Periodic Breathing and O_2 Saturation in Relation to Sleep Stages at High Altitude

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This study was designed to compare sleep organization at high altitude (HA) and sea level (SL) and to estimate the extent periodic breathing (PB) negatively influences arterial O_2 saturation (Sa_{O_2}). Six lowlanders were studied at SL and after 3 weeks spent at 3,800 m (La Paz, Bolivia). Three EEG leads, EOG, submental EMG, chest and abdominal motion, temperature of ventilated gas, and Sa_{O_2} were polygraphically recorded. Comparison of HA and SL data disclosed that: 1) Sleep organization was identical, with the same percentage of REM and stage 4. 2) PB (cycle length: 20 s; central apnea: 9 s) occurred in three subjects during all stages of sleep except REM (43–60% of total sleep). A periodic lowering in heart rate occurred during ventilatory oscillation. 3) During PB, Sa_{O_2} oscillated very regularly from 78–90%, which resulted in a mean Sa_{O_2} value calculated during oscillations similar to that of the non-periodic breathers. We conclude that lung O_2 uptake during PB is preserved.

PERIODIC BREATHING is well documented during sleep at high altitude (7,10,11,17,21–23). However, two questions remain unclear. First, does periodic breathing affect the organization of sleep? This question is still unsolved, mainly due to the experimental conditions during which sleep has been studied at high altitude. Most studies have been carried out during ascents to very high elevations where the difficult living conditions, due to intense muscular activity during the day and to cold and discomfort during the night, might be at least partly responsible for changes in sleep organization. For instance, cold stress may change the percentage of REM (4) or increase the number of awakenings (7,22). Second, to what extent does periodic breathing markedly impair O_2 supply due to the periodic lowering of arterial O_2 saturation during apneas? This question arises from an intriguing remark of West *et al.* (23), who noticed that the climbers with the highest hypoxic ventilatory response, and likely the most marked periodic breathing during sleep, generally tolerated extreme altitude best. The benefit of higher ventilation is evident during daytime, but it may be asked whether the mean arterial O_2 saturation during sleep is as affected by periodic breathing as might be expected.

The objective of the present work was: 1) to compare the organization of sleep in the same subjects under the same experimental conditions; i.e., with identical diurnal physical activity (laboratory work) and identical nocturnal thermal comfort at sea level and after 3 weeks spent at 3,800 m, La Paz, Bolivia; 2) to estimate the extent the mean value of arterial O_2 saturation is altered during unstable breathing periods, which amounts to comparing the level of arterial O_2 saturation in periodic breathers to that of non-periodic breathers at high altitude.

METHODS

The subjects were four men and two women, aged from 30–50 years, and all laboratory workers. During previous sojourns in La Paz, they had never displayed signs of acute mountain sickness or complained of sleep disturbance or lack of freshness on awakening. They were studied 3 weeks after their arrival in La Paz. The study at high altitude was conducted using the same equipment as at sea level. As all subjects had participated several times in sleep protocols, they were observed for one night only. It has been shown that first night effect is reduced in such subjects (19). In addition, owing to their participation in daytime exercise protocols involving arterial blood sampling, it was possible to obtain their Po_2, Pco_2, and pH resting values some hours before the sleep recordings.

The following standard procedures were used for sleep recordings: three EEG channels, one electro-

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oculogram using fronto-temporal leads, and one submental electromyogram. Eye movements were detected by a quartz strain gauge fixed to the eyelid. Chest and abdominal wall motions were monitored with circumthoracic and circumabdominal strain gauges, and nasal air flow temperature with thermistance. All these outputs and those of EKG and actogram were recorded polygraphically using a 10-channel polygraph (Alvar, type REEGA X). Arterial O_2 saturation (Sa_{O_2}) was continuously monitored by an ear oximeter (Hewlett-Packard, Waltham, MA) and recorded separately with a potentiometric Sefram apparatus with a calibration of 25 cm of paper for 100% Sa_{O_2} allowing an accurate measurement of the amplitude of Sa_{O_2} oscillations. EKG-Holter was also recorded throughout the night, to detect the conduction abnormalities and to measure the length of R-R intervals throughout the night.

