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Blood pressure and heart rate during periodic breathing while asleep at high altitude

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Insalaco, Giuseppe, Salvatore Romano, Adriana Salvaggio, Alberto Braghiroli, Paola Lanfranchi, Vincenzo Patruno, Oreste Marrone, Maria R. Bonsignore, Claudio F. Donner, and Giovanni Bonsignore. Blood pressure and heart rate during periodic breathing while asleep at high altitude. *J Appl Physiol* 89: 947–955, 2000.—The ventilatory and arterial blood pressure (ABP) responses to isocapnic hypoxia during wakefulness progressively increased in normal subjects staying 4 wk at 5,050 m (Insalaco G, Romano S, Salvaggio A, Braghiroli A, Lanfranchi P, Patruno V, Donner CF, and Bonsignore G; *J Appl Physiol* 80: 1724–1730, 1996). In the same subjects (n = 5, age 28–34 yr) and expedition, nocturnal polysomnography with ABP and heart rate (HR) recordings were obtained during the 1st and 4th week to study the cardiovascular effects of phasic (i.e., periodic breathing-dependent) vs. tonic (i.e., acclimatization-dependent) hypoxia during sleep. Both ABP and HR fluctuated during non-rapid eye movement sleep periodic breathing. None of the subjects exhibited an ABP increase during the ventilatory phases that correlated with the lowest arterial oxygen saturation of the preceding pauses. Despite attenuation of hypoxemia, ABP and HR behaviors during sleep in the 4th wk were similar to those in the 1st wk. Because ABP during periodic breathing in the ventilatory phase increased similarly to the ABP response to progressive hypoxia during wakefulness, ABP variations during ventilatory phases may reflect ABP responsiveness to peripheral chemoreflex sensitivity rather than the absolute value of hypoxemia, suggesting a major tonic effect of hypoxia on cardiorespiratory control at high altitude.

hypobaric hypoxia; cardiovascular system; hyperventilation; respiratory pause

WE CONDUCTED EXPERIMENTS TO study cardiorespiratory interactions during wakefulness and sleep in conditions of environmental hypobaric hypoxia in a group of normal subjects during a 4-wk sojourn at 5,050 m. The main goals of our project were *1*) to study the relationship between the ventilatory and cardiovascular responses to hypoxia during wakefulness and sleep and *2*) to assess whether and how acclimatization modifies these responses.

We have already published the results of hypoxic tests obtained during wakefulness in normal subjects at sea level and at 5,050 m. Both the ventilatory and systemic pressor responses to hypoxia progressively increased from those measured at sea level vs. those measured during the 1st and 4th week at high altitude. In addition, the systemic pressor response, but not the heart rate (HR) response, was closely related to the ventilatory response to hypoxia (12).

Sleep studies showed that the major phenomenon occurring at high altitude, in relation to the state of hypocapnic hypoxia, was periodic breathing during non-rapid eye movement (NREM) sleep (1, 2, 15, 19, 24, 25). In a study of the same subjects from the wakefulness study, the amount of periodic breathing during sleep was shown to increase over 4 wk at 5,050 m, apparently in contrast to the concomitant improvement in mean arterial oxygen saturation (Sa_{O_2}) (19). These data, together with the increased ventilatory response to hypoxia found during wakefulness (12), suggested a heightened responsiveness to hypoxia caused by a 4-wk exposure to high altitude. However, the question of whether the observed increase in the amount of periodic breathing during sleep was also associated with changes in the behavior of cardiovascular variables during sleep was not addressed.

Few data are available on cardiovascular variables during sleep-induced periodic breathing in normal subjects at high altitude; HR was found to decrease during the respiratory pause of periodic breathing cycles proportionally to the Sa_{O_2} fall, but data on arterial blood pressure (ABP) behavior were not reported (16). Conversely, data on ABP and HR behavior are available for periodic breathing during sleep in subjects with con-

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gestive heart failure (6, 8, 21, 23). These studies showed ABP and HR fluctuations during the periodic breathing cycles with the lowest values found during apnea and the highest during hyperpnea. A similar pattern of ABP and HR fluctuations during periodic breathing was also described in a subject affected by central alveolar hypoventilation (3).

The pathogenetic mechanisms of cardiocirculatory oscillations during periodic breathing are not defined. ABP and HR fluctuations occurring during periodic breathing in pathological conditions were not influenced by the levels of hypoxemia (3, 6). However, patients with chronic heart failure and displaying periodic breathing during sleep are often old; increased circulatory time and abnormal autonomic function can be shown in these patients, which may influence HR and ABP behaviors. Therefore, the pattern and the pathogenetic factors of ABP and HR during periodic breathing could be partially different in normal vs. ill subjects. On one hand, in normal subjects at high altitude, the sensitivity of HR depression to desaturation during periodic breathing was reported to be related to the ventilatory response to hypoxia during wakefulness at sea level, suggesting an effect of peripheral chemoreceptors (16). On the other hand, in awake normal subjects at sea level, voluntary periodic breathing without significant Sa_{O_2} changes caused ABP fluctuations, suggesting entrainment of ABP to ventilation (14). Therefore, the role of Sa_{O_2} changes in the pathophysiology of periodic breathing-induced ABP and HR changes in normal subjects has not been well established.

