

ORIGINAL RESEARCH

Circadian and Sex Differences After Acute High-Altitude Exposure: Are Early Acclimation Responses Improved by Blue Light?

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Objective.—The possible effects of blue light during acute hypoxia and the circadian rhythm on several physiological and cognitive parameters were studied.

Methods.—Fifty-seven volunteers were randomly assigned to 2 groups: nocturnal (2200–0230 hours) or diurnal (0900–1330 hours) and exposed to acute hypoxia (4000 m simulated altitude) in a hypobaric chamber. The participants were illuminated by blue LEDs or common artificial light on 2 different days. During each session, arterial oxygen saturation (SpO₂), blood pressure, heart rate variability, and cognitive parameters were measured at sea level, after reaching the simulated altitude of 4000 m, and after 3 hours at this altitude.

Results.—The circadian rhythm caused significant differences in blood pressure and heart rate variability. A 4% to 9% decrease in waking nocturnal SpO₂ under acute hypoxia was observed. Acute hypoxia also induced a significant reduction (4%–8%) in systolic pressure, slightly more marked (up to 13%) under blue lighting. Women had significantly increased systolic (4%) and diastolic (12%) pressures under acute hypoxia at night compared with daytime pressure; this was not observed in men. Some tendencies toward better cognitive performance (d2 attention test) were seen under blue illumination, although when considered together with physiological parameters and reaction time, there was no conclusive favorable effect of blue light on cognitive fatigue suppression after 3 hours of acute hypobaric hypoxia.

Conclusions.—It remains to be seen whether longer exposure to blue light under hypobaric hypoxic conditions would induce favorable effects against fatigue.

Key words: altitude shift work, intermittent hypoxia, altitude acclimatization, heart rate variability, attentional blink, blue light illumination

Introduction

Exposure to altitude inflicts many environmental stresses on the human body derived from factors such as low temperatures, high doses of solar and ionizing radiation, strong winds, and low absolute humidity.¹ However, most of the problems that occur at high altitude are attributable to the hypobaric hypoxia caused by the decrease in atmospheric pressure.

Thousands of workers in the Americas and Central Asia routinely perform activities requiring periods of a few hours at high altitudes followed by a return to low altitudes or even to sea level on a shift-work model (mining, transport, astronomical facilities, etc.), or rapid ascent and descent to moderate and even high altitudes (rescue, defense, etc.). Because of the short duration of the latter type of exposure, workers rarely present severe symptoms of acute mountain sickness (AMS) as a consequence of their exposure to hypobaric hypoxia. However, the effects of hypoxia on some organs involved in the execution of complex tasks (ie, brain, peripheral

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nerve, and even the heart, which performs brain perfusion) cannot be neglected. Acute hypoxia exposure may manifest early in terms of cognitive or alertness parameters, potentially altering proficiency at complex tasks. The temporary and mild character of these alterations, and their spontaneous resolution in most cases, do not contribute to a proper evaluation of the reduced performance and productivity loss during the first hours or days of altitude exposure. Previous reports have shown a decrease in physical capacity associated with short periods of altitude exposure^{2,3} and deleterious effects on neurobehavioral responses^{4,5} that could increase the risk of work-related accidents, especially for those commuting between places at different altitudes. All these factors may contribute to a high rate of transience in the workforce at high altitude because of intolerance to hypobaric hypoxia.⁶ Moreover, the incidence of vehicle rollover accidents (especially during descent) may be exacerbated by hypoxia because of a decrease in perception, mental concentration, and reaction speed, resulting in a reduced ability to drive vehicles or control heavy machinery.⁷ Recent research by our group revealed a high frequency of cardiac arrhythmic events during car descents from 5050 m to 2950 m.⁸

As a consequence, some countries have developed laws to protect workers at altitude. In Chile, since December 2012, legislation recognizes disorders resulting from hypobarism and requires companies operating at altitude to provide adequate education and preventive measures for their workers. To mitigate these problems, some strategies have been proposed for high-altitude working facilities, such as 1) the installation of base camps at lower altitudes for sleep and leisure⁹⁻¹¹; 2) the use of physiological preacclimation strategies, such as hypobaric chambers¹²; 3) the use of portable canned oxygen for pulse delivery, as used, for example, by visitors to the ALMA telescope site (5050 m); or 4) oxygen enrichment of workplaces.¹³⁻¹⁶

The application of blue light illumination has proved to be a very effective way of improving the regulation of circadian rhythms.¹⁷⁻²⁰ In this context and in the search for new preventive strategies to optimize human labor at altitude, the idea has emerged that blue light could have favorable effects at high altitude. For this reason, our group recently tested blue LED installations in the driver cabins of trucks used for the transportation of mining material for their effects on driver alertness during the night (Behn et al, unpublished data). The physiological basis of this methodology is derived from studies in mammals that demonstrate that the retinohypothalamic tract is involved in the regulation of circadian rhythms by light.²¹ The final step in the regulation loop is the production and rhythmic secretion of melatonin from the

pineal gland via a circuit that allows for the light-dark cycle to be sensed. The circuit involves the activity of the so-called intrinsically photosensitive retinal ganglion cells of the retina.²² These cells are projected to the suprachiasmatic nucleus²³ and ultimately have afferent connections to the pineal gland, where melatonin is produced.^{24,25} The secretion of melatonin can be inhibited by light, but not all wavelengths inhibit it. Wavelengths above 530 nm have no suppressive effects, whereas the blue band (wavelengths between 446 and 477 nm) has been found to be the optimal range for melatonin inhibition.¹⁷ Exposure to blue light has several physiological effects aside from the suppression of melatonin secretion, including increases in body temperature, alterations of cognitive performance, and fatigue during the night.²⁶ Moreover, melatonin has been experimentally demonstrated to increase the ventilatory response to hypoxia.²⁷ On the other hand, it has been reported that color vision can be adversely affected at high altitude, especially discrimination along the tritan (blue) axis,²⁸ which could be related to abnormal melatonin release and wakeful status under such conditions.

