1,2       | 0,68      | 0,6-0,8      | Creatinine mg% 1,2 | 1,0-1,4 | 0,93      | 0,7-1,4 | ns |
| 0,03    | 36,5       | 36-37         | 20        | 12,0-30,0    | Urea mg% 53  | 47-59 | 45        | 26-61   | ns |
| 0,01    | 6,55       | 5,6-7,5       | 4,36      | 3,7-5,2      | Uric acid mg% 5,1 | 8,3-1,9 | 4,6       | 3,7-5,2 | ns |
| ns      | 17,5       | 14-21         | 48,5      | 30-77        | NT-proBNP pg/ml 61,5 | 41-82 | 67,8      | 29-129 | ns |

\( \bar{x} = \) mean of the value found

Sleep Sci. 2020;13(2):138-144
These values did not show differences between the groups when returning from the mountain, probably due to the strenuous exercise and the notable increase of uric acid in all the participants. This phenomenon could be explained because lactate inhibits the elimination of uric acid, while insulin stimulates its reabsorption. Under conditions of tissue hypoxia, ATP is consumed, and the isoform of xanthine oxidase is induced resulting in a local increase in uric acid. This mechanism can occur in hypoxia due to acute exposure to altitude but also in sleep apnea, congenital cyanotic heart diseases and heart failure.

In the OSA group, there was a greater erythropoietic response, probably due to increased cellular hypoxia. The OSA group was overweight prior to exposure to hypobaric hypoxia and the inflammatory effects of sleep apnea.

Bloch et al. described the effect of altitude in OSA patients. At sea level, this group of patients presented apneas and hypopneas associated with intermittent hypoxemia caused by upper-airway collapse. A hypobaric hypoxia setting would promote central apneas and obstructive events that result in intermittent combinations and sustained hypoxemia, as we also observed in our study. In our OSA group, this phenomenon is related to higher initial desaturation and the difference between groups becomes larger at each altitude level (steeper negative slope in the regression line).

REI worsened at higher altitudes for both groups but presented a positive slope of 0.0169 in the OSA group vs 0.0029 in the non-OSA group. There are two pieces of data that suggest that acetazolamide may lower REI in high-altitude settings. Its effect is stronger in patients without OSA. At moderate altitudes, PB improves gradually. However, above 3,730 m.a.s.l, with 2-week acclimatization, PB seemed unrelated to AMS symptoms. In our study, despite progressive acclimatization, high-altitude PB did not disappear at higher altitudes. DR of the OSA group was lower than that of the non-OSA group, as observed in other studies. The existence of pre-existing sleep apnea could mean respiratory center more unstable due to silent disease.

The use of positive pressure devices is difficult in high-altitude settings due to the lack of electric power and proper infrastructure. In general, these devices are not used for this type of activities. The use of supplemental oxygen is recommended > 6,000 m.a.s.l. Many mountaineers, however, refuse to use it. Therefore, acetazolamide is one of the few therapeutic alternatives available both for OSA and non-OSA mountaineers.

Lack of awareness and knowledge about sleep disorders is particularly concerning in mountaineering, skiing and other activities practiced at high altitudes. Sustained hypoxia is a highly prevalent pathology that induces a strong sympathetic activity, a heart rate increase and systemic hypertension. In stable respiratory systems, changes are minimal. In our non-OSA group, disturbances led to hypopneas with a crescendo-decrescendo pattern of PB and a DR closer to 1 (mean value: 0.8). The OSA group, however, had a higher preexisting disturbance that led to frequent central apneas and a DR close to 0.5.

Nocturnal respiratory disturbances measured in the OSA group evidenced lower average O2 saturations, as compared to the non-OSA group. These events may have cognitive consequences and lead to a slow response in risky situations and poorer motor skills during exhausting activities like high-altitude mountaineering.

Under these conditions, it is possible to produce a rapid adrenaline hormone response and a transient increase in plasma cortisol concentrations. Hypoxia, even for a few hours, is enough to induce significant changes in the number of neutrophils and lymphocytes, as we observed.

It has been suggested to remain at an altitude greater than 4000 m.a.s.l. It is associated with an increase in plasma concentrations of IL-6 and the IL-1 receptor antagonist. This situation was observed on return, being higher in the participants with OSA (Table 1). The increase of C-reactive protein (CRP) that is associated with the development of pulmonary edema, did not manifest itself in our participants.

The circadian phase of cortisol was maintained during the expedition, except in those who received corticosteroids as part of treatment by AMS, evidence of the action of cortisol increased by activation of hypoxia-inducible factors. Despite the high degree of demand for the test, no significant changes were observed in the NT-proBNP, nor correlation with the maximum blood pressure values.

Limitations
As in other studies conducted during this type of expeditions, our study included a small number of participants. In addition to this, the OSA group presented baseline REI values of 5-15, which evidence a mild respiratory sleep disorder. To confirm our findings, it would be necessary to analyze larger populations with mild OSA.

CONCLUSION
Pre-existing mild respiratory sleep disorders in amateur mountaineers makes them prone to experiencing lower O₂ saturations and instability of the respiratory control system evidenced by a lower duty ratio.

Mountaineers who snore and have a high BMI should undergo a clinical examination, complete sleepiness questionnaires, and perform a sleep study before making an ascent so as to assess their respiratory risk. These recommendations should also be considered for other high-altitude sports and activities such as skiing, trekking or visiting places located at high altitudes.

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Effect of mild obstructive sleep apnea in mountaineers

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