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EC NEUROLOGY
Research Article

Sleep at High Altitude in Marathon Sky Runners

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Received: February 19, 2016; **Published:** May 23, 2016

Abstract

Introduction: Homeostatic changes and disturbed sleep are common causes of discomfort after rapid ascent to high altitude. This study reports the changes polysomnographic variables during 30-42h of acclimatization at 3480m in adult Sky marathon runners (maximal aerobic power 59.8 ± 1.7 ml/kg/min) controlled for diet and acclimatization. Light-dark and jet-lag effects were excluded by location of the study.

Results: %Spa O_2 recorded during sleep at 3480m was significantly lower than sea-level values. During 30-42h of acclimatization at 3480m, there was a significant increase in the power of low-voltage high frequency bands and periodic breathing during slow wave and REM sleep. Significant changes in heart rate and R-R interval were recorded: the power of low-voltage frequency bands decreased during arousal; the average of the total power increased significantly during stage N2 sleep and Very Low Frequency increased during stage N3 Non Rapid Eye Movement sleep.

Conclusion: Altitude-induced changes in homeostasis, periodic breathing, heart rate with arrhythmias, and arousal may exert a protective effect and prevent excessive oxygen deprivation during sleep. These responses can result from direct and/or indirect stimulation of the brain stem and hypothalamic reticular activating system involved in the metabolic integration of autonomic control, behavioral and cortical arousal.

Keywords: Sleep; Spectral EEG analysis; Periodic breathing; Heart rate variability; Endurance athletes

Abbreviations: EEG: Electroencephalography; SWS: Slow Wave Sleep; NREM: Non Rapid Eye Movement; REM: Rapid Eye Movement; %Spa O2: Percentage of Peripherical Oxygen Saturation

Introduction

Barometric pressure decreases exponentially with altitude, triggering physiologic responses to compensate for tissue hypoxia. Exposure to natural hypobaric-hypoxemia precipitates symptoms of impaired neuronal function, including widespread slowing of electroencephalographic (EEG) activity and sleep disturbances [1-7]. Altitude-related changes in sleep stages during earlier expeditionary climbs [4,9,10,11] and during simulated hypoxia in hypobaric chambers [4,28] are well documented. Shorter duration of stages N3 and N4 of slow-wave sleep (SWS) between 2800m and 6220m has also been described [4,9] surprisingly, no changes in Slow Wave Sleep (SWS) or Non-Rapid Eye Movement (NREM) sleep in decompression chambers simulating conditions between 3505m and 7620m have been reported [4]. A reduction in rapid-eye-movement (REM) sleep at altitude has been reported by some authors [4,7] but not by Normand *et al*. [12].

Periodic breathing is a common benign symptom in mountain climbers at high altitude [4,7,10]. Periodic breathing has not been reported to occur during stage N4 SWS or REM sleep by some authors [7,9] whereas others have reported central sleep apneic episodes during stage N2 SWS and REM sleep [3,4,10]. Metabolic balance changes inducing increased heart rate and ventilation [4,13,14] could also be responsible for sleep disturbances, arousal, and wakening at altitude. Nonetheless, marked changes, both medically safe and unsafe, and

fluctuations in autonomic cardiovascular regulation can ensue from altitude exposure [2] and increase the risk of heart attack. This has been evaluated by spectral analysis of variability in the R-R wave interval by means of the high-frequency rhythm, which chiefly reflects the respiration-driven vagal modulation of sinus rhythm, and the non-respiratory low-frequency rhythm (LF), which reflects sympathetic modulation of the heart and baroreflex responsiveness to variations in blood pressure [2,15-19]. Thermoregulation-related heart-rate variability, termed very low frequency fluctuation (VLF), may also change during sleep at altitude.

In view of the direct and indirect effects of relative hypoxia on the central nervous system and the cardiovascular, respiratory and renal systems [1,13], this study reports the changes EEG, ventilation, and heart rate during hypoxic-hypobaric exposure to 3480m in metabolically Table 1 and anthropometrically characterized endurance athletes controlled for diet and acclimatization. Light-dark and jet-lag effects were excluded by location of the study site.

Materials and Methods

Subjects

Six healthy adult male endurance athletes (Sky runners, best marathon performance under 3 hours at sea level) (CS, DC, MR, GM, MG, SS) volunteered to participate in the study. They were informed of the potential discomfort associated with the experiments, were clinically tested for their performance at high altitude, and were familiarized with the procedures for polygraphic recordings [20-25]. The subjects were requested to refrain from use of medications and alcohol at least 2 days prior to and during the experimental sleep recording sessions. The sessions were carried out in different experimental sections.

Consent was obtained from the subjects prior to each experimental session for all other procedures. The study protocol was approved by the International Medical Association of the Federation of Sport at Altitude. The subjects never sojourned at an altitude > 2000 m during the 15 days preceding the expedition.

Local time and barometric pressure (PB) at 122m (Department of Biomedical and Clinical Science, Luigi Sacco Hospital, University of Milan, Milan, Italy), hereafter referred to as sea level, at 2050m (Cervinia, Aosta, Valle d'Aosta, Italy) and at 3480m (Plateau Rosà, Cervinia, Aosta, Valle d'Aosta, Italy) were measured using a chronometer and barometer sensors mounted on a portable hemogas analyzer (OptiCCA, Roche-Diagnostics, Basel, Switzerland). The subjects ascended by car from 122 m at 11:00 to 2050 m at 13:00-14:00 and then by cable car to 3480m at about 15:00-16:00. The subjects slept at 3460m. All measurements at altitude were performed at rest in supine position in a dark, silenced room containing two bunk beds plus the polysomnograhic recording equipment.

Percentage of arterial oxygen saturation and R-R at sea level and altitude

In the preliminary pilot study, the percentage of peripheral arterial oxygen saturation (% SpaO2) was recorded in all 6 athletes every 8 seconds using a finger pulse oximeter. Cardiac activity was also measured by direct recording of the R-R intervals every 8 seconds with a Polar vantage heart rate monitor (Polar Electro®, Kampala Finland) or indirectly by calculating it from the heart rate (beat per minutes) with a pulse oximeter. Recordings were performed during sleep at sea level (122m) and during 32-41h of acclimatization at 3480m.

Subjective perception of sleep quality

Before and after the end of the initial polysomnographic recordings, each such subject was administered a self-report questionnaire investigating sleep quality in terms of: 1) sleep latency (minutes delay in falling asleep); 2) total number of hours slept; 3) waking time before expected; 4) number of night wakings; 5) whether or not rested on waking; 6) sleep quality evaluated with a visual analogue scale from 1 to 10, where 1 denotes poor and 10 excellent sleep quality.

Cutaneous temperature in altitude

During the preliminary study, the skin temperature was measured during sleep between 32 and 41h of acclimatization at 3480m in 3 subjects (CS, GM, MR). Temperature electrodes were fixed by means of elastic adhesive tape (Tensoplast, BSN-Medical, Hamburg, Germany) on the skin to the right of the V_4 intercostal cardiac electrode. Signals were collected from the temperature meter sensors connected to a temperature meter (resolution 0.1˚C, Orion Aplus, Thermo Fisher Scientific, Waltham, MA) and averaged every 8 seconds.

