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MECHANISMS OF HYPOXIA-INDUCED PERIODIC BREATHING DURING SLEEP IN HUMANS

BY ANNE BERSSENBRUGGE*, JEROME DEMPSEY*, CONRAD IBER†, JAMES SKATRUD† AND PAMELA WILSON†

*From *The John Rankin Laboratory of Pulmonary Medicine, Department of Preventive Medicine, University of Wisconsin, Madison, WI 53705, U.S.A. and †the William S. Middleton Memorial Veterans Administration Hospital, Madison, WI 53705, U.S.A.*

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SUMMARY

1. Ventilation was studied during wakefulness and sleep in six healthy humans in normoxia (mean barometric pressure (P_B) = 740 torr), and in hypobaric hypoxia (P_B = 455 torr).

2. Hypoxia caused hyperventilation and hypocapnic alkalosis ($\Delta P_{a,CO_2} = -7$ torr) during wakefulness and in all sleep states.

3. Periodic breathing was the predominant pattern of breathing in all stages of non-rapid eye movement (non-r.e.m.) sleep in hypoxia, but was rarely observed during wakefulness or r.e.m. sleep.

4. Periodic breathing was composed of repetitive oscillations of reproducible cycle length characterized by clusters of breaths with augmented inspiratory effort (V_T/T_I) and highly variable distribution of breath-to-breath minute ventilation ($\dot{V}_E$) and tidal volume (V_T), which alternated regularly with prolongations of the expiratory pause of the last breath of each cluster (apnea duration = 5–18 sec).

5. Hypoxia-induced periodic breathing was eliminated by: (a) acute restoration of normoxia coincident with a 3–6 torr increase in P_{a,CO_2}; and (b) augmented F_{I,CO_2} (at constant arterial oxygen saturation) which rapidly and reversibly eliminated apneas and stabilized breathing pattern with a < 2 torr increase in P_{a,CO_2}. If hypocapnia was prevented (by augmented F_{I,CO_2}) during acute induction of hypoxia in non-r.e.m. sleep, periodic breathing was also prevented.

6. We propose that the genesis of hypoxia-induced periodic breathing requires the combination of hypoxia and hypocapnia. Periodicity results from oscillations in CO_2 about a CO_2-apnea threshold whose functional expression is critically linked to sleep state.

INTRODUCTION

Periodic breathing during sleep at high altitudes has been known to occur in normal man since the 1890's (Kellogg, 1971). Several papers on this subject have appeared

Address correspondence to: Dr Anne Berssenbrugge, Department of Preventive Medicine, 504 N. Walnut Street, Madison, WI 53705, U.S.A.

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recently (Reite, Jackson, Cahoon & Weil, 1975; Weil, Kryger & Scoggen, 1978; Sutton, Houston, Mansell, McFadden, Hackett, Rigg & Powles, 1979), but quantification of periodic breathing has been confined to the analysis of oscillations in arterial oxygen saturation (S_{a,O_2}). Breath-to-breath measurements of ventilation in normal humans during wakefulness at high altitude have demonstrated the presence of both short- and long-term oscillations (Waggener, Brusil, Kronauer & Gabel, 1977; Brusil, Waggener, Kronauer & Gulesian, 1980), but analogous studies during sleep are not available. Thus, a detailed quantitative description of breath-to-breath changes in ventilation and breathing pattern during sleep in hypoxia has yet to be made. Further, little is known concerning the specific effects of individual sleep stage on periodic breathing.

The mechanism of hypoxia-induced periodic breathing is also unclear. Implicit in the ventilatory response to hypoxia is enhanced peripheral chemoreceptor feed-back resulting from hypoxia itself, and decreased central chemoreceptor feed-back resulting from the attendant hyperventilation and hypocapnic alkalosis. Based on control system theory, which predicts oscillatory behaviour under conditions of negative feed-back instability, a number of models have been proposed to explain the occurrence of periodic breathing secondary to instability in the chemical feed-back control of ventilation (Millhorn & Guyton, 1965; Cherniack & Longobardo, 1973; Khoo, Kronauer, Strohl & Slutsky, 1982).

The objectives of the present studies were to quantitate the effect of hypoxia on ventilation in each sleep state, with particular emphasis on the stability of breathing, and to assess the relative contributions of hypoxia and hypocapnic alkalosis to the genesis of hypoxia-induced periodic breathing.

METHODS

Seven healthy males (ages 22–34 yr) native to sea-level and with normal cardiopulmonary history and function participated in this study. Informed consent was obtained. All sleep studies were conducted during normal sleep times (between 10 p.m. and 7 a.m.). Subjects were allowed to sleep no more than 4 hr on the night preceding the sleep study. Sea level sleep studies for each subject were conducted over two consecutive nights. The first night allowed the subject to become accustomed to sleeping with monitoring equipment in the laboratory environment, and only data collected from the second night were analysed.

Protocols

Protocol 1: control normoxia studies. Six subjects were studied during wakefulness and sleep near sea level (mean barometric pressure (P_B) = 740 torr). Awake measurements were collected over a period of 30–60 min just prior to the sleep portion of the study. Subjects were then allowed to fall asleep and were monitored continuously over the next 8 hr. Subjects were studied awake and asleep predominantly during air breathing. Intermittently, oxygen and variable mixtures of CO_2-enriched air were administered for 10–15 min periods. All gas mixtures including air as the baseline condition were delivered via nasal cannulae at a flow rate of 5 l./min.

Protocol 2: hypobaric hypoxia studies. The effect of hypobaric hypoxia on ventilation during wakefulness and sleep was studied in the same six subjects using an altitude chamber in which barometric pressure was maintained at 455 torr (equivalent to 4300 m altitude). Subjects were brought to altitude thirty minutes before data collection, and Protocol 1 was repeated with the following modifications: (a) during administration of CO_2, additional nitrogen was bled into the inspired gas mixture to maintain constant mean S_{a,O_2}; and (b) awake measurements were also collected in the morning, following the sleep portion of the study, at 7–9 hr hypoxic exposure.

Protocol 3: acute hypoxia studies. The effect of acute hypocapnic and isocapnic hypoxia on ventilation was studied in one additional subject using a ventilation hood canopy, as described by Sorkin, Rapoport, Falk & Goldring (1980), which allowed precise control of inspired gas mixtures. Compressed air was used as the flushing gas, and was delivered at a flow rate of greater than 70 l./min to prevent accumulation of CO_2 within the hood. Control normoxic values of ventilation were collected while the canopy was flushed with compressed air. Acute hypoxia was induced by adding 100% N_2 to the flushing gas in amounts sufficient to lower F_{I,O_2} to approximately 12·5%. Isocapnic hypoxia was induced by bleeding in sufficient CO_2 in addition to nitrogen to prevent end-tidal CO_2 (P_{ET,CO_2}) from changing from mean normoxic levels. When CO_2 was either added to or removed from the inspirate during a background of hypoxia, appropriate adjustments of F_{I,N_2} were made to maintain mean S_{a,O_2} levels constant.

Measurements

All calibrations and measurements were performed with the subject in the supine position.

