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Arterial Blood Gases and Pulmonary and Systemic Arterial Pressure During Sleep in Chronic Obstructive Pulmonary Disease

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Summary: In order to determine the effects of sleep on arterial blood gas tensions, as well as pulmonary and systemic hemodynamics in patients with chronic obstructive pulmonary disease (COPD), blood gases and pulmonary and systemic arterial pressures were measured during monitored sleep in 12 patients suffering from COPD. Alveolar hypoventilation and pulmonary hypertension progressively worsened from wakefulness through the successive stages of slow-wave sleep and were significantly aggravated during REM sleep. The mean pulmonary arterial pressure increased from an average value of 37 mm Hg in wakefulness to 55 mm Hg during REM sleep. The $Paco_2$ values increased from 49.7 to 57.4 mm Hg, and Pao_2 decreased from 56.2 to 42.8 mm Hg. Maximum increase of $Paco_2$ and maximum decrease of Pao_2 during sleep were significantly greater in COPD patients than in a control group of normal subjects. Systemic arterial pressure decreased during sleep, but not significantly. In patients with COPD, sleep—and particularly REM sleep—negatively affects alveolar ventilation and pulmonary pressure. These patients may therefore be predisposed to attacks of right ventricular cardiac failure during sleep.
Key Words: Sleep—Chronic obstructive pulmonary disease—Alveolar ventilation during sleep—Pulmonary artery pressure—Systemic arterial pressure.

The effect of sleep on alveolar ventilation in the normal individual is the subject of controversy. According to some authors, a certain amount of alveolar hypoventilation appears during sleep due to a diminished ventilatory response to carbon dioxide relative to wakefulness (Robin et al., 1958; Birchfield et al., 1959; Bulow, 1963). Other authors (Mangold et al., 1955; Duron, 1972) observed no significant differences between waking and sleeping alveolar ventilation. We have previously documented (Coccagna et al., 1971, 1976*a*) that in the normal individual:

1. Alveolar ventilation decreases significantly during sleep, but the $Paco_2$ values

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never exceeded 42.3 mm Hg; gas analysis values obtained during the various stages of sleep do not differ significantly from each other.

2. Pulmonary artery pressure increases slightly and significantly during sleep, but never exceeds normal values; there are no significant differences between pressure values taken during the different stages of sleep.

3. Systemic arterial pressure decreases progressively and significantly in the successive stages of slow wave sleep; during rapid eye movement (REM) sleep, values are similar to those in stage 2 sleep.

In individuals with chronic hypercapnia secondary to chronic obstructive pulmonary disease, in whom ventilatory response to CO_2 is diminished during wakefulness (Prime et al., 1954; Fishman et al., 1955), markedly aggravated hypoventilation is expected during sleep. This prediction has been confirmed by Robin, but other authors (Pierce et al., 1966; Interiano et al., 1972; Koo et al., 1975) have failed to observe that the increase in $Paco_2$ during sleep in patients with chronic pulmonary insufficiency is significantly greater than in normal subjects.

This report describes a study of blood gases analysis and of pulmonary and systemic arterial pressures during monitored sleep in chronic obstructive pulmonary disease (COPD).

MATERIALS AND METHODS

Twelve male patients from 39 to 68 years of age affected by chronic airway obstruction secondary to chronic bronchitis and emphysema entered the study. Two other patients were excluded from this series, because during the polygraphic recording they did not sleep enough, and all the stages were not present in their sleep. All patients gave a history of chronic cough, mucopurulent sputum production, and increasing dyspnea on exertion; all were in a stable clinical state at the time of the study. Eight were being treated with adrenergic bronchodilators, antibiotics, or both; two were taking small doses of cortisone (triamcinolone). No patient took sedative or analgesic drugs.

The patients' average ratio of forced expiratory volume to forced vital capacity in 1 sec was 42% (extreme values 28% and 69%). $Paco_2$ during wakefulness ranged from 43 to 59 mm Hg. All patients consented to polygraphic recording of spontaneous nocturnal sleep. The recording began at about 11:00 p.m. and ended at 7:00 a.m. the following morning. Any therapy was interrupted at least 8 hr before the beginning of the study, and no medication was given to induce sleep.