Capillary Survey																																	
	n	**122m**			**n**	**2050m**			vs 122 m	**n**	**3480m 6 h (*)**			vs 122 m	vs 2050 m	**n**	**3480m 30 h (^)**			vs 122 m	vs 2,050 m	vs 3480 m -6h	**n**	**3480m 40 h (°)**			vs 122 m	vs 2,050 m	vs 3480 m-6h	vs 3480 m30h
pO_2	4	71,4	±	6	5	58,18	±	2	üüü	5	39,89	±	4,5	üüü	XXX	10	45,32	±	4,2	üüü	XXX	3	10	49,49	±	4	üüü	XXX	333	T
SO_2%	4	93,9	±	2,19	5	91,32	±	1,52	ü	5	77,7	±	6,3	üüü	XXX	10	83,55	±	4,82	üüü	XXX	3	10	86,45	±	3,51	üüü	XXX	333	
pCO_2	4	41,21	±	3,38	5	34,74	±	3,32	ü	5	33,65	±	0,86	üüü		10	29,33	±	2,61	üüü	XXX	333	10	28,02	±	2,33	üüü	XXX	333	
tCO_2	4	29,87	±	1,45	5	27,22	±	1,81	ü	5	27,16	±	1,38	ü		10	24,25	±	1,8	üüü	XXX	333	10	22,77	±	1,75	üüü	XXX	333	T
tHb	4	15,73	±	1,45	5	16,62	±	1,14		5	15,64	±	1,96			10	15,90	±	1,50				10	16,41	±	1,28				
pH	4	7,46	±	0,02	5	7,50	±	0,02	ü	5	7,51	±	0,02	üü		10	7,52	±	0,02	üüü			10	7,51	±	0,03	üüü			
HCO_3^-	4	28,63	±	1,39	5	26,14	±	1,75	ü	5	26,12	±	1,33	ü		10	23,36	±	1,73	üüü	XXX	333	10	21,92	±	1,70	üüü	XXX	333	T
BE	4	4,35	±	0,77	5	3,30	±	1,32		5	3,54	±	1,60			10	1,68	±	1,42	üü	X		10	0,41	±	1,57	üüü	XXX	333	T
Na^+	4	139,75	±	2,22	5	138,96	±	1,62		3	141,50	±	0,50		X	7	141,28	±	1,49	ü	X		7	139,57	±	1,36			3	T
K^+	4	4,33	±	0,37	5	5,06	±	0,93		3	4,25	±	0,05			7	5,23	±	0,63	ü	X	3	7	05:23	±	0.047	ü		3	
Ca^{++}	4	1,18	±	0,02	5	1,19	±	0,03		3	1,19	±	0,01			7	1,21	±	0,04				7	1,20	±	0,06				
La	3	0.71	±	0.1	5	0.96	±	0.24		3	0.84	±	0.24			5	0.92	±	0.36				5	0.6	±	0.25		X		
BE	4	4.1	±	0.77	5	3.48	±	1.49		5	3.34	±	1.8			10	1.7	±	1.39	üü			10	1.32	±	0.9	üüü	X		
BB	n.r.	n.r.	±	n.r	5	52.02	±	1.55		n.r.	n.r.	±	n.r			4	50.8	±	2				4	49.33	±	2.32				
BEact	n.r.	n.r.	±	n.r	5	3.82	±	1.27		n.r.	n.r.	±	n.r			4	2.53	±	1				4	1.63	±	1.13				
BEef	n.r.	n.r.	±	n.r	5	3.7	±	2.65		n.r.	n.r.	±	n.r			4	1.48	±	1				4	1.93	±	1.44				

Table 1: *Haematochemical values changes at 122 metres and during acclimatisation at 3480 metres of altitude.*

Anthropometric and skin fold thickness variables

Anthropometric and skin fold thickness variables were measured once in 5 subjects (CS, DC, GM, MR, SS), including weight (kg), height (cm), and skin fold thickness (mm) at multiple sites (cheek, neck, chest, subscapula, abdomen, flank, ileum, triceps, patella and calf) by taking the adipose skin with one hand and measuring it with calipers. Body-mass index (BMI, kg/m^2), body surface (m^2), percentage and thickness of adipose tissue, lean mass and fat mass (kg) were calculated by computer (Microsoft Excel).

Polysomnographic recordings

During the pilot study, 6 subjects (C.S, DC, MR, GM, MG, SS) were recorded 14 times to familiarize them with the experimental setting. Here, we are presenting the final polysomnographic data acquired with the Somnological 3 software system (Embla Systems, Broomfield, CO) in 3 subjects. At the time of the final polysomnographic recording in the 3 subjects (CS, MR, GM), the age range was 38-41 years, the average body weight was 67.6 kg, the BMI was 21.4 ± 1.0 and the maximal aerobic power at sea level was about 59.8 ± 1.7 ml/kg/min.

The initial polysomnographic recording time at 122 m was 00:10:15 ± 0:45:52 on average and the final time of recording was 07:30:44 ± 0:51:11. The local PB measured in the evening at 23:19 ± 0:08:30 was 738.3 ± 0.06 mm Hg. Polysomnographic recordings were also performed during acclimatization between 30-32 and 38-41h after reaching 3480m. Recordings at altitude started at approximately 00:26:30; the average local PB recorded at 22:31 ± 0:25 was 495.9 ± 4.6 mm Hg. Polysomnographic recording ended in the morning at 07:23:13 ± 0:32:23. The local average PB at 9:55 ± 1:01:31 was 495.5 ± 4.1mm Hg.

Electroencephalographic recordings (EEGs, μV/cm) were performed according to the international 10-20 system for standardized EEG electrode placement with seven silver chloride (Ag/Ag/Cl) cupped electrodes. Before application, the electrodes were cleaned with a NaCl salt solution. Four EEG recording electrodes were positioned in F_3, F_4, P_3, P_4, two were placed in A_1 and A_2 on the mastoid skull, and one ground electrode was positioned in C_z.

Electrooculograms (EOG_L and R, μV/cm) were recorded using two small disposable electrodes ($DBlueSensor_{22x28\ mm}$, Embla) placed in the right up- and the left down- orbital regions. Sub mental electromyograms (EMG-Sub, μV/cm) were recorded by means of two Ag/AgCl cupped electrodes fixed 1 cm apart on the right and left sides under the chin. Two disposable electrodes were fixed on the central ventral mass of the left tibial muscle (EMG-Tib, μV/cm, Flex-El adult EKG electrodes, Embla) spaced 1.5 cm apart. Electrocardiograms (EKG, mV/cm) were recorded with a bipolar derivation from two cardiac electrodes placed in V2 in the fourth left intercostal region along the sternum, and in V4 in the fifth left intercostal region on the hemi cleavear line. Thoracic and abdominal respiratory activity was recorded using two respiratory effort sensor bands, the one fixed along the mammary line for recording thoracic respiratory activity (TA, μV/cm) and the other along xifoid line for recording abdominal activity (AA μV/cm) (Respiratory Effort kit, Medcare Flaga, Iceland). Respiratory air flow was recorded using a nasal cannula (Nasal Oral Pressure Cannula, Medcare) and the snoring episodes using a piezo snoring sensor (Medcare) fixed medially to the left sternocleidomastoid muscle with insulating tape. Decubitus position was recorded by means of a thorax position sensor band (Medcare). The percentage of arterial peripheral oxygen saturation (%$SpaO_2$) was recorded with an oximeter (Flex Sensor 8000J, Nonin, Minneapolis, MN) fixed over the middle finger of the left hand with elastic adhesive tape (Tensoplast, BSN-Medical). All electrodes were positioned after having cleaned the skin with an approximately 100% alcohol and ether solution and added conductive paste or gel (EEG Astromed-Grass paste, Grass Technologies, Warwick, RI; Ultra sonar or EKG gel, Parker Laboratories, Fairfield, NJ) often mixed with a 0.9% physiological NaCl solution. All electrodes and sensors were fixed with insulating tape (Tensoplast, BSN-Medical) and/or an appropriate tubular elastic net bandage (Presteril, Corman, Milan). Polysomnographic EEG, EOG, EMG (sub and TA), EKG signals were amplified and acquired at a sampling rate of 200 Hz for subsequent off-line analysis according to standard criteria (Medcare Flaga). Respiratory flow signals were acquired at a sampling rate of 20 Hz, thoracic and abdominal activities at 10 Hz and the snoring signal at 100 Hz.

Analysis and Statistics

Polysomnographic data: Recordings were scored according to standard criteria in 30-s artifact-free epochs [12]. For macro structural polysomnographic analysis, EEG traces were filtered between 0.3 and 49 Hz, EOGs with a filter < 10 Hz, EMGs with a filter < 5 Hz, snoring signals with a low-cut filter of 7 Hz. Each behavioral wakening during sleep was counted as an arousal if EMG activation, eye movement and alpha EEG activity were present.

Spectral EEG analysis of NREM and REM sleep was carried out on EEG signals registered in P_4-A_1 and in several different epochs and stages in 3 subjects (CS, MR, GM): stage S2 (number of epochs, n_{122m} = 283.3 ± 118.11; n_{3480m} = 305.7 ± 87.32), stage S3 + S4 (n_{122m} =121.7 ± 47.88; n_{3480m} = 59.0 ± 43.92), tonic REM (n_{122m} = 48.0 ± 28.35; n_{3480m} = 31.3 ± 13.01) and phasic REM (n_{122m} = 45.3 ± 22.55; n_{3480m} = 31.7 ± 17.90) by means of Hypno lab® software developed by Raffaele Ferri (1997). Spectral EEG analysis was performed for the following frequency power bands: 0.25-2.5 Hz (*delta1*); 2.5-4.5 Hz (*delta2*); 4.5-7.5 Hz (*theta*); 7.5-11.5 Hz (*alpha*); 11.5-15 Hz (*sigma*); 15-25 Hz (*beta*); 25-35 Hz (*gamma1*) and 35-49 Hz (*gamma2*). As previously shown (Ferri *et al*., 1997), signal frequency, percentage power spectrum and absolute power spectrum were automatically calculated in 30-s signal epochs for each power band. The power band ratio between *beta/delta1, beta/delta2, beta/theta, gamma1/delta1, gamma1/delta2, gamma2/delta1, gamma2/delta2, gamma1/theta, gamma2/theta, beta/sigma, gamma1/sigma and gamma2/sigma* was also calculated using absolute power spectrum values and per cent spectrum [26].