Our hypothesis was that blue light decreases the state of drowsiness, presumably by reducing the secretion of melatonin, especially at night, and therefore improves cognitive performance indicators. The main objective of this study was to detect, by means of measuring non-invasive physiological parameters and psychological testing, the signs of cognitive fatigue and poor acclimatization to high altitude conditions, and to evaluate the possible positive effect of blue light in the early phase of accommodation. Thus, we tested the possible alterations of mental concentration and alertness of subjects under hypobaric hypoxic conditions in daytime and nighttime scenarios.

Methods

SUBJECTS

This study was conducted in accordance with the Helsinki Declaration concerning the ethical principles of human experimentation. A total of 57 healthy volunteers (25 men and 32 women) were randomly selected from a group of college students. **Table 1** shows the anthropometric data of the participants in this study. They were initially given a general information session and personal interview. All subjects underwent a baseline hypoxia tolerance test and were asked not to ingest alcohol and caffeine for 12 hours before each session of the study.

LIGHTING

The lighting level inside the hypobaric chamber was measured using a light meter (PCE 172; PCE Instruments,

Table 1. Select characteristics of the study participants

Characteristic	Men (n=25)	Women (n=32)
Age (years)	23.8 ± 4.2	22.0 ± 3.5
Weight (kg)	71.4 ± 9.8	57.8 ± 7.4
Height (cm)	175 ± 8	166 ± 6
BMI (kg/m ²)	23.2 ± 2.7	20.9 ± 2.4
% Smokers	16.0	18.8

Values are reported as mean ± SD.

BMI, body mass index.

Jupiter, FL) and followed the guidelines established by the European Union for workplace lighting. To meet the recommendations, the incident light was adjusted at 3 different points to 30 lux at 20 cm from the edge of the working table, ensuring uniform lighting conditions inside the hypobaric chamber. Measurements were performed under 2 experimental lighting conditions: 1) normal artificial lighting (NAL) produced by 5 “incandescent-like” (380–750 nm) soft-white halogen roof lamps (2700 K); and 2) blue light (bLED) produced by 2 strips of narrow-wavelength (465–475 nm) blue LEDs placed along the roof of the chamber. According to the literature, this is within the optimal range for effects on humans.^{29–31}

HYPOXIA EXPOSURE

The participants were scheduled for 2 simulated altitude exposure sessions on different days in a hypobaric chamber located at the Bellvitge Health Campus of the University of Barcelona. They were randomly assigned to 1 of 2 groups: nocturnal (11 men and 19 women) or diurnal (14 men and 13 women). The experimental schedule for the nocturnal group was from 2200 to 0230 hours; the diurnal schedule was from 0900 to 1330 hours. A small group (5–6 subjects) took part in each session. At the first session, a full medical examination, including medical history and physical characteristics, was performed. The subjects were allocated to their posts within the hypobaric chamber, and the first set of measurements was performed.

Cardiovascular parameters (heart rate, blood pressure, and arterial oxygen saturation [SpO₂]) were measured before each set of cognitive and heart rate variability (HRV) tests. Once finished, the door of the hypobaric chamber was closed and simulated altitude exposure commenced. The simulated ascent to 4000 m took 20 minutes; simulated altitude lasted for 3 hours, and the final repressurization period was 20 minutes. Either NAL or bLED was used as the only source of illumination in each session. The order of the type of light was randomly

assigned to each group to avoid any psychological bias. All the parameters studied were obtained under 3 different conditions: at sea level (A0); 15 minutes after arrival at a simulated altitude of 4000 m (A1); and after 3 hours of simulated altitude exposure (A2).

MEASUREMENT PROTOCOL

The subjects were at rest and silent for 10 minutes during heart rate monitoring for subsequent HRV analysis. All subjects then proceeded to complete 2 tests to measure concentration and mental fatigue. First, all the subjects performed the d2 attention test together.³² After a short period of relaxation, the attentional blink test³³ was performed.

ANALYSIS OF HEART RATE VARIABILITY

Heart rate variability was measured by means of a Polar Team2 Pro System (Polar Electro Inc, Lake Success, NY). This system has several Team2 transmitters, which send the signal to the receiver unit via Bluetooth technology, thus allowing simultaneous monitoring of several subjects. Beat-to-beat heart rate (R-R interval) was recorded for each individual for at least 5 minutes. The data were analyzed by means of Kubios software (University of Eastern Finland, Kuopio, Finland).³⁴ We evaluated variations of HRV by time and frequency domain methods. In the time domain methods, we analyzed the following statistical measurements: standard deviation of all R-R intervals (SDNN); the square root of the mean squared differences of successive R-R intervals (RMSSD), expressed in milliseconds; and the proportion of heart beats with a duration 50 ms longer or shorter than the successive interval (pNN50), expressed as a percentage. We also analyzed the areas of the spectral peaks of very-low-frequency (VLF), low-frequency (LF), and high-frequency (HF) components expressed as a percentage. The LF/HF ratio, for analysis of the sympathetic–parasympathetic balance, was also calculated. The power spectrum density was estimated using fast Fourier transformations.