Sleep stage was monitored by recording electroencephalograms (e.e.g.), electro-oculograms (e.o.g.), and electromyograms (e.m.g.) on a polygraph (Grass model 7-D). Sleep stages were classified by the criteria of Rechtschaffen & Kales (1968) and were grouped as follows: wakefulness, Stage I, Stage II, Stages III and IV together, and rapid eye movement (r.e.m.) sleep.

S_{a,O_2} was monitored continuously by an ear oximeter (Hewlett-Packard, model 47201A). Ventilation was monitored by inductance plethysmography (Ambulatory Monitoring, Inc., Respitrace). The output from the respitrace was calibrated by the isovolume technique of Konno & Mead (1967) in conjunction with a spirometer (Ohio Medical, model 800). The sum of the abdominal and rib cage measurements correlated well with the tidal volume measured on the spirometer ($r = 0{\cdot}99 \pm 0{\cdot}01$, mean ± S.D.). Similarly, there was good correlation between the respitrace and the spirometer for individual timing parameters. S_{a,O_2} and ventilation were recorded on a tape recorder (Hewlett Packard, Model 3964A) for subsequent computer analysis.

In Protocols 1 and 2, arterialized venous blood samples were collected over a one-minute period from a catheter placed in a vein on the dorsum of the heated hand (Forster, Dempsey, Thomson, Vidruk & doPico, 1972). The samples were analysed at 37 °C for pH and P_{a,CO_2} with calibrated blood gas electrodes (Radiometer, BMS-3), which were frequently checked with tonometered blood as described previously (Bateman, Musch, Smith & Dempsey, 1980). Samples were generally drawn in pairs and the mean number of blood samples drawn in each sleep study was 10 ± 3 samples during wakefulness and 18 ± 6 samples during sleep. In Protocol 3, end-tidal gases were continuously sampled from nasal prongs (Gothe, Goldman, Cherniack & Mantey, 1982) and analysed for CO_2 and O_2 (Beckman LB-2 and Beckman OM-11).

Data analysis

All ventilatory measurements were quantitated according to sleep stage. Only sections in which the sleep stage was constant for greater than three minutes were analysed to avoid the effect of fluctuating sleep state. Stage I was excluded from the results due to its transient nature. Ventilatory measurements from Stage II, Stage III and Stage IV were subsequently combined to represent non-r.e.m. sleep since no differences were found among these stages.

A program was devised on a digital computer (Digital Equipment Co., Model P.D.P. 1134A) to analyse the ear oximeter and Respitrace signals. S_{a,O_2} was measured at 1 sec intervals and the mean, standard deviation, and maximal and minimal values were determined. Ventilation was analysed for mean values of minute ventilation ($\dot{V}_E$) and frequency (f), and breath-to-breath measurements of $\dot{V}_E$, tidal volume (V_T), inspiratory duration (T_I), expiratory duration (T_E), the duration of the expiratory pause, total breath cycle time (T_{TOT}, measured from the onset of inspiration to the onset of the subsequent inspiration), mean inspiratory flow (V_T/T_I), and 'duty cycle' (T_I/T_{TOT}). The stability of breathing pattern was assessed by: (a) the number and length of expiratory pauses greater than or equal to five seconds in duration (which we defined as apnea); (b) the cycle length of periodic oscillations; and (c) the variation about the mean levels of individual volume and timing components of the breath expressed numerically by the coefficient of variation (i.e., standard deviation/mean × 100).

Statistical differences between mean values for each subject and for the group were determined by paired and unpaired t tests. Differences were accepted as significant if $P < 0{\cdot}05$.

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RESULTS

Sleep in normoxia and in hypoxia

Total sleep time during normoxia was $3{\cdot}5 \pm 0{\cdot}4$ hr (mean $\pm$ S.E. of mean), and the proportion of time spent in light sleep (Stages I and II), slow wave sleep (Stages III and IV), and r.e.m. sleep were 61, 25, and 15%, respectively. As compared to normoxia, during hypoxia total sleep time was unchanged ($3{\cdot}7 \pm 0{\cdot}5$ hr). However, the percentage of time spent in light sleep was increased to 83%, while that spent in slow-wave sleep and r.e.m. sleep were decreased to 13 and 4%, respectively. During hypoxia, symptoms of acute mountain sickness were mild and confined to fatigue and headache.

Sleep stage effects on ventilation during normoxia and during hypoxia

Normoxia. The effects of sleep stage on breathing in normoxia are summarized for all subjects in Table 1A. During non-r.e.m. sleep, $\dot{V}_E$ decreased, P_{a,CO_2} increased ($+2{\cdot}2$ to $+5{\cdot}2$ torr), arterial pH fell, and mean S_{a,O_2} was unchanged (range 96–98%) as compared to wakefulness. This relative hypoventilation during non-r.e.m. sleep occurred in the absence of any consistent change in V_T or breathing cycle timing. During r.e.m. sleep, further significant changes in the magnitude of any of these variables were not observed.

Examples of breathing patterns for non-r.e.m. and r.e.m. sleep during normoxia are illustrated in Fig. 1; breath-to-breath variability is summarized for all subjects by the mean intrasubject coefficients of variation (c.v.) listed in Table 1A. The greatest breath-to-breath variability occurred during r.e.m. sleep in which breathing pattern was characterized by random erratic variations in both the volume and timing of breaths (see Fig. 1). During non-r.e.m. sleep, breathing pattern was characterized by consistent tidal excursions and mean intrasubject c.v. values of V_T, T_I, and T_E which were $\leqslant \pm 19\%$ (Table 1A). During r.e.m. sleep, these coefficients of variation were increased substantially. In normoxia, expiratory pauses ($\geqslant 5$ sec, i.e. apneas) were absent during both wakefulness and sleep in the majority of subjects studied,

Hypoxia. The effect of sleep on breathing during hypoxia for all subjects is summarized in Table 1B. Awake measurements were obtained in all subjects in the morning following the sleep portion of the hypoxia study (7–9 hr hypoxia). As compared to normoxic wakefulness, mean S_{a,O_2} was decreased, $\dot{V}_E$ was increased, P_{a,CO_2} was decreased to $33{\cdot}4 \pm 1{\cdot}0$ torr, and pH_a was increased to $7{\cdot}46 \pm 0{\cdot}008$. In four subjects, arterialized blood was also collected during wakefulness prior to the sleep portion of the study at 0·5–1·5 hr of hypoxia; at this time P_{a,CO_2} was $37{\cdot}7 \pm 1{\cdot}0$ torr and pH_a was $7{\cdot}44 \pm 0{\cdot}004$. These comparisons of pre- and post-sleep awake show that ventilatory acclimatization to hypoxia was occurring during sleep over the course of the night.