Respiratory profile analysis

In the final study involving 3 subjects (CS, MR, GM), oxygen desaturation was detected when oxygen saturation fell by at least 4.0%. A sleep apnea event was defined as a 10.0-s interval and if the signal dropped below 10.0% of the reference amplitude. A hypopnea event was detected when the signal dropped below 70.0% of the reference amplitude. For a hypopnea event to be scored, a desaturation event had to occur no later than 20.0 seconds after the start of hypopnea.

Spectral analysis of heart rate variability (HRV)

Cardiovascular variability was analyzed [2,16,19] during sleep at 122m and at 3480m using Somnological 3 (Embla) and the heart rate variability (HRV) software packages [27].

Measurements of heart rate variability in both the power and frequency domain were calculated for 3 subjects (CS, MR, GM) and included: the average of the R-R interval, the standard deviation of all R-R intervals (SDNN), the square root of the mean of the sum of the squares of the differences between adjacent R-R intervals (RMSSD), the number of pairs of adjacent R-R intervals differing more than 50 ms in the entire analysis interval (NN50 count), the percentage NN50 of total HR, the mean of the standard deviations of all R-R intervals from 300 msec to 5 minute segments (SDANN) and the average of the total power of the very low- (VLF), low- (LF), high- (HF) frequency power [27].

Statistical analysis

Differences between conditions were assessed using Student's unpaired and paired t-tests. A probability lower than $P < 0.05$ was accepted as significant.

Results

Anthropometry and plicometry

At the time of the final study, 5 of the 6 subjects weighed 65.8 ± 4 kg, of which 58.3 ± 4.2 kg was their lean body mass and 11.4 ± 2.1 kg the percentage of adipose tissue. The excess adipose tissue was 0.9 ± 1.3 kg. The height was 176 ± 3.7 cm and the BMI was 21.2 kg/m^2. The aerobic power at sea level was about 61.4 ml $Kg^{-1}min^{-1}$.

Sleep quality

In the pilot study involving on all 6 subjects, 65% took longer than usual to fall asleep, 30% woke up 2h before the expected time and 60% woke up more than once during the night. Sleep quality was perceived as significantly poorer ($P < 0.025$), the duration of sleep was shorter and 60% of the subjects felt poorly restored on waking up.

Polysomnographic data

In the pilot study, EEG, EMG, EOG, EKG and respiratory activity were recorded in all 6 subjects during sleep at 122m and during 30-32 to 39-41h of acclimatization at 3480m by means of a portable polysomnographic system equipped with Lab View software (National-Instruments, Austin TX). Sleep was generally characterized by a significant reduction in total sleep time of about 38.5% (P< 0.0021). REM sleep decreased by about 10.3% (P< 0.0226) and non-REM sleep decreased by about 28.3% (P< 0.0151). A parallel increase in wakefulness (38.8%; P< 0.01) was noted. REM sleep episodes were shorter and fragmented at 3480m as compared to sea-level sleep. In comparison to sea level there were less numbers of REM than in altitude. SWS and REM latency increased but not significantly. Sleep was characterized by periodic breathing. During sleep, the average skin temperature recorded near the V4 intercostal chest space during 30-41h of acclimatization at 3480m was in average 35.2 ± 0.7°C.

In the present study, we highlight the data obtained in 3 (CS, GM, MR) of the 6 subjects. Figures 1 and 2 show the typical polysomnographic changes in stage 2 NREM (or SWS, S2) and REM sleep, illustrating the short arousal anticipated by spindle activity in both conditions.

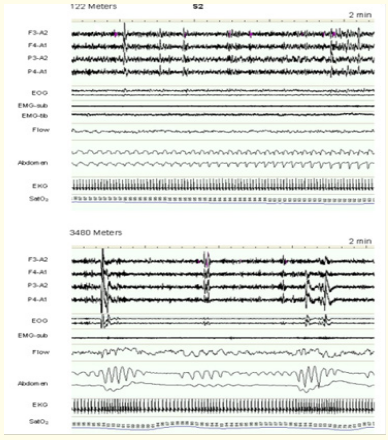

Figure 1: *Examples of recordings during stage 2 (N2) of NREM or SWS sleep (Stage S2) sleep in a subject at 122m (PB about 738 mm Hg) and at 3480m (PB about 494 mm Hg).*

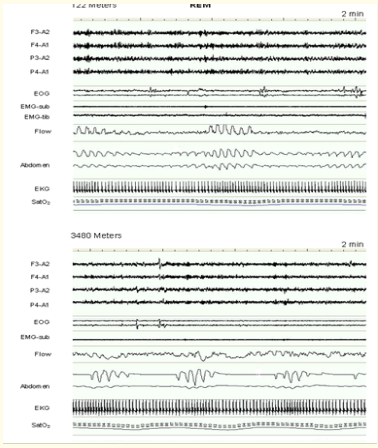

Figure 2: *Examples of recordings during REM sleep in a subject at 122m (PB about 738 mm Hg) and at 3480m (PB 494 mm Hg).*

	General			WAKE		SWS												REM			
	Minutes			Events		Minutes							%			Events		Minutes		%	Events
				Number of	Awakening											Spindles		Average of			Number of
Subjects	SP[1]	TST[2]	WASO[3]	Awakenings	Index	S1	S2	S3	S4	S3+S4	S1	S2	S3	S4	S3+S4	in S2	Index x[(4)]	REM	N-REM	REM	REM
122m																					
C.S.	404.5	373.0	31.5	16	2.57	20	200	38.5	47	85.5	5.4	53.6	10.3	12.6	22.9	531	159.3	12.3	67.5	18.1	5
M.R.	482.0	468.5	13.5	6	0.77	14	272.5	39	24.5	63.5	3	58.2	8.3	5.2	13.5	321	70.68	23.8	118.5	25.3	5
G.M.	429.6	356.5	64.6	10	0.83	16.5	244.5	26.5	16.5	43	4.6	68.6	7.4	4.6	12.0	538	132.02	12.1	52.5	14.7	4
Mean	438.7	399.3	36.5	10.7	1.4	16.8	239.0	34.7	29.3	64.0	4.3	60.1	8.7	7.5	16.1	463.3	120.7	16.1	79.5	19.4	4.7
SD	39.54	60.47	25.92	5.03	1.02	3.01	36.56	7.08	15.81	21.25	1.22	7.68	1.48	4.46	5.91	123.31	45.39	6.70	34.60	5.41	0.58
3480m																					
C.S.	425.1	273.5	151.6	19	3.95	25.5	168	19	33.5	52.5	9.3	61.4	6.9	12.2	19.1	580	207.14	11.8	27.5	10.1	2
M.R.	375.9	357.4	18.5	12	2.01	21	258	12.5	17.5	30	5.9	72.2	3.5	4.9	8.4	531	123.49	8.7	48.5	13.5	5
G.M.	441	366.5	74.5	7	1.15	15.5	253	22	16.5	38.5	4.2	69	6	4.6	10.6	617	146.32	19.7	59.5	16.2	3
Mean	414.0	332.5	81.5	12.7	2.4	20.7	226.3	17.8	22.5	40.3	6.5	67.5	5.5	7.2	12.7	576.0	159.0	13.4	45.2	13.3	3.3
SD	33.94	51.27	66.83	6.03	1.43	5.01	50.58	4.86	9.54	11.36	2.60	5.55	1.76	4.30	5.65	43.14	43.24	5.67	16.26	3.06	1.53
P	0.6064	0.2252	0.3538	0.5286	0.0984	0.2588	0.3930	0.1220	0.2217	0.1322	0.2423	0.2005	0.0833	0.1917	0.0868	0.1503	0.0868	0.7269	0.2652	0.2630	0.2697

Table 2: *Alterations of sleep architecture indexes at 122 and at 3480 meters of altitude.*

Sleep alteration after 32-4h of acclimatization to 3480m in the 3 subjects (CS, GM, MR) was characterized by a non-significant reduction in total sleep time and an increase in cortical and behavioral ultra short, short and long-lasting arousal during sleep, increased wakenings and the awakening index [15], increased duration of phase N1 and decreased duration of phases N2, N3 and N4. The percentages of N1 and N2 also increased, whereas those of N3 and N4 decreased. Stage 2 of NREM sleep was characterized by an increase in spindle activity. A reduction in the average, percentage and number of REM episodes was found Table 2.