D2 ATTENTION TEST

For several years, the d2 attention test has been one of the most useful tools for assessing concentration and selective attention. It assesses the control of attention, error rate, work rate, and concentration fluctuation. In this study, we used the Spanish adaptation.³⁵

Before the test, a clear explanation was given and a practice test was performed. The test consists of 14 lines of the letters “d” and “p” in Courier font accompanied by a variable number (up to 4) of small dashes in subscript

or superscript positions. There is a time limit of 20 seconds per line to be resolved. The respondent is required to scan the lines and cross out all occurrences of the letter “d” with 2 dashes, while ignoring all other characters. The d2 test design allows 3 components reflecting attention behavior to be identified: the rate or amount of work, the degree of precision in performing the task, and the relationship between these factors. Analyzing the scores from this test, conclusions can be drawn about the degree of activity, the stability and consistency in the task, and fatigue and attentional inhibition efficiency.³⁵ In this study, 2 main parameters obtained from the d2 test were considered: the total effectiveness (TOT) was calculated as the total number of items processed minus error scores, and the concentration index (CON) was calculated as the difference between correct and incorrect answers.

ATTENTIONAL BLINK TEST

The attentional blink (AB) test was first described by Raymond et al.³³ The AB test is based on the assumption that there is a known decline in visual performance during task execution. This is attributable to the consumption of resources by other concurrent tasks, when the 2 are out of synchronization. This phenomenon is observed when using the paradigm of rapid serial visual presentation (RSVP): When a series of visual stimuli is presented in rapid succession in the same spatial location, subjects often fail to detect the second target when it is presented between 200 and 500 ms after the first one. The RSVP is often used to study visual perception, both in psychophysics and cognitive psychology,³⁶ and in this case it is used to establish whether there is a decline in visual perception and thus in the nervous system that controls the body.

In this test, 2 condition responses were used: simple and dual tasks. In the simple task, participants were required to indicate at the end of each visual representation series of letters, without any time limit, whether a target stimulus (the letter “X”) appeared, which occurred in 50% of the series. In the double response task, subjects were asked to detect 2 different targets, for example, whether a letter “O” appeared after an “X.” In this second task, it becomes clear that performance is out of the range expected by chance. The software automatically computed the number of right answers (RA) and the reaction time (RT, expressed as $\times 100$ ms) in the second task.

STATISTICAL ANALYSIS

The data were analyzed using SigmaPlot 12 software (Systat Software Inc, San Jose, CA). Multiple comparisons

were performed by 3-way analysis of variance (3-way ANOVA) with the factors L (light, with levels bLED and NAL), H (hypoxia, with levels A0, A1, and A2), and S (schedule, with levels day and night). The power analysis for the ANOVA test was automatically performed according to the following adjustments: minimum detectable difference in means of 0.8, expected standard deviation of residuals at 0.3, and alpha of 0.05. Holm-Sidak and paired *t* tests were used as post-hoc analysis for pairwise comparisons within levels. Differences were considered statistically significant when the probability value was $< .05$. Unless otherwise indicated, values are expressed as mean \pm SD.

Results

Mean data and SD for all physiological parameters are presented in Table 2 (men) and Table 3 (women), and cognitive parameters are given in Table 4. Statistical significance for the interaction (3-way ANOVA) between the 3 factors in the experimental design (light, hypoxia, and schedule) is presented in the corresponding columns on the left. Significant differences after the post-hoc analysis are shown as superscripts according to the code explained in the footnotes of each table.

PHYSIOLOGICAL PARAMETERS

As expected, hypoxia was followed by a marked reduction in SpO_2 . In both men and women, this decrease in SpO_2 was significantly pronounced at night under simulated altitude conditions (A1 and A2) in comparison to daytime. This finding was not evident under normoxic conditions, and no effect was observed regarding lighting conditions.

Blood pressure behaved differently depending on sex. In men there were no significant differences in systolic and diastolic pressures between the day and night schedules (Table 2). However, in women significant increases of systolic pressure were observed at night at A0 with bLED and at A1 under both lighting conditions, and for diastolic pressure in all cases (Table 3). Moreover, hypoxia induced a significant reduction in systolic pressure (4%–8%), which was slightly more marked under bLED lighting (4%–13%). This effect of hypoxia was not observed for diastolic pressure.

Heart rate was always higher at night and also, as expected, under the 2 hypoxic conditions studied. Regarding HRV, some differences again appeared depending on sex. SDNN was significantly higher during the night in men but not in women. Nevertheless, women showed a significant reduction of this parameter at night at A2 under both lighting conditions, and a significant reduction in RMSSD and pNN50 was also evident in women at night under all conditions. VLF and HF

Table 2. Physiological parameters in men exposed to 2 kinds of light under normobaric normoxic and hypobaric hypoxic conditions

