CHEST™

Cerebral Oxygenation in Patients With OSA

Effects of Hypoxia at Altitude and Impact of Acetazolamide

Silvia Ulrich, MD; Yvonne Nussbaumer-Ochsner, MD; Irena Vasic, MD; Elisabeth Hasler, MD; Tsogyal D. Latshang, MD; Malcolm Kohler, MD; Thomas Muehlemann, PhD; Martin Wolf, PhD; and Konrad E. Bloch, MD, FCCP

BACKGROUND: Sleep-disordered breathing may impair cerebral oxygenation in patients with OSA syndrome, in particular during altitude travel. We studied cerebral tissue oxygenation (CTO) at low and moderate altitude in patients with OSA and evaluated whether acetazolamide improved CTO.

METHODS: Eighteen patients with OSA living at < 600 m discontinued CPAP therapy during studies in Zurich (490 m) and during two sojourns of 3 days in the Swiss Alps (2 days at 1,860 m and 1 day at 2,590 m) separated by a 2-week washout period at < 600 m. Patients received acetazolamide (2 × 250 mg/d) or placebo at altitude in a randomized, double-blind, crossover design. Nocturnal polysomnography, including CTO monitoring by near-infrared spectroscopy (NIRS), was performed.

RESULTS: At 490 m, medians of CTO, peripheral oxygen saturation as measured by pulse oximetry (Spo_2), and apnea/hypopnea index were 65%, 93%, and 57.3/h, respectively. At 2,590 m, on placebo, the corresponding values were 59%, 86%, and 86.4/h, respectively ($P < .05$, all corresponding comparisons). Acetazolamide increased CTO and Spo_2 at 2,590 m by mean values of 2% (95% CI, 0%-4%) and 2% (95% CI, 1%-3%), respectively, and reduced the apnea/hypopnea index by 23.4/h (95% CI, 14.0-32.8/h) ($P < .05$, all changes). Cerebral total hemoglobin concentration, a NIRS-derived surrogate reflecting regional cerebral blood volume, increased by a similar degree in response to apneas at 490 m and 2,590 m and during acetazolamide and placebo treatment.

CONCLUSIONS: In patients with OSA staying at altitude, nocturnal cerebral and arterial oxygenation were reduced in association with exacerbated sleep apnea. Acetazolamide partially improved CTO, Spo_2, and sleep apnea without impairing the cerebral blood flow response to apneas.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00714740; URL: www.clinicaltrials.gov

CHEST 2014; 146(2):299-308

Manuscript received December 16, 2013; revision accepted April 1, 2014; originally published Online First May 8, 2014.

ABBREVIATIONS: AHI = apnea/hypopnea index; CtHb = total hemoglobin concentration; CTO = cerebral tissue oxygenation; NIRS = near-infrared spectroscopy; $Ptcco_2$ = Pco_2 from transcutaneous capnography; Spo_2 = peripheral oxygen saturation as measured by pulse oximetry

AFFILIATIONS: From the Pulmonary Division and Sleep Disorders Centre (Drs Ulrich, Nussbaumer-Ochsner, Vasic, Hasler, Latshang, Kohler, and Bloch), and the Biomedical Optics Research Laboratory, Division of Neonatology (Drs Muehlemann and Wolf), University Hospital Zurich; and the Zurich Centre for Human Integrative Physiology and Zurich Centre for Interdisciplinary Sleep Research (Drs Kohler and Bloch), University of Zurich, Zurich, Switzerland.

Drs Ulrich and Nussbaumer-Ochsner share first authorship of this manuscript.

FUNDING/SUPPORT: Grant support was provided by the Swiss National Science Foundation and by the Zurich Lung League.

CORRESPONDENCE TO: Konrad E. Bloch, MD, FCCP, Pulmonary Division and Sleep Disorders Centre, University Hospital Zurich, Rämistrasse 100, CH-8091 Zurich, Switzerland; e-mail: konrad.bloch@usz.ch

DOI: 10.1378/chest.13-2967

OSA syndrome affects 5% to 10% of the population in many Western countries.[1] The disorder is characterized by repetitive upper-airway occlusion during sleep, resulting in apneas/hypopneas, arterial oxygen desaturation, and sleep disruption. As a consequence, patients with OSA suffer from excessive daytime sleepiness, cognitive impairment, and reduced quality of life. Moreover, they are at increased risk of experiencing cardiovascular and cerebrovascular diseases.[2,3] Studies at low altitude suggest that cerebral oxygenation and cerebrovascular autoregulation are impaired in patients with OSA during sleep and that some patients have structural and metabolic alterations of the brain.[4-6] Therefore, patients with OSA may be particularly susceptible to the adverse effects of hypobaric hypoxia at altitude, which impairs cerebral oxygenation and cerebrovascular autoregulation even in healthy subjects.[7,8]

In a previous study, we observed that untreated patients with OSA staying at an altitude of 1,860 m and 2,590 m experienced an exacerbation of sleep-related breathing disturbances with pronounced nocturnal hypoxemia when compared with values near sea level.[9] In a subsequent randomized, placebo-controlled trial, we found that acetazolamide (500 mg/d), taken as the sole therapy by patients with OSA during a stay at 1,860 m and 2,590 m, partially improved nocturnal arterial oxygen saturation and sleep apnea.[10] In another study, acetazolamide (750 mg/d) combined with computer-controlled nocturnal CPAP therapy completely normalized the breathing disturbances of patients with OSA during an altitude sojourn.[11] Therefore, computer-controlled nocturnal CPAP therapy and acetazolamide have been recommended as the preferred treatment of patients with OSA staying at moderate altitude for a few days.[12]

Acetazolamide promotes renal elimination of bicarbonate, thereby inducing a metabolic acidosis.[10] The resulting stimulation of ventilation increases arterial oxygen saturation but enhances the altitude-induced hyperventilation and hypocapnia, which may reduce cerebral blood flow and oxygenation.[13] Whether such possible undesirable effects of acetazolamide occur in patients with OSA at altitude has not been evaluated.