This paper reports the detailed analysis of ABP and HR data during NREM sleep periodic breathing at high altitude in normal subjects and the relationship of these data with Sa_{O_2} changes, to possibly identify phasic (i.e., periodic breathing-dependent) vs. tonic (i.e., acclimatization dependent) effects of hypoxia on cardiovascular variables during sleep. Our experimental design of paired studies at two different times of acclimatization allows comparisons between different levels of hypoxemia and chemoreceptor sensitivity. Paired nocturnal and daytime data allow the correlation of ABP and HR behaviors during sleep with cardiorespiratory responses during wakefulness.

METHODS

We studied five healthy normotensive (ABP of <140/90 mmHg) Caucasian adults (3 men and 2 women) aged 28–34 yr, height of 171.2 ± 11.3 cm, and weight of 65.6 ± 18.0 kg (means ± SD). Experiments were performed at sea level and at an altitude of 5,050 m (410 Torr) in the "Pyramid," a heated, well-equipped laboratory at Lobuche, Nepal (in the Himalayas). The altitude was reached after 6 days of trekking from an altitude of 2,800 m. Sojourn at this altitude lasted 4 wk.

The protocol included a progressive isocapnic hypoxic rebreathing test obtained from awake patients in the morning and a full polysomnographic study obtained from sleeping subjects at night. Each subject underwent the full protocol three times: at sea level and during the 1st and 4th wk at high altitude, respectively. In addition, an adapted polysomnography was performed before the sea level study so that subjects could become accustomed to the instrumentation. The subjects were instructed not to ingest alcohol or caffeine on the days of the studies. Hypoxic rebreathing test methods were described in detail previously (12). The present paper reports the analysis of cardiocirculatory data obtained from the polysomnographic studies performed at altitude.

All subjects gave informed consent, and the protocol was approved by the Italian National Research Council Ev-K2 scientific committee.

Polysomnography. The following parameters were continuously monitored during nocturnal sleep: C3A2, C4A1, O1A2, and O2A1 electroencephalograms (EEGs); right and left electrooculograms; and chin electromyogram by an Oxford tape recorder (Medilog 9000). Oxyhemoglobin saturation (Sa_{O_2}) was measured by a pulse oximeter (Ohmeda Biox 3740); inspired and expired air flows were detected by nasal prongs connected with a pressure transducer (HP 47304A); abdomen and rib cage movements were detected by inductive plethysmography (Respitrace). ABP was continuously recorded by a self-calibrating finger photoplethysmograph (Finapres 2300, Ohmeda). The finger cuff was kept at heart level, and the accuracy of the measurement was controlled by an aneroid sphygmomanometer at the beginning of each study. A modified precordial lead allowed electrocardiograms to be recorded with an Oxford tape recorder (Medilog 9000). The signals were recorded on an eight-channel (HP3968A) and a four-channel (HP3964A) magnetic tape recorder. Airflow was recorded on both tape recorders to synchronize all signals.

Data analysis. ABP, abdomen and rib cage movements, airflow, and Sa_{O_2} signals were digitized at a sampling rate of 200 Hz and stored in a computer (Digital ALPHAstation 500). Sleep was staged according to standard rules (18). Results of sleep scoring were previously reported (19).

We considered periodic breathing to be the cyclic increase in the amplitude of thoracoabdominal movements, followed by a decrease and then by a respiratory pause (absence of both airflow and thoracoabdominal movements) lasting at least 4 s. In each periodic breathing cycle, we measured the duration of the ventilatory phase and the duration of the respiratory pause. We also measured, after accounting for the instrument and circulatory delay times, highest and lowest Sa_{O_2} values in each cycle as well as their difference (ΔSa_{O_2}). All systolic and diastolic ABP values were analyzed and all HR values were calculated from the pulse intervals between two consecutive heart beats. Time of occurrence of each ABP and HR measurement of a periodic breathing cycle was referenced to the beginning of the respiratory pause (*time 0*). A superimposition of all ABP and HR values according to *time 0* of all periodic breathing cycles was performed in each subject, and means and SD were evaluated for periods of 1 s.

Linear regression analysis was performed between systolic ABP and HR vs. time during both the ventilatory phase and the respiratory pause for each periodic breathing cycle.

To evaluate the amplitude of ABP variations, we took into account *1*) the value at the beginning of ventilation, *2*) the highest value, and *3*) the value at the end of the pause. The amplitude of HR variation (ΔHR) was calculated as the difference between mean HR values during ventilatory phase (HRv) and during respiratory pause (HRp).

Mean amplitudes of the ABP and HR variations associated with periodic breathing during the 1st and 4th wk at high altitude were correlated with ABP and HR responses to progressive hypoxia measured in the awake subjects from the same expedition, as previously reported (12).