Spectral analysis

EEG spectral analysis in 3 subjects (CS, GM, MR) revealed that during 32 to 41h of acclimatization at about 3480m sleep stages N3 and N4 were characterized by a significant reduction in the percentages of the power of delta2 activity (P< 0.0251) Table 3 and 4 and an increase in the power of the high-frequency (beta and gamma) bands. During the tonic phase of REM sleep, there was a significant decrease in the absolute power of the very slow delta wave component (P< 0.0082) and the beta component (P< 0.0194) Table 3 and 4. There was a nearly significant decrease in the percentage of alpha activity (P< 0.0566). Phasic REM sleep was characterized by a significant reduction in the power of the theta band (P< 0.0054) and the percentage of the power of the sigma band (P< 0.0106).

Comparison between EEG data recorded at sea level and at altitude showed that during stage 2 NREM sleep the ratio of the absolute power of the spectra of beta/delta1 and gamma1/theta increased significantly (P< 0.0262 and P< 0.02, respectively), as did the percentages of beta/delta1 (P< 0.0147) and gamma1/theta (P< 0.0415) Tables 3 and 4. The percentages of the ratio of the power of the gamma2/delta2 (P< 0.0246) and of the gamma2/theta (P< 0.0412) were significantly increased during phases S3 and S4 of NREM sleep.

In comparison to sea-level data, during tonic REM at altitude there was an increase in the ratio of beta/delta1 (P< 0.0117) and gamma1/theta (P< 0.0055) and in the percentages of the ratio of beta/delta1 (P< 0.0359) and gamma1/theta (P< 0.0353). Phasic REM at altitude was characterized by an increase in the power of beta/sigma (P< 0.030), the percentage of beta/theta (P< 0.0379) and the ratio of the beta/sigma (P< 0.0410) Tables 3 and 4.

Respiratory activity

In the pilot study, the average of the percentages of peripheral arterial oxygen saturation recorded in all 6 subjects during 32-41h of sleep and acclimatization at 3480 m was significantly lower on average than sea-level values (%$SpaO_2$; n = 6, mean ± SEM: 79.98 ± 2.4 vs. 94.9 ± 1.27; t = 12.98; P< 0.0005). The present study involving 3 subjects confirmed a significant reduction in %$SpaO_2$ during sleep (P< 0.0479) Table 5.

Figures 1, 2 illustrates the changes in respiratory activity patterns during both stage N2 NREM (N2) and REM sleep at sea level and at 3480 m (local P_B 494 mm Hg). During 32-41h of acclimatization, NREM and REM sleep at altitude were characterized by a significant increase in periodic breathing. Periodic breathing was characterized by three to five rapid breaths (hyperpnea), followed by 10 to 20s of no breathing (apnea). Tachypneic episodes were occasionally seen, with transient signs of arousal lasting several seconds. Altered respiration and arousal were not always strictly related. Signs of arousal were seen to precede and/or occur parallel to and/or following hyperapneic episodes.

During both NREM and REM sleep at altitude, the number of apnea-hypopnea episodes and their index increased (P< 0.0259 and P< 0.0159, respectively) Table 5. REM sleep at a local PB of 495 mm Hg was characterized by an increase in the number of central apneas (CA; P< 0.0041). Analysis of periodic breathing episodes in all 3 subjects at altitude revealed a constant, repeatable reduction in the areas under inspiration signals, particularly in stage N2 NREM sleep. These changes were also evident during REM sleep but significantly so in 2 of the 3 subjects Table 6. The inspiration signal slopes changed in 2 of the 3 subjects during both NREM and REM sleep Table 6. Stage N2 NREM sleep was characterized by an increase in the inspiration signal slope of the preceding deepest inspiration, while the deepest inspiration and the following one decreased significantly at altitude compared to sea level. Analysis of breathing patterns during REM sleep at altitude showed wide variability among the subjects. In one subject, all components of the inspiration signal slope were significantly decreased, whereas in another subject all the inspiration signal slopes were increased, but only the inspiration signal slope preceding the deepest was significantly increased Table 6.

				mV²								%							
Sleep	Metres	Subject	#	δ	δ	θ	α	β	β	γ	γ	δ	δ	θ	α	β	β	γ	γ
stage			Epochs	0.25-2.5	2.5-4.5	4.5-7.5	7.5-11	11.5-15	15-25	25-35	35-50	0.25-2.5	2.5-4.5	4.5-7.5	7.5-11	11.5-15	15-25	25-35	35-50
S2																			
	122																		
		C.S.	157	139.7	75.9	71.0	60.5	51.9	57.2	36.3	41.4	25.5	14.3	13.6	11.7	9.8	10.7	6.7	7.5
		M.R.	302	124.0	112.3	118.8	98.7	88.6	109.5	52.2	46.6	16.3	15.0	15.8	13.1	11.8	14.7	7.0	6.2
		G.M.	391	116.8	89.6	69.5	63.1	59.2	72.4	41.5	33.9	20.8	16.2	12.6	11.5	10.6	13.1	7.4	7.8
		Mean	283.3	126.9	92.6	86.4	74.1	66.6	79.7	43.3	40.6	20.9	15.2	14.0	12.1	10.8	12.8	7.1	7.2
		SD	118.1	11.7	18.4	28.0	21.3	19.4	26.9	8.1	6.4	4.6	1.0	1.6	0.9	1.0	2.0	0.3	0.8
	3480																		
		C.S.	241	113.5	65.9	62.0	63.6	56.5	54.8	31.7	35.8	22.5	13.6	13.0	13.6	11.8	11.6	6.6	7.4
		M.R.	405	121.0	109.5	103.1	95.2	85.8	120.5	52.9	44.0	16.2	14.8	14.1	13.0	11.7	16.7	7.4	6.1
		G.M.	271	101.6	91.4	73.4	64.8	54.6	76.5	46.0	60.1	17.5	16.0	13.0	11.5	9.6	13.6	8.1	10.6
		Mean	305.7	112.0	88.9	79.5	74.5	65.6	83.9	43.5	46.6	18.7	14.8	13.4	12.7	11.0	13.9	7.4	8.0
		SD	87.3	9.8	21.9	21.2	17.9	17.5	33.5	10.8	12.4	3.3	1.2	0.6	1.1	1.2	2.6	0.8	2.3
P				0.157	0.402	0.352	0.856	0.759	0.386	0.946	0.615	0.162	0.180	0.422	0.452	0.775	0.139	0.297	0.477
S3+S4																			
	122																		
		C.S.	160	219.6	96.9	79.5	55.2	51.6	61.0	42.3	49.6	33.8	15.2	12.5	8.6	7.9	8.8	6.2	7.2
		M.R.	137	195.2	131.4	125.9	113.2	87.1	99.0	47.2	43.7	22.6	15.6	15.1	13.6	10.5	11.9	5.6	5.2
		G.M.	68	198.8	120.4	76.6	61.1	75.7	69.5	36.8	37.8	29.2	17.8	11.4	9.0	11.2	10.3	5.5	5.6
		Mean	121.7	204.5	116.2	94.0	76.5	71.5	76.5	42.1	43.7	28.5	16.2	13.0	10.4	9.8	10.3	5.8	6.0
		SD	47.9	13.2	17.6	27.7	31.9	18.1	20.0	5.2	5.9	5.6	1.4	1.9	2.8	1.7	1.5	0.4	1.0
	3480																		
		C.S.	99	309.7	102.8	74.9	56.2	53.8	60.3	45.1	51.9	40.5	13.8	10.0	7.5	7.3	8.0	6.0	6.9
		M.R.	66	275.7	147.0	127.7	105.8	94.4	114.9	64.1	72.5	26.8	14.6	12.9	10.9	9.6	11.8	6.4	7.2
		G.M.	12	151.9	105.5	82.4	64.2	64.0	74.4	54.1	62.2	23.2	16.1	12.5	9.8	9.7	11.3	8.1	9.3
		Mean	59.0	245.8	118.4	95.0	75.4	70.7	83.2	54.4	62.2	30.1	14.8	11.8	9.4	8.9	10.4	6.8	7.8
		SD	43.9	83.0	24.8	28.6	26.7	21.1	28.3	9.5	10.3	9.1	1.2	1.6	1.7	1.4	2.0	1.2	1.3
P				0.449	0.828	0.782	0.759	0.910	0.302	0.122	0.152	0.711	0.025	0.412	0.424	0.064	0.930	0.342	0.260
REM (Tonic)																			
	122																		
		C.S.	38	74.7	51.6	60.7	74.1	45.0	59.4	33.8	34.9	17.0	12.0	14.2	17.3	10.4	13.7	7.7	7.9
		M.R.	80	90.7	78.3	82.0	85.9	71.8	116.6	56.6	51.8	13.6	12.4	13.1	13.7	11.5	18.6	9.0	8.0
		G.M.	26	69.4	62.1	53.5	60.7	47.9	67.0	37.8	35.8	16.0	14.3	12.3	14.0	11.0	15.5	8.5	8.3

