HIGHLIGHTED TOPIC | Hypoxia 2015

Sleep at high altitude: guesses and facts

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Submitted 8 June 2015; accepted in final form 13 July 2015

Lowlanders commonly report a poor sleep quality during the first few nights after arriving at high altitude. Polysomnographic studies reveal that reductions in slow wave sleep are the most consistent altitude-induced changes in sleep structure identified by visual scoring. Quantitative spectral analyses of the sleep electroencephalogram have confirmed an altitude-related reduction in the low-frequency power (0.8-4.6 Hz). Although some studies suggest an increase in arousals from sleep at high altitude, this is not a consistent finding. Whether sleep instability at high altitude is triggered by periodic breathing or vice versa is still uncertain. Overnight changes in slow wave-derived encephalographic measures of neuronal synchronization in healthy subjects were less pronounced at moderately high (2,590 m) compared with low altitude (490 m), and this was associated with a decline in sleep-related memory consolidation. Correspondingly, exacerbation of breathing and sleep disturbances experienced by lowlanders with obstructive sleep apnea during a stay at 2,590 m was associated with poor performance in driving simulator tests. These findings suggest that altitude-related alterations in sleep may adversely affect daytime performance. Despite recent advances in our understanding of sleep at altitude, further research is required to better establish the role of gender and age in alterations of sleep at different altitudes, to determine the influence of acclimatization and of altitude-related illness, and to uncover the characteristics of sleep in highlanders that may serve as a study paradigm of sleep in patients exposed to chronic hypoxia due to cardiopulmonary disease.

altitude; hypoxia; sleep; insomnia

WORLDWIDE AN INCREASING NUMBER of persons is traveling to altitude for professional and leisure activities, and several millions of people permanently reside in mountain areas at high altitude (8, 16). Whether and to which extent acute or chronic exposure to hypobaric hypoxia at altitude affects sleep, an essential element of human well-being, is still uncertain. Relatively few scientific studies have investigated the impact of altitude exposure on subjective sleep quality and on characteristics of sleep measured by objective means. Presumably, the sleep of travelers arriving from lowlands at high altitude is poor in the first few nights but improves with acclimatization (33). Whether sleep is disturbed by a direct effect of the reduced barometric pressure and the consecutive hypoxia, or whether other factors play an important role including the excitement or stress of being in an unusual environment, physical stimuli such as noise, uncomfortable temperature, and sleeping conditions, is uncertain (34). Moreover, high-altitude periodic breathing, a pattern of breathing with waxing and waning of ventilation that commonly occurs even in healthy persons at elevations above 1,500 m, and acute altitude-related illness may also affect sleep (14). Insomnia has been considered a manifestation of acute mountain sickness (43) although this has been challenged recently (15, 28).

Despite the common belief that sleep quality at altitude is poor, the scientific evidence to support this notion is still modest. Based on observational studies, many of them performed in only a few healthy young men, it has been assumed that the main changes in sleep structure at altitude consisted in a reduction of deep sleep and an impairment of sleep continuity (Fig. 1). These concepts have been endorsed by several narrative reviews (42, 54, 55). Recent investigations including a few randomized trials have provided more robust and quantitative data on the changes of sleep at high altitude. The purpose of the current work was therefore to perform a systematic analysis of the scientific literature on sleep at altitude to summarize the established facts and to identify areas that might benefit from a corroboration of current assumptions by further research.

The topics that we address specifically include characteristics of sleep in newcomers at high altitude, changes in sleep...
during altitude acclimatization, treatments of altitude-induced sleep disturbances, sleep in patients with respiratory disease traveling to altitude, and sleep in highlanders.

**Systematic Search of the Literature**

A systematic search of the literature was performed (last retrieval on May 30, 2015) using the PubMed and the MEDLINE database (http://www.ncbi.nlm.nih.gov/pubmed/). The search terms and the number of returned articles are listed in Table 1. Titles and abstracts of the retrieved publications were studied. Articles were further analyzed if the following criteria were met: original investigations in adult humans; sleep assessment by either polysomnography, actigraphy, or standardized questionnaires; the study design, altitude, and setting were reported; and the results with appropriate statistics were reported. Data from these studies are described in this review.

A further, detailed analysis of all studies using polysomnography in at least 10 participants in addition to fulfilling the criteria mentioned above was performed. The results of this analysis are presented in Tables 2–4. The minimally required number of 10 participants was derived by a power calculation assuming a minimal important difference of 5% in slow wave sleep, a SD of 7%, a power of 0.8, and an alpha level of 0.05 based on data from a previous study (24).