Table 1. *Data relevant to periodic breathing during NREM sleep in each subject during the 1st and 4th wk of sojourn in hypoxic environmental conditions*

Subject No.	Gender		PB, %NREM sleep	Ventilatory Phase Duration, s	Respiratory Pause Duration, s	Highest Sa_{O_2}, %	Lowest Sa_{O_2}, %	ΔSa_{O_2}, %
1	M	1st wk	35.2	12.2 ± 2.0	10.3 ± 2.4	85 ± 2	81 ± 2	5.4 ± 1.4
		4th wk	75.5	11.2 ± 2.0	14.2 ± 2.2	91 ± 2	88 ± 2	2.6 ± 1.0
2	M	1st wk	85.7	8.3 ± 1.4	8.0 ± 1.4	80 ± 4	74 ± 4	6.1 ± 1.4
		4th wk	95.3	8.7 ± 1.2	10.5 ± 1.5	84 ± 3	77 ± 3	6.8 ± 1.9
3	M	1st wk	78.5	9.8 ± 1.7	11.1 ± 3.2	78 ± 3	70 ± 2	8.6 ± 3.2
		4th wk	81.8	8.9 ± 1.7	10.9 ± 2.1	86 ± 2	80 ± 2	6.3 ± 1.0
4	F	1st wk	5.6	8.1 ± 2.0	10.0 ± 1.2	73 ± 2	69 ± 3	4.6 ± 2.7
		4th wk	15.1	8.4 ± 1.9	11.6 ± 2.6	82 ± 2	79 ± 1	2.7 ± 1.4
5	F	1st wk	46.9	8.3 ± 1.8	11.5 ± 2.2	85 ± 2	81 ± 3	3.4 ± 0.8
		4th wk	82.5	8.9 ± 1.3	12.9 ± 1.8	87 ± 1	83 ± 1	4.5 ± 0.9

Values are means ± SD. M, male; F, female; NREM, non-rapid eye movement; PB, periodic breathing; Sa_{O_2}, arterial oxygen saturation; ΔSa_{O_2}, Sa_{O_2} drop during respiratory pause.

Values are reported as means ± SD. Student's *t*-test, either paired or unpaired, was used to test the differences between means, as appropriate. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed by using the StatView statistical package (version 4.5, Abacus Concepts).

RESULTS

Baseline sea level polysomnographic studies did not show any apneic activity, either central or obstructive, in any subject. At high altitude, no obstructive apneas were observed, but all subjects spent a variable amount of non-REM sleep breathing periodically (Table 1). Analysis of periodic breathing during sleep was previously published (19). Briefly, periodic breathing occurred in all NREM sleep stages, but *stages 3–4* were completely absent in four subjects during the 1st wk and in one subject during the 4th wk of the sojourn. EEG arousals occurred in 25% of the ventilatory phases of periodic breathing cycles. Both the percentage of time spent in periodic breathing and the Sa_{O_2} values during NREM sleep were higher during the 4th wk vs. the 1st wk of the sojourn.

Figure 1 shows typical ABP and Sa_{O_2} behaviors during periodic breathing in one subject. During periodic breathing cycles, both ABP and HR always fluctuated synchronously with respiratory changes, showing an increase during the ventilatory phase followed by a decrease. ABP behavior was similar in all subjects (Fig. 2). ABP increased progressively during the ventilatory phase and always reached the highest level shortly before the beginning of the respiratory pause, when it started to decrease smoothly. Noticeable, very high ABP levels were reached during the ventilatory phase in some subjects.

HR behavior exhibited a higher intersubject variability than ABP, although it was usually comparable between studies in each subject (Fig. 3). HR reached a peak before the end of the ventilatory phase and then decreased suddenly in most cases. All subjects showed a similar relationship between ABP and HR during the ventilatory phase. ABP and HR increased in a parallel fashion during most of the ventilatory phase, but HR dropped while ABP was still increasing. On average, the HR peak occurred 2.8 s (range was 2.1–3.5 s) and 2.6 s (range was 2.2–2.9 s) before the ABP peak at 1 and 4 wk at altitude, respectively.

HR during the respiratory pause showed a decreasing, increasing, or stable pattern. In fact, linear regression analysis of HR vs. time during the respiratory pause on the 614 periodic breathing pauses selected from studies during the 1st wk showed a significant HR decrease in 7.0% of periodic breathing pauses, an increase in 44.6%, and no change in 48.4%. In the 1,043 periodic breathing pauses analyzed from studies during the 4th wk, the percentages were as follows: 20.5% decreasing, 25.4% increasing, and 54.1% with no significant change. Moreover, during the respiratory

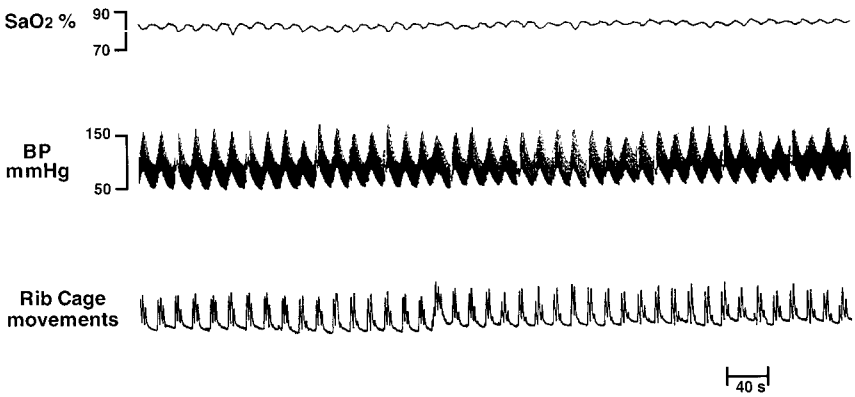

Fig. 1. Chart recording of arterial blood pressure behavior during periodic breathing in one subject. Respiratory pause is shown by the absence of rib cage movements. Sa_{O_2}, arterial oxygen saturation; BP, systemic arterial blood pressure. Note how systemic arterial blood pressure increases during the ventilatory phase and decreases during the respiratory pause.

