Refer to: Guilleminault C, Eldridge FL, Simmon FB, et al: Sleep apnea syndrome—Can it induce hemodynamic changes? West J Med 123:7-16, Jul 1975

Sleep Apnea Syndrome

Can It Induce Hemodynamic Changes?

CHRISTIAN GUILLEMINAULT, MD, *Stanford,*
FREDERIC L. ELDRIDGE, MD, *Chapel Hill, North Carolina,*
F. BLAIR SIMMON, MD, *and* WILLIAM C. DEMENT, MD, *Stanford*

Of 250 patients referred to the Stanford Sleep Disorders Clinic, 35 were diagnosed for a sleep induced apnea syndrome. Thirty of them (27 adults and 3 children) were nonobese and complained of a sleep disorder. In 12 patients (9 adults and 3 children) extensive cardiorespiratory workups were done during sleep and wakefulness. Three types of sleep induced apnea syndrome were identified: diaphragmatic (or central), obstructive and mixed. The diaphragmatic type was predominant in sleep apnea insomnia; obstructive was predominant in sleep apnea hypersomnia. Hemodynamic changes were documented during sleep. Tracheostomy, done in two cases, improved the sleep induced symptomatology.

IN 1956 Burwell and co-workers[1] coined the term "Pickwickian" to describe the cardiorespiratory syndrome of obesity. Extensive studies have since been made on the cardiorespiratory dysfunctions in these patients. In 1969 Lugaresi and co-workers[2] reported the findings from a detailed clinical investigation of a *nonobese* hypersomniac patient and showed that the same sleep related respiratory abnormalities previously reported only in Pickwickian patients were present. In 1970, Coccagna and co-workers[3] postulated the existence of a more general "hypersomnia-hyperventilation syndrome" based on a review of the literature and their own case material. They pointed out that patients classified as Pickwickian, Ondine's Curse[4] or "hypersomnia with periodic respiration"[2] presented three common findings: (a) daytime hypersomnolence, (b) respiratory abnormalities during sleep and (c) hypotonia of the nasopharyngeal muscles during sleep. More recently, respiratory abnormalities during sleep have also been described in nonobese patients classified as rapid eye movement (REM) narcoleptics and insomniacs.[5,6]

From the Sleep Disorders Clinic, Stanford University School of Medicine (Drs. Guilleminault and Dement); the Department of Physiology, University of North Carolina School of Medicine, Chapel Hill (Dr. Eldridge); and the Department of Otolaryngology, Stanford University School of Medicine (Dr. Simmon).

Submitted April 18, 1975.

This research was supported by National Institutes of Neurological Disease and Stroke Grant NS 10727; Research Scientist Development Award MH 05804 (Dr. Dement); Public Health Services Grant NS 09390; and Public Health Service Research Grant N. R.R.-70 from the General Clinical Research Centers, Division of Research Resources.

Information and reprint requests should be addressed to: C. Guilleminault, MD, Sleep Disorders Clinic and Laboratory, Stanford University School of Medicine, Stanford, CA 94305.

ABBREVIATIONS USED IN TEXT

EEG = electroencephalogram
EKG = electrocardiogram
EMG = electromyogram
EOG = electro-oculogram
NREM = nonrapid eye movement
PAP = pulmonary arterial pressure
REM = rapid eye movement

The purpose of the present paper is to report clinical studies that confirm and extend these observations. The occurrence of sleep-related, repetitive apneic episodes in a large case series of nonobese patients who initially were known to complain only of a sleep problem will be reported. In addition, respiratory and pulmonary arterial pressure (PAP) abnormalities during sleep and wakefulness in a subsample of this population will be emphasized.

Methods

Case Finding Techniques

A total of 250 consecutive patients referred to the Stanford Sleep Disorders Clinic underwent continuous polygraphic recording, including respiratory variables, for at least one full night. In all cases, the patients were fully awake at the beginning of the study and had a period of wakefulness in the morning before the tests were terminated. In addition, many had spontaneous periods of wakefulness of varying lengths in the middle of the night.