Variable	3-way ANOVA			bLED						NAL					
	L	H	S	A0		A1		A2		A0		A1		A2	
				Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night
SpO ₂ (%)	NS	<i>bc</i>	<i>e</i>	99 ± 1	98 ± 1	83 ± 5 ^f	74 ± 5 ^{fh}	82 ± 4 ^f	75 ± 5 ^{fh}	99 ± 1	98 ± 1	84 ± 6 ^f	75 ± 6 ^{fh}	81 ± 3 ^f	77 ± 6 ^{fh}
HR (bpm)	NS	<i>bc</i>	<i>e</i>	71 ± 8	79 ± 12 ^h	77 ± 8 ^f	90 ± 18 ^{fh}	76 ± 6 ^f	89 ± 17 ^h	69 ± 9	76 ± 9 ^h	76 ± 8 ^f	86 ± 13 ^{fh}	74 ± 10 ^f	87 ± 17 ^{fh}
SP (mm Hg)	NS	<i>bcd</i>	NS	132 ± 10	136 ± 13	123 ± 10 ^f	130 ± 13 ^f	115 ± 15 ^{fg}	121 ± 13 ^{fg}	129 ± 9	133 ± 16	122 ± 14 ^f	127 ± 20	118 ± 10 ^f	121 ± 14 ^f
DP (mm Hg)	NS	NS	NS	77 ± 7	74 ± 6	74 ± 11	72 ± 10	70 ± 10	69 ± 7	76 ± 6	79 ± 18	72 ± 8	73 ± 17	72 ± 9	77 ± 18
HRV															
SDNN	<i>a</i>	NS	<i>e</i>	59 ± 23	76 ± 31 ^h	61 ± 20	73 ± 28 ^h	59 ± 14	64 ± 22 ^h	59 ± 16	88 ± 31 ^h	60 ± 17	73 ± 26 ^h	59 ± 18	81 ± 29 ^{hi}
RMSSD (ms)	NS	NS	NS	49 ± 28	50 ± 26	46 ± 23	42 ± 20	40 ± 13	39 ± 10	48 ± 20	70 ± 31	49 ± 20	45 ± 29	35 ± 14	55 ± 23
pNN50 (%)	NS	<i>c</i>	NS	27 ± 20	24 ± 18	17 ± 11 ^f	17 ± 15 ^f	15 ± 9 ^f	15 ± 13 ^f	28 ± 17	32 ± 21	20 ± 12	23 ± 17	13 ± 10 ^{fg}	20 ± 15
VLF (%)	NS	NS	<i>e</i>	20 ± 15	34 ± 19	25 ± 12	31 ± 18	21 ± 12	30 ± 18	22 ± 12	22 ± 14	24 ± 10	26 ± 17	27 ± 16	37 ± 16 ^h
LF (%)	NS	<i>cd</i>	NS	43 ± 17	42 ± 19	48 ± 9	53 ± 19	61 ± 16 ^{fg}	54 ± 19	46 ± 18	47 ± 19	45 ± 14	49 ± 23	57 ± 17 ^{fg}	51 ± 19
HF (%)	NS	<i>cd</i>	<i>e</i>	38 ± 22	25 ± 14 ^h	27 ± 12 ^f	17 ± 5 ^h	18 ± 9 ^{fg}	16 ± 6	32 ± 19	30 ± 16	32 ± 17	25 ± 20	16 ± 8 ^{fg}	14 ± 8
LF/HF	NS	NS	NS	2.9 ± 3.6	2.7 ± 3.1	3.4 ± 4.3	2.9 ± 1.0	4.9 ± 4.1	4.3 ± 4.8	3.2 ± 4.6	2.4 ± 1.9	2.3 ± 2.5	2.4 ± 2.0	4.6 ± 2.9	5.0 ± 3.8

All data are mean ± SD. Multiple comparisons were performed by a 3-way analysis of variance (3-way ANOVA) with factors L (light, with levels bLED and NAL), H (hypoxia, with levels A0, A1, and A2), and S (schedule, with levels day and night). Holm-Sidak and paired *t* tests were used in post-hoc analysis for pairwise comparisons within levels.

bLED, blue LED; NAL, normal artificial light; A0, at sea level; A1, 15 minutes after ascent to simulated altitude of 4000 m; A2, 3 hours of simulated altitude of 4000 m; SpO₂, arterial saturation; NS, not significant; HR, heart rate; SP, systolic blood pressure; DP, diastolic blood pressure; HRV, heart rate variability; SDNN, standard deviation of R-R intervals; RMSSD, square differences of successive R-R intervals; pNN50, differences of successive intervals greater than 50 ms; VLF, very low frequency; LF, low frequency; HF, high frequency.

^a bLED vs NAL, *P* < .05, 3-way ANOVA.

^b A0 vs A1, *P* < .05, 3-way ANOVA.

^c A0 vs A2, *P* < .05, 3-way ANOVA.

^d A1 vs A2, *P* < .05, 3-way ANOVA.

^e day vs night, *P* < .05, 3-way ANOVA.

^f vs A0, *P* < .05, Holm-Sidak and paired *t* tests.

^g vs A1, *P* < .05, Holm-Sidak and paired *t* tests.

^h vs day, *P* < .05, Holm-Sidak and paired *t* tests.

ⁱ vs bLED, *P* < .05, Holm-Sidak and paired *t* tests.