During both non-r.e.m. and r.e.m. sleep in hypoxia, $\dot{V}_E$ and S_{a,O_2} were decreased and P_{a,CO_2} was increased as compared to wakefulness in hypoxia; and hyperventilation and respiratory alkalosis were found relative to sleep in normoxia (Table 1). The most striking effect of hypoxia during sleep was the occurrence of periodic breathing during all stages of non-r.e.m. sleep in all subjects; an example of which is illustrated in Fig. 2 (upper panel). Periodic breathing was characterized by repeated clusters of two to five

TABLE 1. The effect of sleep stage on ventilation in normoxia and hypoxia

		Breath-to-breath measurements									Expiratory pause (≥ 5 sec)	
		$\dot{V}_E$ (l./min)	f (no./min)	V_T (l.)	V_T/T_I (l./sec)	T_I (sec)	T_E (sec)	P_{a,CO_2} (torr)	pH	S_{a,O_2} (%)	Length (sec)	no./hr
	n	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}$	$\bar{x}\pm$S.E.*
A. Normoxia												
awake	5	5·9±0·4	14·9±1·4	0·41±20	0·30±16	1·4±17	2·8±20	40·7±1·2	7·40±0·01	98±0·3	—	0
non-r.e.m.‡	6	5·2±0·4	13·4±0·9	0·39±19	0·26±21	1·6±15	3·0±19	44·4±1·2	7·37±0·01	97±0·3	8·3	1±1
r.e.m.	4	4·8±0·5	12·9±1·4	0·38±35	0·27±29	1·5±28	3·3±42	43·4±0·7	7·36±0·01	97±0·1	9·0	26±20
B. Hypoxia												
awake	5	8·6±1·0	14·3±1·9	0·61±27	0·44±20	1·4±22	3·1±33	33·4±1·0	7·46±0·01	78±1·2	7·2	27±19
non-r.e.m.‡	6	7·1±0·2	9·3±1·2	0·83±37	0·53±30	1·5±20	5·6±88	36·7±1·0	7·44±0·01	66±2·0	10·8	145±15
r.e.m.	4	6·9±0·4	15·4±0·6	0·45±31	0·35±22	1·3±22	2·6±49	37·1±1·6	7·42±0·01	60±1·1	9·6	6±5

* $\bar{x}\pm$S.E. = grand mean ± intersubject standard error of the mean.

† $\bar{x}\pm$c.v.% = grand mean ± grand mean of intrasubject coefficients of variation.

‡ non-r.e.m. values represent averaged all night measurements from Stages II, III & IV non-r.e.m. sleep. (Values listed for each condition are based on a mean of 80 min of ventilatory analyses (range 30–173 min)).

TABLE 2. The effect of O_2 administration on ventilation during non-r.e.m. sleep in normoxia and hypoxia

	Breath-to-breath measurements									Expiratory pause (≥ 5 sec)	
	$\dot{V}_E$ (l./min)	f (no./min)	V_T (l.)	V_T/T_I (l./sec)	T_I (sec)	T_E (sec)	P_{a,CO_2} (torr)	pH	S_{a,O_2} (%)	Length (sec)	no./hr
	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$c.v.%†	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}\pm$S.E.*	$\bar{x}$	$\bar{x}\pm$S.E.*
A. Normoxia‡	5·1±0·5	12·4±1·2	0·41±20	0·27±20	1·6±15	3·4±23	42·7±1·0	7·36±0·01	97±0·2	11·0	6±4
Normoxia + O_2§	5·1±0·5	12·9±1·2	0·40±20	0·25±22	1·7±18	3·1±17	43·3±1·0	7·35±0·01	99±0·0	—	0
B. Hypoxia ‡	6·9±0·3	8·8±0·6	0·81±35	0·60±28	1·3±18	5·7±87	36·6±0·7	7·44±0·01	63±1·9	10·1	183±9
Hypoxia + O_2‖	5·6±0·4	14·5±0·4	0·39±18	0·31±17	1·3±16	2·9±17	40·8±0·8	7·40±0·01	97±04	—	0

* $\bar{x}\pm$S.E. = grand mean ± between trial standard error of the mean.

† $\bar{x}\pm$c.v.% = grand mean ± grand mean of within trial coefficients of variation.

‡ Means of measurements taken within 1·5 hr of each oxygen administration.

§ Means from five trials of increased F_{I,O_2} in four subjects.

‖ Means from eight trials of increased F_{I,O_2} in five subjects.

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breaths, interspersed with regularly spaced expiratory pauses and associated with large swings in S_{a,O_2}. The over-all cycle length of these periodic breathing episodes was $21{\cdot}2 \pm 1{\cdot}8$ sec (range 17–28 sec) and was highly reproducible within each subject throughout non-r.e.m. sleep (mean intrasubject c.v. = $\pm 7\%$). The proportion of time spent in expiratory pause accounted for almost half of this cycle length and the mean

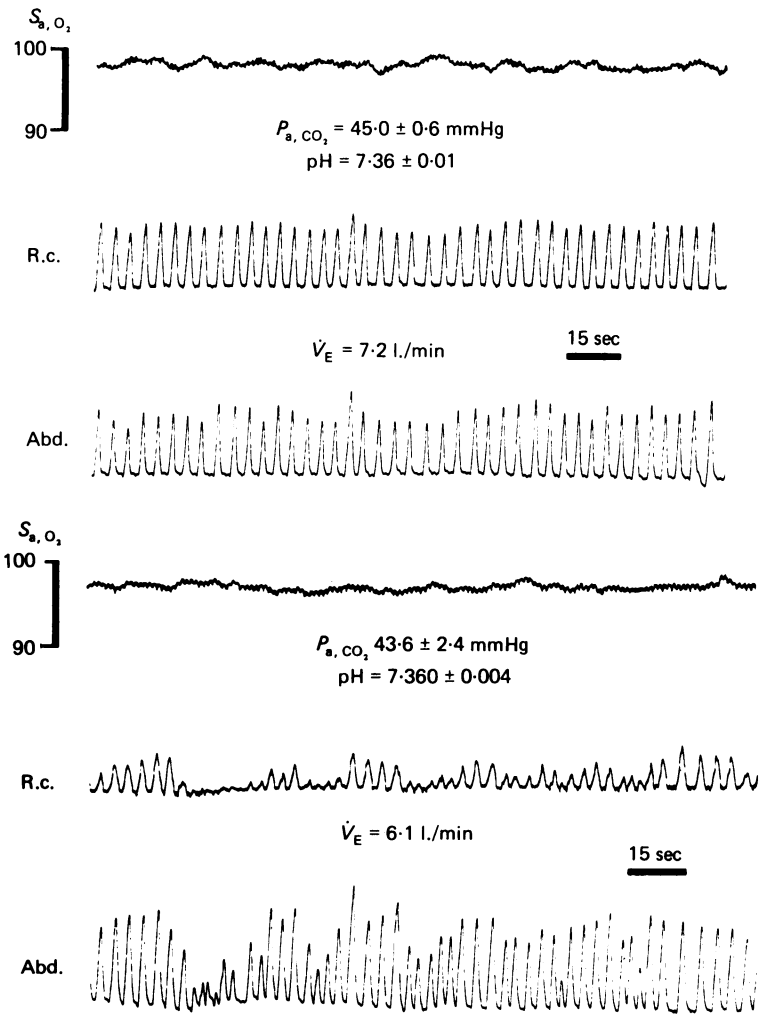

Fig. 1. Representative tracings of S_{a,O_2}, and rib cage (R.c.) and abdominal (Abd.) movements taken from one subject during sleep in normoxia. Upper panel, non-r.e.m. sleep; Lower panel, r.e.m. sleep.