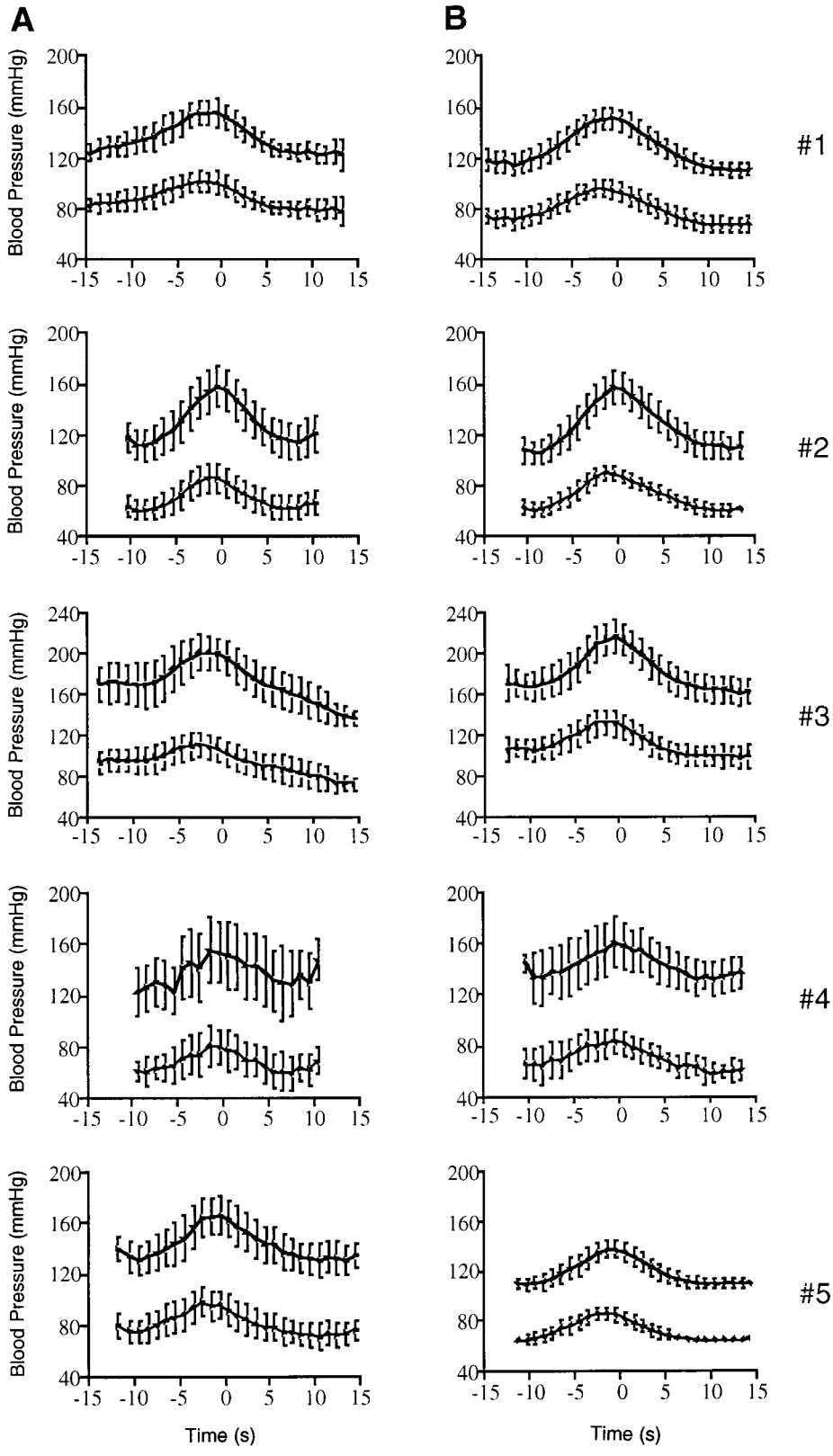

Fig. 2. Mean values of systolic and diastolic blood pressure for 1-s intervals and their temporal relationship to ventilatory phase and respiratory pause for each subject during the 1st wk (*A*) and 4th wk (*B*) of sojourn at high altitude. *Time 0* indicates the beginning of the respiratory pause. Negative time values are relevant to the ventilatory phase. Values are means ± SD; numbers at *right* indicate subject number.

pause, no significant relationships were found in any subject between ΔSa_{O_2} (the drop of Sa_{O_2} due to respiratory pause) or lowest Sa_{O_2} and the slope of HR vs. time during the pause. Mean HRp was significantly lower than HRv in all subjects at both times (Fig. 4). ΔHR was linearly correlated to HRv in four subjects: higher HRv values were followed by larger reductions in HR. No correlation between ΔHR and duration of