Table 3. Physiological parameters in women exposed to 2 kinds of light under normobaric normoxic and hypobaric hypoxic conditions

Variable	3-way ANOVA			bLED						NAL					
				A0		A1		A2		A0		A1		A2	
	L	H	S	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night
SpO ₂ (%)	NS	abc	d	99 ± 1	99 ± 1	84 ± 3 ^e	80 ± 7 ^{eg}	81 ± 6 ^{ef}	76 ± 6 ^{efg}	98 ± 3	99 ± 1	84 ± 6 ^e	79 ± 6 ^{eg}	81 ± 5 ^e	80 ± 4 ^{eg}
HR (bpm)	NS	ab	d	78 ± 11	84 ± 11 ^g	84 ± 11 ^e	93 ± 10 ^{eg}	85 ± 10 ^e	96 ± 8 ^{efg}	75 ± 10	87 ± 6 ^g	80 ± 10 ^e	91 ± 8 ^{eg}	86 ± 13 ^{ef}	95 ± 9 ^{eg}
SP (mm Hg)	NS	ab	d	115 ± 11	120 ± 15 ^g	106 ± 7 ^e	116 ± 12 ^{eg}	106 ± 9 ^e	110 ± 11 ^{ef}	115 ± 11	119 ± 14 ^e	108 ± 7 ^e	113 ± 12 ^{eg}	111 ± 20	110 ± 11 ^e
DP (mm Hg)	NS	NS	d	71 ± 7	78 ± 10 ^g	68 ± 7	75 ± 14 ^g	69 ± 9	76 ± 13 ^g	70 ± 11	76 ± 9 ^g	66 ± 6	77 ± 14 ^g	69 ± 7	80 ± 15 ^g
HRV															
SDNN	NS	ab	NS	57 ± 22	65 ± 17	52 ± 21	67 ± 32	51 ± 21	48 ± 21 ^{ef}	62 ± 22	71 ± 20	64 ± 31	81 ± 61	55 ± 24	46 ± 25 ^{ef}
RMSSD (ms)	NS	NS	d	52 ± 30	42 ± 17	41 ± 26	35 ± 19	41 ± 25	25 ± 12 ^g	54 ± 27	43 ± 16	51 ± 32	48 ± 39	46 ± 23	25 ± 19 ^g
pNN50 (%)	NS	ab	d	28 ± 19	20 ± 16	14 ± 14 ^e	13 ± 14	13 ± 10 ^e	7 ± 9 ^{ef}	26 ± 21	22 ± 13	20 ± 18	13 ± 16 ^e	20 ± 16	7 ± 13 ^{efg}
VLF (%)	NS	NS	d	18 ± 10	35 ± 19 ^g	26 ± 13	44 ± 16 ^g	20 ± 13	42 ± 13 ^g	23 ± 13	46 ± 17 ^g	25 ± 13	47 ± 22 ^g	19 ± 10	46 ± 16 ^g
LF (%)	NS	b	NS	39 ± 9	38 ± 15	43 ± 11	36 ± 13	53 ± 16 ^e	42 ± 11	36 ± 14	33 ± 10	39 ± 14	31 ± 12	46 ± 12 ^e	40 ± 12
HF (%)	NS	b	d	43 ± 15	27 ± 14 ^g	32 ± 20 ^e	20 ± 7 ^g	28 ± 14 ^e	16 ± 6 ^g	42 ± 22	21 ± 11 ^g	36 ± 22	22 ± 14	36 ± 16	14 ± 6 ^g
LF/HF	NS	b	NS	1.3 ± 1.7	2.1 ± 1.8	2.5 ± 2.6	2.2 ± 1.5	2.9 ± 3.0	3.1 ± 1.6 ^e	1.5 ± 1.6	1.9 ± 0.9	2.1 ± 2.2	1.8 ± 1.2	2.2 ± 1.9	3.8 ± 2.9 ^e

All data are mean ± SD. Multiple comparisons were performed by a 3-way analysis of variance (3-way ANOVA) with factors L (light, with levels bLED and NAL), H (hypoxia, with levels A0, A1, and A2), and S (schedule, with levels day and night). Holm-Sidak and paired *t* tests were used in post-hoc analysis for pairwise comparisons within levels.

bLED, blue LED; NAL, normal artificial light; A0, at sea level; A1, 15 minutes after ascent to simulated altitude of 4000 m; A2, 3 hours of simulated altitude of 4000 m; SpO₂, arterial saturation; NS, not significant; HR, heart rate; SP, systolic blood pressure; DP, diastolic blood pressure; HRV, heart rate variability; SDNN, standard deviation of R-R intervals; RMSSD, square differences of successive R-R intervals; pNN50, differences of successive intervals greater than 50 ms; VLF, very low frequency; LF, low frequency; HF, high frequency.

^a A0 vs A1, *P* < .05, 3-way ANOVA.

^b A0 vs A2, *P* < .05, 3-way ANOVA.

^c A1 vs A2, *P* < .05, 3-way ANOVA.

^d day vs night, *P* < .05, 3-way ANOVA.

^e vs A0, *P* < .05, Holm-Sidak and paired *t* tests.

^f vs A1, *P* < .05, Holm-Sidak and paired *t* tests.

^g vs day, *P* < .05, Holm-Sidak and paired *t* tests.