number of pauses per hour was 145 ± 15 with an average duration of 10·8 sec (range 5–18 sec) (Table 1B). During hypoxic non-r.e.m. sleep, V_T, V_T/T_I, and T_E were increased, f and T_I/T_{TOT} were decreased, and T_I was unchanged relative to normoxic non-r.e.m. sleep. Similar changes of smaller magnitude were also found when comparing hypoxia-induced periodic breathing to a regular pattern of breathing

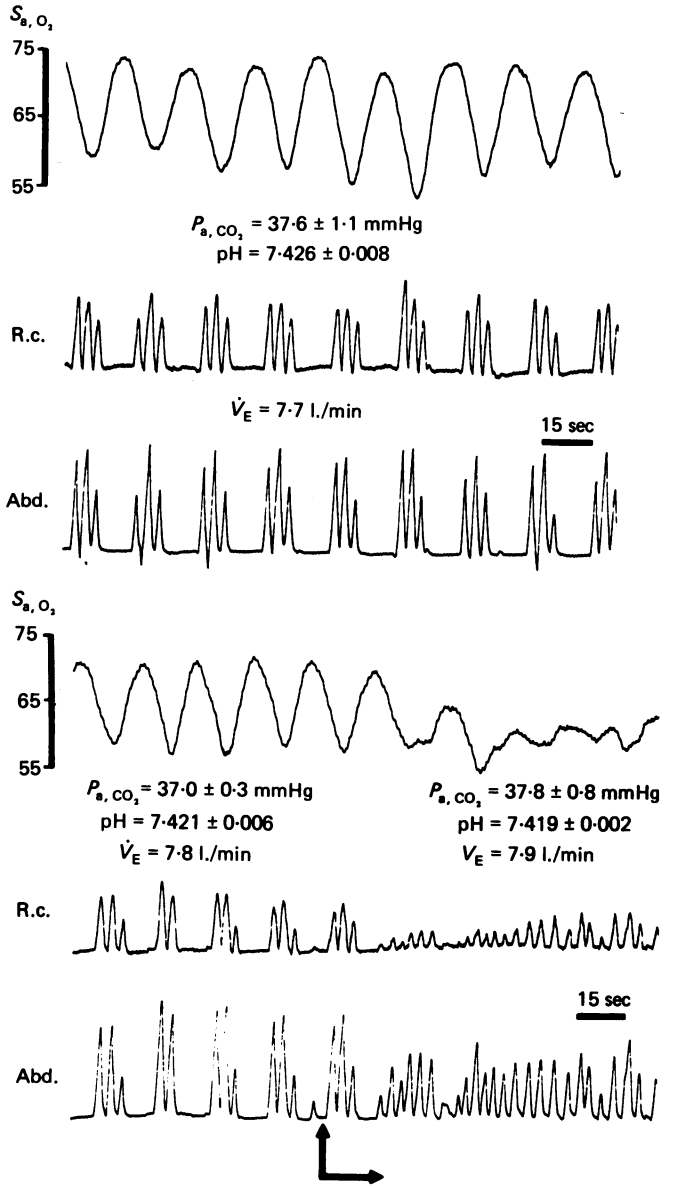

Fig. 2. Representative tracings of S_{a,O_2}, and rib cage (R.c.) and abdominal (Abd.) movements during sleep in hypoxia taken from the same subject shown in Fig. 1. Upper panel, non-r.e.m. sleep; Lower panel, spontaneous transition from non-r.e.m. to r.e.m. sleep (at arrow).

during wakefulness in hypoxia. Breath-to-breath variability increased during hypoxic non-r.e.m. sleep, reflecting the periodic pattern of breathing. Thus, the mean intrasubject c.v.s for V_T, T_I, and T_E were increased during hypoxic non-r.e.m. sleep relative to normoxic non-r.e.m. values (Table 1).

During wakefulness in hypoxia, periodic breathing was observed in only one

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subject. This subject accounted for 65% of the total number of expiratory pauses found in all subjects during wakefulness (see Table 1B). During the transition from wakefulness to non-r.e.m. sleep in hypoxia, the development of frank periodic breathing with apneas was generally preceded by initially mild oscillations in V_T which progressively increased in magnitude. The first apnea occurred following a sequence of relatively large V_Ts, at which point periodic breathing and apneas were usually self-sustaining.

R.e.m. sleep in hypoxia was not accompanied by periodic breathing in any of the four subjects analysed. Fig. 2 (lower panel) illustrates the stabilization of breathing pattern during a spontaneous transition from non-r.e.m. to r.e.m. sleep. Relative to non-r.e.m. sleep in hypoxia, during r.e.m. sleep: (a) P_{a,CO_2}, pH and $\dot{V}_E$ were unchanged; (b) f and T_I/T_{TOT} increased, and V_T, V_T/T_I and S_{a,O_2} decreased and (c) expiratory pauses were virtually eliminated (mean no./hr = 6 ± 5) (Table 1B). The random variations in the volume and timing of breaths typical of breathing pattern during normoxic r.e.m. sleep persisted in hypoxia (Fig. 1 *vs.* Fig. 2) and mean intrasubject c.v.s. for V_T, V_T/T_I, T_I and T_E were unchanged (Table 1). Thus, the occurrence of periodic breathing during hypoxia was confined to non-r.e.m. sleep, although equivalent levels of hypoxia-induced hyperventilation and respiratory alkalosis occurred in all sleep states.

Effects of oxygen administration during sleep

Oxygen was administered via nasal catheter during non-r.e.m. sleep in normoxia and in hypoxia. An example is shown in Fig. 3, and mean steady-state data are summarized in Table 2. In normoxia augmented F_{I,O_2} increased mean S_{a,O_2} to 99%, but had no major effect on either the magnitude or the variability of any of the respiratory variables (Table 2A).

During the periodic breathing of non-r.e.m. sleep in hypoxia, augmenting F_{I,O_2} caused a gradual increase in S_{a,O_2} (time to 90% S_{a,O_2} = 1·2–4·0 min), and eliminated periodic breathing (Fig. 3). This transition from a periodic to a regular pattern of breathing was generally characterized by (a) a progressive drop in $\dot{V}_E$ during breathing clusters; (b) an initial prolongation of the duration of the expiratory pause, followed by shortening and disappearance when $S_{a,O_2} \geqslant 91\%$; and (c) elimination of cyclical oscillations in V_T which occurred within 0·3–2·0 min of the cessation of apneas. Steady-state values obtained 5 min following the onset of increased F_{I,O_2} are shown in Table 2B): S_{a,O_2} increased from 63 to 97%, $\dot{V}_E$ decreased, P_{a,O_2} increased (+2·7 to +6·3 torr) and pH_a decreased. The addition of O_2 during periodic breathing altered breathing pattern both by decreasing inspiratory 'effort' and by changing cycle timing secondary to the removal of apneas. Thus V_T, V_T/T_I, and T_E decreased, f and T_I/T_{TOT} increased, and T_I was unchanged. The stabilizing effects of increased F_{I,O_2} on breath-to-breath variability during hypoxia are reflected by the reduced mean intrasubject c.v.s listed in Table 2B.