Calibrations were performed while the subject was lying in bed, and waking data were taken just before the light was turned off. At both sea level and high altitude, the subjects were allowed to sleep as much as they liked.

Sleep recordings were visually scored by sleep physiologists, using 30-s epochs according to the usual criteria of Rechtschaffen and Kales (16). For stage 4 scoring, the minimum delta wave amplitude criterion of 75 μV was not used. For slow-wave sleep, staging was entirely based on the percentage of time occupied by delta waves (stage 4: more than 50%). The beginning of REM sleep was defined from the first simultaneous occurrence of the three main criteria: stage 1, abolition of muscle tone, and rapid eye movements. REM sleep was divided into tonic and phasic epochs according to the absence or presence of rapid eye movements.

During non-periodic breathing, the mean ventilatory rate was calculated by sampling 10 successive ventilatory cycles every 3 min during stages 1, 2, 3, and 4. During phasic REM, the ventilatory rate was calculated taking into account all ventilatory cycles occurring during one sequence of eye movements, except when the rate became too irregular and made the measurements inaccurate. During tonic REM, the ventilatory rate was easier to measure because ventilatory cycles were more regular.

Periodic breathing was characterized by the regular alternation of apnea and ventilatory activity. Apnea was of central origin, as indicated by the absence of signals in the outputs of nasal thermistance, and the thoracic and abdominal strain gauges. It was followed by 3–4 breaths (5 at the end of the night): one apnea and one ventilatory burst determined a periodic ventilatory cycle, the duration of which was defined as the cycle time. The length of the cycle time and that of its corresponding apnea were measured during the different episodes of periodic breathing.

The episodes of periodic breathing were accompanied by oscillations in Sa_{O_2}. In order to obtain a more condensed expression of Sa_{O_2} changes during the night, the average value of Sa_{O_2} was calculated over 5-min periods in the following manner: when Sa_{O_2} did not oscillate, the average value of Sa_{O_2} was directly measured on the paper recordings during 5-min periods. When Sa_{O_2} oscillated in the three periodic breathers, the maximum and minimum values of each oscillation were measured over 5-min periods and averaged. Then the mean value of Sa_{O_2} during these 5-min periods was computed by integrating Sa_{O_2} as a function of time.

The mean Sa_{O_2} computed during the oscillation episodes in the three periodic breathers enabled the time course of the mean Sa_{O_2} to be calculated for all six subjects throughout the night. As the duration of sleep was not exactly the same for all subjects, the subject with the shortest period of sleep (6 h) determined the mean. Thus, the mean arterial Sa_{O_2} was computed by averaging the data acquired for the six subjects during the first 5 h of sleep; the values of the sixth hour of sleep were obtained by averaging the last hour of sleep for each of the six subjects in order to show the slow rise of Sa_{O_2} before awakening which is present in the six subjects.

The mean heart rate was computed in the same way as the mean Sa_{O_2}. To define more precisely the time course of heart rate changes during a periodic ventilatory cycle, the mean heart rate was computed beat-by-beat during 10 sequential periodic ventilatory cycles.

The statistical comparisons were carried out using paired *t* tests since the subjects served as their own controls.

RESULTS

Sleep organization: At high altitude and sea level, the subjects stated that they slept well despite the occasional discomfort due to the ear oximeter. They fell asleep after 2–10 min in the dark (lights were switched out at about 11 p.m.). An example of a hypnogram at high altitude and sea level is shown in Fig. 1. The duration of waking time during the night varied greatly both at high altitude (range: 8–79 min) and sea level (21–77) with a mean duration of 40 min. Under both conditions, the highest value was observed in the oldest man (50 years). It is superior to the upper limit of the normal male subjects of this age range (24) and probably could be attributed to the discomfort due to the ear oximeter, since this subject did not complain about usual sleep. The data characterizing sleep organization (Table I) did not differ at high altitude and at sea level. In particular, the sleep length was not modified, the same percentages were recorded for REM and stage 4 under both conditions, and the disruptions were not more frequent at high altitude.