Polygraphic monitoring included simultaneous recording of the electroencephalogram, electro-oculogram, and electromyogram (chin muscles) for identification of sleep stages according to the criteria of Rechtschaffen and Kales (1968). Stages 3 and 4 of deep slow sleep were considered together.

Airflow through the upper airway was recorded by means of thermocouples placed in front of the mouth and in one nostril. Thoracic movements were recorded using an expandable tube attached to a belt around the thorax and connected to a piezoelectric transducer. Systemic arterial pressure was recorded by percutaneous cannulation of a radial artery with Teflon tubing, and pulmonary arterial pressure was recorded with a Grandjean microcatheter positioned in the

artery through an antecubital vein. The catheter and the Teflon needle were connected to Statham P23-Db transducers which were, in turn, connected to manometric preamplifiers of the polygraph. The arm in which the pulmonary catheter and the Teflon needle were inserted was strapped to the side of the bed to restrict movement. A three-way stopcock permitted intermittent flushing of the lines and sampling of blood from the radial artery catheter for blood gas analysis. During the course of the night, an average of 13 arterial blood samples were drawn during wakefulness and the various stages of sleep for gas analysis; values were measured immediately using a radiometer apparatus.

The polygraphic control allowed us to determine that the drawing of arterial blood samples during sleep did not cause the patients to arouse or change the sleep stage; when this occurred, the blood sample was discarded.

The values of the pulmonary and systemic arterial pressures were read every 30 sec during quiet wakefulness and during the different stages of sleep. Waking values of pulmonary and systemic arterial pressures and of arterial blood gases are the mean values obtained before the beginning of sleep (starting at least 20 min after the preparation of the patient was completed) and at least 3 min after a reawakening at night and in the morning.

Using identical methods of polygraphic recording during sleep, we have studied these same physiological variables in a group of healthy control subjects. The systemic arterial pressure and arterial blood gases were determined in eight male subjects aged 28 to 68, while the pulmonary artery pressure was recorded in four men and one woman from our laboratory staff, aged 30 to 50.

To evaluate whether eventual changes of sleep pattern in the patient group and in the control group (control group A) were due to the particular procedure of polygraphic recording, we studied sleep parameters in eight other normal male subjects between ages 25 and 45 in whom the polygraphic recordings included only the recording of electroencephalogram, electro-oculogram, and the electromyogram of a chin muscle (control group B).

The statistical analyses were performed by analysis of variance. The averages shown in Table 1 were compared with a multiple comparison test (Tukey's test).

RESULTS

Sleep Changes

Sleep parameters of both patients and control groups are shown in Table 1. Both patients and control group A subjects had very disturbed sleep with respect to control group B. The only important differences between the first two groups were the total sleep time, sleep latency, and the number and duration of nocturnal awakenings. In patients, nocturnal awakenings were often caused by excessive coughing and the necessity to expel secretions.

The percent duration of different sleep stages did not differ substantially in the patients and in control group A, whereas these groups showed a reduction of stages 3 and 4 with a concomitant increase in stages 1 and 2 and a smaller decrease in REM sleep relative to control group B.

TABLE 1. *Sleep parameters of patients and control groups*

Parameter	Patients	Control groups	
		A	B
Recording time (hr)	7.5	7.5	8.5
Sleep time (hr)	4.9 (2.3–6.3)	5.4 (3.2–6.5)	7.5 (6.5–8.5)
Sleep (% of recording time)	66 (30–84)	72 (42–86)	84 (73–94)
Sleep latency (min)	45 (18–80)	32 (10–72)	20 (3–45)
1st REM latency (min)	125 (88–160)	107 (80–147)	84 (50–199)
Awakenings after sleep onset (*N*)	4.5 (3–9)	3.5 (3–5)	2.3 (0–4)
Sleep stages (%)			
1	18 (6–30)	16 (4–25)	11 (2–20)
2	49 (30–64)	46 (29–59)	37 (25–54)
3–4	17 (8–25)	20 (10–31)	29 (12–46)
REM	16 (6–24)	18 (10–23)	23 (15–32)

Extreme values are reported in parentheses.