Therefore, the aim of the current study was to noninvasively monitor nocturnal cerebral tissue oxygenation (CTO) using near-infrared spectroscopy (NIRS) in patients with OSA participating in a randomized, placebo-controlled trial of acetazolamide during a stay at moderate altitude.[10] Total hemoglobin concentration (CtHb) was also monitored by NIRS as a surrogate measure reflecting changes in regional cerebral blood volume in response to apneas/hypopneas.[6,14,15] We hypothesized that cerebral oxygenation during nights spent at 2,590 m would be decreased compared with nights at 490 m, and that acetazolamide would mitigate the altitude-related reduction in cerebral oxygenation.

Materials and Methods

This study was performed as part of a randomized, placebo-controlled, double-blind trial evaluating the effects of acetazolamide in patients with OSA during an altitude sojourn. The experimental design, patient selection, and results of sleep and nocturnal breathing pattern analysis have been published.[10] Data on CTO, the topic of the current study, were not part of the previous report. The protocol was approved by the institutional ethics committee (Kantonale Ethikkomission Zürich, EK-1522), and subjects gave written informed consent to participate.

Patients

Patients with OSA to whom CPAP therapy had been administered were asked to participate if they were 20 to 80 years of age and living at an altitude below 600 m, and if the diagnosis of OSA was documented by medical records and a history of excessive sleepiness in association with an apnea/hypopnea index (AHI) $>$ 20/h before initiation of CPAP treatment. The following conditions excluded patients from study admission: a current oxygen desaturation index ($>$ 3%) $<$ 15/h during ambulatory nocturnal peripheral oxygen saturation as measured by pulse oximetry (Spo_2) or an obstructive AHI $<$ 10/h after 3 nights of CPAP withdrawal at 490 m; unstable cardiovascular disease; any lung disease; internal medical, neurologic, or psychiatric disease; or use of drugs that interfere with sleep and control of breathing.

Study Design and Protocol

From August to October 2008, we performed a randomized, placebo-controlled, double-blind, crossover trial evaluating the effects of acetazolamide in patients with OSA staying at altitude while discontinuing their CPAP therapy. The trial comprised baseline evaluations for 1 day in Zurich (490 m [barometric pressure, 717 mm Hg], either before or after altitude studies), and two altitude sojourns, lasting for 3 days each, in Alpine villages at 1,860 m (Davos Schatzalp [607 mm Hg], 2 days) and at 2,590 m (Davos Jakobshorn [554 mm Hg], 1 day), respectively, separated by a 2-week washout period at $<$ 600 m.

Patients were randomized to receive acetazolamide (250 mg, bid) during the first altitude sojourn, and identical-looking placebo tablets during the second altitude sojourn, or vice versa, according to a randomized, balanced block design (Fig 1). Because only one NIRS device was available, only one-half of the study participants, determined at random, underwent NIRS recordings (Fig 1). Transportation between study locations was by train, bus, and cable car. CPAP therapy was discontinued for 3 nights before beginning the studies and during altitude sojourns.

Assessments

Patients underwent daily questionnaires and clinical examinations. Polysomnography was performed from approximately 10:00 PM to 6:00 AM, as described previously.[10] In addition to standard measurements, it

included Pco_2 from transcutaneous capnography ($Ptcco_2$) and continuous NIRS monitoring. NIRS noninvasively measures concentrations of oxygenated and deoxygenated hemoglobin in the cerebral tissue by transluminating the skull by a light source placed on the skin and recording the reflected light in the near-infrared range. Cerebral tissue oxygen saturation (oxygenation) and CtHb are derived mathematically (see later data analysis).[16] A miniaturized, battery-powered NIRS device designed at our center was used.[17,18] Its optical probe comprised two pairs of light sources emitting at 760 and 870 nm, respectively, and two light sensors (source-detector distances of 14 and 22 mm, respectively) monitoring two superficial regional brain volumes, within a distance of 4 cm. The NIRS device was fixed and secured with elastic bandages high on the forehead where bone thickness is at its minimum and sinuses are avoided. NIRS data were transmitted by wireless connection to a personal computer and were recorded continuously at a rate of 1 Hz during the entire sleep study.

Data Analysis and Statistics

Polysomnography was analyzed according to standard criteria, as described previously,[10,11,19] by an investigator blinded to the location, treatment, and clinical data. Tracings of variables derived by NIRS (ie, regional CTO [CTO = ratio of oxygenated/(oxygenated + deoxygenated) hemoglobin concentration] and regional total cerebral tissue hemoglobin concentration [CtHb = oxygenated + deoxygenated hemoglobin concentration]) were inspected visually on a computer screen, along with finger Spo_2. Technical failures and occasional motion artifacts defined by loss of signal or brisk changes of the NIRS or Spo_2 signals were excluded from analysis. Individual mean values and SDs of CTO and Spo_2 from overnight recordings were determined. The response to apneas/hypopneas was evaluated in three consecutive obstructive apnea/hypopnea cycles during non-rapid eye movement sleep. Mean values were recorded for the apnea/hypopnea cycle time and for the following variables quantifying the extent and dynamic changes of cerebral and arterial oxygenation and of regional cerebral blood volume (Fig 2): baseline values of CTO and Spo_2; desaturation amplitude; time from beginning of desaturation to the nadir; rise in CtHb, a surrogate of regional cerebral blood volume changes; and time from start of CTO drop to the CtHb peak.