		Mean	48.0	78.3	64.0	65.4	73.6	54.9	81.0	42.8	40.8	15.6	12.9	13.2	15.0	11.0	15.9	8.4	8.1
		SD	28.4	11.1	13.5	14.8	12.6	14.7	31.0	12.2	9.5	1.7	1.2	0.9	2.0	0.6	2.5	0.6	0.2
	3480																		
		C.S.	18	62.2	44.6	51.2	58.8	33.9	54.4	28.4	29.6	17.0	12.2	14.1	16.2	9.3	15.0	7.9	8.2
		M.R.	32	79.3	66.1	72.5	76.1	66.5	111.0	56.4	45.2	13.8	11.6	12.7	13.3	11.6	19.4	9.8	7.9
		G.M.	44	60.3	56.8	50.0	55.0	42.4	63.6	43.6	54.2	14.2	13.4	11.8	12.9	10.0	14.9	10.2	12.7
		Mean	31.3	67.3	55.8	57.9	63.3	47.6	76.3	42.8	43.0	15.0	12.4	12.9	14.1	10.3	16.4	9.3	9.6
		SD	13.0	10.4	10.8	12.7	11.2	16.9	30.3	14.0	12.4	1.8	0.9	1.2	1.8	1.2	2.5	1.2	2.7
P				0.008	0.059	0.063	0.066	0.060	0.019	0.982	0.817	0.465	0.335	0.143	0.057	0.205	0.484	0.160	0.400
REM (Phasic)																			
	122																		
		C.S.	22	75.8	48.0	56.4	62.2	42.2	60.7	34.5	36.2	17.7	11.7	13.9	15.4	10.1	14.6	8.2	8.5
		M.R.	67	83.7	73.7	77.8	83.5	70.0	112.1	56.3	50.3	13.3	12.2	12.9	13.9	11.7	18.6	9.2	8.1
		G.M.	47	70.6	67.5	58.0	60.3	45.3	64.7	36.4	34.9	16.1	15.5	13.3	13.8	10.3	14.8	8.3	8.0
		Mean	45.3	76.7	63.1	64.1	68.7	52.5	79.1	42.4	40.5	15.7	13.1	13.3	14.4	10.7	16.0	8.6	8.2
		SD	22.5	6.6	13.4	11.9	12.9	15.2	28.6	12.1	8.5	2.2	2.1	0.5	0.9	0.9	2.3	0.6	0.3
	3480																		
		C.S.	12	72.3	48.4	50.5	65.5	35.2	56.6	27.9	30.5	18.7	12.5	13.0	16.9	9.1	14.6	7.3	7.9
		M.R.	36	92.6	70.3	73.1	80.8	63.5	111.7	57.0	46.7	15.5	11.9	12.4	13.6	10.7	18.7	9.6	7.8
		G.M.	47	72.3	58.2	52.2	56.2	42.9	65.1	44.2	57.8	16.0	13.0	11.6	12.6	9.6	14.5	9.9	12.9
		Mean	31.7	79.1	59.0	58.6	67.5	47.2	77.8	43.0	45.0	16.7	12.4	12.3	14.4	9.8	16.0	8.9	9.5
		SD	17.9	11.7	11.0	12.6	12.4	14.6	29.7	14.6	13.7	1.7	0.6	0.7	2.3	0.8	2.4	1.4	2.9
P				0.579	0.285	0.005	0.653	0.069	0.444	0.891	0.672	0.265	0.559	0.086	0.993	0.011	0.788	0.696	0.530

Table 3: *Power (μV2) and Percentages of EEG power (P4-A1) at 122 and 3480 meters of altitude.*

				mV^2												%											
			n.	b/d1	b/d2	b/q	g1/d1	g1/d2	g2/d1	g2/d2	g1/q	g2/q	b/s	g1/s	g2/s	b/d1	b/d2	b/q	g1/d1	g1/d2	g2/d1	g2/d2	g1/q	g2/q	b/s	g1/s	g2/s
Sleep stage	Metres	Subject	Epochs																								
S2																											
	122																										
		C.S.	157	0.409	0.753	0.805	0.260	0.478	0.296	0.511	0.006	0.583	1.101	0.699	0.797	0.419	0.750	0.785	0.264	0.471	0.296	0.494	0.031	0.554	1.087	0.683	0.766
		M.R.	302	0.883	0.975	0.922	0.421	0.465	0.376	0.439	0.007	0.392	1.236	0.589	0.526	0.899	0.980	0.929	0.429	0.468	0.382	0.444	0.057	0.395	1.243	0.593	0.529
		G.M.	391	0.619	0.808	1.042	0.355	0.463	0.290	0.597	0.009	0.487	1.223	0.701	0.572	0.630	0.807	1.039	0.357	0.458	0.377	0.590	0.050	0.623	1.232	0.699	0.738
		Mean	283.3	0.637	0.845	0.923	0.345	0.469	0.321	0.516	0.007	0.488	1.187	0.663	0.632	0.649	0.846	0.918	0.350	0.466	0.352	0.509	0.046	0.524	1.187	0.658	0.678
		SD	118.1	0.2	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.1
	3480																										
		C.S.	241	0.483	0.831	0.884	0.279	0.480	0.316	0.511	0.008	0.578	0.970	0.561	0.634	0.515	0.850	0.888	0.295	0.487	0.331	0.509	0.040	0.571	0.979	0.561	0.629
		M.R.	405	0.996	1.101	1.169	0.437	0.483	0.363	0.513	0.010	0.427	1.405	0.616	0.513	1.034	1.130	1.184	0.458	0.500	0.378	0.524	0.073	0.433	1.428	0.632	0.523
		G.M.	271	0.753	0.837	1.042	0.453	0.504	0.592	0.627	0.010	0.819	1.402	0.844	1.102	0.775	0.845	1.040	0.465	0.507	0.607	0.624	0.059	0.814	1.406	0.844	1.101
		Mean	305.7	0.744	0.923	1.032	0.390	0.489	0.424	0.550	0.009	0.608	1.259	0.674	0.750	0.775	0.942	1.037	0.406	0.498	0.439	0.552	0.057	0.606	1.271	0.679	0.751
		SD	87.3	0.3	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.2	0.3	0.1	0.3	0.3	0.2	0.1	0.1	0.0	0.1	0.1	0.0	0.2	0.3	0.1	0.3
P				0.026	0.109	0.273	0.239	0.208	0.411	0.246	0.020	0.375	0.549	0.906	0.632	0.015	0.098	0.248	0.164	0.077	0.352	0.152	0.042	0.273	0.472	0.813	0.673
S3+S4																											
	122																										
		C.S.	160	0.278	0.630	0.768	0.192	0.436	0.226	0.532	0.003	0.624	1.183	0.819	0.961	0.260	0.578	0.701	0.183	0.408	0.212	0.495	0.021	0.572	1.114	0.786	0.910
		M.R.	137	0.508	0.754	0.786	0.242	0.359	0.224	0.375	0.004	0.347	1.137	0.542	0.501	0.526	0.759	0.786	0.250	0.361	0.230	0.374	0.035	0.344	1.129	0.538	0.495
		G.M.	68	0.350	0.577	0.906	0.185	0.306	0.190	0.480	0.005	0.493	0.918	0.486	0.500	0.353	0.577	0.902	0.187	0.306	0.193	0.478	0.031	0.494	0.921	0.488	0.504
		Mean	121.7	0.378	0.654	0.820	0.207	0.367	0.213	0.462	0.004	0.488	1.079	0.616	0.654	0.380	0.638	0.796	0.207	0.358	0.212	0.449	0.029	0.470	1.055	0.604	0.636
		SD	47.9	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.2	0.3	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.2	0.2
	3480																										
		C.S.	99	0.195	0.587	0.806	0.146	0.439	0.168	0.602	0.003	0.693	1.121	0.838	0.965	0.198	0.583	0.802	0.147	0.433	0.170	0.595	0.020	0.686	1.098	0.814	0.939
		M.R.	66	0.417	0.782	0.900	0.232	0.436	0.263	0.502	0.003	0.568	1.218	0.679	0.768	0.439	0.803	0.914	0.238	0.436	0.268	0.496	0.034	0.557	1.227	0.666	0.748
		G.M.	12	0.490	0.705	0.903	0.356	0.513	0.410	0.657	0.006	0.755	1.161	0.845	0.972	0.487	0.702	0.900	0.351	0.506	0.401	0.649	0.039	0.742	1.160	0.836	0.956
		Mean	59.0	0.367	0.691	0.870	0.245	0.462	0.280	0.587	0.004	0.672	1.167	0.787	0.902	0.375	0.696	0.872	0.245	0.458	0.280	0.580	0.031	0.662	1.162	0.772	0.881
		SD	43.9	0.2	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.0	0.1	0.1	0.2	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.1	0.1	0.1	0.1
P				0.896	0.527	0.286	0.627	0.252	0.498	0.056	0.912	0.088	0.425	0.227	0.209	0.952	0.241	0.196	0.604	0.196	0.457	0.025	0.551	0.041	0.286	0.218	0.182
REM (Tonic)																											
	122																										
		C.S.	38	0.795	1.151	0.979	0.453	0.655	0.468	0.557	0.013	0.576	1.320	0.751	0.776	0.805	1.143	0.964	0.453	0.643	0.463	0.543	0.057	0.555	1.319	0.742	0.759