The polygraphic variables related to monitoring states of sleep and wakefulness were exactly the same in all patients.[7] The electroencephalogram (EEG) was always recorded from the standard C_3/A_2 or symmetrical C_1/A_1 placements of the International 10-20 System.[7] The electro-oculogram (EOG) was recorded either bipolarly from electrodes at the right and left outer canthi, or monopolarly with each canthus referred to the opposite ear lobe. Two closely approximated submental electrodes recorded the digastric electromyogram (EMG). Each successive 30 seconds of polygraphic recording was assigned to a specific category of sleep and wakefulness according to rules and definitions set forth in an internationally recognized standard sleep stage scoring manual.[7]

Four polygraphic tracings were routinely devoted to respiration using thoracic and abdominal mercury strain gauges and buccal and nasal thermistors. This simple respiratory technique does not interfere with the sleep of patients and, at the same time, gives an adequate differentiation between those patients with normal respiration and those whose respiration during sleep is pathological. The polygraphic data from patients were compared with published data on respiration during sleep in normal adults[8-10] and with recordings made on our own normal control groups (5 young adults and 12 older persons ranging from 40 to 60 years of age). The comparisons indicated that the above technique for recording respiration during sleep and wakefulness was an accurate and reliable case finding procedure.

The 250 patients fell almost entirely into three groups: patients complaining of insomnia, patients complaining of daytime sleepiness and long nocturnal sleep times (hypersomnia), and patients who complained of daytime sleep attacks associated with disrupted nocturnal sleep. REM narcolepsy was by far the most prevalent condition in the latter group. All ages were represented, with a peak in the range of 40 to 60 years old. Except for obese patients, sleep related respiratory abnormalities were not usually suspected by the referring physician, the patient or the staff of the Stanford Sleep Disorders Clinic.

Experimental Protocol

When positive findings were obtained in the case finding study, the patient was encouraged to participate in additional evaluations. Thus, in a subsample of the case series, very extensive hemodynamic and pulmonary data were gathered. The size of this subsample (12 patients) was severely limited by many factors. Among them were the availability of testing facilities, the willingness of the patients to undergo additional tests and their ability to be available on the required dates and, finally, a variety of constraints imposed by considerations involving use of human subjects.

Using the simple recording technique described previously, two all-night recordings first were made for each patient in the subsample to confirm sleep pathology and respiration problems during sleep. In patients with complaint of excessive daytime sleep (hypersomniacs or REM narcoleptics) during this two-day period, one 24-hour continuous recording was made to determine the number of sleep attacks during the daytime and to evaluate the severity of the daytime sleepiness. Respiration was also recorded during daytime naps throughout this 24-hour period.

Evaluation during wakefulness. Following this

initial two-day assessment period, all patients followed a four-day 24-hour protocol. During the day, patients were given pulmonary function tests *during wakefulness* that included spirometric tests; studies of lung volume, elastic recoil, air flow resistance and arterial blood gases, and an exercise study which compared rest and three grades of exercise. Also CO_2 response curve and posthyperventilation breathing tests as described by Plum[11] were done. We made certain that patients were awake during respiratory evaluations, although it was often a problem in hypersomniacs. In addition, all patients in the subsample were given careful laryngologic examinations to determine that there was no evident obstruction of the upper airway.

On the last day of the evaluation, cardiac catheterization was carried out in all patients except children. In each adult patient, a catheter was placed in the brachial artery, and a Swan-Ganz catheter was positioned in the pulmonary artery. Continuous recording of pulmonary arterial pressure was made during the subsequent 14 hours which included substantial periods of both wakefulness (in a resting position) and sleep. Arterial blood samples were drawn at various strategic moments throughout the procedure.

Evaluation during sleep. During the first two experimental nights standard sleep measurements were recorded. Respiration was recorded using strain gauges and thermistors, and 200 micron wire electrodes were inserted in intercostal muscles for analysis of EMG during respiratory movements and apneic episodes.

In each patient, on the third and fourth nights, a catheter tip pressure transducer was positioned in the esophagus to record endoesophageal pressure. Peripheral air flow was analyzed using buccal and nasal thermistors as well as a carbon dioxide (CO_2) pickup placed in the oropharynx. The CO_2 pickup measured the percentage of carbon dioxide in the expired air flow. An ear oxymeter continuously measured arterial oxygen saturation. During night four, using the brachioarterial catheter, arterial blood samples were drawn throughout the night for independent validation and calibration of the ear oxymeter.