Both in the patients and in control group A the pattern of sleep varied notably from one subject to another; next to relatively good sleepers, there were very poor sleepers. These differences were not correlated with the gravity of respiratory insufficiency. In all patients, EEG tracing both in wakefulness and in sleep was normal.

Hemodynamic and Ventilatory Changes

The results obtained are presented in Table 2 and Fig. 1. In patients with COPD, alveolar hypoventilation worsened progressively and significantly through the successive stages of slow-wave sleep (from stage 1 to stages 3–4), and was aggravated further during REM sleep. [$Paco_2$: W < stage 2 ($p < 0.001$), stages 3–4 < stage REM ($p < 0.01$); Pao_2: W > stage 2 ($p < 0.01$), stage 3–4 > stage REM ($p < 0.001$); pH: W > stage 2 ($p < 0.01$)]. In COPD patients, the mean $Paco_2$ maximum increase (± SEM) during sleep, compared to values recorded during wakefulness was 10.6 mm Hg (± 0.49); the difference between these two values was significant ($p < 0.001$). Similarly, the mean Pao_2 maximum decrease (± SEM) in patients was 15.9 mm Hg (± 1.34) and 5.5 mm Hg (± 2) in the control group; this difference was also statistically significant ($p < 0.01$). The mean maximum decrease of pH was the same in patients and in the control group (0.04).

Pulmonary artery pressure increased progressively through the successive stages of slow-wave sleep (from stage 1 to stages 3–4); a further conspicuous increase occurred during REM sleep [PAP (max, min, and mean): W < stage 2 ($p < 0.05$), stages 3–4 < stage REM ($p < 0.001$)]. Using multiple regression analysis, we correlated blood gas values for each sleep stage with corresponding pulmonary artery pressure values. Progressive pulmonary arterial pressure increases during specific sleep stages correlated with Pao_2 changes and were less dependent on $Paco_2$ or pH changes.

Systemic arterial pressure decreased during sleep in COPD patients; nevertheless, in contrast to what was observed in normal controls, this pressure drop was not statistically significant.

TABLE 2. *Behavior of the systemic and pulmonary arterial pressures and of the arterial blood gases during sleep in patients affected with chronic obstructive pulmonary disease and in normal subjects (mean values ± SEM)*[a]

	W	Stage 1
	Subjects affected with COPD	
Systemic artery pressure	127.6 ± 3.59 / 69.3 ± 2.21	125.2 ± 3.40 / 67.9 ± 2.12
Pulmonary artery pressure (mean)	59.2 ± 4.09 / 29.9 ± 2.28 (37.0 ± 2.48)	61.6 ± 4.19 / 30.6 ± 2.12 (38.1 ± 3.14)
$Paco_2$	49.7 ± 1.59	—
Pao_2	56.1 ± 1.26	—
pH	7.34 ± 0.0046	—
	Normal subjects	
Systemic artery pressure	129.1 ± 5.23 / 60.2 ± 4.77	125.1 ± 5.60 / 57.2 ± 4.75
Pulmonary artery pressure	17.9 ± 4.63 / 8.2 ± 2.40	19.4 ± 4.28 / 8.9 ± 2.25
$Paco_2$	36.3 ± 0.80	—
Pao_2	81.3 ± 2.92	—
pH	7.36 ± 0.0050	—