Nonnormally distributed data are summarized as medians (quartiles), normally distributed data as means (95% CIs). Effects of altitude and of acetazolamide were evaluated by Wilcoxon matched pairs tests and by computing mean differences with 95% CIs. A probability of $P < .05$ was considered statistically significant.

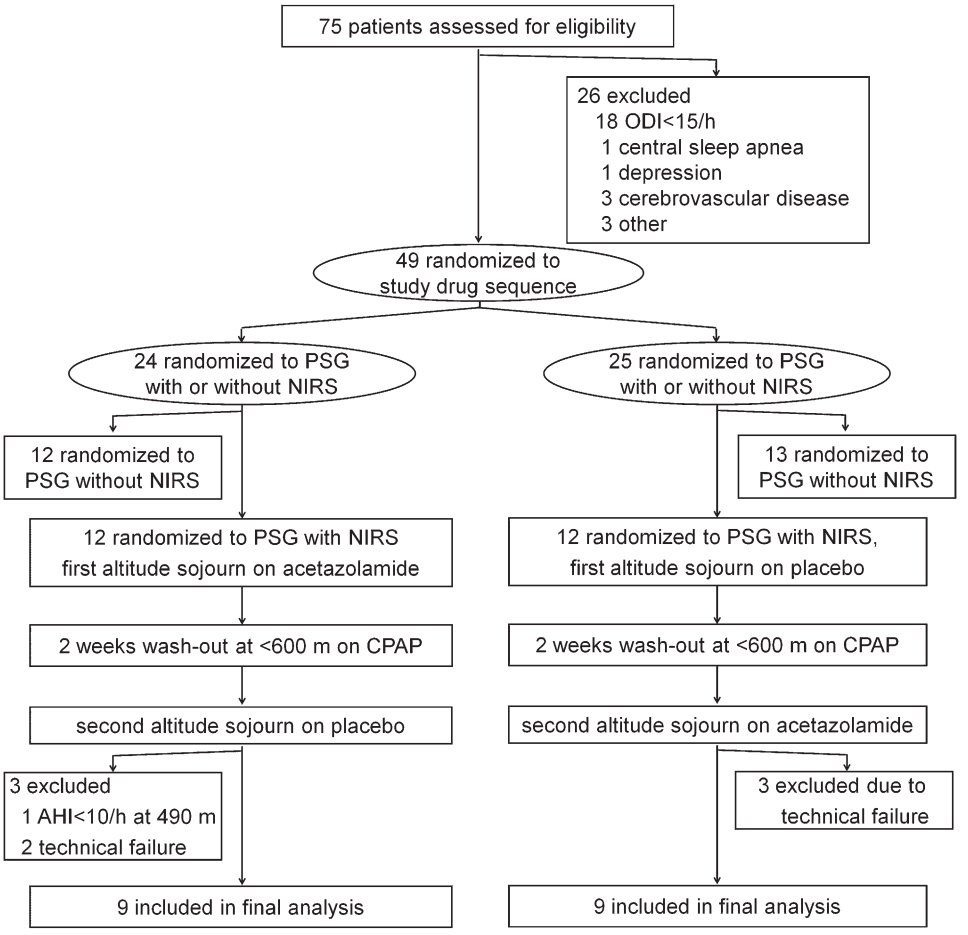

Figure 1 – *Patient flow. Patients were randomized to a study drug sequence (either acetazolamide or placebo during the first altitude sojourn) and to PSG with or without NIRS monitoring. AHI = apnea/hypopnea index; NIRS = near-infrared spectroscopy; ODI = oxygen desaturation index (> 3%); PSG = polysomnography.*