Definition of Pathological Apneas

An apnea was specifically defined as a cessation of air flow at nose and mouth enduring for a *minimum* of 10 seconds. Apneic events shorter than ten seconds were ignored. An abnormal sleep apnea syndrome was diagnosed if a patient showed a minimum of 30 apneic episodes during seven hours of nocturnal sleep. In addition, the apneic episodes had to occur in nonrapid eye movement (NREM) sleep as well as in REM sleep, and some of the episodes that occurred during NREM periods had to appear in a repetitive sequence. Apneic episodes seen at the onset of sleep or occurring simultaneously with a burst of rapid eye movement are not pathologic.[12]

Three types of apnea have been defined using strain gauge and thermistor recordings made mainly in Pickwickian patients.[13] Specific definitions of types of apnea used in our clinical investigations were consonant with previous guidelines. *Central apnea* was defined by the absence of airflow (indicated by a flat tracing in *both* nasal and buccal thermistors) accompanied by absence of respiratory efforts (indicated by flat tracings in the abdominal and thoracic strain gauges). An esophageal pressure transducer gave a somewhat more reliable recording of respiratory effort, and the cessation of air exchange was confirmed by an ear oxymeter. *Obstructive or upper airway* apnea* was defined for intervals of ten seconds or longer during which there was an absence of airflow (determined by flat tracings in both nasal and buccal thermistors) while the thoracic and abdominal strain gauges showed persistent respiratory effort. Once again, if in place, the esophageal pressure transducer gave a clearer measure of respiratory effort. When micro-wire needle electrodes were inserted in the intercostal muscles, they showed a cessation of intercostal activity during a central apnea; during an upper airway apnea, they generally showed a persistent rhythmic activity which tended to increase in intensity as the apnea progressed. A *mixed or complex apnea* was defined for all intervals of ten seconds or longer during which there was a complete cessation of airflow accompanied by an absence of respiratory effort in the early part of the apneic episode and a resumption of respiratory effort in the latter part. In other words, a mixed apnea had the appearance of a central apnea giving way to an upper airway apnea. The reverse order never seemed to occur.

Two sources of artifact were troublesome. First, prolonged upper airway apnea was accompanied

*We prefer the term "upper airway" apnea, to the widely used "obstructive" apnea. The latter has the unfortunate connotation of a physical obstruction to many, such as intrathoracic goiter, tracheal constriction and the like. These physical obstructions would also be present during wakefulness whereas the functional apneas under consideration appear to be present only during sleep.

by increasing respiratory effort with recruitment of accessory mechanisms that frequently led to fairly vigorous rhythmic body movement. This movement, in turn, often produced artifactual rhythmic deflections on the thermistors tracings. Second, the mercury strain gauges around thorax and abdomen occasionally went out of adjustment leading to an artifactually flat tracing. As indicated earlier, patients were recorded at least one night with intraesophageal pressure transducer and ear oxymeter which greatly increased the reliability of the respiratory evaluation.

Results

General Observations

On the basis of all-night polygraphic recordings, 35 of the 250 patients referred for evaluation of a sleep disorder complaint were diagnosed as having an abnormal sleep apnea syndrome. In nearly every case, the sleep related apneic condition was unambiguously pathological, well beyond the previously stated criteria. Repetitive episodes were seen in NREM sleep and hundreds of individual apneas were tabulated. In every one of the 35 cases, apneic episodes were present only during sleep; spontaneous or induced awakenings were always associated with the resumption of normal respiration. In particular, the fairly lengthy periods of polygraphic wakefulness at the beginning and end of the all-night recording sessions were characteristically associated with rhythmic breathing.

Although the gender of the total patient population was equally distributed, only one of the 35 sleep apnea patients was female. Thirty of the 35 were *not* obese (normal statistical values corrected for height and age were used[14] and the diagnosis of obesity was applied only to patients who were more than 25 percent overweight). Interestingly enough, the proportion of obese patients was slightly higher in the 215 patients who had normal respiration during sleep. The ages of the 35 sleep apnea patients ranged from 9 to 70, with the majority in their forties and fifties. Ten were initially referred with the complaint of insomnia, 14 with uncomplicated daytime sleepiness, and 11 were classified by us as REM narcoleptics.

An important observation was that 16 of the nonobese sleep apnea patients had a moderate essential hypertension and 3 of the 16 had some EKG abnormalities.

Experimental Protocol

Twelve patients were available for further studies. In addition to the previously mentioned factors that influenced their ability to participate, an attempt was made to restrict the subsample to patients who did not have any cardiac abnormality or hypertension during the daytime when first seen in the Sleep Disorders Clinic. The exclusion criteria were not rigid, however, and the final sample included one patient with abnormal findings on an electrocardiogram (EKG) and one with moderate hypertension.

None of the 12 patients was obese. Three were children aged 9, 11 and 15 years. The latter was the only female in the entire group. All three children were enuretics. One of the 12 was 70 years old and the remaining 8 ranged from 35 to 59 years old (mean = 48 years). Two patients complained of insomnia, 5 presented REM narcolepsy, and 5 patients, including the 3 children, presented hypersomnia.