		M.R.	80	1.285	1.488	1.422	0.625	0.723	0.571	0.691	0.016	0.632	1.624	0.789	0.722	1.367	1.508	1.423	0.657	0.725	0.588	0.684	0.104	0.612	1.618	0.778	0.696
		G.M.	26	0.966	1.079	1.252	0.544	0.608	0.515	0.706	0.018	0.668	1.399	0.788	0.746	0.967	1.085	1.261	0.533	0.598	0.518	0.695	0.079	0.675	1.405	0.774	0.752
		Mean	48.0	1.015	1.239	1.218	0.541	0.662	0.518	0.651	0.016	0.625	1.447	0.776	0.748	1.046	1.246	1.216	0.548	0.656	0.523	0.641	0.080	0.614	1.447	0.765	0.736
		SD	28.4	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.2	0.0	0.0	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.0	0.1	0.2	0.0	0.0
	3480																										
		C.S.	18	0.875	1.221	1.063	0.457	0.638	0.476	0.555	0.017	0.579	1.604	0.838	0.873	0.885	1.232	1.066	0.465	0.647	0.484	0.560	0.063	0.583	1.611	0.846	0.881
		M.R.	32	1.400	1.679	1.531	0.712	0.854	0.570	0.778	0.019	0.623	1.670	0.849	0.680	1.409	1.669	1.525	0.715	0.847	0.571	0.774	0.111	0.618	1.674	0.850	0.679
		G.M.	44	1.055	1.120	1.274	0.724	0.768	0.898	0.874	0.021	1.084	1.502	1.030	1.278	1.051	1.108	1.265	0.720	0.759	0.894	0.867	0.089	1.076	1.493	1.023	1.270
		Mean	31.3	1.110	1.340	1.289	0.631	0.753	0.648	0.736	0.019	0.762	1.592	0.906	0.944	1.115	1.336	1.286	0.633	0.751	0.650	0.734	0.088	0.759	1.593	0.906	0.943
		SD	13.0	0.3	0.3	0.2	0.2	0.1	0.2	0.2	0.0	0.3	0.1	0.1	0.3	0.3	0.3	0.2	0.1	0.1	0.2	0.2	0.0	0.3	0.1	0.1	0.3
P				0.012	0.158	0.110	0.216	0.239	0.412	0.227	0.005	0.431	0.182	0.150	0.375	0.036	0.150	0.169	0.244	0.181	0.419	0.173	0.035	0.376	0.187	0.122	0.326
REM (Phasic)																											
	122																										
		C.S.	22	0.800	1.265	1.075	0.455	0.719	0.478	0.612	0.014	0.643	1.438	0.818	0.859	0.822	1.250	1.052	0.461	0.702	0.478	0.591	0.059	0.613	1.439	0.808	0.838
		M.R.	67	1.340	1.522	1.441	0.673	0.764	0.601	0.724	0.017	0.647	1.602	0.804	0.719	1.400	1.526	1.442	0.695	0.759	0.611	0.717	0.108	0.630	1.589	0.790	0.694
		G.M.	47	0.916	0.958	1.114	0.515	0.539	0.494	0.627	0.016	0.601	1.428	0.804	0.771	0.922	0.957	1.116	0.518	0.537	0.497	0.627	0.069	0.601	1.436	0.806	0.774
		Mean	45.3	1.019	1.248	1.210	0.548	0.674	0.525	0.654	0.016	0.630	1.490	0.809	0.783	1.048	1.244	1.203	0.558	0.666	0.529	0.645	0.079	0.615	1.488	0.801	0.769
		SD	22.5	0.3	0.3	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.1	0.3	0.3	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.1
	3480																										
		C.S.	12	0.783	1.169	1.121	0.386	0.576	0.422	0.552	0.016	0.604	1.607	0.792	0.867	0.785	1.173	1.130	0.390	0.583	0.425	0.562	0.061	0.612	1.603	0.797	0.869
		M.R.	36	1.206	1.589	1.528	0.616	0.811	0.504	0.780	0.016	0.639	1.759	0.898	0.735	1.211	1.579	1.515	0.618	0.806	0.504	0.774	0.098	0.631	1.754	0.896	0.731
		G.M.	47	0.901	1.120	1.248	0.612	0.760	0.799	0.847	0.017	1.107	1.518	1.031	1.347	0.908	1.120	1.247	0.617	0.761	0.806	0.847	0.078	1.107	1.515	1.030	1.345
		Mean	31.7	0.963	1.293	1.299	0.538	0.716	0.575	0.727	0.016	0.784	1.628	0.907	0.983	0.968	1.291	1.297	0.542	0.717	0.579	0.728	0.079	0.783	1.624	0.908	0.982
		SD	17.9	0.2	0.3	0.2	0.1	0.1	0.2	0.2	0.0	0.3	0.1	0.1	0.3	0.2	0.3	0.2	0.1	0.1	0.2	0.1	0.0	0.3	0.1	0.1	0.3
P				0.292	0.611	0.073	0.867	0.730	0.730	0.467	0.433	0.477	0.030	0.312	0.399	0.284	0.571	0.038	0.806	0.656	0.739	0.375	0.971	0.422	0.041	0.257	0.357

Table 4: *EEG power ratio and percentages during sleep at 122 and at 3480 metres.*

Metres	TST									REM		
	%	Events								Events		
Subject	$SpaO_2$ [1]	OD[2]	A + H[3]	CA[4]	Apnea Related to Desaturation	OD Index [5]	A + H Index [6]	CA Index [7]	A related to OD Index	CA in REM [10]	CA in REM Index [11]	Arousals in REM [12]
122												
C.S.	95.0	165	72	36	25	0.17	0.19	0.10	0.07	6	0.09	12
M.R.	97.3	36	50	14	7	0.08	0.11	0.03	0.01	5	0.02	8
G.M.	97.7	14	41	33	5	0.04	0.12	0.09	0.01	1	0.02	2
Mean	96.7	71.7	54.3	27.7	12.3	0.1	0.1	0.1	0.0	4.0	0.0	7.3
SD	1.46	81.57	15.95	11.93	11.02	0.07	0.05	0.04	0.03	2.65	0.04	5.03
3,480												
C.S.	82.5	106	122	41	27	0.39	0.45	0.15	0.10	14	0.51	4
M.R.	72.3	97	96	71	51	0.27	0.27	0.20	0.14	14	0.29	3
G.M.	83.5	233	117	115	106	0.64	0.32	0.31	0.29	11	0.18	3
Mean	79.4	145.3	111.7	75.7	61.3	0.4	0.3	0.2	0.2	13.0	0.3	3.3
SD	6.20	76.05	13.80	37.22	40.50	0.19	0.09	0.08	0.10	1.73	0.17	0.58
P	0.048	0.457	0.026	0.169	0.230	0.125	0.016	0.096	0.178	0.004	0.062	0.270

***Table 5**: Respiratory indexes at 122 and 3480 meters of altitude.*

[1]percentage peripheral oxygen saturation; [2]episodes of oxygen Desaturation during TST; [3]episodes of apnoeas and hypopnoeas during TST; [4]episodes of central apnoea; [5]oxygen Desaturation episodes per minute; [6]apnoeas and hypopnoeas episodes per minute; [7]central apnoea episodes per minute. [8]number of arousals per minute referred to TST; [9]number of arousals per minute referred to NREM sleep stage S2; [10]central apnoeas during REM period; [11]central apnoeas in REM per minute; [12]arousals during REM; [13]arousals during REM period per minute.