	Stage 2	Stage 3–4	Stage REM
	Subjects affected with COPD		
Systemic artery pressure	124.2 ± 3.10 / 66.2 ± 1.87	124.5 ± 3.08 / 66.2 ± 1.68	125.6 ± 2.66 / 65.7 ± 1.90
Pulmonary artery pressure (mean)	63.5 ± 4.58 / 30.9 ± 2.53 (40.3 ± 3.55)	67.2 ± 4.82 / 32.6 ± 2.86 (44.8 ± 3.77)	79.3 ± 5.19 / 37.7 ± 3.03 (55 ± 3.80)
$Paco_2$	53.4 ± 1.52	54.5 ± 1.94	57.4 ± 1.71
Pao_2	52.6 ± 2.06	50.2 ± 2.30	42.8 ± 2.54
pH	7.32 ± 0.0036	7.31 ± 0.0075	7.30 ± 0.0051
		Normal subjects	
Systemic artery pressure	118.8 ± 6.49 / 54.8 ± 5.11	112.0 ± 5.93 / 52.1 ± 5.32	120.8 ± 5.75 / 58.8 ± 5.10
Pulmonary artery pressure	23.0 ± 5.47 / 10.7 ± 2.95	23.4 ± 5.59 / 11.9 ± 3.80	23.2 ± 5.55 / 10.9 ± 2.92
$Paco_2$	39.5 ± 0.79	39.4 ± 0.75	39.3 ± 0.78
Pao_2	77.4 ± 2.16	77.3 ± 2.34	78.7 ± 3.28
pH	7.33 ± 0.010	7.33 ± 0.0070	7.33 ± 0.0069

[a] The significance of the difference of the values between the different stages of sleep are reported in the text. W, wakefulness.

Alveolar hypoventilation and pulmonary hypertension tended to worsen through the course of the night. In specific sleep stages, values were altered more during the second half of the night than during the first half. Blood gases and pulmonary arterial pressure were obtained at times of awakening during the course of the night and in the morning; these results were always more abnormal than those recorded before sleep onset.

DISCUSSION

The procedure used in the present study presents several possible limitations that need definition. The fact that subjects were tested during only one night's

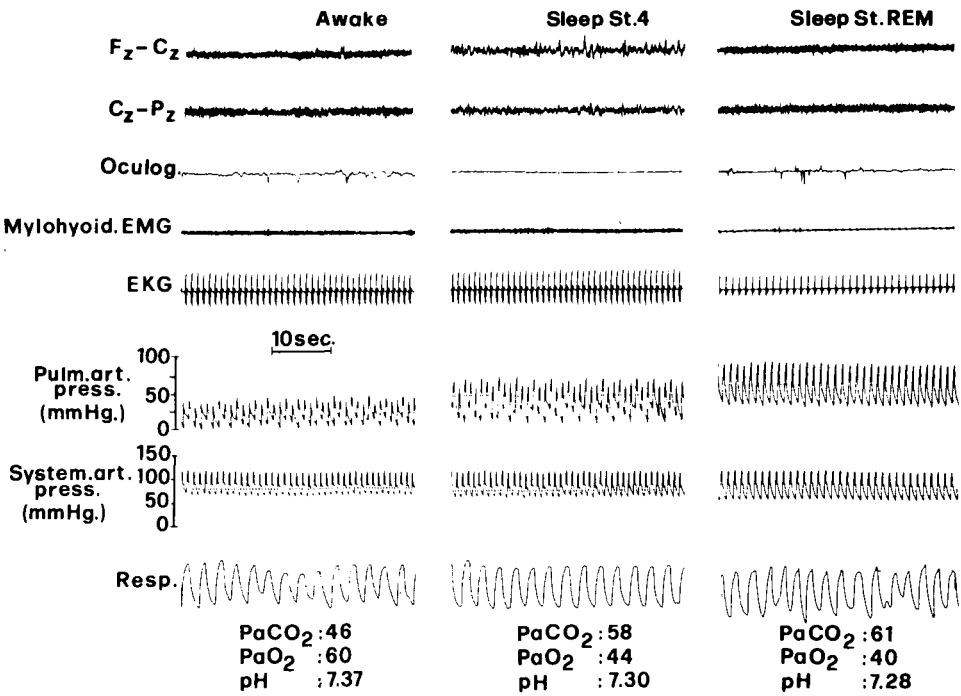

FIG. 1. Simultaneous recording of the EEG, horizontal oculogram, electromyogram of the myelohyoid muscle, EKG, pulmonary and systemic arterial pressure, and thoracic respiration. Pulmonary artery pressure and alveolar hypoventilation increased during slow-wave sleep (stage 4) and further increased during REM sleep. Blood gases were obtained immediately before or after the respective fragments of polygraphic tracing.

sleep, and with the use of a rather complex polygraphic recording technique, poses several problems in interpretation, not only of the parameters of sleep, but also of the blood gas analysis. Both variables can be artificially modified by the patient's emotional state, due either to the effect of the first night in the laboratory or of the preparational procedures of the subject for the recording. However, this same complexity of the polygraphic recording makes more than one recording session impossible to obtain.