**Table 1. Systematic literature research on sleep at altitude assessed by polysomnography**

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<th>Search Terms</th>
<th>PubMed Search Details</th>
<th>Returned Articles</th>
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<tr>
<td>5 Polysomnography and altitude</td>
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<td>7 Polysomnography and hypobaric hypoxia</td>
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<td>Total number of titles and abstracts screened</td>
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<tr>
<td>1–8 All</td>
<td>Number of articles containing polysomnographic data from altitude studies on at least 10 adult humans and summarized in Table 2</td>
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J Appl Physiol • doi:10.1152/japplphysiol.00448.2015 • www.jappl.org
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<tr>
<th>Reference</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Latshang et al. 2013 (24)</td>
<td>Randomized crossover. 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m.</td>
<td>Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</td>
<td>lb</td>
<td>51</td>
<td>Healthy men living below 800 m, age 24 yr.</td>
<td>Time at altitude 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m. Sleep Sleep efficiency, %: 490 m 97*; 1,630 m 1st night 98*; 2nd night 99*; 2,590 m 1st night 98*; 2nd night 98*. NREM 3 and 4, %: 490 m 24*; 1,630 m 1st night 24*; 2nd night 24*; 2,590 m 1st night 20*; 2nd night 21*. REM, %: 490 m 19*; 1,630 m 1st night 22*; 2nd night 20*; 2,590 m 1st night 20*; 2nd night 22*. Arousal index, 1/h: 490 m 8.3; 1,630 m 1st night 7.7*; 2nd night 7.7. Breathing SpO2, %: 490 m 96; 1,630 m 1st night 94*; 2nd night 94*. AH1, 1/h: 490 m 4.6; 1,630 m 1st night 7.0*; 2nd night 5.4*; 2,590 m 1st night 13.1*; 2nd night 8.0*. *P &lt; 0.05 vs. 490 m.</td>
<td>The main sleep disturbance at 1,650 m and 2,590 m consisted in a decrease in deep NREM sleep stages 3 and 4, see Fig. 2. Effects of acclimatization, are outlined in Table 3. Vigilance and cognitive performance during daytime tests did not show significant changes at altitude. However, slight impairments in postural control were noted (47).</td>
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<tr>
<td>Stadelmann et al. 2013 (48). Data collected during study by Latshang et al. 2013 (24).</td>
<td>Randomized crossover. 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m.</td>
<td>Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</td>
<td>lb</td>
<td>44</td>
<td>Healthy men living below 800 m, age 24 yr.</td>
<td>Time at altitude 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m. Sleep EEG, power spectral analysis Central (C3A2) slow wave activity (0.8–4.6 Hz), compared with 490 m, % change: 1,630 m 1st night -16; 2nd night -13; 2,590 m 1st night -15; 2nd night -14. Breathing See Ref. 24.</td>
<td>Quantitative spectral analysis of frontal and central EEG derivations revealed an altitude-dependent decrease in slow wave activity. In addition, there was a slight but statistically significant increase in the number of sleep cycles at higher altitudes and with longer stay at altitude. Effects of acclimatization are outlined in Table 3.</td>
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<tr>
<td>Stadelmann et al. 2014 (49). Data collected during study by Latshang et al. 2013 (24).</td>
<td>Randomized crossover. 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m.</td>
<td>Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</td>
<td>lb</td>
<td>20</td>
<td>Healthy men living below 800 m, age 24 yr. Subset of participants in study by Latshang et al. (24).</td>
<td>Time at altitude 1 day at 490 m, 2 days at 1,630 m, 2 days at 2,590 m. Sleep EEG, power spectral analysis Comparison of EEG power spectral density during epochs containing periodic breathing without arousals and periods with normal breathing but arousals reveal similar qualitative changes. Breathing See Ref. 24.</td>
<td>Data suggest that visual scoring of EEG arousals according to conventional criteria may miss subtle EEG changes at altitude.</td>
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<td>Tseng et al. 2014 (52).</td>
<td>Observational. 1 night at 9 m, 2 nights at 3,150 m, 1 night at 9 m.</td>
<td>Field study. Studies at Taipei and at Mountain Ho-Huan, Taiwan.</td>
<td>4</td>
<td>40</td>
<td>Healthy subjects, 14 men, age 39.9 yr.</td>
<td>Time at altitude 9 m before and after altitude exposure: T0 and T3 and at 3,150 m (day 1 and 2: T1 and T2). Sleep Sleep efficiency, %: 9 m T0 and T3 86 and 87; 3,150 m T1 and T2 82* and 84. NREM 3 and 4: 9 m T0 and T3 7 and 9; 3,150 m T1 and T2 7* and 7*. REM, %: 9 m T0 and T3 7 and 16; 3,150 m T1 and T2 14 and 7.</td>
<td>Minor although significant changes at altitude include alterations in sleep efficiency, slow wave sleep, and arousal index. This paper also contains a comparison of data on subjects without and with acute mountain sickness during the stay at 3,150 m.</td>
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<tr>
<td>Reference</td>
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<td>Participants</td>
<td>Main Results</td>
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</table>
| Nussbaumer-Ochsner et al. 2012 (39). | Design observational. 1 night at 490 m, night 1 and 3 at 4,559 m. |        | 4   | 16 healthy mountaineers, age 45 yr.       | **Time at altitude**  
1 day at 490 m, 3 days at 4,559 m.  
Sleep  
Sleep efficiency, %: 490 m 93; 4,559 m night 1 69*; night 3 75.  
Stage 3 and 4, %: 490 m 18; 4,559 m night 1 6; night 3 11%.  
REM, %: 490 m 8; 4,559 m night 1 1*; night 2 2%.  