Because of the previously mentioned artifacts, we will present quantitative data only from these 12 patients.

Clinical symptomatology. Although none of the patients in the subsample was either aware of or complained of any respiratory problem, we learned from the patients' spouses (or mothers in the three children) that the patients were very loud snorers, and that the history of snoring had always preceded the sleep complaint. Several patients were also described as having a snorting or gasping respiration during sleep. The shortest interval reported between the onset of snoring and the onset of a sleep complaint was two years. Polygraphic recordings confirmed that snoring occurred as patients began to breathe at the end of each apneic episode.

Sleep pathology and sleep recordings. The polygraphic recordings confirmed the clinical diagnosis of insomnia, REM narcolepsy, and hypersomnia in the respective patients. An abnormal sleep structure was also present in each case; despite the three different clinical complaints, a great reduction or a complete absence of stage 3 and 4 NREM (slow wave) sleep occurred in all 12 patients. The definition of sleep stages was difficult in patients presenting predominantly obstructive apnea, since the resumption of respiration was usually accompanied by snorting and movement artifact which

made the polygraphic recordings difficult to evaluate. All of the patients, even those complaining of insomnia, were difficult to awaken during the apneic episodes, and, if suddenly awakened, were completely disoriented and unable to cope with the surrounding reality. Their sleep was very agitated, and frequently these patients presented abnormal movements before resuming respiration at the end of apnea. These movements were either simple movements of the feet and hands, best described as a "flapping tremor," or were of a greater magnitude involving the whole body. (Fifteen minutes after sleep onset the bed usually looked like a battlefield.)

The fewest apneic episodes recorded on a single night was 68 and the most was 682. Apnea ranged in duration from 10 to 190 seconds. However, each of the categories of sleep disorders differed slightly in the mean duration of an apnea: insomniacs on the average having the longest apneic episodes (mean = 44 seconds) and REM narcoleptics having the shortest (mean = 19 seconds). The duration of apneic episodes varied widely in each patient. No explanation for the continuous intrasubject variations as yet has been found. The three types of sleep disorders also differed in the type of predominant apnea they presented; though all three types of apnea were seen in all cases, central apnea was predominant in insomniacs while the predominant apnea for hypersomniacs and REM narcoleptics was obstructive (see Table 1).

Hypersomniacs, REM narcoleptics and insomniacs behaved differently at the end of an apneic episode. When hypersomniac patients resumed breathing, the EEG usually changed from a theta rhythm to a slow alpha which looked like stage 1 NREM sleep. However, sleep stages were difficult to identify in these recordings since the apneas were predominantly obstructive and caused artifact in the recordings. Hypersomniac patients seldom presented short alpha arousals at the end of an apneic episode. The digastric EMG, which during the episode was very low and similar to that of REM sleep, suddenly increased at the end of the apneic episode.

In the REM narcoleptics, who also presented predominantly obstructive apneas, the sleep recordings were similar to those of the hypersomniacs. However, the former more frequently presented short alpha arousals (arousals with alpha rhythm in the EEG) than did the hypersomniacs. In addition, longer awakenings which are part of the classical symptom of disrupted nocturnal sleep in REM narcolepsy more frequently followed the end of an apneic episode in REM narcoleptics than in hypersomniacs.

Since the insomniacs presented predominantly nonobstructive apneas, sleep stages were more easily identified in their recordings than in those of the hypersomniacs and REM narcoleptics. Of the three sleep disorders, insomniacs most frequently presented alpha arousals at the end of an apneic episode. However, occasionally only a lightening of sleep, a change from NREM stage 2 to stage 1, rather than a complete arousal occurred. For reasons that we have been unable to determine, after repetitive apneic episodes insomniac patients awakened completely. Neither the number of previous apneic episodes nor the duration of any given apneic episode appeared to be related to the awakenings. The patients stayed awake for 10 to 60 minutes and presented three to six such waking periods per recording night.

Blood gas values during sleep. Blood gas values showed extreme fluctuations during the repetitive sleep apneic episodes. Oxygen levels reached high values of 96 mm of mercury following resumption of respiration and fell as low as 40 mm of mercury at the end of an apneic episode. Concurrently measured carbon dioxide pressure (PCO_2) ranged from levels near 40 mm of mercury up to 60 mm of mercury during the longest apnea. Most of the data were from the nine adults. In the three chil-

TABLE 1.—*Types of Apnea Presented by the Patients Studied*

Patient Population	*Mean total of apneic episodes per night*	*Mean duration of each apnea (seconds)*	*Mean percent of apnea occurring during NREM sleep*	*Type of predominant apnea as percent of total apneas**
Insomniac, N=2	236	44.0	87.5	Diaphragmatic (central) 95.0
Hypersomniacs, N=5	474	31.3	88.5	Obstructive 85.4
REM narcoleptics, N=5	220	19.0	93.2	Obstructive 49.2

*Though all three types of apnea (diaphragmatic [central], obstructive and mixed) were seen, values are given only for the *predominant* type of apnea observed in each classification.

dren, the brachio-arterial catheter was not left overnight, but samples were drawn during wakefulness and one daytime nap.

