Respiratory Function during Sleep in Patients with Chronic Obstructive Lung Disease *

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Hypoventilation of normal persons during sleep causes the arterial carbon dioxide tension to rise (1–9). Hypoventilation during sleep is accentuated when the respiratory center is further depressed by opiates (10); it might be suspected that carbon dioxide retention during sleep would be similarly accentuated in patients with chronic hypercapnia. Indeed, available evidence suggests that such patients with chronic obstructive pulmonary disease demonstrate even more marked hypoventilation while asleep than that seen in normal persons (11, 12). This study was undertaken to determine the extent of hypoventilation in sleeping patients with chronic obstructive pulmonary disease. The study also presented the opportunity to determine the mechanisms responsible for the hypoxia sometimes seen in such patients (13) and to determine the ventilatory pattern during sleep.

Methods

The only criteria for selection of subjects were availability and the presence of severe chronic airway obstruction. The first 11 patients were studied during the evening hours. These patients were brought to the laboratory shortly before their accustomed hour of sleep (8 to 11 p.m.). The next 8 patients were studied in the early afternoon after a light lunch (1 to 3 p.m.). No

medication was given any patient to induce sleep, and all other medications were withheld for the 4 hours before the onset of the study.

When each patient reported to the laboratory, aerosol bronchodilator (2.5 mg isoproterenol and 5.0 mg cyclopentamine) was administered by an intermittent positive pressure breathing device. Approximately 15 minutes after the termination of the bronchodilator treatment, the patient performed a forced spirogram, and the various timed segments, flow rates, and volumes were determined in the usual way (14). Parietal and occipital electroencephalogram (EEG) electrodes were then attached with electrode cream; electrocardiogram electrodes were fastened in position at the shoulders and thighs with bentonite paste and colloiden gel. A pneumatic cuff pressure transducer apparatus was connected to the patient's chest for the subsequent determination of respiratory movement. The patient was then placed in bed, and all of this apparatus was connected to a multichannel direct-writing recorder. When it was determined that all systems were operative, a Cournand needle was placed in a brachial artery, and that arm was secured with tape to a padded board. The patient was allowed to return to a stable state of basal respirations at which time base-line blood for gas analysis was drawn during EEG-monitored wakefulness. The lights were then subdued, and the patient was left undisturbed. During the entire study the patient was observed by one of the investigators, who noted changes in the patient's position, respiration, and clinical alertness. The recorder paper ran at 25 mm per second during most of the study period.

Blood for gas analysis was periodically drawn into sealed, heparinized syringes that were then occluded with a mercury cap. Analytic determinations were carried out within 15 minutes of obtaining each specimen. pH was measured at 37° C with a Sands type Metrohm electrode and arterial carbon dioxide tension (Pa_{CO_2}) with a Severinghaus electrode (15); the output of each of these electrodes was read with a model C33B Vibron electrometer. Oxygen saturation was measured by determining the ratio of the light intensities diffusely backscattered from whole blood at 2 wavelengths of light on each of two American Optical Company oximeters and was required to measure within 1% on the two machines. These oximeters were regularly standardized with a Clark oxygen electrode.

Others have emphasized (4, 7) that the breath-by-breath analysis of expired CO_2 by a rapid-acting infrared spectrophotometer is the ideal way of following the level of CO_2 for an extended period of time. Unfortunately, this method is not satisfactory in patients with lung disease who have uneven ventilation-perfusion relationships; in such patients, the end-tidal CO_2 is not an adequate reflection of Pa_{CO_2}. We have therefore relied on multiple samples of arterial blood. An average of 10.7 samples of blood was obtained from the nocturnal sleepers during the study or a sample every 12 minutes. An average of 5.3 samples or a sample every 15.5 minutes was collected from day sleepers. Although instantaneous changes in blood gases may have been missed, this sampling technique is certainly sufficient to determine trends.