Arousal index, l/h: 490 m 5.4; 4,559 m night 1 3*; night 2 4%.  
Breathing  
SpO₂, %: 490 m 96; 4,559 m night 1 67*, night 3 71*.  
AHI, l/h: 490 m 0.1; 4,559 m night 1 60.9*; night 3 86.5%.  
*P < 0.05 vs. 490 m; ¶P < 0.05 vs. day 1 at same altitude. | Symptoms of AMS and of disturbed sleep were significantly reduced in the morning after the 3rd vs. the 1st night at 4,559 m. |
| Muhm et al. 2009 (30). | Design randomized crossover. Exposure to simulated altitude of 305 m and 2,438 m for 18 h each. Washout period of >3 wk. |        | 1b  | 20 healthy men, age 44.1 yr.             | **Time at altitude**  
18 h at 305 m and at 2,438 m, respectively.  
Sleep  
Sleep efficiency, %: 305 m 87; 2,438 m 84.  
Slow wave sleep, %: 305 m 3; 2,438 m 2.  
REM, %: 305 m 17; 2,438 m 17.  
Arousal index, l/h: 305 m 139; 2,438 m 152.  
SpO₂, %: 305 m 92; 2,438 m 86.  
Breathing  
SpO₂, %: 305 m 92; 2,438 m 86*.  
Oxygen desaturation index (>3%), l/h: 305 m 3; 2,438 m 12*.  
*P < 0.05 vs. 305 m | Objective and subjective measurements of sleep quantity and quality did not change significantly with changes in simulated altitude nor did postsleep neurobehavioral performance or mood. |
| Beaumont et al. 2004 (3). | Design randomized, placebo-controlled, crossover. Sleep studies during 4 nights, separated by 1 wk washout in normobaric conditions. Treatment with zolpidem 10 mg, zaleplon 10 mg, placebo at simulated 4,000 m, respectively. |        | 4 (altitude effect) 1b (drug effect) | 12 healthy men, age 29.9 yr. | **Time at altitude**  
1 night at 80 m, 3 nights at simulated 4,000 m.  
Sleep  
Sleep efficiency, %: 80 m 87; 4,000 m: placebo 81; zaleplon 84; zolpidem 85.  
NREM 3 and 4, %: 80 m 23; 4,000 m: placebo 38%; zaleplon 20; zolpidem 24%.  
REM, %: 80 m 17; 4,000 m: placebo 7%; zaleplon 10%; zolpidem 10%.  
Arousal index, l/h: NA.  | Minor effect of hypobaric hypoxia on slow wave and REM sleep. Accordingly, the effect of drugs was also minor. The drugs did not induce any significant changes in oxygen saturation or periodic breathing. |
<table>
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<th>Reference</th>
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<th>Participants</th>
<th>Main Results</th>
<th>Comments</th>
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<tr>
<td>Beaumont et al. 2007 (4).</td>
<td><strong>Design</strong> Randomized, placebo-controlled crossover. 5 days at 1,000 m, 3 periods of nights at 3,613 m with washout phase. <strong>Setting</strong> Field study. Military School in the French Alps. Nights 1–3 to test zolpidem 10 mg, zaleplon 10 mg, placebo. Washout phase of at least 1 wk between treatment nights.</td>
<td>4 (altitude effect) 1b (drug effect)</td>
<td>12</td>
<td>Healthy military trainees, age 22.2 yr.</td>
<td><strong>Time at altitude</strong> 1 night at 1,000 m, 3 periods of 3 consecutive nights at 3,613 m, 1 night on placebo, 1 night on zolpidem, 1 night on zaleplon. <strong>Sleep</strong> Sleep efficiency, %: 1,000 m: placebo 91%; zaleplon 93%; zolpidem 93%. Arousal, 1/h: NA NREM 4 (SWS NA), %: 1,000 m: placebo 12%; zaleplon 15%; zolpidem 17. <strong>Breathing</strong> SpO₂, %: 1,000 m 96; 3,613 m: placebo 83%; zaleplon 84%; zolpidem 82%. *P &lt; 0.05 vs. 1,000 m; ¶P &lt; 0.05 vs. placebo.</td>
<td>Altitude exposure was associated with a significant reduction in NREM sleep stage 4 and in sleep efficiency, and this was partially reversed with zolpidem. Nocturnal SpO₂ was not affected by either drug.</td>
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<td>Nussbaumer-Ochsner et al. 2010 (37).</td>
<td><strong>Design</strong> Randomized crossover. 1 day at 490 m, 2 days at 1,860 m, 2 days at 2,590 m. Discontinuation of CPAP therapy during study. <strong>Setting</strong> Field study. University Hospital Zurich, mountain hostels in Swiss Alps.</td>
<td>1b</td>
<td>34</td>
<td>Patients with obstructive sleep apnea syndrome living at &lt;600 m, age 62 yr. Discontinued their CPAP therapy during the study period.</td>
<td><strong>Time at altitude</strong> 1 day at 490 m, 2 days at 1,860 m, 2 days at 2,590 m. <strong>Sleep</strong> Sleep efficiency, %: 490 m 86; 1,860 m 1st night 82; 2nd night 79%; 2,590 m 1st night 78%; 2nd night 71%. NREM 3 and 4, %: 490 m 14; 1,860 m 1st night 12; 2nd night 14; 2,590 m 1st night 6%; 2nd night 9%. REM, %: 490 m 13; 1,860 m 1st night 13; 2nd night 13; 2,590 m 1st night 10; 2nd night 10. Arousal index, 1/h: 490 m 35.5; 1,860 m 1st night 41.8%; 2nd night 45.5%; 2,590 m 1st night 51.3%; 2nd night 49.3%. <strong>Breathing</strong> SpO₂, %: 490 m 94; 1,860 m 1st night 90%; 2nd night 90%; 2,590 m 1st night 86%; 2nd night 87%. AHI, 1/h: 490 m 51.2; 1,860 m 1st night 85.1%; 2nd night 68.5%; 2,590 m 1st night 90.3%; 2nd night 88.6%. *P &lt; 0.05 vs. 490 m; P = NS night 2 vs. 1 at same altitude.</td>
<td>Patients with obstructive sleep apnea syndrome discontinuing their CPAP therapy experience pronounced hypoxemia and exacerbation of sleep apnea during a stay at moderate altitude.</td>
</tr>
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</table>
The literature research provided 14 original publications with data from nocturnal polysomnography at altitude. Two of these (5, 30) used a hypobaric chamber to simulate altitude exposure, and the other 12 studies were field studies [11 performed in the Alps and 1 in Taiwan (52)]. Ten of the 14 papers reported data on healthy subjects and 4 on patients with obstructive sleep apnea. Due to the inhomogeneity of the studies a pooled analysis was not feasible. The study design and setting, the Oxford Center of Evidence-Based Medicine evidence level (40), the number of participants, and the main outcomes were extracted and tabulated for these polysomnographic studies.