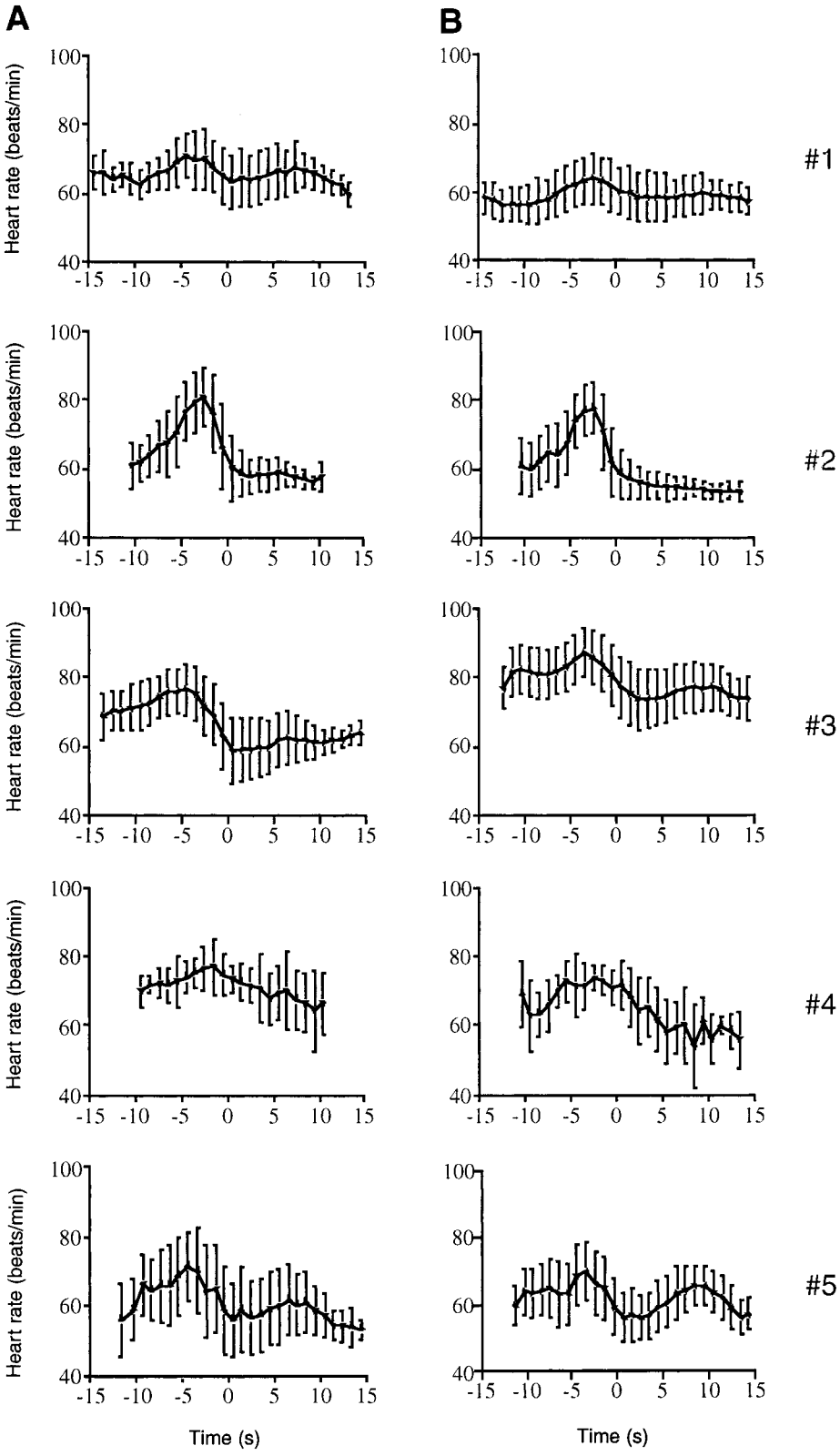

Fig. 3. Mean values of heart rate, for 1-s intervals, and their temporal relationship to ventilatory phase and respiratory pause for each subject during the 1st wk (*A*) and 4th wk (*B*) of sojourn at high altitude. *Time 0* indicates the beginning of the respiratory pause. Negative time values are relevant to the ventilatory phase. Values are means ± SD; numbers at *right* indicate subject number.

respiratory pause was found in any subject. A significant relationship between ΔHR and ΔSa_{O_2} was observed only in *subject 3* during both the 1st wk (intercept of −1.28 for beats/min, slope of −1.11 for beats/mean% $P < 0.0001$) and 4th wk (intercept of 3.52 for beats/min, slope of −1.77 for beats/min% $P < 0.0001$) of sojourn. In summary, there was no consistent relationship between ΔHR during the respiratory pause and either time or Sa_{O_2}.