The electroencephalograms were read by an independent observer who noted the depth of sleep every 12.5 seconds according to the criteria of Loomis, Harvey, and Hobart (16), as modified by Simon and Emmons (17). By these criteria stage 0 corresponds to wakefulness, stage A to drowsiness, stage B to a transition state, stage C to light sleep, stage D to deep sleep, and stage E to very deep sleep.

Student's t test was used to determine the significance of the difference between the various observations reported (18). Results were considered not significant if the likelihood of occurrence by chance alone was greater than 5% (p > 0.05). Since there was no statistical difference between the day and night sleepers as regards any measurement of waking ventilation or any of the sleeping functions, these groups will be reported together.

Results

The age, ventilatory functions, and blood gas values while awake of the 19 men in this study are recorded in Table I. All of the patients had severe obstructive ventilatory defects. There was no correlation between the magnitude of the ventilatory defect in each patient and the change with sleep of the various functions reported. Only two patients (10 and 18) had normal oxygen saturations ($\geq 95\%$) while awake. Ten patients had definite hypercapnia while awake ($Pa_{CO_2} > 45$ mm Hg).

Despite the various monitoring equipment used, no patient failed to sleep. Only one (Patient 1) failed to reach stage C of sleep or deeper; conversely, only one (Patient 14) reached stage E of sleep. The nocturnal subjects were asleep on the average longer than the afternoon sleepers (136 and 83 minutes, respectively).

In each case the Pa_{CO_2} rose during sleep (Table II). In no case was this rise greater than 12 mm Hg, and the mean maximal rise was 6.6 mm Hg. The mean maximal fall in pH was 0.02. The mean maximal rise in calculated plasma bicarbonate concentration was 2 mEq per L, which

TABLE I

*Pulmonary functions and blood gases in subjects while awake**

Patient	Age	PVC	FVC	FEV$_{1.0}$	FEF$_{25-75}$%	FIF	Wake Sa$_{O_2}$	Wake Pa$_{CO_2}$	Wake pH
	years	L	L	L	L/sec	L/sec	%	mm Hg	
1	67	4.07	3.60	1.54	0.58	3.30	91	39	7.40
2	59	4.33	4.25	1.02	0.42	3.39	92	44	7.36
3	62	3.86	2.28	0.83	0.20	2.24	94	45	7.41
4	61	4.16	3.10	1.32	0.43	4.43	83	54	7.39
5	74	3.35	2.14	0.90	0.40	1.69	83	61	7.39
6	61	3.89	3.71	1.30	0.33	5.16	94	41	7.45
7	71	3.56	2.66	0.94	0.35	3.14	92.5	51	7.36
8	54	4.03	1.89	0.40	0.14	1.34	93.5	44	7.41
9	58	4.33	2.88	0.73	0.26	2.17	82.5	72	7.35
10	74	3.64	2.04	0.93	0.44	2.16	95	33	7.43
11	61	4.12	1.66	0.34	0.16	0.82	87	45	7.38
12	51	4.52	3.16	0.96	0.31	4.37	84	57	7.40
13	68		2.44	0.64	0.29	4.60	93	44	7.42
14	47	4.13	2.67	1.03	0.31	4.01	88	61	7.43
15	59						94	49	7.39
16	65	4.23	3.70	1.95	0.75	2.80	93.5	46	7.37
17	57	3.95	2.96	1.78	0.78	2.63	94	36	7.39
18	69	3.22	1.35	0.70	0.38	2.63	96	37	7.38
19	59	3.60	2.02	1.40	1.07	2.60	94	44	7.46
Average	62	3.94	2.69	1.03	0.39	2.97	90.7	47.5	7.39

* Abbreviations: PVC, predicted vital capacity; FVC, forced vital capacity; FEV$_{1.0}$, forced expiratory volume in 1.0 second (normal value, > 75% of FVC); FEF$_{25-75}$%, forced expiratory flow during the first one-fourth of the vital capacity (normal range, 4.5 to 10.7); FIF, forced inspiratory flow (normal range, 4.2 to 5.9); Sa$_{O_2}$, oxygen saturation (normal value, $\geq 95\%$); Pa$_{CO_2}$, arterial carbon dioxide tension (normal value, 40 ± 5).