### Sleep in Newcomers at Altitude

Questionnaire evaluations suggest that sleep disturbances at high altitude are common. For example, 46% of 100 Iranian ski tourists reported frequent awakenings and other subjective sleep disturbances (Groningen insomnia score >6) they perceived in the first night after arriving at a hotel at 3,500 m (17). Similarly, among 305 Chinese soldiers transported from 500 m to 3,700 m in Lhasa, 32% suffered from insomnia in the first night at altitude (Athens insomnia scale score >6), and 74% of 246 workers air lifted to the South Pole at 2,835 m reported difficulty sleeping in the first week (1). As subjective perception and neurophysiologic correlates of sleep may differ considerably at altitude (36), it is important to consider both subjective reports and objective assessments when evaluating altitude effects on sleep.

The results of our systematic analysis of the literature on polysomnographic sleep studies in newcomers at altitude are provided in Tables 1–4. In the largest study evaluating alterations in sleep structure induced by traveling to altitude (i.e., ascent from 490 m, to 1,630 m, and 2,590 m), the main changes observed in 51 healthy young men (median age 24 y) included a slight reduction in deep sleep (Fig. 2A), i.e., a reduction of 3% in non-rapid eye movement (NREM) sleep stages 3 and 4 at 2,590 m, but no significant changes in sleep efficiency and arousals (24). In the same study, power density spectra of frontal and central electroencephalogram derivations revealed a reduction in slow wave activity (0.8–4.6 Hz) during NREM sleep by ~4% in the first night at 1,630 m and by ~15% at 2,590 m (Fig. 2B) (48); additional altitude-related changes that have not been described previously, included a decrease in theta activity (4.6 to 8.0 Hz) and an increase in spindle peak height and frequency at 2,590 m. Reductions in slow wave and theta activity were also noticed during rapid eye movement (REM) sleep (48). Nevertheless, subjective sleep quality was not significantly impaired, and daytime tests of vigilance and cognitive performance did not reveal any altitude-related decrements at 1,630 m and 2,590 m (24). A more pronounced reduction in deep sleep was observed in other studies performed at higher altitude, i.e., a 12% reduction in NREM stages 3 and 4 at 4,559 m along with a 5% reduction in REM sleep. This was associated with subjective insomnia and symptoms of acute mountain sickness reported by the mountaineers (39).

Early studies have suggested that a pronounced sleep fragmentation was a characteristic change occurring with exposure to hypobaric hypoxia (2). However, these observations obtained in only five subjects confined to a hypobaric chamber for several weeks while being exposed to extremely low baromet-

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### Table 2—Continued

<table>
<thead>
<tr>
<th>Design and Setting</th>
<th>Study using transcranial near-infrared spectroscopy during sleep. In patients with obstructive sleep apnea discontinuing CPAP therapy during the study period.</th>
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<td><strong>Participants</strong></td>
<td>n=18</td>
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<tr>
<td><strong>FIM</strong></td>
<td>1b</td>
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</table>

| **Reference**      | Bloch KE et al. 2012 (53).                                                                           |
| **Setting**        | University Hospital Zurich, mountain huts in Swiss Alps.                                           |
| **Design**         | Controlled trial, level 4, case–series, CPAP, continuous positive airway pressure, AH, apnea/hypopnea index, REM, rapid eye movement sleep, NREM, non-rapid eye movement sleep, SpO2, mean nocturnal arterial oxygen saturation. |

**Main Results**

- P = 0.05 vs. 490 m; ¶ P = 0.05 vs. 490 m at same altitude.
- Sleep disturbance scores: 0.8–4.6 Hz, 4.6 to 8.0 Hz, 4.6 to 8.0 Hz.
- Increase in spindle peak height and frequency at 2,590 m.
- Reduction in slow wave activity (0.8–4.6 Hz) during NREM sleep by ~4% in the first night at 1,630 m and by ~15% at 2,590 m.
- Additional altitude-related changes including a decrease in theta activity (4.6 to 8.0 Hz) and an increase in spindle peak height and frequency at 2,590 m.
Fig. 2. Data from a randomized trial evaluating effects of altitude on sleep and cognitive performance in 51 healthy men. A: this shows the decrease in nocturnal oxygen saturation and the increase in the apnea/hypopnea index at the higher altitudes (left: 1,630 m and 2,590 m compared with 490 m), and the corresponding changes in deep sleep (right); the number of arousals is similar at the three altitudes (†P < 0.05 vs. 490 m, ††P < 0.05 vs. 490 m and 1,650 m). B: spectral plots of power density from frontal (F3A2; left) and central electroencephalographic derivations (C3A2; right) that quantify the reduction in slow wave activity (0.8–4.6 Hz) and the increase in the spindle frequency range (10–15 Hz) at the higher altitudes (1,630 and 2,590 m, nights 1 and 2, N1 and N2, compared with a night at 490 m). C: Pre-sleep (left) and post-sleep (right) performance in a visual-motor task are illustrated. The decrement of overnight memory consolidation at 2,590 vs. 490 m is reflected in the increase in directional error in 264 movements at 2,590 vs. 490 m. A–C are reproduced in modified form with permission from Latshang et al. (24), Stadelmann et al. (48), and Tesler et al. (51).
periodic breathing triggers arousals from sleep or, vice versa, sleep fragmentation promotes instability of ventilatory control remains controversial. Both spontaneous arousals not associated with central apnea and arousals following apneas of periodic breathing have been described (19). However, the observation that the amount of high-altitude periodic breathing in mountaineers arriving at 4,559 m increased with acclimatization over the course of 3 nights (i.e., the apnea/hypopnea index increased from 60.9/h in the 1st to 86.5/h in the 3rd night at 4,559 m) while the arousal index decreased over the same period (from 17.9/h to 5.7/h) suggests independent physiologic mechanisms (39). Correspondingly, in healthy newcomers at 2,590 m, the arousal index determined by visual EEG analysis was not different from that at 490 m (i.e., 7.7/h at 2,590 m vs. 8.3/h at 490 m) although the apnea/hypopnea index had increased significantly (13.1/h at 2,590 m vs. 4.6/h at 490 m) (24). Quantitative electroencephalogram analysis in the same study revealed that spectral EEG signatures during periodic breathing without visually scored arousals were similar to those of sleep periods without periodic breathing but with visually scored arousals (46, 49). Therefore, high-altitude periodic breathing seems to be associated with EEG alterations not apparent during visual inspection using standard criteria (46). Subtle changes in electrical brain activity induced by exposure to even mild hypobaric hypoxia may thus reflect cortical dysfunction at altitude. Sophisticated, quantitative measurement techniques are required to detect these effects.