Effects of CO_2 administration during sleep

To examine the role of hypocapnic alkalosis on the occurrence of periodic breathing in hypoxia, we measured the effect of increased F_{I,CO_2} at constant S_{a,O_2} on breathing pattern in four subjects both in normoxia and in hypoxia. Mean steady-state data

for all trials of CO_2 administration are summarized in Table 3, and examples in hypoxic non-r.e.m. sleep are illustrated in Fig. 4.

During normoxic non-r.e.m. sleep, augmenting F_{I,CO_2} increased P_{a,CO_2} (+0·2 to +1·5 torr), decreased pH_a, and increased $\dot{V}_E$, (Table 3A). The major effect of CO_2 on breathing pattern was confined to increases in V_T and V_T/T_I whereas parameters of cycle timing (f, T_I, T_E, and T_I/T_{TOT}) did not change, and mean intrasubject c.v.s for V_T, V_T/T_I, and T_I were all reduced.

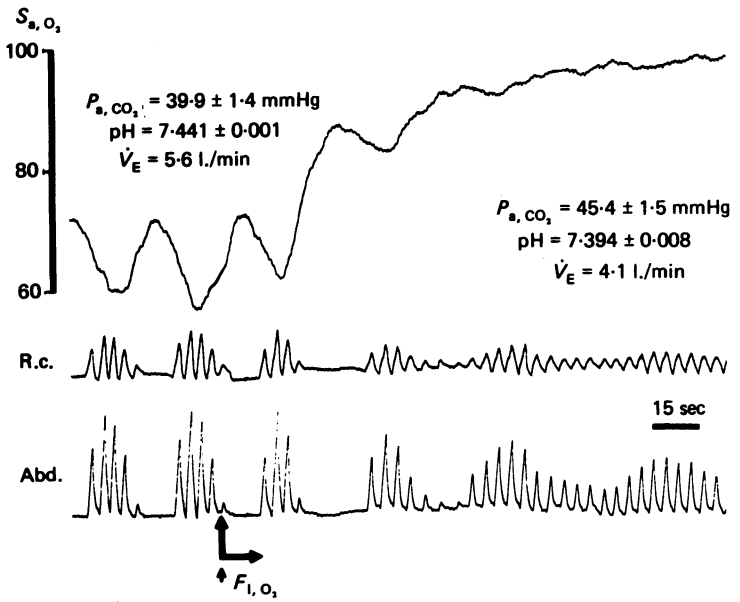

Fig. 3. Representative tracings of S_{a,O_2} and rib cage (R.c.) and abdominal (Abd.) movements during acute restoration of normoxia in hypoxic non-r.e.m. sleep. F_{I,O_2} was increased at arrow.

During hypoxic non-r.e.m. sleep, CO_2 was administered while mean S_{a,O_2} was held constant. Augmented F_{I,CO_2} increased P_{a,CO_2} (+0·3 to +2·8 torr), decreased pH_a, and increased $\dot{V}_E$, while S_{a,O_2} was unchanged (Table 3B). Thus hypocapnic alkalosis persisted in these subjects during increased F_{I,CO_2}, relative to their normoxic non-r.e.m. values (Table 3B *vs.* Table 1A). The most striking effect of CO_2 on breathing pattern in hypoxia was the removal of apneas and stabilization of breathing pattern. Apneas were eliminated within 15 sec of the onset of CO_2 administration, and cyclic oscillations in V_T were eliminated within 1–2 min (Fig. 4, upper panel). Conversely, apneas returned within 30 sec of the termination of CO_2 administration (Fig. 4, lower panel). When augmented F_{I,CO_2} converted breathing from a periodic to a stable pattern in hypoxia, T_E decreased; f and T_I/T_{TOT} increased; and T_I, V_T/T_I, and V_T were unchanged (Table 3B). The stabilizing effect of CO_2 on breath-to-breath variability in hypoxia is summarized by the mean intrasubject c.v.s for V_T, V_T/T_I, T_I, and T_E which were all decreased (Table 3B).

The effect of increased F_{I,CO_2} during r.e.m. sleep in normoxia was measured in three trials in three subjects, and the mean data are summarized in Table 3C. Analogous

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TABLE 3. The effect of CO_2 administration on ventilation during sleep in normoxia and hypoxia

			Breath-to-breath measurements						Expiratory pause (≥ 5 sec)	
	$\dot{V}_E$ (l./min) $\bar{x}\pm$S.E.*	f (no./min) $\bar{x}\pm$S.E.*	V_T (l.) $\bar{x}\pm$C.V.%†	V_T/T_I (l./sec) $\bar{x}\pm$C.V.%†	T_I (sec) $\bar{x}\pm$C.V.%†	T_E (sec) $\bar{x}\pm$C.V.%†	P_{a,CO_2} (torr) $\bar{x}\pm$S.E.*	pH $\bar{x}\pm$S.E.*	S_{a,O_2} (%) $\bar{x}\pm$S.E.*	Length (sec) $\bar{x}$	no./hr $\bar{x}\pm$S.E.*
Non-r.e.m.											
A. Normoxia‡	5·1 ± 0·6	12·7 ± 1·2	0·40 ± 23	0·27 ± 21	1·7 ± 16	3·3 ± 18	45·0 ± 0·7	7·36 ± 0·01	97 ± 0·2	6·8	1 ± 1
Normoxia + CO_2§	7·6 ± 0·9	12·2 ± 1·2	0·62 ± 13	0·38 ± 12	1·7 ± 12	3·4 ± 15	46·0 ± 0·8	7·35 ± 0·01	97 ± 0·2	8·4	2 ± 2
B. Hypoxia‡	7·1 ± 0·2	9·7 ± 0·5	0·75 ± 37	0·53 ± 27	1·4 ± 21	4·9 ± 93	36·7 ± 0·7	7·44 ± 0·01	67 ± 0·3	9·5	163 ± 9
Hypoxia + CO_2‖	11·2 ± 0·5	16·2 ± 0·8	0·71 ± 14	0·49 ± 13	1·5 ± 12	2·3 ± 18	38·1 ± 0·7	7·42 ± 0·01	69 ± 1·8	—	0
R.e.m.											
C. Normoxia‡	5·1 ± 0·6	12·6 ± 1·9	0·40 ± 36	0·30 ± 28	1·4 ± 28	3·5 ± 47	43·6 ± 0·9	7·36 ± 0·01	97 ± 0·2	9·0	35 ± 25
Normoxia + CO_2¶	7·9 ± 1·1	14·5 ± 2·4	0·56 ± 31	0·36 ± 29	1·6 ± 20	2·8 ± 44	45·3 ± 1·0	7·34 ± 0·01	97 ± 0·1	7·1	23 ± 19

* $\bar{x}\pm$S.E. = grand mean ± between trial standard error of the mean.
† $\bar{x}\pm$C.V.% = grand mean ± grand mean of within trial coefficients of variation.
‡ Means of measurements taken within 30 min of each CO_2 administration.
§ Means from six trials of CO_2 in three subjects.
‖ Means from nine trials of CO_2 in four subjects.
¶ Means from three trials of CO_2 in three subjects.