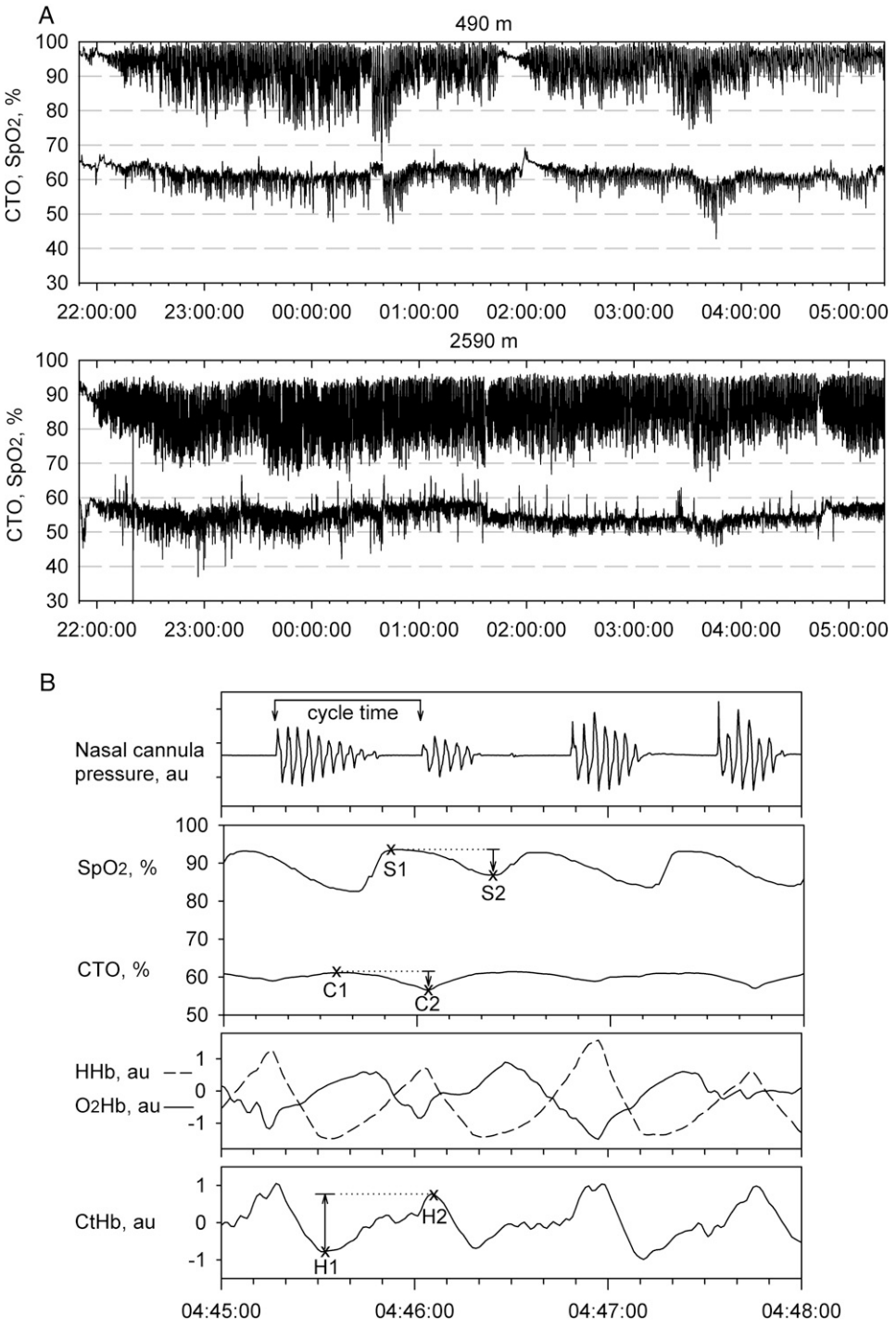

Figure 2 – *Nocturnal NIRS and finger SpO2 recordings in a patient at 490 m and at 2,590 m (on placebo). A, Entire nights (7.5 h) with large swings of finger SpO2 and more moderate swings of CTO that depart from lower baseline levels. B, 3-min episode of the recording at 2,590 m. Nasal cannula pressure swings show several apnea/hyperpnea cycles and corresponding changes in SpO2, CTO, O2Hb, HHb, and CtHb. Variables listed in Table 2 are marked: SpO2 baseline (S1); SpO2 nadir (S2); SpO2 desaturation amplitude = difference in amplitude between S1 and S2; SpO2 desaturation time to nadir = difference in time between S1 and S2; CTO baseline (C1); CTO nadir (C2); CTO desaturation amplitude = difference in amplitude between C1 and C2; CTO desaturation time to nadir = difference in time between C2 and C1; CtHb rise in amplitude = H2 − H1; CtHb time from start of CTO drop from baseline (C1) to CtHb peak = difference in time between H2 and C1. au = arbitrary units; CtHb = total hemoglobin concentration; CTO = cerebral tissue oxygenation; HHb = deoxygenated hemoglobin; O2Hb = oxygenated hemoglobin; SpO2 = peripheral oxygen saturation as measured by pulse oximetry. See Figure 1 legend for expansion of other abbreviations.*

Results

Figure 1 illustrates the patient flow. A total of 24 patients underwent polysomnography with NIRS recordings. Data from one patient had to be excluded after study completion according to the predefined criteria because baseline polysomnography at 490 m revealed an obstructive AHI < 10/h; data from five patients had to be excluded because of technical failures or insufficient quality of NIRS or Spo_2 recordings. The final analysis included data from 18 patients (one woman). The median (quartiles) age of the study participants was 61 years (58-65 years), BMI was 32 kg/m^2 (31-38 kg/m^2), and the AHI during CPAP withdrawal was 57.3/h (46.5-67.3/h).

Effects of Altitude on Cerebral and Arterial Oxygenation, Breathing, and Sleep

The results of the sleep studies are summarized in Table 1. In patients using placebo at 2,590 m, nocturnal CTO, Spo_2, and $Ptcco_2$ were significantly reduced compared with the corresponding values at 490 m. The variability of CTO quantified by the SD remained unchanged at 2,590 m, whereas the SD of Spo_2 was larger than at 490 m. This was consistent, with a significantly higher AHI (median of 86.4/h) at 2,590 m than the corresponding value at 490 m (57.3/h) related to an increase in central AHI. There was a 10% decrease in sleep efficiency and a 3% reduction in slow-wave sleep at 2,590 m compared with 490 m, whereas changes in rapid eye movement sleep were not statistically significant.

Effects of Acetazolamide on Cerebral and Arterial Oxygenation, Breathing, and Sleep at 2,590 m

Acetazolamide significantly increased CTO and Spo_2 compared with values during placebo treatment at 2,590 m. The increase was similar for CTO and Spo_2, so the differences between CTO and Spo_2 remained unchanged. Acetazolamide reduced the total and the central AHI and increased the total sleep time and sleep efficiency (Table 1).

Cerebral and Arterial Oxygenation During Apnea/Hypopnea Events at 490 m and 2,590 m During Placebo and Acetazolamide Treatment

The effects of apneas/hypopneas on variables derived by NIRS, Spo_2, and $Ptcco_2$ are summarized in Table 2 and illustrated in Figure 3. For this analysis, data were available from 13 patients who had obstructive apneas/hypopneas and corresponding NIRS and Spo_2 recordings of satisfactory quality at 490 m and from 18 patients studied at 2,590 m on placebo and 17 patients on acetazolamide. Compared with 490 m, baseline values of CTO, Spo_2, and $Ptcco_2$ were significantly lower at 2,590 m during placebo treatment. In addition, apnea/hypopnea-related CTO and Spo_2 desaturations were larger at 2,590 m, although the apnea/hypopnea cycle time was shorter. Therefore, the slopes of CTO and Spo_2 desaturations were steeper and the nadirs occurred earlier at 2,590 m compared with 490 m (Fig 3). Apnea/hypopnea events were associated with a similar increase in CtHb at 490 m and at 2,590 m during placebo treatment, but the increase in CtHb relative to the corresponding (greater) drop in CTO was reduced at 2,590 m (Table 2).