Consistent with an unfavorable effect of altitude on sleep, overnight changes in slow wave-derived measures of neuronal synchronization (i.e., overnight decrements in the slope of slow waves) were less pronounced at 2,590 m than corresponding baseline measures at 490 m and this was associated with a decline in the sleep-related memory consolidation assessed by a visual-motor learning task (Fig. 2C) (51). Impairment in postural control observed at 2,590 m during the same study further supports a role of even mild hypoxia and possibly sleep disturbances in causing central nervous performance decrements (47) even though vigilance and cognitive function were not noticeably affected in certain tests (24). In turn, studies performed at higher altitude (3,800 m and 3,900 m) have revealed cognitive impairment and improvement of sleep and periodic breathing by nocturnal oxygen enrichment that were followed by subsequent improvements in daytime performance in neuropsychological tests (26, 27).

### Changes in Sleep During Altitude Acclimatization

Data on the effects of altitude acclimatization on sleep structure are very scant (Table 3). In healthy mountaineers ascending rapidly from 490 m to 4,559 m a reduction of total sleep time, sleep efficiency, and deep sleep (NREM stages 3 and 4) and a significant increase in arousals and pronounced periodic breathing were noted in the first night at high altitude (39). The changes in sleep structure were partially normalized in the third night at 4,559 m in association with an improvement in nocturnal arterial oxygen saturation while periodic breathing increased even further (39). At an altitude of 3,150 m (52) and at 2,590 m (24), no significant changes in sleep structure between the first and second nights

<table>
<thead>
<tr>
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<tr>
<td>Latshang et al. 2013 (24).</td>
<td>See Table 2.</td>
<td>1b</td>
<td>51</td>
<td>Healthy men.</td>
<td>See Table 2.</td>
<td>Acclimatization (days at altitude) was a significant independent predictor of the %NREM sleep stages 3 and 4, of the %time with wakfulness after sleep onset, and of the AHI when controlling for several covariables.</td>
</tr>
<tr>
<td>Stadelmann et al. 2013 (48). Data collected during study by Latshang et al. (24).</td>
<td>See Table 2.</td>
<td>1b</td>
<td>44</td>
<td>Healthy men.</td>
<td>See Table 2.</td>
<td>Quantitative spectral analysis of frontal and central EEG derivations revealed that the altitude dependent decrease in slow wave activity was more pronounced in the first compared to the second night at altitude. In addition, the increase in the number of sleep cycles at higher altitudes was more pronounced in the first compared to the second night.</td>
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<td>Tseng et al. 2014 (52).</td>
<td>See Table 2.</td>
<td>4</td>
<td>40</td>
<td>Healthy men and women.</td>
<td>See Table 2.</td>
<td>There was no statistically significant difference between sleep variables in the first and second night at 3,150 m suggesting no effect of acclimatization.</td>
</tr>
<tr>
<td>Nussbaumer-Ochsner et al. 2012 (39).</td>
<td>See Table 2.</td>
<td>4</td>
<td>16</td>
<td>Healthy mountaineers.</td>
<td>See Table 2.</td>
<td>Acclimatization from day 1 to day 3 at 4,559 m was associated with an increase in deep sleep (NREM stages 3 and 4) and REM sleep and in the AHI while the arousal decreased.</td>
</tr>
<tr>
<td>Nussbaumer-Ochsner et al. 2010 (37). See also Table 2.</td>
<td>See Table 2.</td>
<td>1b</td>
<td>34</td>
<td>Patients with obstructive sleep apnea.</td>
<td>See Table 2.</td>
<td>In patients with obstructive sleep apnea syndrome living near sea level and discontinuing their continuous positive airway pressure therapy during altitude travel there was no difference in sleep characteristics between the first and second night at 1,860 and 2,590 m, respectively.</td>
</tr>
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Numbers in the participants and results columns are means or medians; n = number of participants. Abbreviations: see Table 2.
were noted. Based on the cited studies (24, 39, 52) one might hypothesize that the effects of acclimatization on sleep are altitude dependent. In this context it is interesting to note that the progression or regression of high-altitude periodic breathing during acclimatization seems also to depend on the altitude: Thus at 4,559 m (39) and at altitudes from 4,497 to 6,825 m (6), the amount of high-altitude periodic breathing (expressed as apnea/hypopnea index or percentage of the nighttime with periodic breathing) increased with the time spent at altitude (6). Conversely, in studies at 1,650 and 2,590 m (24) and at 3,450 m (20), high-altitude periodic breathing decreased from the first to the second night. Assuming a sleep disruptive effect of high-altitude periodic breathing (as discussed above), these observations offer a possible explanation of the altitude-dependent differential effect of acclimatization on sleep structure. The varying tendency to breathing instability (periodic breathing) during the initial and prolonged exposure to moderate or high altitude may be related to changes in the balance between the ventilatory sensitivity to hypoxia and hypocapnia (12). In other studies that reported repeated sleep studies in lowlanders during more prolonged sojourns at higher altitudes, the independent effect of acclimatization was difficult to assess because of progressive increases in altitude over the course of a trek in the Himalayas (18) or because of inadequate sample size and nonstandardized sleep scoring (44).