Beat-by-beat systolic ABP showed a significant linear correlation with time both during the ventilatory phase

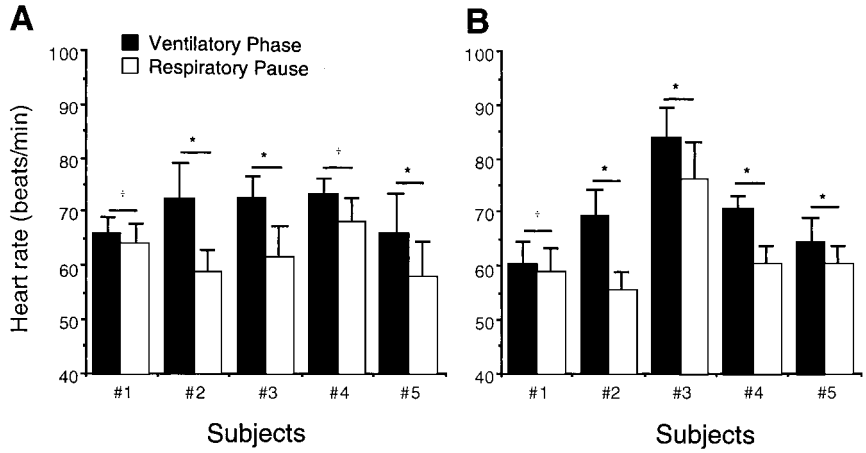

Fig. 4. Mean heart rate during ventilatory phase and respiratory pause for each subject during the 1st wk (*A*) and 4th wk (*B*) of sojourn at high altitude. Values are means ± SD. *$P < 0.0001$; †$P < 0.01$.

and the respiratory pause in each periodic breathing cycle. In all subjects, there was a high degree of cycle-to-cycle variability in the rate of change of increasing (range of 0.8–14.8 mmHg/s) and decreasing (range of −0.7 to −11.4 mmHg/s) ABP during both the 1st and 4th wk of sojourn. However, the rates of ABP decrease or ABP increase were significantly related to the respective intercept in all except one subject (i.e., the higher the ABP peak in the ventilatory phase, the faster the decrease during respiratory pause; the lower the ABP at the end of the pause, the faster the increase during the ventilatory phase).

Table 2 summarizes the relationships between the extent of ABP fall from the peak level to the end of the pause (ΔABPp) and pause duration or ΔSa_{O_2}. In all subjects, ΔABPp correlated at both times of sojourn to pause duration but inconsistently to ΔSa_{O_2}. During both the 1st and 4th wk at altitude, there was no correlation between the ABP rise from the end of the pause to the peak value during ventilation (ΔABPv) and the lowest Sa_{O_2} of the preceding pause.

Mean ΔABPv increased from the 1st to the 4th week in *subjects 1–3* ($P < 0.0001$), decreased in *subject 5* ($P < 0.0001$), and did not change in *subject 4*. In each subject, these same variations had been observed in the response to progressive hypoxia during wakefulness (12). Similar relationships were found in all subjects between mean ΔABPv and either the ventilatory or ABP response to hypoxia during wakefulness (Fig. 5).

The same analysis on the mean increase in HRv did not show any significant change from the 1st to the 4th wk in any subject and no relationship with the HR response to progressive hypoxia during wakefulness.

DISCUSSION

The aim of this study was to possibly identify phasic (i.e., periodic breathing-dependent) vs. tonic (i.e., accli-

Table 2. *Changes in systolic and diastolic blood pressure vs. arterial oxygen desaturation and time during respiratory pause*

	1st wk								4th wk							
	ΔSystolic BP vs. ΔSa_{O_2}				ΔDiastolic BP vs. ΔSa_{O_2}				ΔSytolic BP vs. ΔSa_{O_2}				ΔDiastolic BP vs. ΔSa_{O_2}			
Subject No.	Slope, mmHg/%	Intercept, mmHg	r^2	P	Slope, mmHg/%	Intercept, mmHg	r^2	P	Slope, mmHg/%	Intercept, mmHg	r^2	P	Slope, mmHg/%	Intercept, mmHg	r^2	P
1				NS				NS				NS				NS
2	2.64	29.81	0.09	<0.0001	1.36	19.13	0.08	<0.0001				NS				NS
3	3.51	16.85	0.53	<0.0001	1.86	12.61	0.40	<0.0001	3.82	21.45	0.10	<0.0001	2.27	22.27	0.06	<0.0001
4				NS	2.84	13.90	0.53	0.026				NS				NS
5				NS				NS	1.63	24.9	0.08	0.0097				NS

	1st wk								4th wk							
	ΔSystolic BP vs. t pause				ΔDiastolic BP vs. t pause				ΔSystolic BP vs. t pause				ΔDiastolic BP vs. t pause			
Subject No.	Slope, mmHg/s	Intercept, mmHg	r^2	P	Slope, mmHg/s	Intercept, mmHg	r^2	P	Slope, mmHg/s	Intercept, mmHg	r^2	P	Slope, mmHg/s	Intercept, mmHg	r^2	P
1	1.33	23.25	0.10	0.016	1.30	12.58	0.14	0.004	1.17	27.98	0.11	<0.0001	0.67	21.66	0.08	0.0003
2	5.20	4.41	0.37	<0.0001	2.74	5.57	0.34	<0.0001	3.94	8.11	0.31	<0.0001	2.35	5.15	0.28	<0.0001
3	3.55	7.55	0.54	<0.0001	1.84	8.17	0.39	<0.0001	2.67	26.11	0.23	<0.0001	2.35	10.70	0.31	<0.0001
4	4.77	−19.42	0.58	0.017	3.80	−10.97	0.50	0.032	2.50	4.02	0.28	0.016	2.63	0.71	0.25	0.026
5	1.72	20.54	0.20	0.0003	1.37	14.35	0.19	0.0004	1.76	9.44	0.40	<0.0001	1.54	6.02	0.32	<0.0001

ΔSystolic BP and Δdiastolic BP, differences between peak systolic and diastolic blood pressure and their values at the end of the pause; t pause, pause duration; NS, not significant.