In comparison with placebo, acetazolamide increased the baseline values of both CTO and Spo_2 at 2,590 m, and it prolonged the apnea/hypopnea cycle time and the time to the CTO and Spo_2 desaturation nadirs, resulting in a reduced slope of Spo_2 desaturations (Fig 3). The increase in CtHb in response to CTO desaturations occurred significantly earlier during acetazolamide compared with placebo treatment (Fig 3, Table 2), and the CtHb increase tended to be greater ($P = .14$) despite a more pronounced hypocapnia during acetazolamide treatment (Table 2). The ratio of CtHb increase to CTO decrease remained unchanged by acetazolamide.

Discussion

The current randomized, crossover trial demonstrates that patients with OSA discontinuing their CPAP therapy during a stay at moderate altitude experience a reduction of both cerebral (CTO) and arterial oxygen saturation (Spo_2) in association with exacerbated sleep apnea caused by central apneas/hypopneas. In a randomized, placebo-controlled, double-blind comparison, our trial further shows that acetazolamide taken during an altitude sojourn partially prevents the fall in nocturnal CTO and Spo_2 and reduces the breathing disturbances of otherwise untreated patients with OSA. Acetazolamide did not adversely affect the changes in the NIRS-derived measures of the cerebrovascular response to apneas/hypopneas (ie, the changes in CtHb), suggesting that the regulation of cerebral blood flow was not altered by the drug although it enhanced hypocapnia at altitude. The results of the current trial, therefore, suggest that patients with OSA unable to have CPAP therapy administered during an altitude sojourn may benefit from acetazolamide therapy.

TABLE 1] Cerebral and Arterial Oxygenation, Breathing, and Sleep at 490 m and 2,590 m; Effect of Acetazolamide (n = 18)

Variable	490 m, Off CPAP, Median (Quartiles)	2,590 m, Placebo, Median (Quartiles)	2,590 m-490 m, Δ (95% CI)	2,590 m, Acetazolamide, Median (Quartiles)	Acetazolamide-Placebo at 2,590 m, Δ (95% CI)
CTO, mean, %	65 (63; 68)	59 (56; 62)	−6[a] (−8 to −4)	61 (59; 64)	2[a] (0 to 4)
CTO, SD of mean, %	2 (2; 3)	3 (2; 5)	0 (−1 to 2)	3 (3; 4)	0 (−1 to 1)
Spo_2 nocturnal, %	93 (92; 94)	86 (84; 87)	−7[a] (−9 to −6)	89 (86; 90)	2[a] (1 to 3)
Spo_2, SD of mean, %	3 (2; 3)	5 (3; 6)	2[a] (1 to 3)	4 (3; 5)	−1 (−2 to 0)
Difference Spo_2-CTO, %	28 (25; 30)	27 (22; 31)	1 (−2 to 4)	25 (24; 29)	0 (−3 to 2)
$Ptcco_2$, mm Hg	48 (45; 50)	39 (37; 40)	−9[a] (−11 to −2)	37 (35; 41)	−1 (−4 to 2)
AHI total, 1/h	57.3 (46.5; 67.3)	86.5 (70.0; 117.0)	36.4[a] (27.1 to 45.8)	67.4 (52.3; 91.5)	−23.4[a] (−32.8 to −14.0)
AHI obstructive, 1/h	49.6 (42.2; 62.2)	61.3 (33.9; 75.0)	1.3 (−9.3 to 11.8)	48.2 (35.7; 76.3)	−0.2 (−10.9 to 10.5)
AHI central, 1/h	0.8 (0.2; 1.8)	30.7 (21.2; 48.2)	35.2[a] (22.4 to 48.0)	8.6 (5.0; 17.5)	−23.2[a] (−33.1 to −13.3)
Total sleep time, min	293 (221; 329)	274 (237; 386)	11 (−27 to 50)	397 (323; 422)	90[a] (55 to 124)
Sleep efficiency, %	65 (54; 84)	53 (44; 69)	−10[a] (−16 to −3)	74 (59; 84)	17[a] (11 to 23)
Slow-wave sleep, %	8 (2; 15)	5 (0; 10)	−3[a] (−6 to −1)	1 (0; 10)	0 (−2 to 2)
REM sleep, %	8 (4; 12)	4 (0; 12)	0 (−5 to −5)	10 (0; 12)	0 (−5 to 5)

AHI = apnea/hypopnea index; CTO = cerebral tissue oxygenation; $Ptcco_2$ = Pco_2 from transcutaneous capnography; REM = rapid eye movement; Spo_2 = peripheral oxygen saturation as measured by pulse oximetry.
[a]$P < .05$.