Table 4. Cognitive parameters in men and women exposed to 2 kinds of light under normobaric normoxic and hypobaric hypoxic conditions

Variable	Sex	3-way ANOVA			bLED						NAL					
		L	H	S	A0		A1		A2		A0		A1		A2	
					Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night
d2 test																
TOT	Men	NS	<i>b</i>	<i>d</i>	546 ± 78	475 ± 107 ^g	581 ± 69 ^e	544 ± 85 ^e	573 ± 82 ^e	530 ± 93 ^e	530 ± 85	501 ± 120	572 ± 77 ^e	541 ± 77	562 ± 90 ^e	529 ± 87
	Women	NS	<i>bc</i>	<i>d</i>	555 ± 70	482 ± 125 ^g	609 ± 42 ^e	546 ± 92 ^{eg}	598 ± 44 ^e	531 ± 95 ^{eg}	577 ± 72	462 ± 127 ^g	618 ± 36 ^e	520 ± 111 ^{eg}	613 ± 35 ^e	487 ± 114 ^{fg}
CON	Men	NS	<i>b</i>	NS	230 ± 45	217 ± 42	250 ± 39 ^e	246 ± 36 ^e	244 ± 40 ^e	241 ± 37 ^e	219 ± 47	227 ± 50	243 ± 46 ^e	244 ± 34	243 ± 48 ^e	241 ± 35
	Women	NS	<i>bc</i>	<i>d</i>	231 ± 47	219 ± 48	266 ± 31 ^e	248 ± 37 ^e	256 ± 35 ^e	243 ± 35 ^e	249 ± 46	206 ± 47 ^g	271 ± 26 ^e	234 ± 41 ^g	269 ± 24 ^e	223 ± 39 ^g
AB																
RT (s)	Men	<i>a</i>	NS	<i>d</i>	3.5 ± 0.3	3.1 ± 0.3 ^g	3.4 ± 0.2	3.0 ± 0.3 ^g	3.3 ± 0.3	2.9 ± 0.3 ^g	3.4 ± 0.3	2.9 ± 0.2 ^g	3.2 ± 0.3	2.8 ± 0.1 ^g	3.3 ± 0.3	2.8 ± 0.1 ^g
	Women	NS	<i>bc</i>	<i>d</i>	3.4 ± 0.3	3.0 ± 0.4 ^g	3.2 ± 0.4 ^e	2.9 ± 0.4 ^{eg}	3.2 ± 0.3 ^e	2.9 ± 0.4 ^g	3.6 ± 0.3	3.0 ± 0.2 ^g	3.5 ± 0.3 ^e	2.8 ± 0.3 ^{eg}	3.3 ± 0.3 ^e	2.8 ± 0.2 ^{eg}
RA (%)	Men	NS	NS	NS	95 ± 2	95 ± 4	95 ± 4	93 ± 6	94 ± 5	93 ± 5	95 ± 4	95 ± 8	97 ± 4	94 ± 4	96 ± 4	95 ± 5
	Women	NS	NS	<i>d</i>	91 ± 14	84 ± 24	92 ± 11	85 ± 22	94 ± 12	86 ± 21 ^g	94 ± 9	88 ± 12	93 ± 9	87 ± 14	95 ± 9	88 ± 15

All data are mean ± SD. Multiple comparisons were performed by a 3-way analysis of variance (3-way ANOVA) with factors L (light, with levels bLED and NAL), H (hypoxia, with levels A0, A1, and A2), and S (schedule, with levels day and night). Holm-Sidak and paired *t* tests were used in post-hoc analysis for pairwise comparisons within levels.

bLED, blue LED; NAL, normal artificial light; A0, at sea level; A1, 15 minutes after ascent to simulated altitude of 4000 m; A2, 3 hours of simulated altitude of 4000 m; NS, not significant; TOT, total effectiveness; CON, concentration index; AB, attentional blink; RT, reaction time; RA, right answers.

^a bLED vs NAL, *P* < .05, 3-way ANOVA.

^b A0 vs A1, *P* < .05, 3-way ANOVA.

^c A0 vs A2, *P* < .05, 3-way ANOVA.

^d day vs night, *P* < .05, 3-way ANOVA.

^e vs A0, *P* < .05, Holm-Sidak and paired *t* tests.

^f vs A1, *P* < .05, Holm-Sidak and paired *t* tests.

^g vs day, *P* < .05, Holm-Sidak and paired *t* tests.

showed opposite trends: VLF increased at night whereas HF decreased. The effects of hypoxia on HRV were especially notable after 3 hours of hypoxia (A2). Significant reductions were observed in both men and women in pNN50 and HF, along with significant increases in LF. Moreover, the LF/HF ratio presented higher values at A2 in both men and women, although they were only statistically significant in women. Regarding the effect of bLED on HRV, the only significant difference with respect to NAL was a reduction in SDNN in men at night after 3 hours of hypobaric exposure (A2), and not significantly lower values in the time domain parameters (RMSSD and pNN50) also at night and A2.

COGNITIVE PARAMETERS

Although bLED did not show any statistically significant differences in the parameters derived from the d2 test (TOT and CON), there was a slight tendency for both parameters to increase at day (Table 4). The parameters of this test showed significantly higher values in women (both in normoxia and hypoxia and in both lighting conditions) in the daytime. Surprisingly, TOT and CON increased significantly under hypoxic conditions. RT in the AB test was significantly higher in both men and women in the daytime and presented a significant increase in men as a result of bLED illumination; post-hoc multiple comparison test detected global significant differences for light factor.

Discussion

The protocol of hypobaric hypoxia (short-term artificial hypoxia conditions in a hypobaric chamber) was designed to avoid the risk of severe AMS symptoms in the subjects. Moreover, this approach allows us to isolate hypoxia effects from other environmental factors (such as cold, dry atmosphere, or strong wind) and also to overcome the difficulties of performing a similar study under real field conditions (eg, work schedule, additional stress, and time availability). Altitude hypoxia is an environmental factor that strongly affects human body functions, eliciting a series of compensatory physiological responses, such as tachycardia and hyperventilation (for an extensive review, see West et al¹). These cardiorespiratory responses are driven by general and sustained sympathetic activation that favors the occurrence of fatigue.³⁷ A total of 41.7% of Chilean mineworkers declared physical/physiological or psychological/cognitive fatigue at geographical altitude, which is a positive predictor for AMS.³⁸ The role of bLED as a possible fatigue regulator has been studied and can be considered as well established at sea

level.^{18,31,39,40} However, the feasibility of applying it at high altitude has not been verified, and the possible effects of bLED illumination on shift work at altitude are not known.