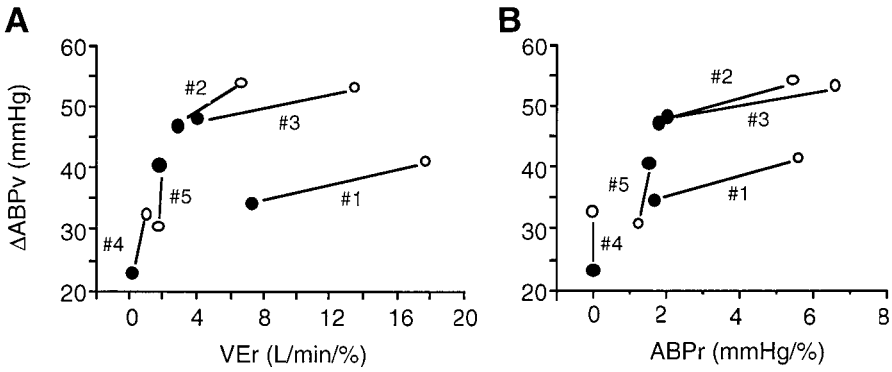

Fig. 5. Relationship between mean nocturnal increase in systolic arterial blood pressure during the ventilatory phase (ΔABPv) and the mean ventilatory response (VEr; *A*) and systolic arterial blood pressure response (ABPr; *B*) to progressive hypoxia during wakefulness in the 1st wk (●) and 4th wk (○) at high altitude.

matization-dependent) effects of hypoxia on cardiovascular variables during sleep with the use of a detailed analysis of ABP and HR data during sleep-induced periodic breathing at high altitude in normal subjects. The similar behavior of ABP and HR during sleep in the 1st and 4th wk of acclimatization, despite different levels of Sa_{O_2}, argues against a major role of phasic changes of Sa_{O_2} in periodic breathing-related cardiovascular changes. Our results suggest that chronic hypoxia may exert a tonic effect on peripheral chemoreceptors, as indicated by the increased ventilatory and ABP response to hypoxia during wakefulness (12) and by the relationship between wakefulness and sleep data.

In summary, normal subjects at high altitude are exposed to repetitive hypertensive events during periodic breathing while asleep. Our analysis of the HR and ABP swings during periodic breathing at high altitude shows that, in normal subjects, both HR and ABP fluctuate with ventilation, with an increase whenever ventilation is resumed after a respiratory pause, as it occurs during periodic breathing in various pathological conditions (3, 6, 7, 23). Both ABP and HR behaviors were highly reproducible in each subject and similar at both stages of acclimatization. ABP always changed in a continuous and gradual fashion, increasing in the ventilatory phase and decreasing during the respiratory pause. A 4-wk period of acclimatization was associated with an improvement in hypoxemia, but the amount of periodic breathing during NREM sleep increased and hypertensive events tended to increase in both frequency and severity. As for HR changes, the periodic breathing-induced HR peak always preceded the ABP peak. HR responses were different from ABP in that they usually showed brisk changes, i.e., sudden HR drops during the ventilatory phases, as well as periods with minor changes during respiratory pauses.

Several factors could influence cardiocirculatory behavior during the ventilatory phase of periodic breathing. A stimulus for the ABP increase soon after a respiratory pause could be represented by hypoxia, since it is often suggested as a main factor of ABP postapneic increase (22). Our results regarding ΔABPv do not provide a straightforward indication about the role of hypoxemia on the ABP rise during the ventilatory phase. The apparent lack, in each subject, of a correlation between ΔABPv and the lowest Sa_{O_2} in each cycle does not suggest a primary role of hypoxemia in the ABP increase during ventilatory phases. This would be in agreement with previous studies showing that ABP oscillations occurring with periodic breathing respiration during sleep were not blunted when Sa_{O_2} swings were strongly attenuated by oxygen administration (3, 6). Studies in healthy subjects also showed ABP and HR fluctuations similar to ventilatory fluctuations during voluntary normoxic periodic breathing (14). However, we cannot exclude that the narrow range of Sa_{O_2} values following pauses (Table 1) could account at least in part for the lack of significant correlations between ΔABPv and Sa_{O_2}. Hypoxia could also be involved in the increasing HR trend during the ventilatory period because it causes HR to accelerate through stretch receptor stimulation while ventilation is maintained (pulmonary inflation reflex) (4).