				Area under			**Inspiration signal**	
				Inspiration ignal			Slope	
Sleep stage	Metres	Subject	Preceding	The deepest	Following	Preceding	The deepest	Following
			The deepest		The deepest	The deepest		The deepest
S2								
	122	C.S.	209.252	601.596	340.009	0.492	1.138	0.932
	3480		85.989	156.049	104.694	0.747	0.762	0.621
P			0.0081	3.08E-06	0.0001	0.0621	0.0001	0.0009
	122	M.R.	70.962	76.200	80.061	0.202	0.319	0.249
	3480		41.759	46.060	26.434	0.214	0.236	0.175
P			0.0282	0.0130	3.22E-06	0.8372	0.1644	0.1531
	122	G.M.	79.710	429.304	348.260	0.401	0.868	0.649
	3480		67.026	112.693	83.609	0.410	0.502	0.431
P			0.2089	1.04E-22	5.09E-18	0.8074	2.77E-14	2.00E-07
REM								
	122	C.S.	100.778	458.313	149.396	0.341	0.753	0.645
	3480		113.447	196.893	139.615	0.841	0.917	0.735
P			0.5365	0.1233	0.8118	1.15E-05	0.0994	0.3785
	122	M.R.	38.399	49.343	33.475	0.204	0.236	0.192
	3480		11.228	15.624	12.766	0.087	0.110	0.079
P			8.73E-07	4.97E-07	9.73E-05	4.58E-07	3.20E-07	1.19E-06
	122	G.M.	80.000	123.828	134.063	0.338	0.334	0.260
	3480		43.969	134.405	68.539	0.271	0.357	0.289
P			0.0197	0.8797	0.0103	0.4352	0.7642	0.7091

***Table 6:** Periodic breathing at 122m and at 3480m.*

Cardiovascular activity

Changes in the resting EKG recorded in the 3 subjects (CS, GM, MR) during sleep were evident after 32-42h of acclimatization at 3480m and at local PB of 494 mm Hg, with an increase in the resting heart rate and sign of sinus arrhythmia during periodic breathing. A decrease in heart-rate frequency was recorded just before the apnea period and an increase was observed during maximum ventilatory effort peaks.

Comparison of the sea-level heart-rate variability (HRV) in the 3 subjects during the deep phases (N3 and N4) of NREM sleep showed that the standard deviation of all R-R intervals were significantly lower than that recorded during arousals with awakening period (SDNN; P< 0.0158).

There was an increase in the number of pairs of adjacent R-R intervals differing more than 50 milliseconds in the entire analysis interval in phase N2 NREM sleep in comparison to that recorded during arousal with awaking periods (P< 0.0323). The average of very low frequency (VLF) significantly decreased during stages N3 and N4 of NREM sleep (P< 0.0204) in comparison to that observed during the arousal and awakening periods. The VLF in REM sleep increased significantly (P< 0.0256) in comparison to that recorded during stages 3 and 4 of NREM sleep. The average of the total power decreased during stages N3 and N4 of NREM sleep (P< 0.0247) in comparison to that recorded during arousal and awaking periods during sleep. The total power was also decreased from stages N2 to N3 + 4 (P< 0.0399) but increased when comparing REM versus stages N3 + 4 (P< 0.0213). The ratio between low- and high-frequency (LF/HF) during stages N3 and N4 was significantly lower than that recorded during arousal and awakening periods (P< 0.0393).

Comparison of the HRV characteristics during sleep during 32-42h of acclimatization at 3480m showed that the VLF was significantly lower than that recorded during arousal and awakening periods (N2: P< 0.0504; N3 and N4: P< 0.0004); the VLF component was significantly increased from stages N3 + 4 to REM sleep (P< 0.0006); the average total power was significantly decreased between the awakening periods and stage N2 (P< 0.0204) and stages N3 + 4 (P< 0.0008) NREM sleep and between stage N2 and stages N3 + 4 NREM sleep (P< 0.0289). Comparison of stage 2 NREM sleep and REM sleep at altitude showed an increase in the total power (P< 0.0431). This increase was more evident when comparing the total power of stages 3 and 4 NREM versus REM sleep (P< 0.0023).

The average of the R-R intervals in the 3 subjects was significantly reduced during the arousal and awaking periods at altitude compared to sea-level values (mean ± SEM: 1.208 ± 71 vs. 962 ± 104, P< 0.0128). During awakening from sleep at altitude, there was a significant reduction in the low frequency (LF) between 0.04-0.15 Hz (8.427 ± 3.190 vs. 5.367 ± 1.366, P< 0.0298). The average of the R-R intervals during stage N2 NREM sleep at altitude was significantly lower than the sea-level values (mean ± SEM, 1.303 ± 62 vs. 1.079 ± 64; P< 0.0206) as was the total power (23.814 ± 12.019 vs. 18.203 ± 10.368; P< 0.0078). The mean of the R-R intervals recorded in stages N3 and N4 at altitude (1.278 ± 39 vs. 1.017 ± 55; P< 0.0054) was significantly lower than the sea-level values, as was the power of the VLF band between 0.003 and 0.04 Hz (5.344 ± 4.173 vs. 3.644 ± 3.454; P< 0.05471). During REM sleep, the average of R-R variability dropped from 1.270 ± 67 at sea level to 1016 ± 78 at altitude (P< 0.0473).

The present study was performed in the field and is preliminary descriptive in nature; nonetheless, the results demonstrate that many physiological, EEG, respiratory and cardiovascular changes occur during 6 to 42h of acclimatization at an altitude of approximately of 3500m and a P_B of 495 mm Hg in anthropometrically and plicometrically characterized marathon runners.

Discussion

Polysomnographic data

In the preliminary pilot study involving all 6 subjects, the significant changes we found in NREM and REM sleep stages are shared by some authors [4,7-11,28], though the results of our final study are consistent with the results reported by other authors that showed no significant changes in sleep between 3505 and 7620m [4]. Nevertheless, all the variables in the present study were strictly monitored and controlled for metabolic/anthropometrical characteristics, diet and acclimatization. The experiments were performed in a domestic location so as to also preclude light-dark and jet-lag effects. Importantly, all subjects were familiar with the experimental setting. So the

decrease of REM in altitude might involve the sufferance of the pontine geniculate occipital formation, the cerebellum, the amigdala and the intralaminar thalamus.

Spectral analysis

The main result of this study was that after 32-42h of acclimatization at 3480m there was a decrease in the amplitude and the power of the very slow frequency bands [29] and an increase in the power of the low-amplitude high-frequency (beta and gamma) bands during SWS. These data indicate activation of the thalamic and extra thalamic mechanisms underlying cortical arousal [15,30], where the latter may be more sensitive to decreases in arterial oxygen saturation. REM sleep at 3480m was characterized by a disruption in the balance of the power of the frequencies that normally occur during this sleep stage, including the changes in the ratio between the power of the delta and theta and the beta and gamma frequency bands. These changes during sleep could result from alterations in chemical secretion from the brainstem reticular formation and basal forebrain, which are responsible for cortical arousal (when exposed for about 35 h to a P_B of about 480 mm Hg), but without substantially changing the macrostructures of sleep and behavior. In agreement with Ferri [26], we can not exclude that alteration of the ratio between the power of the low- and high-frequency activities observed during NREM and REM sleep at altitude could be specifically due to an alteration in the excitability of the thalamocortical system during the light phases of NREM sleep. We should also mention that the energy dissipation (for review, see 31) required for giving rise to slow versus high-frequency EEG activity during REM sleep might become more sensitive at a PB of 480 mm Hg.