TABLE 2] Cerebral and Arterial Oxygenation During Apneas/Hypopneas at 490 and 2,590 m

Variable	490 m, Off CPAP (n = 13), Median (Quartiles)	2,590 m, Placebo (n = 18), Median (Quartiles)	2,590 m-490 m, Δ (95% CI)	2,590 m, Acetazolamide (n = 17), Median (quartiles)	Acetazolamide-Placebo at 2,590 m, Δ (95% CI)
CTO baseline, %	67 (63; 71)	61 (56; 64)	−8[a] (−14 to −2)	67 (62; 68)	5.2[a] (1.1 to 9.3)
CTO desaturation amplitude, %	3 (2; 4)	5 (3; 7)	3[a] (0 to 6)	4 (3; 4)	−2 (−5 to 3)
CTO desaturation time to nadir, s	18 (16; 23)	18 (14; 19)	−2.8 (−8.1 to 2.5)	21 (17; 24)	4.4[a] (2.2 to 6.6)
CTO desaturation slope, %/s	−0.17 (−0.14; −0.23)	−0.34 (−0.21; −0.41)	−0.25[a] (−0.04 to −0.46)	−0.18 (−0.14; −0.24)	0.16 (−0.02 to 0.34)
Spo_2 baseline, %	98 (96; 98)	89 (86; 92)	−9[a] (−13 to −4)	93 (92; 93)	4[a] (1 to 7)
Spo_2 desaturation amplitude, %	9 (6; 14)	13 (10; 14)	3[a] (2 to 6)	13 (6; 9)	−1 (−3 to 4)
Spo_2 desaturation time to nadir, s	23 (21; 33)	17 (14; 21)	−10 (−16 to 4)	24 (17; 30)	6[a] (2 to 10)
Spo_2 desaturation slope, %/s	−0.31 (−0.27; −0.49)	−0.78 (−0.43; −0.96)	0.42[a] (0.23 to 0.60)	−0.54 (−0.34; −0.61)	0.21[a] (0.04 to 0.38)
Δ Desaturation amplitude Spo_2-CTO, %	6[b] (4; 5)	10[b] (4; 12)	−1 (−5 to 4)	7[b] (3; 13)	1 (−5 to 6)
CtHb increase amplitude, au	18.9 (15.4; 22.1)	16.7 (13.8; 21.4)	−0.5 (−6.2 to 5.3)	18.6 (15.5; 26.8)	4.1 (−3.4 to 11.5)
CtHb increase slope, au/s	1.28 (0.84; 1.56)	1.17 (0.77; 1.79)	0.32 (−0.32 to 0.96)	1.44 (0.97; 1.92)	0.43 (−0.3 to 1.2)
CtHb time from start of CTO drop to CtHb peak, s	21.7 (16.7; 23.3)	24.3 (18; 29)	−2.6 (−10.3 to 5.1)	17.8 (9.7; 26.8)	−5.3[a] (−10.2 to −0.3)
CtHb increase/CTO drop, au/%	6.6 (5.6; 7.3)	2.6 (2.1; 5.6)	−3.3[a] (−5.2 to −1.4)	5.4 (3.8; 9.1)	5.2 (−1.9 to 12.2)
Apnea/hypopnea cycle time, s	40.9 (35.4; 46.5)	30.8 (27.4; 34.1)	−8.8[a] (−17.5 to −0.1)	39.6 (33.5; 45.7)	8.8[a] (5.1 to 12.5)
$Ptcco_2$, mm Hg	41 (38; 44)	31 (27; 34)	−10[a] (−13 to −8)	29 (27; 31)	−2[a] (−3 to −0)

Variables were measured during three consecutive obstructive apneas/hypopneas per patient. Variables are illustrated in Figures 2 and 3. au = arbitrary units; CtHb = total hemoglobin concentration, the surrogate of cerebral blood volume in au. See Table 1 legend for expansion of other abbreviations.

[a]$P < .05$.

[b]$P < .05$ for difference Spo_2-CTO.

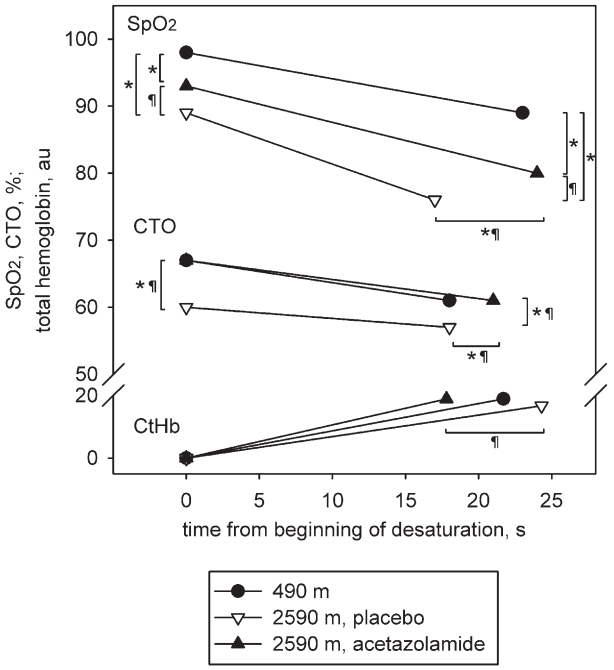

Figure 3 – *Variables derived from SpO2, CTO, and CtHb during apnea/hypopnea events. Medians for the group of patients at 490 m and at 2,590 m are shown for baseline values at the beginning of apneas/hypopneas (time = 0, corresponding to S1, C1, and H1 in Figure 2) and for subsequent changes to nadirs (CTO, SpO2) and peaks (CtHb), corresponding to S2, C2, and H2, respectively, in Figure 2. SpO2 and CTO measured at 2,590 m, on placebo (▽ connected with lines), depart from lower baseline values and drop to deeper nadirs at the end of apneas, compared with corresponding values at 490 m (● connected with lines). Acetazolamide partially restores SpO2 and CTO (▲) toward values measured at 490 m; moreover, acetazolamide treatment results in CtHb, the surrogate of cerebral blood volume, reaching its peak earlier after the fall of CTO, compared with placebo. *P < .05 vs 490 m; ¶P < .05 vs placebo. For clarity of presentation, medians are shown without quartiles; corresponding data are listed in Table 2. See Figure 2 legend for expansion of abbreviations.*