Another possible factor is a central influence on the cardiocirculatory and respiratory activities, as suggested by the observation of simultaneous changes in ventilation and ABP during periodic breathing in congestive heart failure or after stroke (6, 7), similar to our observations in normal subjects at high altitude. Such central influences, as previously suggested (6, 7), could be represented by arousals (5), a well-recognized cause of HR and ABP increase during sleep. However, in our subjects, we previously showed that only a minority of ventilatory phases were associated with EEG-detectable arousals during sleep-induced periodic breathing at 1 and 4 wk at altitude (19). Furthermore, Trinder et al. (21) reported that ABP augmentations after apneas were similar if apneas occurred during continuous wakefulness or during sleep, no matter if sleep was undisturbed or interrupted by EEG arousals. Therefore, it is possible that central influences other than arousal mechanisms take place. For example, central influences could be associated with sympathetic activation, which has been proven to determine postapneic blood pressure rise in several different conditions, like breath-holds or Müller maneuvers performed during wakefulness (13, 17), or obstructive sleep apneas (20).

An additional factor operating during the ventilatory phase could be the arterial baroreflex, whose activation is suggested by the sudden drop of HR in the second portion of the ventilatory phase while ABP is still increasing. Baroreflex activation may also be involved

in the modulation of the rate of rise of ABP in relationship to the ABP level immediately preceding the ventilatory phase: little arterial baroreceptor stimulation could be present at low levels of ABP, resulting in a lower braking effect and in a faster subsequent rate of rise of ABP.

Similar to the ventilatory phase, factors like hypoxemia and baroreceptor activity could influence cardiocirculatory behavior during the respiratory pause. A possible hypothesis is that hypoxia played a role in the HR decrease, since hypoxia induces bradycardia in the absence of ventilation (diving reflex) (4). However, HR and Sa_{O_2} in the periodic breathing cycles had very different time courses, which could not warrant any correlation between the level of hypoxemia and that of bradycardia. In fact, the lowest HR was only rarely recorded at the end of the respiratory pause, when the Sa_{O_2} level is lowest. A significant correlation between HR reduction in the respiratory pause and hypoxemia was found in only one of our subjects. Similarly, Masuyama et al. (16) found a significant correlation in only three of their seven normal subjects sleeping at high altitude, and Franklin et al. (6) did not find any relationship between oxygen desaturation and HR in patients with periodic breathing or previous stroke. Altogether, the available evidence does not support a major role of hypoxemia in modulating cardiovascular variables during respiratory pauses. Conversely, an important role of baroreflex activity is suggested by the inverse relationship between the ABP level reached during the ventilatory phase and the subsequent rate of ABP fall during the pause. In addition, the variable HR trend during the respiratory pause could be secondary to a variable modulation of baroreflex activity controlling the ABP fall.

The hypothesis of a tonic as opposed to a phasic effect of hypoxia in cardiovascular modulation during sleep at high altitude can be inferred on the basis of some pieces of evidence. First, as already mentioned, persistence of nocturnal ABP peaks with similar or even higher values at the 4th wk than at the 1st wk of altitude was associated with an increased ventilatory ABP response to progressive isocapnic hypoxia during wakefulness (12). Second, HR behavior during sleep with periodic breathing was unrelated to peripheral chemoreflex sensitivity similar to daytime data. Third, the amount of periodic breathing during NREM sleep increased despite improved Sa_{O_2} (19). Altogether, the close relationship between the diurnal and nocturnal data suggests a common pathogenetic mechanism responsible for our findings. We hypothesize that the cardiovascular effects of periodic breathing may remain unchanged with acclimatization because they result from the balance between the level of phasic hypoxemia during sleep and the changes in ventilatory and cardiovascular responsiveness to hypoxia: the first improves during sojourn at 5,050 m, but the second one is potentiated by chronic exposure to hypoxia, accounting for the similar ABP behavior observed in the 1st and 4th wk as well as for the apparent independence of cardiovascular changes from the Sa_{O_2} level during sleep. Finally, intermittent nocturnal hypoxia in patients with the obstructive sleep apnea syndrome was shown to be associated with a tonic increase in daytime sympathetic activity (20) and ABP response to hypoxia (9), suggesting a role of nocturnal hypoxemia in modulating the ABP response to hypoxia during both wakefulness and sleep.

Other physiological changes, in addition to the ones in hypoxic responsiveness, could take place in a month of sojourn at high altitude and deserve mention, among them an increase in hemoglobin concentration and variations in cerebral blood flow (10) and autonomic nervous system activity (11). Although, to our knowledge, the adaptations of the arterial baroreflex during sleep at high altitude have not been studied, it is likely that they occur in a 1-mo period together with changes in the vagal tone (11). Therefore, some changes in the amplitude of HR and ABP fluctuations could also have occurred as a consequence of baroreceptor gain variations. Further studies are needed to address this issue.

In summary, we have shown during sleep at high altitude in normal subjects the occurrence of periodic breathing-related repetitive hypertensive events and ABP and HR swings that are synchronous with the ventilatory cycle but are different in their pattern of fluctuations. The temporal relationship between ABP and HR variations during periodic breathing suggests the active intervention of the arterial baroreflex in cardiocirculatory control. ABP variations during ventilatory phases seem to reflect the responsiveness of ABP to peripheral chemoreflex sensitivity rather than the absolute value of hypoxemia, suggesting a major tonic effect hypoxia on cardiorespiratory control at high altitude.

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