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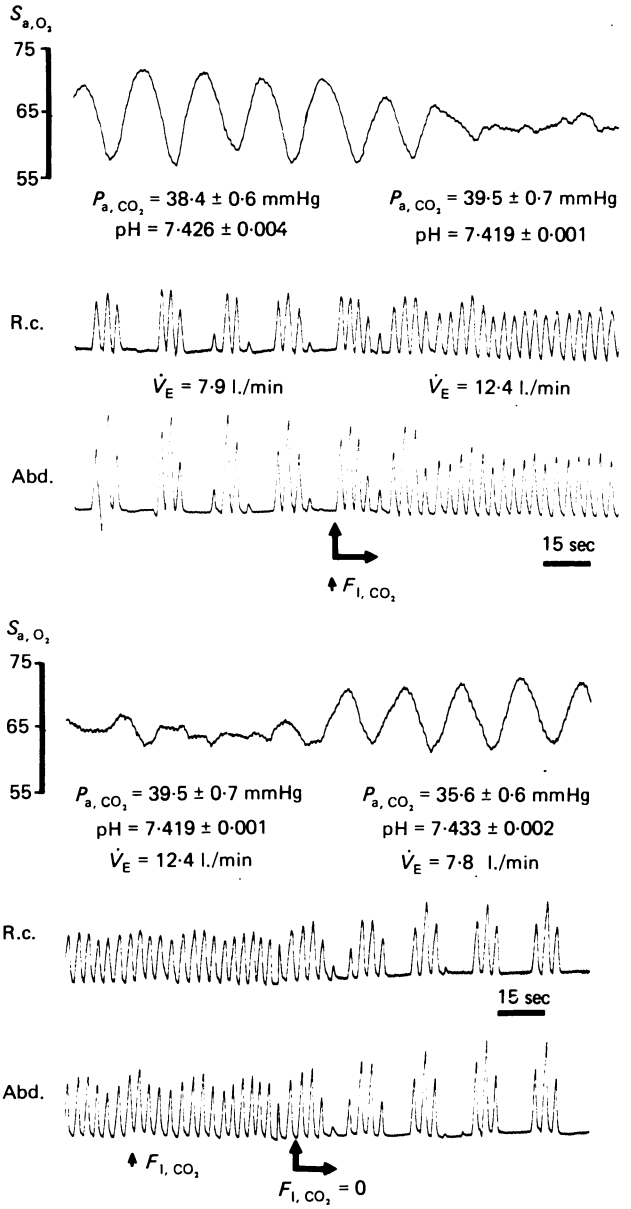

Fig. 4. Representative tracings of S_{a,O_2}, and rib cage (R.c.) and abdominal (Abd.) movements taken from one subject during administration of CO_2 in hypoxic non-r.e.m. sleep. Upper panel, CO_2 is added at arrow; Lower panel, CO_2 is removed at arrow.

data in hypoxic r.e.m. sleep was not obtained. Addition of CO_2 during r.e.m. sleep increased P_{a,CO_2} (+1·3 to +2·4 torr), decreased pH_a, and increased $\dot{V}_E$. The increase in $\dot{V}_E$ was accompanied by an increase in T_I/T_{TOT}, however, consistent changes in V_T, V_T/T_I, T_I, T_E or f were not found. During r.e.m. sleep, breath-to-breath variability was unaffected by CO_2 administration. Thus, in contrast to marked reductions found

during either normoxic or hypoxic non-r.e.m. sleep, the addition of CO_2 during r.e.m. sleep had little effect on the already substantial values of mean intrasubject c.v. for all breath-to-breath parameters; and further did not eliminate the expiratory pauses (Table 3C).

Effects of acute hypocapnic and isocapnic hypoxia

In order to examine the relationship of breath-to-breath changes in CO_2 and O_2 with the development of hypoxia-induced periodic breathing, we induced acute hypoxia by lowering F_{I,O_2} (12·5 %) using a ventilation hood canopy, and monitored the time course of changes in P_{ET,O_2}, P_{ET,CO_2}, and ventilatory pattern in one subject.

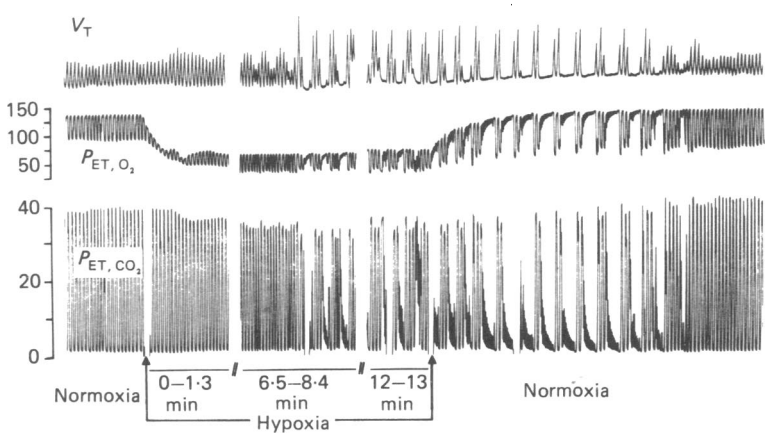

Fig. 5. Representative tracings of V_T, P_{ET,O_2}, and P_{ET,CO_2} during acute induction of hypocapnic hypoxia during non-r.e.m. sleep. Hypoxia (F_{I,O_2} = 12·5 %) was initiated at the first arrow and terminated at the second arrow.

The results during non-r.e.m. sleep are illustrated in Fig. 5. We observed the following: (1) with acute induction of hypoxia, P_{ET,O_2} decreased, $\dot{V}_E$ increased, and P_{ET,CO_2} gradually fell; (2) the pattern remained rhythmic until P_{ET,CO_2} had dropped approximately 4 torr below normoxic values; (3) cyclic oscillations in V_T preceded periodic breathing with apneas; (4) the first apnea occurred following a large V_T (and a low P_{ET,CO_2}), and thereafter periodic breathing and apneas were self sustaining (within 8 min of initiation of hypoxia); and (5) restoration of normoxia caused an initial prolongation of the duration of apneas followed by shortening and elimination of apneas, and stabilization of breathing pattern correlated with progressive increases in both P_{ET,CO_2} and P_{ET,O_2}.

With acute induction of isocapnic hypoxia (during which P_{ET,CO_2} was held at normocapnic levels by augmenting F_{I,CO_2}) (Fig. 6): (1) pattern remained rhythmic for the 20-min duration of isocapnic hypoxia; and (2) when CO_2 flow through the hood was discontinued, P_{ET,CO_2} decreased 3–4 torr, and periodic breathing gradually developed in the absence of any change in mean S_{a,O_2}.

DISCUSSION

We have quantitated hypoxia-induced periodic breathing, and examined the roles of both sleep state and hypocapnic alkalosis in its occurrence. In general, we have found that: (a) periodic breathing consists of periods of augmented inspiratory effort alternating with periods of apnea; and (b) the maintenance of rhythmic breathing in hypoxia was dependent upon the neurophysiologic state of the higher C.N.S.