TABLE II

Blood gases during sleep

Patient	Maximal Pa_{CO_2} during sleep	Maximal Pa_{CO_2} rise during sleep	Lowest pH during sleep	Maximal pH fall during sleep	Lowest Sa_{O_2} during sleep	Maximal Sa_{O_2} fall during sleep	Maximal Pa_{O_2} fall during sleep
	mm Hg	*mm Hg*			%	%	*mm Hg*
1	45	6	7.39	0.01	89.0	2.0	4
2	53	9	7.33	0.03	82.0	10.0	18
3	55	10	7.36	0.05	87.0	7.0	16
4	64	10	7.37	0.02	77.0	6.0	6
5	65	4	7.38	0.01	73.0	10.0	9
6	42	6	7.42	0.03	91.0	3.0	8
7	58	7	7.32	0.04	88.0	4.5	9
8	49	5	7.40	0.01	91.0	2.5	7
9	74	7	7.34	0.01	63.0	19.5	16
10	42	9	7.37	0.01	92.5	2.5	9
11	48	3	7.35	0.03	83.5	3.5	5
12	65	7	7.37	0.03	77.0	7.0	8
13	47	3	7.41	0.01	92.0	1.0	2
14	68	10	7.38	0.05	79.0	9.0	10
15	50	1	7.39	0.00	94.0	0.0	0
16	49	5	7.36	0.01	91.0	2.5	6
17	48	12	7.38	0.01	93.0	1.0	3
18	39	1	7.36	0.02	96.0	0.0	0
19	55	11	7.40	0.06	91.0	3.0	6
Average	53	7	7.37	0.02	85.7	4.9	7

is well within the expected rise for this degree of acute hypercapnia (19). The Pa_{CO_2} was higher in the deeper stages of sleep (Figure 1); the variability in Pa_{CO_2} at any particular stage of sleep was large in some patients.

In 17 of the 19 subjects the oxygen saturation during one or more of the samples taken while subjects were sleeping was lower than values while they were awake (Table II). There was considerable variability in the oxygen saturation during the course of the sleeping period. In some cases the oxygen saturation remained below the waking level during the entire period of sleep and rose on waking to values before sleep, whereas on other occasions, the oxygen saturation fell and then rose again to waking values during the course of sleep. These fluctuations did not correlate with movement or position. There was a tendency for the patients with the lowest waking oxygen saturations to have the greatest falls in sleeping saturations, but this was not invariable (Tables I and II). The oxygen tension did not fall progressively with the deeper levels of sleep; indeed, the lowest tensions occurred in stage B, and the tensions returned toward waking values in stages C and D (Figure 1). The very large falls in oxygen saturation are misleading in terms of altered pulmonary function. Since the oxygen saturations
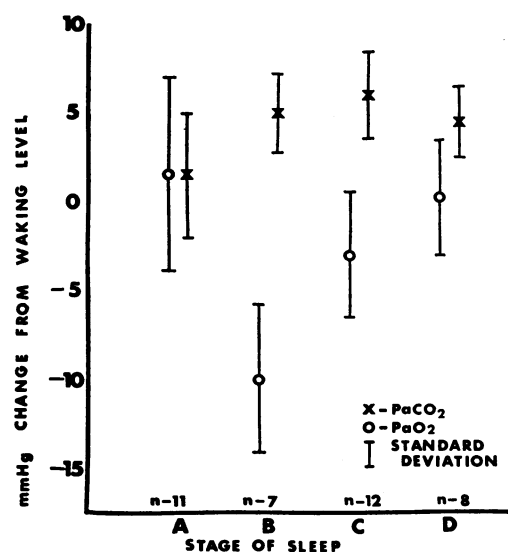

FIG. 1. CHANGES IN BLOOD GAS TENSIONS WITH SLEEP. Only the blood samples obtained after the patient had been in a single stage of sleep for at least 4 minutes were recorded. Levels of significance between the means follow (see Methods for explanation of stages of sleep). Pa_{O_2}—stages A to B, B to C, and B to D, $p < 0.001$; stage A to C, $p < 0.05$; stage C to D, $0.1 > p > 0.05$. All other relationships of Pa_{O_2} were not significantly different. Pa_{CO_2}—stages A to B and A to C, $p < 0.001$; stage A to D, $0.1 > p > 0.05$. All other relationships of Pa_{CO_2} were not significantly different.