ARTERIAL OXYGEN SATURATION

Inspired P_{O_2} decreases with barometric pressure; at a simulated altitude of 4000 m, it is approximately 90 mm Hg, which corresponds to 60% of the inspired P_{O_2} at sea level.⁴¹ This fall in P_{O_2} is responsible for the well-known reduction in Sp_{O_2} provoked by acute hypobaric conditions. As expected, we found a reduction of Sp_{O_2} levels in hypobaric conditions (Tables 2 and 3) in agreement, for example, with the diurnal values (81%–85%) found by Shen et al⁴² in a recent field study at 4000 m.

One of the interesting findings in the present study is the circadian effect reflected in the Sp_{O_2} levels recorded at night under hypobaric conditions (A1 and A2): There was a significant decrease, 4% to 9%, in absolute Sp_{O_2} values. It is important to note that all subjects were awake and had no apparent signs of periodic breathing. This effect was not apparent under normoxia (A0), when the values fell in the normal range of saturation under sea-level conditions (98%–100%) both during the day and at night.

A circadian rhythm in peak expiratory flow has been reported, an indicator of bronchial diameter. Reinberg et al⁴³ reported a 10% reduction in peak expiratory flow between 2300 hours and 0700 hours. Adamczyk et al⁴⁴ also reported significant reductions in several respiratory parameters such as tidal volume, minute ventilation, and mean inspiratory flow at night. This circadian rhythm could play a role in explaining the more marked reductions in Sp_{O_2} at night during acute hypoxia. An alteration in oxygen-conducting pathways from atmosphere to blood, such as a reduction in bronchial diameter, could have a greater effect during acute hypoxia, when the fall in environmental P_{O_2} compromises oxygen homeostasis, than in normoxia, thereby explaining the differences found between night and day in hypoxia but not in normoxia.

BLOOD PRESSURE

Our results show a circadian rhythm in systolic and diastolic blood pressure in women, with significant increases in almost all situations at night. This agrees with the results reported by Hermida et al,⁴⁵ who found 2 peaks of arterial pressure values at 4 hours and 12 hours (before night rest) after waking, but is in clear contrast with the circadian rhythm described by Cagnacci et al,⁴⁶

who reported a decline in blood pressure at night that is enhanced by the prolonged administration of melatonin.

In men, we also obtained higher values at night, but they were not significant, introducing a source of variation between men and women in the present study that contrasts with the previously reported circadian decline in young men.⁴⁷ Regarding the effect of acute hypoxia on systolic and diastolic arterial pressure, our results contrast with those obtained at similar altitudes by other authors. Wolfel et al⁴⁸ reported a rise in systemic blood pressure in men after 2 days at 4300 m and attributed the increase to sympathetic activity. Rapid ascents to 4559 m (in <28 hours or after being airlifted by helicopter) have also been reported to result in significant increases both in systolic and diastolic blood pressures.^{49,50} However, it should be noted that all of these studies were only of men, with a wide range of ages, who were exposed under natural hypoxic conditions.

In contrast, in a study performed in a hypobaric chamber, at a simulated altitude of 4800 m and with the same short hypoxic exposure time of 3 hours as that used in the present study, Loshbaugh et al⁵¹ reported no significant increases in mean blood pressure (calculated from systolic and diastolic measurements) in 6 men and 3 women with the same mean age as the subjects participating in our study. Thus, a possible explanation for the contrasting results obtained in our hypobaric chamber could be both the short time of hypoxic exposure (3 hours) and the fact that under field exposure there is a wide range of environmental variables (eg, temperature) that cannot be controlled and could play a role in arterial blood pressure changes.

HEART RATE

The protocol of acute hypobaric hypoxia followed in this research showed significant increases in heart rate in all cases, ranging from 7% to 13%. These higher heart rates were observed immediately after reaching the simulated altitude of 4000 m (A1) and lasted for the entire 3 hours of hypoxia (A2). This observation has been repeatedly confirmed, both in the field and in simulated altitude (see, for example, Naeije⁵²), and leads to an increase in cardiac output and therefore higher oxygen delivery to tissues. Our results also show a circadian rhythm in heart rate, with significant increases at night that range from 8% to 18% when compared with daytime. The circadian rhythm of heart rate has been extensively studied, and clear diurnal and nocturnal variations have been reported and attributed to increased sympathetic activity during the day.⁵³

Our results in normoxia (A0) are in close agreement with a study by Hermida et al⁴⁵ in white men and women of the same age, with increases of between 8% and 16% at night. Moreover, our results show that the circadian rhythms are maintained in hypobaric hypoxia, both immediately after reaching 4000 m (A1, with increases of 11%–14% at night) and after 3 hours of exposure (A2, with increases of 10%–18% at night). Finally, we must conclude that there is no effect of bLED on heart rate, either when compared with NAL or regarding circadian rhythm.