Non-periodic breathing at high altitude and sea level: As no significant difference was found between the ventilation rate recorded for the four sleep stages at high altitude and sea level, all values were averaged for each condition and reported as the non-REM (NREM) ventilation rate. Mean ventilation rates at high altitude vs. sea level were: Waking state: 15.9 ± 0.8/min vs. 15 ± 1.2, NREM: 15.8 ± 0.9/min vs. 14.6 ± 1.0, phasic REM: 18.8 ± 1.4/min vs. 17.1 ± 1.2, and tonic REM: 16.3 ± 0.9/min vs. 14.8 ± 1.0. The ventilation rates therefore tended to be higher at high altitude than at sea level but the difference never reached the significance level. During the phasic phase of REM, the ventilation rate was significantly higher than during the tonic phase at high altitude ($p < 0.05$) and sea level ($p < 0.01$).

Periodic breathing at high altitude: At high altitude,

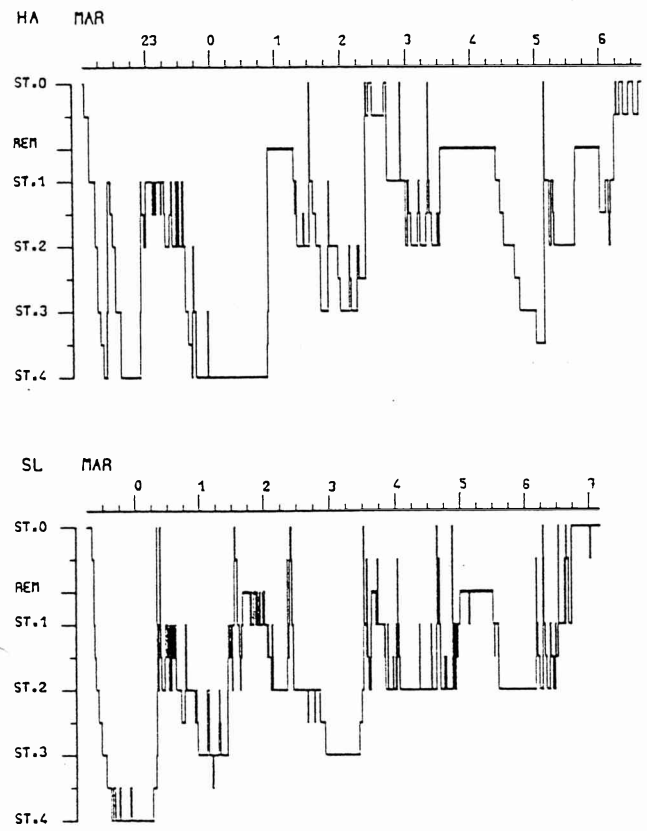

Fig. 1. Hypnogram recorded in subject HM at high altitude (HA) and sea level (SL).

three subjects, HN (aged 30, a smoker), HM and OB (both aged 38, non smokers) displayed periodic breathing during 4–5 episodes of about 1 h each. Hence, they spent 48, 43, and 60% of the total sleep period in periodic breathing, respectively. The first delayed inspiration inaugurating the first episode of periodic breathing appeared suddenly, only 1–2 min after the subject had fallen asleep. The end of an episode was as sudden as its beginning. Periodic breathing occurred during all stages of sleep except REM, and its features are reported in Table II. Apnea was definitely of central origin since ventilation arrest was observed in the three recordings of the ventilation rate. The values for cycle length and apnea were very close for the three subjects. Owing to the lengthening of the ventilatory burst, the duration of the cycle time tended to increase by 10–25% as a function of the number of periodic breathing episodes during the night (Table II), whereas the duration of apnea changed less, so that the apnea/cycle time ratio decreased towards the end of the night.

At high altitude, true periodic breathing episodes were accompanied by regular oscillations in S_aO_2 which were quite different from the erratic changes accompanying irregular ventilation without apnea, displayed by all subjects during REM (Fig. 2). The recordings of S_aO_2 in Fig. 2 show that 20-s oscillations were grouped into spindle-shaped waning and waxing bursts lasting 4–5 min. These spindles existed in the three periodic breathers, especially at the beginning of each episode of periodic breathing, but they were particularly clear and frequent in subject HN. No periodic changes in S_aO_2 were detected at sea level.