TABLE III

Heart rates during sleep

Patient	EEG stage of sleep*				
	0	A	B	C	D
3	74.1	78.6	73.0	72.6	
4	86.2	82.0	84.0	82.4	
5		110.3	107.0	108.5	
6	85.8	81.5	82.8	79.0	
7	85.2	83.1	80.2	79.8	
8	69.0	70.5	64.8	64.1	62.8
9	97.8	94.6		97.4	93.5
10	69.0	71.6	72.8	73.5	
11	76.6	72.4		67.8	
12			87.6	89.5	
13		75.6	77.8	73.0	
14		106.0	103.0	101.5	106.4
15		74.2	75.8	72.8	
16		64.7	66.9	68.1	
17		74.8	73.6		
18		94.2	90.7	87.7	
19		93.7	91.6	89.0	
Average	80.4	82.9	82.1	81.4	

* See Methods for explanation.

tended to be rather low in the waking state, the large changes in saturation were brought about by relatively small changes in the arterial oxygen tension (Pa_{O_2}) because of the shape of the oxygen dissociation curve. In addition, the changing pH associated with the rising Pa_{CO_2} shifts the dissociation curve to the right. The mean maximal change in Pa_{O_2} from wake to sleep was only 7.4 mm Hg (SD ± 5.0).

The heart rate during sleep was quite variable from subject to subject, but it remained relatively stable in any given subject. Replicate measurements were available for all patients at several stages of sleep, and the range in pulse rate for an individual in one stage of sleep averaged 8.7 beats per minute. There was no significant change in pulse rate from wake to sleep (p > 0.5). Moreover, during sleep there was no consistent tendency for the heart rate to change (mean change from stage A to stage C, − 1.5, p > 0.7) (Table III). Patients with a mean sleeping oxygen saturation of less than 85% had a mean sleeping pulse greater than 81, whereas only two of the twelve patients with a mean arterial oxygen saturation during sleep greater than 85% had this high a mean pulse rate (p < 0.01).

The respiratory rate was not only quite variable from subject to subject, but also varied considerably from time to time in any individual subject. For any one individual during sleep the range in

respiratory rate averaged 6.3 breaths per minute. There was no significant change in respiratory rate as the subject passed from wakefulness to sleep (p > 0.3) (Table IV). Moreover, there was no consistent tendency for respiratory rate to change in relation to changes in the depth of sleep (mean change from stage A to stage C, 1.8, p > 0.3). The variability in the respiratory rate tended to occur as a subject changed from one level of sleep to another. As a subject remained in any level of sleep, the respiratory rate became monotonously regular. Patients with an oxygen saturation greater than 85% had a mean sleeping respiratory rate of 18.1 (SD ± 2.9), whereas patients with a sleeping oxygen saturation of less than 85% had a mean sleeping respiratory rate of 25.8 (SD ± 6.4, p < 0.001).