HEART RATE VARIABILITY

As previously described, acute altitude exposure induced a marked decrease in HRV.^{54–56} We found some significant circadian changes in HRV that could reflect variations in autonomous nervous system activity. Especially in women, a significantly lower beat-to-beat HRV (ie, a reduction in parameters such as RMSSD and pNN50) together with a significant decrease in HF at night may indicate reduced vagal activity that matches the significant increases in heart rate discussed above. We also found a significant reduction in VLF at night in both men and women.

Although the physiological mechanisms underlying VLF oscillations are still unclear, fluctuations of thermoregulatory activity and parasympathetic outflow have been proposed as potential factors⁵⁷ and could explain these results. Hypobaric hypoxia had significant effects on HRV, especially after 3 hours of exposure (A2): we found decreases in parameters reflecting parasympathetic modulation (pNN50 and HF) and increases in LF and the LF/HF ratio. All these results are indicative of activation of the sympathetic tone and a vagal withdrawal response, in agreement with previous work on acute hypoxia at rest.^{58–61} Apart from a significant reduction in SDNN in men at night after 3 hours of hypobaric exposure, in the present study we did not find any clear-cut trend in the effect of bLED illumination on HRV. These findings suggest a negligible effect of blue light on HRV, at least in the first 3 hours of exposure.

COGNITIVE PERFORMANCE

Beside the effects of hypobaric hypoxia on physiological parameters, a variety of effects on neuropsychological functions have also been reported that have mostly been attributed to cerebral hypoxia and the resulting functional and structural cerebral alterations. Some studies have demonstrated short-term visual and spatial memory deterioration when ascending over 2500 m,^{62,63} with particularly notable effects over 4500 m.⁶⁴ Those studies also found a reduction in the speed and precision of

motor capacity in comparison to sea level conditions. Language disorders, such as aphasias and deficiencies in comprehension, have also been reported in mountaineers, which affect them in an altitude-dependent pattern.^{65,66} A decrease in reaction time, psychomotor ability, and mental efficiency is also a common finding in altitude-exposed subjects in both experiments performed in hypobaric chambers^{67,68} and during mountain expeditions.⁶⁹ Moreover, a rapid ascent to altitude is associated with decreased function and cognitive performance in subjects trained in specific jobs, showing deterioration in accuracy tests and a decrease in execution speed caused by hypoxia.⁷⁰

On the other hand, it has been established that the circadian cycle is sensitive to blue light exposure.¹⁷ Blue light increases alertness of subjects, in association with a higher subjective feeling of vigil and low levels of fatigue at night,^{31,40,71} although there is a significant decrease in subjective sleepiness during 460-nm light exposure compared with 550-nm light exposure and no light, starting 30 minutes after lights on.⁷² The use of enriched blue light has been generalized in places of work, such as in the cabins of heavy vehicles or aircrafts,³¹ because of a demonstrated effect of reducing fatigue in workers. However, to our knowledge, no previous studies assessed the potential positive effects of blue light under acute hypobaric hypoxia. It is important to note that hypoxic conditions greatly alter most physiological control mechanisms; for this reason, it is necessary to confirm the putative positive effects of blue light, which have been well established at sea level, under these environmental conditions.

Although our results are statistically insignificant, a tendency to solve the d2 attention test with better cognitive performance was detected in some cases. Thus, in men, the overall TOT and CON tended to be higher (2%–5%) when the test was executed under bLED in the day (Table 4). In women, bLED resulted in a tendency to improve cognitive performance with increases in TOT and CON from 4% to 8%; however, in this case, this was true when the d2 test was performed at night (Table 4). Moreover, in women there is a significant difference (both in normoxia and hypoxia and in both lighting conditions) in cognitive performance: they perform better in the d2 test during the daytime than at night.

A surprising finding of our study is that for both lightings, TOT and CON were significantly improved under hypoxic conditions. We believe that this finding arises from an important limitation of the study: a probable training effect derived from the repeated, close in time executions of the d2 test. This effect would be the reason for consistently better performance in subsequent tests compared with the first one. This is also an

important methodological limitation to be considered for d2 test field applications (ie, altitude workers).

Regarding the results of the AB test, significantly lower RT scores were found at night in both men and women. This finding agrees with studies that demonstrate that the circadian fluctuations of serial-visual performance in a vigilance task have an interval for maximum speed execution between 1900 hours and 2100 hours.⁷³ However, in women the significant reduction in RT found at night is accompanied by a loss of effectiveness (lower RA) in comparison with daytime. Contrasting the trend observed in parameters from the d2 test, RT significantly increased in men under bLED illumination, indicating another difference between the sexes and questioning the usefulness of bLED in reaction tasks.

Conclusions

In conclusion, we observed significant circadian rhythm differences in physiological parameters such as blood pressure, heart rate, and HRV, which are maintained in acute hypoxia after 3 hours of exposure. Moreover, a circadian effect on SpO₂ under acute hypoxia conditions has been observed, with significant decreases at night. Sex differences were also evident, with different behavior in the physiological and cognitive parameters after hypoxia. Some tendencies toward better cognitive performance from the d2 attention test under bLED illumination were seen, although when considered with the physiological parameters and reaction time, there was no conclusive favorable effect of bLED on fatigue suppressive effects after 3 hours of acute hypobaric hypoxia. It remains to be seen whether exposure times to bLED longer than 3 hours under hypobaric hypoxic conditions would induce favorable effects against fatigue. These conclusions are limited by the present study design, mainly the short-term hypoxia exposure to avoid the risk of severe AMS in the subjects owing to the lack of acclimatization.

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