During periodic breathing, S_aO_2 oscillated between 83 and 91% in subject HM, 80 and 90% in OB, and 78 and 88% in HN, who was the smoker. The amplitude of the oscillations tended to decrease at the end of the night in relation to the lengthening of the ventilatory cycle time already mentioned (Fig. 3A, B, C). The mean calculated S_aO_2 in these three subjects formed a smooth continuation of S_aO_2 measured during non-periodic breathing. In the six subjects, the time course of the mean S_aO_2 (Fig. 3D) shows that, during the first 5 min of sleep, S_aO_2 decreased from 88.2 ± 0.6% during the waking state to 87.5 ± 0.7% ($p < 0.05$), then reached 86.0 ± 1.1% ($p < 0.01$) at the 30th min, and remained steady at that level until the end of the first hour of sleep (86.0 ± 1.2%; $p < 0.05$). In fact, all sequential 5-min values during the first hour of sleep were significantly lower from those recorded during the waking state. Thereafter, all subjects displayed changes in S_aO_2 which were not synchronous during the remaining part of the night, except for a sudden rise common to all just before awaking.

Heart rate: Fig. 4 illustrates the mean time course of the heart rate for the six subjects during the night. Resting heart rates were significantly different at high altitude and sea level (69.5 ± 2 beat/min vs. 63 ± 3.4; $p < 0.05$). Under both conditions, heart rate decreased significantly during the night, and at the end of the night fell to 61 ± 3 beat/min at high altitude vs. 55.5 ± 2 at sea level with a significance level of $p < 0.05$ and $p < 0.01$, respectively. It rose suddenly when the subjects awoke. Holter recordings showed no abnormalities except for a few ventricular premature beats in subject OB.

Ventilatory periodicity was accompanied by corresponding periodical changes in the heart rate. The time course of heart rate changes during a ventilatory cycle was characterized by a sudden slow beat. The time course was similar in the three periodic breathers (Fig. 5) whatever the mean level of heart rate. The cardiac beat with the lowest frequency occurred at the end of the ventilatory burst, as shown by the polygraphic recordings.

Diurnal arterial P_{O_2}, P_{CO_2} and pH: The resting values obtained in the three periodic breathers for P_aO_2, P_aCO_2, and pH were, respectively, in subject HM: 59.5 mm Hg, 29.3 mm Hg, 7.440; OB: 58.6, 29.5, 7.444; HN: 55.6, 28.5, 7.445, and did not differ from the three other subjects (mean: 59.4 mm Hg, 29.5 mm Hg, 7.443).

DISCUSSION

The present investigation, which examined the same six subjects at high altitude and sea level, showed that high altitude does not induce any change in sleep organization. The change in breathing pattern in three subjects does not alter the sleep organization observed for these subjects at sea level; the two subjects who did not display stage 4 at high altitude did not display it at sea level, either. The discrepancy between our finding that sleep is normal at 3,800 m and other results which report the disappearance of REM (13) or of stage 4 (17,22) or an increase in the number of disruptions (7,17,22), might be due to altitudes about 1,000 m higher in the areas

TABLE I. ELECTROENCEPHALOGRAPHIC DATA RECORDED DURING SLEEP, AT HIGH ALTITUDE (HA) AND SEA LEVEL (SL).

Characteristics of sleep	HA		SL	
	min	% of TST	min	% of TST
Time in bed (TIB)	451 ± 23		457 ± 15	
Total sleep period (TSP)	442 ± 23		445 ± 16	
Total sleep time (TST)	403 ± 28		402 ± 24	
Nb of stage changes	118 ± 10		108 ± 23	
Sleep efficiency index	0.89 ± 0.03		0.88 ± 0.04	
REM latency	114 ± 21		107 ± 12	
REM	74 ± 7	18	57 ± 8	14
Stage 1	98 ± 13	24	97 ± 17	24
Stage 2	152 ± 13	38	174 ± 12	43
Stage 3	41 ± 6	19	45 ± 8	18
Stage 4	35 ± 12		29 ± 8	

Time in bed (TIB) corresponds to the time with light turned off. Total sleep period (TSP) corresponds to the time elapsed from the first to the last electroencephalographic signs of sleep. Total sleep time (TST) was calculated as the time spent asleep (TSP less waking time during the night). The sleep efficiency index is the ratio TST/TIB. The different stages of sleep are expressed in absolute values and as percentages of TST.

where these studies were carried out. However, they are more likely to be related to the unusual physical or psychological conditions inherent in climbing.