Discussion

Normal subjects consistently show a rise in P_{CO_2} during sleep due to a diminished responsiveness of the respiratory center to carbon dioxide, and the greater the depth of sleep the more marked the rise (3–7). Because this occurs so rapidly with the onset of sleep, it is thought to be a neurogenic effect. Increases in Pa_{CO_2} in normal subjects have been reported as high as 14 mm Hg, and a rise of 10 mm Hg is not uncommon. In the series of normal subjects reported by Robin,

TABLE IV

Respiratory rate during sleep

Patient	EEG stage of sleep				
	0	A	B	C	D
1	13.7	14.9	15.5		
2	20.7	19.5	17.4		
3	15.3	16.1	17.7	16.5	
4	17.9	22.3	23.0	23.0	23.8
5		29.1	27.8	34.3	
6	15.7	21.0	23.5	23.7	
7	16.6	13.8	16.2	16.1	
8	13.3	19.4	20.1	19.9	19.6
9	24.8	20.8		20.1	19.9
10	19.0	16.6	16.4	20.0	
11	15.5	15.9		18.0	
12			13.6	29.2	32.3
13		21.1	21.8	21.0	
14		24.7	33.0	35.5	37.7
15		21.7	21.9	22.5	
16		17.7	15.3	13.9	
17		17.2	16.7	13.3	
18		23.2	18.8	17.5	
19		13.7	16.3	14.2	
Average	17.3	19.3	19.7	21.1	26.6

Whaley, Crump, and Travis (4) the mean maximal rise in Pa_{CO_2} was 8.0 mm Hg, whereas in the series by Birchfield, Sieker, and Heyman (3, 5) the mean rises in Pa_{CO_2} were 5.3 and 4.1 mm Hg. These rises are not significantly different from our mean maximal rise of 6.6 mm Hg (p > 0.2). Moreover, in none of our patients was there a Pa_{CO_2} rise greater than 12 mm Hg. It is not known whether the physiological effects of a given rise in Pa_{CO_2} differ from usual when the initial Pa_{CO_2} is elevated. Nevertheless, our data do not support the contention that the patient with chronic pulmonary disease shows greater CO_2 elevations and a more profound depression of respiratory center sensitivity during sleep than do normal subjects (11, 12).

It would be reasonable to expect depressed ventilation, accompanied by relatively infrequent movement and frequently associated with obstructing mucus in the airways, to be associated with an abnormal distribution of ventilation in relation to blood flow. The Pa_{O_2} fell maximally in the middle stage of sleep and during deeper sleep rose again to waking levels. The initial fall in Pa_{O_2} coincided with the rise in Pa_{CO_2}, but the subsequent rise in Pa_{O_2} occurred despite the persistent elevation of Pa_{CO_2}. Therefore, ventilation-perfusion relationships must have improved in the deeper stages of sleep. This unexpected finding is probably related to a more efficient pattern of ventilation during the deeper stages of sleep. This observation deserves further investigation.

It is apparent from these data that the mean maximal fall in Pa_{O_2} from wake to sleep was only 7.4 mm Hg (SD ± 5.0). Only Birchfield and his associates (3, 5) have reported comparable oxygen saturations and pH during wake and sleep. Of their 22 normal subjects, 14 had a modest reduction in oxygen saturation during sleep. The calculated change in Pa_{O_2} from wake to sleep in these 22 subjects was 4.9 mm Hg. This change in Pa_{O_2} is not significantly different from the change observed in this series (p > 0.3). Thus the hypoxia noted in these patients, as suggested by others (12, 13), is a manifestation of the greater change in oxygen saturation per unit change in Pa_{O_2} when the oxygen saturation is on the steep segment of the oxygen dissociation curve.

It is significant that all of our patients with oxygen saturations less than 85% had a tachycardia during sleep. Severe hypoxia is known to cause tachycardia (20) and pulmonary hypertension (21), and these events are important in the genesis of cor pulmonale. The present data suggest that adequate oxygenation during sleep, if accentuation of hypoventilation did not occur, might defer the appearance of cor pulmonale in patients such as these.

Summary

The heart rate, respiratory rate, and blood gases have been followed during the course of electroencephalogram-monitored sleep in 19 men with chronic obstructive lung disease. No patient had a greater rise in arterial carbon dioxide tension during sleep than occurs in normal subjects. However, the patients had an average maximal decrease in arterial oxygen saturation during sleep of 5%. A significant tachycardia was observed in sleeping patients with an oxygen saturation of less than 85%.

Acknowledgments

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