Respiratory activity

A reduction in pO_2 stimulates ventilation. For a given pCO_2 level, ventilatory augmentation becomes more prominent [32]. During sleep in hypoxic conditions, the pO_2/pCO_2 ventilation curve shifts depending on the pCO2 level and the bicarbonate concentration [33]. After about 35-40h at 3480m, increased ventilation during periodic breathing must, periodically, reduce the pCO_2 and the respiratory drive. In this study, we found that, following 8 s to about 24s of apnea at altitude, there was an increase in pCO2 that probably shifted the pO_2 curve, producing a cyclic increase in ventilation. Alkalosis, pO_2 and the pCO_2 threshold influence the basic respiratory drive. Flattening and shifting of the ventilatory curve in relation to changes in pCO_2 and pO_2 during sleep have been discussed by Weil [4]. One of the main results of the present study is that during sleep at 3480m and after about 35-40h of acclimatization there was a 70-84% reduction in oxygen saturation [12], which is thought to exacerbate periodic breathing [4]. With this study we confirm the observation on periodic breathing that we observed during stage 2 of NREM and REM sleep at altitude [4,7,10,34]. In agreement with Finnegan *et al*. [9] and West *et al*. [7], we did not observe periodic breathing during stage 3-4 NREM sleep. The hypocapnic alkalosis observed during 35-40h of acclimatization at altitude could have been another factor that modulated the periodic breathing. Unlike Normand *et al*. [12], but in agreement with Goldenbergh *et al*. [10], we found that periodic breathing persisted during REM sleep at altitude. In this sleep stage, periodic breathing was characterized by regular alternation of apnea and ventilatory activity. Most of the apnea episodes were of central origin and were followed by 3 to 4 deep breaths. The ventilatory oscillatory activity grouped into spindle-shaped bursts. The morphology of the signals reflecting the periodic breathing observed by the thoraco-abdominal signals at altitude suggests an alteration in oscillatory rhythm and excitability not only of the inspiratory neurons but also of the expiratory neurons located in the pontine bulbar and medullary respiratory network. The rhythm city of the respiratory neurons seems to be greatly disturbed by hypoxic/hypocapnic/hypercapnic oscillatory levels and alkalosis that occurred during brief exposure to a PB of 495 mm Hg. The true periodic breathing at high altitude was characterized by regular oscillation of oxygen saturation, even during REM sleep, which was higher and different from the erratic changes accompanying irregular ventilation without apnea, seldom recorded at low altitude.

Chemical and non-chemical stimuli (still present during the hyperapnea episodes at altitude) have been suggested to be responsible for the changes in the ventilation profile. Response to non-chemical stimuli differs in degree during the different sleep phases at sea level. But during periodic Cheyne-Stokes ventilation at altitude such stimuli can influence the progressive increase in the cyclic activation/deactivation of the medullary respiratory neurons. Alteration of the rhythmic synaptic, inhibition/excitation of the brainstem network, cyclically observed during periodic breathing under hypoxic conditions, has been put forward as one of the factors responsible for perturbation of the respiratory oscillator neurons in the brainstem reticular formation. The respiratory and cardiovascular oscillatory network

neurons are closely linked to and affected by the chemical and sensory afferents. A reduction in or the absence of changes in ventilation during stages N3 and N4 of NREM sleep might also be somehow due to oscillation of pO_2/pCO_2 at a level that substantiates more constant ventilation during sleep. Thus, alterations of the breathing rhythms during different sleep stages in hypoxic conditions may also be linked to modifications of the chemo-, baro- and propioreceptor signals and the vagal and gloss pharyngeal nerves that end in the medulla oblongata, the bulbar-pontin regions, and the hypothalamic regions where the respiratory oscillatory neurons are located and are involved in respiratory rhythmogenesis and cardiovascular control [18,35].

As suggested by Normand *et al*. [12], we agree that the "putative total cost" for cellular survival at altitude might be increased by giving rise to periodic breathing. Nevertheless, periodic changes in ventilation induce opposite changes in the blood pressure of CO_2 and O_2, favoring the oxygen dissociation curve alternatively for oxygen uptake by the lungs during ventilatory bursts and oxygen release to the tissues during apnea periods [5,13,14]. Like Normand *et al*. [12], we observed that at 3480m breathing pattern changes do not seem to deeply alter the marcostructural organization of sleep; however, we found that exposure to a P_B of 450 mm Hg can result in microstructural EEG changes. We agree with Normand *et al*. [10,12] that the discrepancy between our findings and those reported by others might be due to the level of barometric pressure at which the experiments were performed and/or to inadequate acclimatization and/or the ventilatory response characteristics of a single subject [7]. West suggested that athletes with the highest hypoxic ventilatory response at altitude and the most marked periodic breathing during sleep generally tolerate extreme altitude best. The subjects participating in the present study had a similar maximal aerobic power.

Khoo *et al*. [36] demonstrated that at 4500m only less than 52% of transient arousals are correlated with periodic breathing and suggested that arousal promotes periodic breathing but is not necessary for its development. We agree with Khoo *et al*. [36] that the EEG arousal signs were seen to precede parallel to or following the waxing and waning respiratory pattern but were seldom followed by a behavioral awakening Halasaz *et al*. [31].

REM sleep, particularly the phasic phase, was characterized by an irregular breathing pattern. We suggest that the neurons of the mesopontin, dorsal and ventral respiratory neuronal groups can play a pivotal role in generating periodic breathing even during REM sleep. These neuronal groups may collectively play a critical role in integrating the metabolic and non-metabolic signals involved in the induction and maintenance of a particular sleep phase and periodic breathing [34,35,37-41]. In hypoxia conditions, cyclic hypercapnia, hypocapnia and temporary alkalosis may have had a key role in generating and maintaining the periodic breathing that could have been responsible for the EEG instability and cortical arousal signs we observed. At altitude, instability of the EEG and the intrinsic respiratory control mechanism may create a vicious loop that is broken only when arterial oxygen saturation becomes more sufficient and more stable [3,4], together with a physiological level of pCO_2.

Cardiovascular activity

In agreement with Sacknoff *et al*. [19], we found that the mean of the R-R interval variability in the subjects at sea level, at rest and in supine position, during short arousal and awakening from sleep, was between 1208 and 1303 milliseconds. At see level there was a significant reduction in the power of the very low frequency (VLF) band, the total power and the LF/HF ratio between stages N3 and N4 of NREM sleep in comparison with the arousal and awakening periods of sleep. The LH/HF ratio was also significantly lower during stage N2 of NREM sleep than that observed during stages N3 and N4 of NREM sleep. In comparison to stages N3 and N4 of NREM sleep, the VLF and Total Power increased significantly during REM sleep. In agreement with other authors, we suggest that at low altitude the differences in heart rate variability during and between REM and NREM sleep could be mainly due to a higher sympathetic tone during REM sleep and to a high vagal tone during the deep stages of NREM sleep, the former thought to be linked to the brainstem generator triggered by the arousal systems [15,42].

With Lanfranchi *et al*. [2] and Karliner *et al*. [43] we agree that the changes in the resting EKG are evident, even during sleep, at 3480m and PB of 495 mm Hg after 30-40h of acclimatization. The changes consisted of increased resting heart rate in association with signs of sinus arrhythmia, evident during periodic breathing. Analysis of heart rate variability is essential for evaluating the differences in the

autonomic tone of heart rate variability and provides a valuable tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system even in trained aerobic endurance mountain runners. The main periodic fluctuations during sleep were: the sinus arrhythmia (LF) linked with the respiratory rate, the baroreflex-related (LF) and the thermoregulation-related (VLF) heart rate variability [17]. At 3480m after 35-40h of acclimatization at a P_B of about 495 mm Hg, there was a significant decrease in the resting average of the R-R interval length during NREM and REM sleep at 3480m in comparison to sea-level values.

Sleep at altitude was characterized by a significant reduction in the VLF and the total power during stages N2, N3 and N4 of NREM sleep as compared with the VLF and total power recorded during arousal and awaking period during sleep. In comparison to the VLF and total power observed during stages N3 and N4 of NREM sleep, the VLF and total power increased during REM sleep. This suggests that the mechanism underlying thermoregulation-related heart rate variability is more affected during sleep at altitude.

Like Lanfranchi *et al*. [2], we found a significant reduction in the LF component of R-R variability at altitude. The LF component is thought to originate from the spontaneous rhythmic activity of vessel smooth muscle and from rhythmic sympathetic discharges of the central bulbar center. The reduction in the VLF during stages N3 and N4 of NREM sleep may mediate the fluctuation in peripheral vascular resistance, blood pressure, and heart rate frequency controlled and mediated by the sympathetic nervous system [17].

The risk of stroke, heart attack and cardiac failure, common during the second part of the night, can be due to sudden increases in blood pressure and heart rate frequency. The risk of heart attack at altitude can be due to an increase in sympathetic/vagal imbalance peaks particularly during REM sleep.

Conclusion

It has been postulated that changes in atmospheric pressure may influence activation of the reticular activating system even during sleep either directly via carotid baroreceptors [46] or indirectly via carotid and aortic chemoreceptors [41] and central chemoreceptors [32] or trunk propioreceptors. The results of this study involving endurance athletes suggest that changes in the power density of the high-frequency EEG component during sleep and micro arousal with or without awaking might be related to changes in the reticular activating systems including the posterolateral hypothalamus and thalamus [15,31,39,44]. There is evidence that changes in the rhythms of the central nervous system, the cardiovascular, respiratory and renal systems are generated and modified by a common reticular activating system and cardio respiratory network located between the pontomedullary reticular formation and the diencephalon [31,32,45]. This neuronal network may be susceptible to the homeodynamic reflex inputs that act to maintain homeostasis even during sleep [15,17,31-33,40,44].

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