In contrast to the intersubject homogeneity in sleep organization, a wide intersubject variability was observed in ventilatory and cardiac functions compared to sea level. Only three of the six subjects displayed long episodes of marked periodic breathing, but the features of the periodic breathing were similar for the three periodic breathers: apnea of central origin, ventilatory cycle times and apneas of the same duration, and oscillations in S_aO_2 induced by periodic breathing of the same amplitude. The three subjects were males, which is not surprising in view of the finding that testosterone favors periodic breathing during sleep (18). With regard to arterial blood gases and pH, they were similar to the three non-periodic breathers, which means that they had achieved a similar level of ventilatory adaptation to high altitude which, however, was not yet complete since the arterial pH was still slightly alkaline. If we total the apnea periods, these three subjects spent more than 1.5 h without ventilating during the night! Despite such long episodes of periodic breathing, the percentage of the different sleep stages, as well as their occurrence during the night, were unaffected.

Periodic breathing certainly never occurred during REM, because the sudden stop or reappearance of apneas and oscillations in S_aO_2 coincided with the time

TABLE II. FEATURES OF PERIODIC BREATHING AT DIFFERENT TIMES DURING THE NIGHT IN THE THREE PERIODIC BREATHERS.

Subjects	Time of the night	Nb of periodic breathing cycles analyzed	Periodic breathing cycle length (s)	Duration of apnea (s)	Apnea/ cycle ratio	Ventilation burst	
						Duration (s)	Nb of breaths
H.M. 38 yr.	22.00–24.00	119	20.9	9.5	0.45	11.4	3.3
			0.2	0.2			0.06
	1.15–2.00	50	23.4	10.2	0.44	13.2	3.7
			0.4	0.3			0.07
	4.00–5.00	44	23.0	9.6	0.42	13.4	4.0
			0.5	0.4			0.07
O.B. 38 yr.	23.20–24.20	89	19.8	8.2	0.41	11.6	3.9
			0.2	0.2			0.05
	1.35–3.10	58	23.8	10.1	0.42	13.7	3.8
			0.5	0.4			0.16
	5.40–6.15	29	24.5	8.9	0.36	15.7	4.0
			0.7	0.7			0.06
H.N. 30 yr.	23.10–24.00	64	18.2	9.3	0.51	8.9	2.9
			0.2	0.3			0.06
	3.35–4.05	21	20.1	8.8	0.44	11.3	3.2
			0.3	0.3			0.09
	4.30–5.00	38	19.1	8.5	0.45	10.6	3.1
			0.2	0.2			0.04

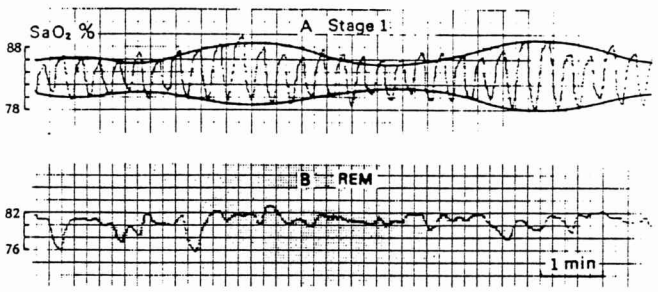

Fig. 2. Changes in O_2 saturation (S_aO_2) at high altitude in subject HN: A, During a periodic breathing episode occurring during stage 1. The groups of 20-s oscillations of S_aO_2 form spindle-shaped traces lasting about 4 min each. B, During a phase of REM. The changes in S_aO_2 display erratic oscillation.

when the subjects fell into or emerged from REM as indicated by EEG. This finding agrees with some authors (2,17,22) but not others (7). Periodic breathing has been reported not to occur during stage 4 sleep (17,22). In the present study, oscillations in S_aO_2 appeared during the first episodes of stage 4 but not during subsequent episodes. Hence, clearer conclusions concerning stage 4 at high altitude require additional investigations.