To our knowledge, the current study is the first to monitor CTO in patients with OSA not only during daytime naps or short periods of nocturnal sleep, but during entire nights. The mean nocturnal CTO of 65% at 490 m (Table 1) is comparable to corresponding values of 65% and 71% to 72% recorded during daytime naps in two previous studies in 13 and eight untreated patients with OSA, respectively.[5,20] We found that CTO dropped to a lesser extent than Spo_2 during nocturnal apneas/hypopneas (ie, 3% vs 9% at 490 m) (Table 2), possibly because of compensatory mechanisms protecting the brain from pronounced hypoxia. Doppler ultrasound measurements have suggested that middle cerebral artery blood flow transiently increases in healthy subjects exposed to hypercapnia or hypoxia[21] and in patients with OSA over the course of obstructive apneas.[4] Other studies in patients with OSA revealed a rise in intracranial pressure during obstructive apneas consistent with a transient increase in intracranial blood volume.[22] Accordingly, CtHb, the NIRS-derived measure of regional cerebral blood volume, increased over the course of apneas/hypopneas in the current study (Fig 3, Table 2).

During the nights at 2,590 m, patients with OSA treated with placebo revealed significantly lower values of CTO and Spo_2 (59% and 86%) compared with the nights at 490 m (CTO and Spo_2 of 65% and 93%, respectively) (Table 1). This was associated with a rise in the AHI, mainly caused by the emergence of central apneas/hypopneas, and a reduction in $Ptco_2$ consistent with hypoxic stimulation of ventilation.[10] To our knowledge, the effect of altitude exposure on CTO during sleep has not been reported in patients with OSA. In 20 healthy volunteers monitored by NIRS during wakefulness at 150 m, and upon arrival at 2,770 m, CTO fell from 70% to 67%, whereas Spo_2 fell from 98% to 92%.[23] The higher values of CTO and Spo_2 in the cited,[23] compared with the current, report may relate to differences in study participants (young, healthy subjects vs older patients with OSA), wakefulness vs sleep state, and differences in NIRS technology.

Although the dips in CTO and Spo_2 that patients with OSA experienced during apneas/hypopneas were greater at 2,590 m than at 490 m, the increases in CtHb were similar at both altitudes (Fig 3, Table 2). Thus, the combination of a reduced baseline CTO with larger, apnea-related dips, and the lack of enhanced blood flow response, may have exposed the brains of patients with OSA to considerable hypoxia at altitude. For comparison, the drop in ipsilateral CTO after unilateral internal carotid artery clamping during endarterectomy was 8%,[24] similar to the drop in CTO that occurred with ascent to 2,590 m in patients with OSA (Fig 3, Tables 1, 2). Moreover, CTO in patients with OSA decreased even further, by a median of 5% during apneas/hypopneas, and in certain patients, the apnea-related drop in CTO exceeded the drop of 13% associated with severe cerebral ischemia and brain dysfunction in neurosurgical patients.[25]

In comparison with placebo, acetazolamide increased the mean nocturnal CTO and Spo_2 by 2%, and it significantly reduced the AHI in patients with OSA during their sojourn at 2,590 m (Table 1). Although the apnea-related rise in CtHb was not statistically significantly increased by acetazolamide, the rise in CtHb in relation to CTO desaturation tended to be greater, and the peak of CtHb was reached earlier after the onset of CTO

desaturations during acetazolamide compared with placebo treatment (Fig 3, Table 2). Acetazolamide improved the AHI at altitude only partially and was mainly related to a significant reduction in central apneas/hypopneas. Nevertheless, the increases in CTO achieved by acetazolamide may still be essential in patients with OSA with preexisting metabolic and structural alterations of the brain,[26,27] cerebrovascular disease, impaired autoregulation due to OSA,[4] and altitude-related hypoxemia.[7]

Our study has several limitations. We purposely excluded patients with unstable cardiovascular disease or lung disease and those older than 80 years who may have been particularly susceptible to the adverse effects of hypoxia. Moreover, a more pronounced exposure to hypoxia was avoided by selecting an only moderately elevated study location and by letting participants acclimatize for 2 days at 1,860 m before ascending further to 2,590 m. Because of logistic limitations, we could not perform NIRS recordings in all patients participating in the trial. We feel that this did not bias the current data because patients were allocated randomly to NIRS recordings. Our data do not allow the determination of the various physiologic factors that may have contributed to changes in CTO at altitude and with acetazolamide therapy, including arterial oxygen saturation and regional changes in cerebral perfusion and metabolism. The signals recorded by certain NIRS devices can be influenced by extracranial vessels,[28] but NIRS accurately tracked trends of changes in cerebral oxygenation in a number of studies in comparison with intracerebral oxygen sensors, jugular venous oxygen saturation, and by evaluating effects of internal carotid artery clamping, and other interventions.[24,25,29,30]

Conclusions

In conclusion, our study shows that untreated patients with OSA experience considerable cerebral hypoxia during overnight sleep, in particular when staying at altitude. If CPAP therapy is not feasible, patients with OSA may benefit from acetazolamide treatment during altitude travel because it prevents precipitous drops in cerebral and arterial oxygenation and improves the breathing disturbances without impairing the cerebrovascular response to apneas.