Sleep Disturbances in Altitude-Related Illness

It is conceivable that altitude-related illness including acute mountain sickness and high-altitude pulmonary edema may interfere with refreshing sleep either directly or through symptoms such as headache, cough, and shortness of breath although there is little robust evidence to corroborate this (Tables 2–4). Mountain travelers with acute mountain sickness at 3,250 m had a minor reduction in REM sleep but an otherwise similar sleep structure compared with controls without acute mountain sickness (52). High-altitude pulmonary edema susceptible subjects revealed a major reduction in sleep efficiency and in deep sleep (NREM 3 and 4) in the first night after ascent to 4,559 m within less than 24 h (Table 4) (38). These changes were similar to those in mountaineers without known susceptibility to high-altitude pulmonary edema in the same setting (Table 2) (39). Since high-altitude pulmonary edema usually develops within 2–4 days after rapid ascent, sleep in the first night at altitude may not have been affected in the participants of the cited study although subtle changes in the nocturnal breathing pattern, i.e., an increase in the breath rate and periodic breathing, were noted (9). The combination of sustained and intermittent hypoxia associated with periodic breathing in the first 1–2 nights at high altitude with the associated surges of pulmonary artery pressure may promote the subsequent development of high-altitude pulmonary edema in susceptible subjects.

Treatment of Altitude-Induced Sleep Disturbances

Several studies have evaluated the effect of hypnotic drugs on altitude-induced sleep disturbances, but only few used polysomnography (Table 4). In a randomized, placebo-controlled hypobaric chamber study simulating an altitude of 4,000 m (3) and a field study in the French Alps at 3,610 m (4), the GABAA agonists zaleplon (10 mg) and zolpidem (10 mg) were evaluated. Zolpidem provided minor although statistically significant improvements in deep NREM sleep (i.e., a 2.6% increase in stage 4 vs. placebo). No impairment of nocturnal oxygen saturation, breathing pattern, or daytime performance in cognitive test batteries was noted with either zaleplon or zolpidem compared with placebo (3, 4). In a study performed in Nepal at 3,540 m, 34 trekkers received either temazepam (7.5 mg) or acetazolamide (125 mg) on the first night at that altitude according to a randomized, double-blind design (50). Participants receiving temazepam reported a better subjective sleep quality and less frequent awakenings to urinate than those receiving acetazolamide. No polysomnographic data were available in that study (50). In climbers staying at Everest base camp at 5,300 m, temazepam (10 mg) improved subjective sleep quality and reduced the cyclic oxygen desaturations due to periodic breathing compared with values during a placebo night without affecting mean nocturnal oxygen saturation (13). However, temazepam (10 mg) did not improve subjectively perceived insomnias nor actigraphic indexes of sleep continuity in 19 trekkers sleeping at 5,000 m in Nepal compared with a control group of 14 trekkers receiving placebo (31). Interpretation of these results is hampered by incomplete data sets, and the small number of participants, some of them also taking acetazolamide.

In high-altitude pulmonary edema susceptible mountaineers, dexamethasone (2 × 8 mg/d) taken before a rapid ascent to 4,559 m resulted in a better subjective sleep quality and a greater total sleep time and sleep efficiency recorded by polysomnography in the first night at altitude compared with participants not receiving the drug (Table 4) (38). Taking dexamethasone before ascent increased the mean nocturnal oxygen saturation and reduced the heart rate at 4,559 m, which is consistent with the beneficial effects of dexamethasone on reducing pulmonary artery pressure and preventing overt high-altitude pulmonary edema (29).

Sleep in Patients with Respiratory Disease Traveling to Altitude

Although patients with disturbances of control of breathing or gas exchange impairment due to respiratory disease may be particularly susceptible to adverse effects of hypobaric hypoxia at altitude, there has been little scientific evidence to counsel these patients regarding the risks of altitude travel and effective measures to prevent them. To address this point, we have performed several randomized, controlled trials in lowlanders with obstructive sleep apnea syndrome (OSA) (Tables 2–4) (25, 35, 37, 53). These studies revealed that OSA patients who discontinued their continuous positive airway pressure therapy when staying in Alpine resorts at an elevation of 1,860 and 2,590 m had pronounced nocturnal hypoxemia and an exacerbation of sleep apnea due to frequent central events (37). This was associated with a reduced cerebral tissue oxygenation (53), decreased sleep efficiency and deep sleep, and more frequent arousals compared with nights at 490 m (37, 53). Moreover, driving simulator performance during daytime was impaired at altitude (37). Continuous positive airway pressure treatment with computer controlled mask pressure (AutoCPAP) combined with acetazolamide improved arterial oxygen saturation and prevented the altitude-induced increase in sleep apnea (25). Another trial suggested that acetazolamide alone may be beneficial for patients with OSA traveling to remote mountain areas where CPAP therapy is not feasible as it improved...
Table 4. Treatment of sleep disturbances at altitude