The main characteristics of the S_aO_2 periodicity were its great degree of regularity, and the occurrence of a peak value higher than that of the waking state, so that the mean calculated S_aO_2 value for periodic breathers was similar to that for non-periodic breathers. It has been suggested that periodic breathing might be beneficial in that it reduces the cost of breathing at high altitude (3), and the present results indeed show that this reduction in ventilation was not accompanied by a deterioration in mean S_aO_2. This can be explained by periodic changes in ventilation that induced opposite changes in P_aCO_2 and P_aO_2 so that the O_2 dissociation curve was alternately shifted to the left, which favors O_2 uptake by the lungs during the ventilatory bursts, and to the right which, conversely, favors O_2 release to the tissue during apneas. These findings imply that satisfactory control of ventilation persists during periodic breathing, a possibility supported by the observation that periodic breathing occurred during all sleep stages but disappeared during REM. It has been shown (9,14) that the activity of various central neuronal processes, including those controlling ventilation, are altered during REM, thereby inducing variability in breathing which is illustrated here by the erratic changes in S_aO_2 observed during REM (Fig. 1).

Although the present study is purely descriptive, some of the findings concerning, in particular, features of periodic breathing, S_aO_2 and heart rate are relevant to some of the mechanisms that determine periodic breathing during sleep at high altitude, as recently reviewed by Lahiri (11). The mean cycle time value of 20 s measured at 3,800 m fits closely the predictive relationship between cycle time and altitude given by Khoo's model (8). Moreover, the lengthening of the cycle time observed at the end of the night, which occurred concomitantly with the decrease in heart rate (Fig. 4) and, consequently, with the increase in the circulatory time lung-chemoreceptors, is consistent with the theoretical basis

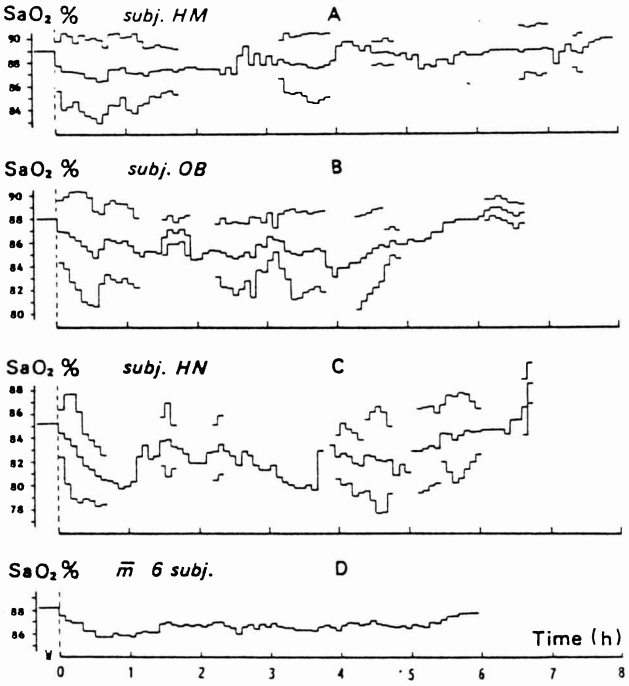

Fig. 3. A, B and C show maximum, minimum, and calculated mean values for O_2 saturation (S_aO_2) over 5-min periods during periodic breathing episodes for three male subjects. Outside these episodes, S_aO_2 did not oscillate and the mean value directly measured is reported. D shows the time course of mean S_aO_2 for all six subjects at high altitude.

of the model. However, the initiation of periodic breathing has not been considered by Khoo *et al.* (8). Our study brings some additional insight concerning what initiates the ventilatory system destabilization. The