The patients appeared calmer than control subjects, because they had previously undergone right heart catheterization and repeated percutaneous arterial punctures.

The abnormalities encountered in the patients' sleep parameters were in large part attributable to the uneasiness induced by the recording technique. This was demonstrated by comparison with the two control groups, even though coughing and bronchial secretions could be responsible for lightening of sleep and repeated nocturnal awakenings. Regarding the arterial blood gas samples, the major problems concerned samples taken during wakefulness, because hyperventilation due to the patient's emotional state could lower $Paco_2$ values artificially.

To limit causes of error as much as possible, blood samples were taken re-

peatedly before sleep, during nocturnal awakenings, and on awakening in the morning, when the patient was apparently tranquil and respiration was regular.

The results on the behavior of alveolar ventilation and pulmonary and systemic arterial pressure confirm a limited pilot study (Coccagna et al., 1976*b*); in COPD, alveolar hypoventilation and pulmonary hypertension are aggravated during slow-wave sleep and worsen further during REM sleep. Koo et al. (1975) reported arterial blood gas and pH changes in COPD during sleep. They polygraphically monitored the electroencephalogram, cardiac rhythm, and respiratory frequency of eight patients during sleep and found that alveolar hypoventilation worsened during REM sleep. Rapid increases in hypoxemia and hypercapnia were associated with this state. These authors, however, did not monitor arterial pressures.

One area of controversy in the literature concerns whether COPD patients present similar or wider variations of blood gas levels during sleep than do normal subjects. Data from our patient group clearly demonstrated marked $Paco_2$ and Pao_2 variations compared to blood gas values during wakefulness contrasted with normal controls previously recorded in our laboratory or those mentioned in the literature (Robin et al., 1958; Birchfield et al., 1959; Bulow, 1963). Robin (1958) reported an increase of approximately 2.5 times in average alveolar carbon dioxide partial pressure during sleep in seven patients, compared to their control group. But Pierce et al. (1966), Interiano et al. (1972), and Koo et al. (1975) found no statistical difference between the maximum increase in $Paco_2$ in their patient groups and the calculated maximum rise observed in the normal sleeping subjects reported by Birchfield et al. (4.1 ± 2.1 mm Hg). Koo et al. (1975) concluded that patients with severe airway obstruction do not show more profound alveolar hypoventilation during sleep than do normal subjects.

In most of these reported studies, sleep was evaluated behaviorally, with the exception of polygraphic monitoring in eight of the 15 patients reported by Koo et al.; the depth of sleep in the remaining seven patients was judged visually. As these authors had no way of establishing the state of sleep in half of their patients, it is possible that blood samples were not drawn during REM sleep, during which state they found, as we confirmed, that alveolar hypoventilation reaches its most pathological levels. If the data from the Koo et al. (1975) study are subdivided into two subgroups—patients polygraphically monitored and those visually observed—the former group had average higher $Paco_2$ values during sleep, which supports our assumption. Clearly, it is necessary to monitor all variables, including sleep, in similar studies.

To conclude, we suggest that sleep, and particularly REM sleep, increases the vulnerability of patients suffering from chronic respiratory insufficiency. This statement has important clinical implications, as REM sleep is particularly abundant during the early morning hours. The progressive nocturnal increase in pulmonary arterial pressure may contribute to the appearance of right ventricular cardiac failure. Further clinical studies are needed to determine whether oxygen therapy during sleep may be helpful in preventing hemodynamic changes observed during sleep in COPD patients.

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