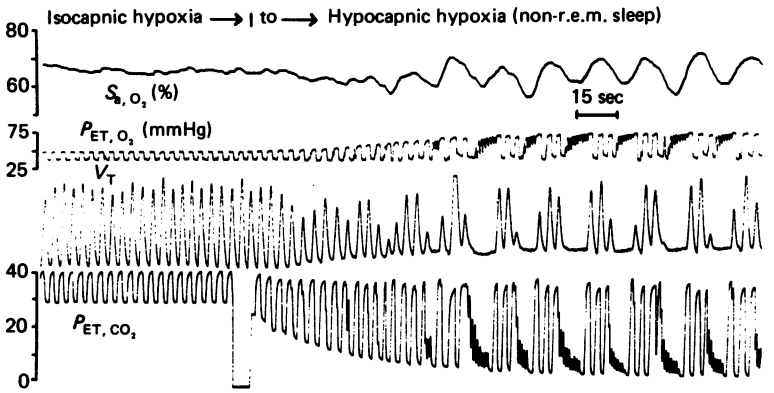

Fig. 6. Representative tracings of S_{a,O_2}, V_T, P_{ET,O_2}, and P_{ET,CO_2} during the last minute of a 15-min interval of isocapnic hypoxia during non-r.e.m. sleep, in which P_{ET,CO_2} was held at normocapnic levels by augmenting F_{I,CO_2}. Augmented CO_2 was halted at the arrow and artifact shown in the P_{ET,CO_2} trace.

intrinsic to wakefulness or r.e.m. sleep. We propose that self-sustained periodic breathing in non-r.e.m. sleep requires the presence of both hypocapnic alkalosis and hypoxia, and results from oscillations in CO_2 about a CO_2-dependent apneic threshold.

Characterization of periodic breathing

Periodic breathing during non-r.e.m. sleep in hypoxia was composed of repetitive breathing oscillations characterized by clusters of two to five breaths which alternated regularly with periods of apnea. The over-all cycle length of the periodic breathing episode and the number of breaths per cluster varied among subjects, but were fairly reproducible within a subject throughout the duration of hypoxic non-r.e.m. sleep. As compared to a rhythmic (non-periodic) pattern of breathing observed in hypoxia, mean $\dot{V}_E$ was essentially unaltered during periodic breathing; however, mean V_T/T_I, V_T, and breath-to-breath $\dot{V}_E$ were always increased indicating that inspiratory effort was augmented during breathing clusters. In some subjects, large variations in V_T were found within clusters and included volumes small enough to approach an estimated physiologic dead space (i.e. $V_T < 35$ ml). No consistent correlation was found between the maximal or minimal inspiratory effort (V_T/T_I) and the relative position of the breath within the breathing cluster. Changes in breathing cycle timing during periodic breathing were confined to the prolongation of the expiratory pause of the last breath in the breathing cluster, resulting in apnea. Virtually all the apneas during periodic breathing appeared to be of the central or non-obstructive type, i.e.

defined by the total cessation of all respiratory movements (Guilleminault, van den Hoed & Mitler, 1978).

Effect of sleep state on periodic breathing

The most stable periods of breathing were observed during normoxic non-r.e.m. sleep. Two exceptions were noted. First, mild oscillations of V_T were sometimes observed in association with rapid fluctuations in sleep state, particularly during sleep onset. However, when sleep stage was stable, breathing pattern was stable. Similar observations have been reported by Bulow (1963). Secondly, in one subject who showed evidence of obstructive breathing, breath-to-breath variability was increased during these episodes. Similar breathing abnormalities in normal subjects during normoxic non-r.e.m. sleep have been reported by Block, Boysen, Wynne & Hunt (1979).

We found that hypoxia caused periodic breathing in the absence of fluctuating sleep states and during all stages of non-r.e.m. sleep. We avoided the effect of fluctuating sleep stages by analysing only those periods of breathing during which sleep stage was constant for greater than 3 min. In hypoxia, we and others have found that the proportion of time spent in light sleep (Stages I and II) was increased, and the proportion of time spent in slow wave sleep (Stages III and IV) was decreased (Reite *et al.* 1975). Nevertheless, four out of five subjects who achieved Stage III/IV non-r.e.m. sleep in hypoxia breathed exclusively in a periodic pattern indicating that a shift to lighter stages of non-r.e.m. sleep was not obligatory in eliciting periodic breathing.

During wakefulness in hypoxia, although frank periodic breathing and associated apneas were generally not observed, breath-to-breath variability of both the volume and timing components was increased in some subjects as compared to normoxic wakefulness. Brusil *et al.* (1980) reported that 25 % of his sojourners at 3050 m altitude showed 'reinforcing oscillations' during which expired breath volume (V_E) and T_{TOT} oscillated out of phase and contributed to increased ventilatory fluctuations. Thus, although hypoxia in the presence of hypocapnic alkalosis may increase variability during wakefulness, it appears that the state of the higher C.N.S. associated with wakefulness contributes significantly to the maintenance of rhythmic breathing (Fink, 1961; Bulow, 1963; Phillipson, 1978; Remmers, 1981) and prevents the occurrence of apneas and periodic breathing (see below).

During r.e.m. sleep, the seemingly random erratic variations in the volume and timing of breaths, typical of breathing pattern in normoxia, was not affected by hypoxic exposure. This type of breathing pattern has been described previously in a variety of species (Bulow, 1963; Remmers, Bartlett & Putnam, 1976; Sullivan, Kozar, Murphy & Phillipson, 1978). Since this variability was not associated with any obvious cyclical waxing or waning, the mechanisms underlying the instability found in r.e.m. sleep may be quite different from those found during periodic breathing. It has been proposed that dependence on classical respiratory afferent stimuli is decreased during r.e.m. sleep and respiratory rhythm is maintained by non-respiratory neural events of the higher C.N.S. (Phillipson, 1978; Remmers, 1981). Depression of vagal and chemoreceptor feed-back during r.e.m. sleep in dogs had little effect on breathing frequency in comparison with its effect during non-r.e.m. sleep, and the irregular pattern of breathing typical of r.e.m. sleep was unaffected (Sullivan

et al. 1978). We have shown that augmentation of the CO_2 stimulus in normoxic r.e.m. sleep increased over-all $\dot{V}_E$ but the random variations in breathing persisted. Therefore, the non-respiratory neural events intrinsic to r.e.m. sleep provide sufficient stimulus to maintain a variable but non-periodic respiratory cycle rhythm, despite alterations in chemical afferent input.

The role of hypocapnic alkalosis in the genesis of periodic breathing in hypoxia

We were able to implicate hypocapnia as a critical link in the genesis of hypoxia-induced periodic breathing during non-r.e.m. sleep in several ways. First, administration of CO_2 (at constant S_{a,O_2}) rapidly and reversibly eliminated periodic breathing during hypoxia even though the increase in P_{a,CO_2} was smaller than 2 torr and thus respiratory alkalosis still persisted (Fig. 4; Table 3). The major effect of augmented CO_2 on breathing pattern in hypoxia was on cycle timing, specifically the elimination of apneas, with little effect on V_T or inspiratory 'effort,' V_T/T_I. Secondly, during acute induction of hypocapnic hypoxia, the development of periodic breathing correlated with a progressive decrease in P_{ET,CO_2} (Fig. 5). Further, the onset of periodic breathing was prevented by the maintenance of isocapnia during hypoxic exposure (Fig. 6). Only when P_{ET,CO_2} was allowed to fall did periodic breathing develop, in the absence of any change in mean S_{a,O_2}. Finally, restoration of normoxia during periodic breathing in hypoxia caused an initial prolongation of the duration of apneas followed by shortening and elimination of apneas; the stabilization of breathing correlated with a 3–6 torr increase in P_{a,CO_2} (Fig. 3, Table 2B), and a progressive increase in P_{ET,CO_2} (Fig. 5). Similar findings on the effect of acute restoration of normoxia on breathing pattern in hypoxic non-r.e.m. sleep have been reported by Gothe *et al.* (1982).