<table>
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<tr>
<th>Reference</th>
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<tr>
<td>Beaumont et al. 2004 (3)</td>
<td>Randomized, placebo-controlled, crossover. Sleep studies during 4 nights, separated by 1 wk washout. Treatment with zolpidem 10 mg, zaleplon 10 mg, placebo at simulated 4,000 m, respectively.</td>
<td>4 (altitude effect) 1b (drug effect)</td>
<td>12</td>
<td>Healthy men.</td>
<td>See Table 2.</td>
<td>Minor effect of hypobaric hypoxia on slow wave and REM sleep. Accordingly, the effect of drugs was also minor and only significant for zolpidem in terms of a slight increase in NREM stage 4 compared to placebo. The drugs did not induce any significant changes in oxygen saturation or periodic breathing.</td>
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<td></td>
<td>Setting Hypobaric chamber simulating 80 m and 4,000 m.</td>
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<td>Beaumont et al. 2007 (4). See also Table 2.</td>
<td>Randomized, placebo-controlled crossover study of zaleplon and zolpidem, respectively, vs. placebo. 5 days at 1,000 m, 3 times 3 nights at 3,613 m using the different drugs, washout phase of at least 1 wk between treatment nights.</td>
<td>4 (altitude effect) 1b (drug effect)</td>
<td>12</td>
<td>Healthy military trainees.</td>
<td>See Table 2.</td>
<td>Exposure to 3,613 m was associated with a significant reduction in NREM sleep stage 4 and in sleep efficiency. This was partially reversed with zaleplon (sleep efficiency) and zolpidem (sleep efficiency and NREM stage 4) compared to placebo at 1,000 m. Nocturnal SpO2 was not affected by either drug.</td>
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<tr>
<td></td>
<td>Setting Field study. Military camps at 1,000 m and 3,613 m.</td>
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</table>
| Nussbaumer-Ochsner et al. 2011 (38). | Randomized study of dexamethasone prophylaxis of high-altitude pulmonary edema. Subjects were randomized to receive dexamethasone 2 × 8 mg/day taken before ascent and during stay at altitude or to the same medication starting on day 2 at altitude only. Outcomes were assessed at 490 m and during night 1 and 3 at 4,559 m. | 3b  | 14 | High-altitude pulmonary edema susceptible but otherwise healthy subjects, age 47 yr. | **Time at altitude**  
1 night at 490 m, 3 nights at 4,559 m.  
**Dexamethasone late group:**  
Sleep  
Sleep efficiency, %: 490 m 91; 4,559 m night 1 65*; night 3 69*.  
Stage 3 and 4, %: 490 m 22; 4,559 m night 1 11*; night 3 20#.  
REM, %: 490 m 6; 4,559 m night 1 2*; night 3 2*.  
Arousal index, 1/h: 490 m 3.0; 4,559 m night 1 8.1*; night 3 6.0.  
**Breathing**  
SpO2, %: 490 m 96; 4,459 m night 1 71*; night 3 80#.  
AHI, 1/h: 490 m 1.9; 4,459 m night 1 91.3*; night 3 9.6#. | Multiple regression analysis controlling for the differences in the nocturnal SpO2 and the AHI suggested an independent effect of dexamethasone in improving sleep efficiency in the first night at 4,559 m. There was no independent effect of the drug on slow wave sleep and arousal index compared to no treatment in the first night at 4,559 m. |
<p>|                            | Setting Field study. In Zurich and Regina Margherita hut at 4,559 m, Swiss/Italian Alps. |     |    |                               |                                                                                                  |                                                                                                   |</p>
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<tr>
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</table>
| Nussbaumer-Ochsner et al. 2012 (35). | Randomized, placebo-controlled, double-blind crossover study of acetazolamide 2 × 250 mg/d during stay at altitude vs. placebo in patients with obstructive sleep apnea. Discontinuation of CPAP therapy during study. 1 day at 490 m, 2 days at 1,860 m, 1 day at 2,590 m. | 1b   | 45  | Patients with obstructive sleep apnea syndrome living at <600 m, age 64 yr. Discontinued their CPAP therapy during the study period. | **Dexamethasone early group:**
Sleep
Sleep efficiency, %: 490 m 96; 4,559 m night 1 95¶; night 3 90*. Stage 3 and 4, %: 490 m 19; 4,559 m night 1 19*; night 3 18*. REM, %: 490 m 10; 4,559 m night 1 1%; night 2 2%. Arousal index, 1/h: 490 m 2.0; 4,559 m night 1 5.6*; night 3 6.2*.
Breathing
SpO₂, %: 490 m 95; 4,559 m night 1 78*; night 3 79*. AHI, 1/h: 490 m 1.7; 4,459 m night 1 85.3*; night 3 52.3*. *P < 0.05 vs. 490 m; ¶P < 0.05 vs. dexamethasone early; #P < 0.05 vs. day 1 at 4,559 m.

| Setting       | Field study. University Hospital Zurich, mountain hostels in Swiss Alps.            |      |     |              | **Time at altitude**
1 day at 490 m, 2 days at 1,860 m, 1 day at 2,590 m. Outcomes assessed at 490 m, 1,860 m 2nd night and 2,590 m 1st night on placebo and acetazolamide, respectively.
Sleep
Sleep efficiency, %: 490 m 78; 1,860 m placebo 72, acetazolamide 81¶; 2,590 m placebo 66*; acetazolamide 77¶.
NREM 3 and 4, %: 490 m 6; 1,860 m placebo 6, acetazolamide 8; 2,590 m placebo 4*; acetazolamide 3*.
REM, %: 490 m 8; 1,860 m placebo 12, acetazolamide 8; 2,590 m placebo 9, acetazolamide 8.
Arousal index, 1/h: 490 m 44.9; 1,860 m placebo 52.8, acetazolamide 47.4; 2,590 m placebo 72.7*¶; acetazolamide 54.9*¶.
Breathing
SpO₂, %: 490 m 93; 1,860 m placebo 89¶; acetazolamide 91*; 2,590 m placebo 85*, acetazolamide 88*¶.
AHI, 1/h: 490 m 51.2; 1,860 m placebo 63.6*, acetazolamide 48.0¶; 2,590 m placebo 86.2*, acetazolamide 61.4*¶.

In patients with obstructive sleep apnea syndrome discontinuing their CPAP therapy during a stay at 1,860 m and 2,590 m acetazolamide 2 × 250 mg/day was superior to placebo in terms of nocturnal oxygen saturation, AHI, sleep efficiency, and arousal index. Therefore, patients with obstructive sleep apnea may benefit from acetazolamide therapy during a stay at altitude if CPAP therapy is not feasible.