Acknowledgments

Author contributions: S. U. and K. E. B. are the guarantors of this study and take responsibility for the content of the manuscript, including the data and analysis. S. U., Y. N.-O., T. D. L., and K. E. B. contributed to the conception and design of the study; S. U., Y. N.-O., T. D. L., and K. E. B. contributed to data acquisition, analysis, and interpretation; S. U., Y. N.-O., T. D. L., and K. E. B. contributed to drafting and critical revision of the manuscript; S.U., Y.N.-O., I. V., E. H., T. D. L., M. K., T. M., M. W., and K. E. B. contributed to approval of the final version to be published; and I. V., E. H., M. K., T. M., and M. W. contributed to critical revision of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

References

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5(2):136-143.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005;365(9464):1046-1053.
3. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol*. 2010;7(12):677-685.
4. Bålfors EM, Franklin KA. Impairment of cerebral perfusion during obstructive sleep apneas. *Am J Respir Crit Care Med*. 1994;150(6 pt 1):1587-1591.
5. Valipour A, McGown AD, Makker H, O'Sullivan C, Spiro SG. Some factors affecting cerebral tissue saturation during obstructive sleep apnoea. *Eur Respir J*. 2002;20(2):444-450.
6. Pizza F, Biallas M, Wolf M, Werth E, Bassetti CL. Nocturnal cerebral hemodynamics in snorers and in patients with obstructive sleep apnea: a near-infrared spectroscopy study. *Sleep*. 2010;33(2):205-210.
7. Subudhi AW, Panerai RB, Roach RC. Effects of hypobaric hypoxia on cerebral autoregulation. *Stroke*. 2010;41(4):641-646.
8. Vuyk J, Van Den Bos J, Terhell K, et al. Acetazolamide improves cerebral oxygenation during exercise at high altitude. *High Alt Med Biol*. 2006;7(4):290-301.
9. Nussbaumer-Ochsner Y, Schuepfer N, Ulrich S, Bloch KE. Exacerbation of sleep apnoea by frequent central events in patients with the obstructive sleep apnoea syndrome at altitude: a randomised trial. *Thorax*. 2010;65(5):429-435.
10. Nussbaumer-Ochsner Y, Latshang TD, Ulrich S, Kohler M, Thurnheer R, Bloch KE. Patients with obstructive sleep apnea syndrome benefit from acetazolamide during an altitude sojourn: a randomized, placebo-controlled, double-blind trial. *Chest*. 2012;141(1):131-138.
11. Latshang TD, Nussbaumer-Ochsner Y, Henn RM, et al. Effect of acetazolamide and autoCPAP therapy on breathing disturbances among patients with obstructive sleep apnea syndrome who travel to altitude: a randomized controlled trial. *JAMA*. 2012;308(22):2390-2398.
12. Latshang TD, Bloch KE. How to treat patients with obstructive sleep apnea syndrome during an altitude sojourn. *High Alt Med Biol*. 2011;12(4):303-307.
13. Ainslie PN, Ogoh S. Regulation of cerebral blood flow in mammals during chronic hypoxia: a matter of balance. *Exp Physiol*. 2010;95(2):251-262.
14. Hayakawa T, Terashima M, Kayukawa Y, Ohta T, Okada T. Changes in cerebral oxygenation and hemodynamics during obstructive sleep apneas. *Chest*. 1996;109(4):916-921.
15. Matsuo A, Inoue Y, Namba K, Chiba H. Changes in cerebral hemoglobin indices in obstructive sleep apnea syndrome with nasal continuous positive airway pressure treatment. *Sleep Breath*. 2011;15(3):487-492.

16. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth*. 2009;103(suppl 1):i3-i13.
17. Muehlemann T, Haensse D, Wolf M. Wireless miniaturized in-vivo near infrared imaging. *Opt Express*. 2008;16(14):10323-10330.
18. Muehlemann T, Reefmann N, Wechsler B, Wolf M, Gygax L. In vivo functional near-infrared spectroscopy measures mood-modulated cerebral responses to a positive emotional stimulus in sheep. *Neuroimage*. 2011;54(2):1625-1633.
19. Rechtschaffen A, Kales A, eds. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, DC: United States Government Printing Office; 1968.
20. McGown AD, Makker H, Elwell C, Al Rawi PG, Valipour A, Spiro SG. Measurement of changes in cytochrome oxidase redox state during obstructive sleep apnea using near-infrared spectroscopy. *Sleep*. 2003;26(6):710-716.
21. Beaudin AE, Brugniaux JV, Vöhringer M, et al. Cerebral and myocardial blood flow responses to hypercapnia and hypoxia in humans. *Am J Physiol Heart Circ Physiol*. 2011;301(4):H1678-H1686.
22. Jennum P, Børgesen SE. Intracranial pressure and obstructive sleep apnea. *Chest*. 1989;95(2):279-283.
23. Imray CH, Barnett NJ, Walsh S, et al. Near-infrared spectroscopy in the assessment of cerebral oxygenation at high altitude. *Wilderness Environ Med*. 1998;9(4):198-203.
24. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. *Stroke*. 2001;32(11):2492-2500.
25. Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke*. 2006;37(11):2720-2725.
26. Tonon C, Vetrugno R, Lodi R, et al. Proton magnetic resonance spectroscopy study of brain metabolism in obstructive sleep apnoea syndrome before and after continuous positive airway pressure treatment. *Sleep*. 2007;30(3):305-311.
27. Macey PM, Henderson LA, Macey KE, et al. Brain morphology associated with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;166(10):1382-1387.
28. Davie SN, Grocott HP. Impact of extracranial contamination on regional cerebral oxygen saturation: a comparison of three cerebral oximetry technologies. *Anesthesiology*. 2012;116(4):834-840.
29. McLeod AD, Igielman F, Elwell C, Cope M, Smith M. Measuring cerebral oxygenation during normobaric hyperoxia: a comparison of tissue microprobes, near-infrared spectroscopy, and jugular venous oximetry in head injury. *Anesth Analg*. 2003;97(3):851-856.
30. Budohoski KP, Zweifel C, Kasprowicz M, et al. What comes first? The dynamics of cerebral oxygenation and blood flow in response to changes in arterial pressure and intracranial pressure after head injury. *Br J Anaesth*. 2012;108(1):89-99.