These findings suggest that during hypoxia-induced periodic breathing, the ventilatory system behaves in a manner consistent with a CO_2-apneic threshold phenomenon which is operating very close to the eupneic P_{CO_2} obtained during non-r.e.m. sleep. Other recent studies performed in our laboratory have provided evidence to support this concept. (Skatrud & Dempsey, 1982). We have demonstrated the consistent occurrence of apneas during non-r.e.m. sleep in normal subjects following passively induced positive pressure hyperventilation in both hyperoxic and hypoxic backgrounds. Significant apnea was consistently produced when P_{ET,CO_2} was reduced to 1–3 torr below spontaneous breathing awake levels, and apneic length was positively correlated with the magnitude of hypocapnia. In hypoxia, both the P_{ET,CO_2} obtained during spontaneous breathing and the CO_2-apnea threshold were decreased as compared to hyperoxia. These findings demonstrate the presence of a highly sensitive CO_2-dependent apneic threshold during non-r.e.m. sleep. Bulow (1963) also reported that apneas were observed during non-r.e.m. sleep in normals following spontaneous sighs which transiently decreased P_{ET,CO_2}. Thus, a functional CO_2-apnea threshold exists in non-r.e.m. sleep which may be a critical factor in the mechanism of periodic breathing during sleep in hypoxia. As discussed above, during the states of wakefulness or r.e.m. sleep, non-chemical influences on inspiratory activity contribute to the maintenance of respiratory cycle rhythm. These influences may prevent the occurrence of periodic breathing and apneas in these states by preventing the expression of a CO_2-apnea threshold.

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Mechanism of hypoxia-induced periodic breathing

We have shown that hypoxia alone, in the absence of hypocapnia, did not elicit periodic breathing (Fig. 6). On the other hand, in the absence of hypoxia, hypocapnia attendant to passive hyperventilation elicited apnea; but the recovery of spontaneous breathing showed a gradual return of V_T towards normal values as P_{ET,CO_2} progressively increased, i.e. self-sustained periodic breathing did not occur (Skatrud & Dempsey, 1982). Similarly, when prolonged hypocapnia was chronically induced in normoxia by administration of medroxyprogesterone acetate or acetazolamide ($\Delta P_{a,CO_2} = -5$ to -12 torr) we observed no effect on the stability or variability of breathing pattern during non-r.e.m. sleep (Skatrud, Dempsey, Iber & Berssenbrugge, 1981; Skatrud & Dempsey, 1983). Thus, the genesis of self-sustained periodic breathing during non-r.e.m. sleep requires the combined influence of both hypoxia and hypocapnia.

Several models have been proposed explaining periodic breathing as the result of instability in the chemical feed-back control of ventilation (Millhorn & Guyton, 1965; Cherniack & Longobardo, 1973; Khoo *et al.* 1982). The model of Cherniack & Longobardo (1973), supported by observations in anaesthetized cats (Cherniack, von Euler, Homma & Kao, 1979), points out the potential for instability created when hypoxic peripheral chemoreceptor stimulation exceeds $CO_2/[H+]$-mediated medullary chemoreception, and emphasizes the importance of the curvilinear response of the peripheral chemoreceptors to increasing hypoxemia in causing this instability in chemical feed-back control. We propose that the combination of augmented peripheral chemoreceptor 'gain' in hypoxia with the hypocapnia-induced apneic threshold in non-r.e.m. sleep provides the basis for explaining: (a) the initial occurrence of apnea; (b) the augmented inspiratory activity that occurs in the subsequent breathing clusters; and (c) the self-sustaining nature of periodic breathing. During conditions of hypoxia and non-r.e.m. sleep, increased peripheral chemoreceptor activity lowers P_{a,CO_2} to near the apneic threshold, thus creating an inherently unstable situation. This instability is clearly manifested in the appearance of regularly occurring cycles of increasing and decreasing V_T (e.g. Fig. 5). A further drop in P_{a,CO_2} below its threshold results in apnea. We do not know the cause of this additional hypocapnia. It may arise simply owing to the duration of hypoxia, which results in increasing ventilation or permits further wash-out of CO_2 stores; or conceivably it may result from the normal variability in breathing that occurs which allows perturbations in V_T (e.g. due to changes in airway mechanics or sighs). During the apnea, further hypoxemia develops which shifts P_{a,O_2} further along that portion of the peripheral chemoreceptor response curve at which 'gain' rapidly increases. This peripheral chemoreceptor gain may be further enhanced by the coincident rise in P_{a,CO_2}. When P_{a,CO_2} eventually exceeds its apneic threshold, rather than a gradual increase in V_T there is ventilatory overshoot characterized by augmented inspiratory effort, increased V_T and hyperventilation during the subsequent breathing cluster which again drives CO_2 below its threshold. The cycle then repeats itself resulting in self-sustaining periodic oscillations.

During hypoxic non-r.e.m. sleep, both the CO_2-apneic threshold and the relative 'gain' of the peripheral chemoreceptors can be altered by an increase or decrease in the net level of respiratory afferent stimuli, and hence, change the nature of periodic

breathing. It has been demonstrated in dogs that metabolic acidosis decreases the CO_2-apneic threshold (Mitchell, Bainton & Edelest, 1966), and we have shown in the passive hyperventilation studies that removal of the hypoxic stimulus with hyperoxia increased the CO_2-apneic threshold (Skatrud & Dempsey, 1982). Accordingly, we attribute the observed pattern of stabilization of breathing with acute restoration of normoxia in hypoxia to the following: the initial transient prolongation of apneic duration results from the increase in the CO_2-apneic threshold; as P_{a,O_2} rises further, the relative 'gain' of the peripheral chemoreceptors decreases (reducing the ventilatory overshoot) and $\dot{V}_E$ falls (allowing a rise in P_{a,CO_2}) both of which act to eliminate apneas and lead to the subsequent stabilization of breathing pattern. Further, the stabilizing effects of medroxyprogesterone acetate and acetazolamide on periodic breathing observed during sleep at high altitude in association with an increase in S_{a,O_2} (Weil *et al.* 1978; Sutton *et al.* 1979) may be similarly explained by the effect of these respiratory stimulants on reducing peripheral chemoreceptor 'gain' and decreasing the CO_2-apneic threshold.

Although we think our data clearly provide evidence supporting the importance of chemical feed-back instability in general and hypocapnic-induced apnea specifically in the genesis of hypoxia-induced periodic breathing during non-r.e.m. sleep, the possibility exists that a direct effect of hypoxia on the central nervous system (Santiago & Edelman, 1976; Gautier & Bonora, 1980) or an effect of hypoxia and/or hypocapnia on upper airway resistance (England, Bartlett & Knuth, 1982) may also exert an influence on hypoxia-induced periodic breathing.

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