Continued
Table 4.—Continued

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<thead>
<tr>
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<tbody>
<tr>
<td>Ulrich et al. 2014 (53). Data collected during study of Nussbaumer-Ochsner et al. 2012 (35) above.</td>
<td>See Table 2 and Nussbaumer-Ochsner et al. 2012 (35).</td>
<td>1b</td>
<td>18</td>
<td>Patients with obstructive sleep apnea syndrome living at &lt;600 m, age 64 yr. Discontinued their CPAP therapy during the study period.</td>
<td>See Table 2 and Nussbaumer-Ochsner et al. 2012 (35).</td>
<td>Study using transcranial near-infrared spectroscopy during sleep. In patients with obstructive sleep apnea staying at 2,590 m, nocturnal cerebral and arterial oxygenation were reduced in association with exacerbated sleep apnea. Acetazolamide partially improved cerebral tissue oxygenation, arterial oxygen saturation, and the AHI without impairing the cerebral blood flow response to apneas.</td>
</tr>
<tr>
<td>Latshang et al. 2012 (25).</td>
<td>Design</td>
<td>Randomized, placebo-controlled, double-blind crossover. Acetazolamide 250 mg in the morning and 500 mg in the evening during stay at altitude vs. placebo. CPAP therapy during stay at altitude. 1 day at 490 m, 2 days at 1,630 m, 1 day at 2,590 m.</td>
<td>1b</td>
<td>51</td>
<td>Patients with obstructive sleep apnea syndrome living at &lt;600 m, age 63 yr.</td>
<td>Time at altitude 2 days at 490 m, 2 days at 1,630 m, 1 day at 2,590 m. Outcomes assessed at 490 m with and without CPAP therapy, and at 1,630 m 2nd night and 2,590 m 1st night on placebo and acetazolamide, respectively. Sleep Sleep efficiency, %: 490 m CPAP 80; 1,630 m, CPAP + placebo 81, CPAP + acetazolamide 87*¶; 2,590 m CPAP + placebo 79; CPAP + acetazolamide 89*. NREM 3 and 4, %: 490 m CPAP 15; 1,630 m CPAP + placebo 13, CPAP + acetazolamide 15; 2,590 m CPAP + placebo 10*, CPAP + acetazolamide 13*. REM, %: 490 m CPAP 19; 1,630 m CPAP + placebo 23, CPAP + acetazolamide 19; 2,590 m CPAP + placebo 17, CPAP + acetazolamide 17. Arousal index, 1/h: 490 m CPAP 15.8; 1,630 m CPAP + placebo 17.4, CPAP + acetazolamide 16.4; 2,590 m CPAP + placebo 16.3, CPAP + acetazolamide 14.1.</td>
</tr>
</tbody>
</table>
arterial and cerebral oxygenation and central sleep apnea and prevented excessive blood pressure rises. These studies in obstructive sleep apnea patients have been reviewed recently (7, 21).

Preliminary studies revealed that lowlanders with chronic obstructive pulmonary disease [COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 2–3] who were normoxemic and did not have sleep apnea at 490 m were significantly more hypoxemic and developed moderate to very severe, predominantly central sleep apnea with reduced sleep efficiency and deep sleep when staying at 1,650 and 2,590 m compared with 490 m (23).

Thus current evidence suggests that patients with obstructive sleep apnea or COPD at lowlands are particularly susceptible to periodic breathing and sleep disturbances when staying at altitude. No other robust data on sleep in altitude travelers with preexisting respiratory or cardiac conditions are available.

Sleep in Highlanders

Virtually no conclusive data on sleep characteristics in highland residents are available. Normand et al. (32) reported that sleep organization assessed in Bolivian highlanders in La Paz at 3,850 m was “roughly” similar in 14 highlanders with polycythemia compared with 6 without polycythemia, but no comparison to measurements in lowlanders was provided. Coote et al. (11) performed polysomnographic studies in 8 Peruvian highlanders (mean hematocrit 58%) at Cerro de Pasco (4,330 m). Sleep efficiency was 91%, the relative duration of deep sleep (NREM stages 3 and 4) was 26%. Again, no comparison to data from lowlanders was performed in the cited and in a similar additional study performed by the same group (10). In Indian soldiers, six of them Ladakhis born and brought up at 3,300-3,800 m, sleep studies were obtained at an altitude of 3,500 m but the data are inconclusive because of the small sample size (45). Our own preliminary data from a study in Kyrgyz highlanders with high-altitude pulmonary hypertension (n = 36) suggest that the time in wakefulness after sleep onset was increased and NREM sleep stages 1 and 2 were increased compared with healthy highlanders (n = 54) and lowlanders (n = 34) (22); highlanders with high-altitude pulmonary hypertension had a significantly higher apnea/hypopnea index compared with both healthy highlanders and lowlanders.

Conclusions

Our review of the scientific literature on sleep and its disturbances at altitude confirm the longstanding notion that mountain tourists commonly perceive sleep disturbances with insomnia and frequent awakenings in the first few nights at altitude. High-altitude insomnia is generally modest, and it may or may not be associated with acute mountain sickness. The most consistent change reported from the few well-designed polysomnographic studies performed in healthy lowlanders arriving at altitude is a decrease in slow wave sleep. This may not only affect subjective well-being but also impair memory consolidation during sleep and possibly vigilance and cognitive and visual-motor performance during daytime. However, the evidence to support these assumptions is still scant. Further studies are required to better quantify the effects of different levels of altitude on sleep in persons of both sexes and of various ages and to elucidate the underlying physiological
mechanisms. Areas of uncertainty that should be addressed by future research relate to the interaction of high-altitude periodic breathing and sleep fragmentation, to the role of hypoxia in impairing daytime performance directly or via sleep disturbance (sleep fragmentation and altered sleep structure), and to changes in sleep with acclimatization. A better evaluation of the efficacy and safety of drugs for treatment of altitude-related sleep disturbances is also required. The research on sleep in high-altitude residents is still at its very beginning but might provide insights that are valuable for the better understanding and treatment of sleep disturbances in patients with chronic hypoxia at lowlands due to cardiac or pulmonary disease. In summary, although recent research has provided several facts that corroborate or refute previous guesses, more research is clearly needed to advance our understanding of various aspects of sleep at altitude.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