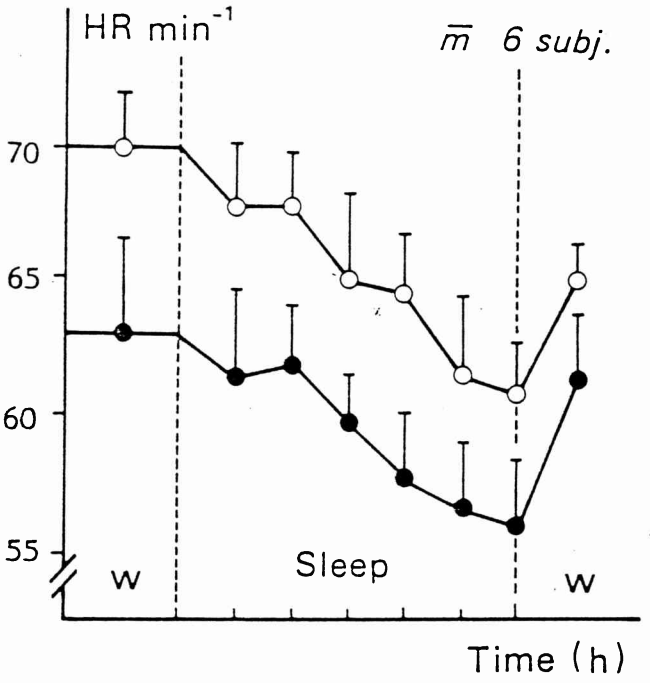

Fig. 4. Time course of the mean heart rate ±1 S.E. for the six subjects, calculated during the waking state (W) and for each hour of sleep at high altitude (○) and sea level (●).

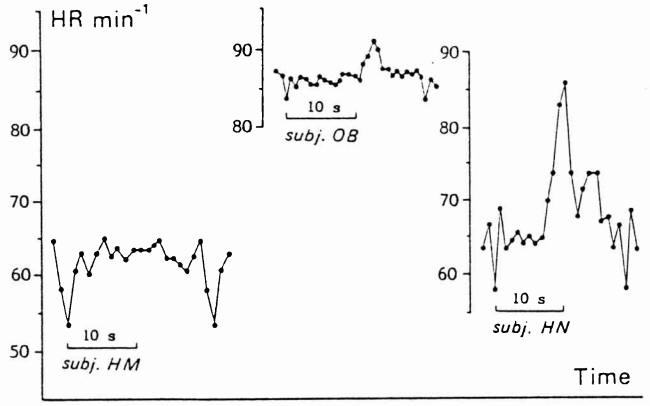

Fig. 5. Time course of heart rate during a periodic ventilatory cycle in subjects HM, OB, and HN. These are mean data calculated for 10 sequential cycles of periodic breathing during the first episode.

wide spindles formed by the 20-s oscillations in the S_aO_2 recordings (Fig. 2) show that slow oscillations were present in the ventilation of our periodic breathers during sleep at high altitude. Chapman *et al.* (5) reported that the spontaneous slow oscillations in ventilation, which are common in sleep and are also present during the waking state (12), can be converted into periodic breathing with apnea when stimuli related to wakefulness are withdrawn suddenly. Such a finding is corroborated by our subjects, who fell asleep and entered periodic breathing at the same time. With the loss of a tonic wakefulness drive, the automatic control of breathing preponderates (6,20). However, a question remains about the changes in the heart rate which accompanied periodic breathing. These ventilatory and cardiac oscillations were compared to Mayer waves described in animals (1), but the assimilation of mechanisms eliciting periodic breathing during sleep at high altitude to those inducing Mayer waves has been questioned by Preiss *et al.* (15), who have proposed a set of hypotheses into which the present study does not allow us to enter.

Our results specifically concern normal lowlanders in the course of adapting to an altitude which is not extreme, but which allows normal physical activity during daytime. They show that the organization of sleep displayed at sea level is altered neither by altitude nor by periodic breathing, whatever the sex and age of the subjects. Periodic breathing is considered a deterioration of respiratory control. However, this deterioration does not induce any sign of energetic maladaptation to high altitude since the control of periodic breathing seems to preserve lung O_2 uptake as shown by the time course of the mean value of S_aO_2 during the night, which is similar in all the subjects, whether periodic or non-periodic breathers.

Nevertheless, impairment in O_2 supply, which cannot be explored in our study, might exist: the periodic sudden lowering in heart rate, which is likely to correspond to a periodic lowering of cardiac output, might affect O_2 delivery to the cells. Another potential consequence of periodic breathing might be the increased erythropoietin production due to the repeated regular falls in P_aO_2 during several hours which might be a more potent stimulus than steady hypoxia.

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