Pulmonary arterial pressure during sleep. Throughout the night, in association with the repetitive apneic episodes, a progressive increase in systolic and diastolic pulmonary arterial pressure was recorded. Pulmonary arterial pressure reached levels as high as 87 mm of mercury (systolic) and 50 mm of mercury (diastolic). The patients who had primarily diaphragmatic (central) apneic episodes showed less severe increases in

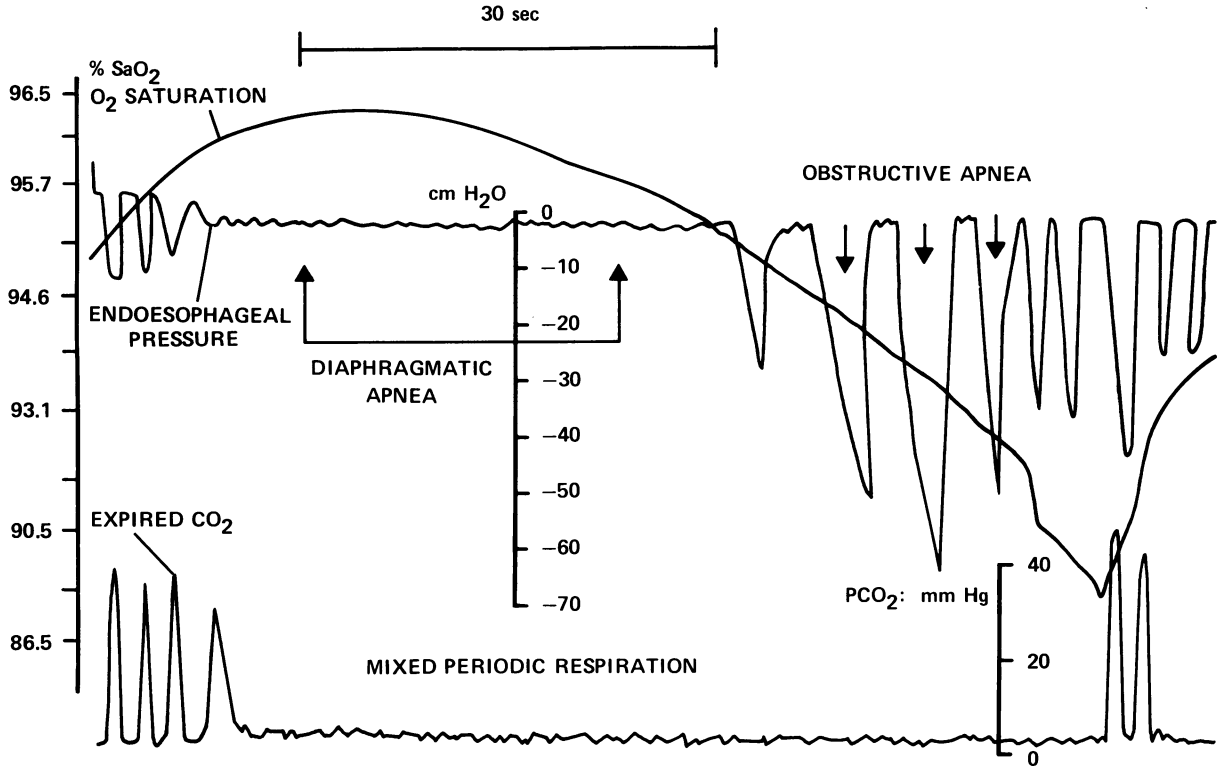

Figure 1.—Polygraphic recording of a mixed type sleep apnea in a 49-year old man whose daytime pulmonary function tests are reported in Table 2. At the beginning of the record there is a "stopped diaphragm" episode; then, on the right half of the recording, one can see that diaphragmatic movements resume (endo-esophageal pressure), but no air flows at the peripheral level. The endo-esophageal pressure progressively increases until, finally, the peripheral obstruction is lifted and air flows normally through nose and mouth.

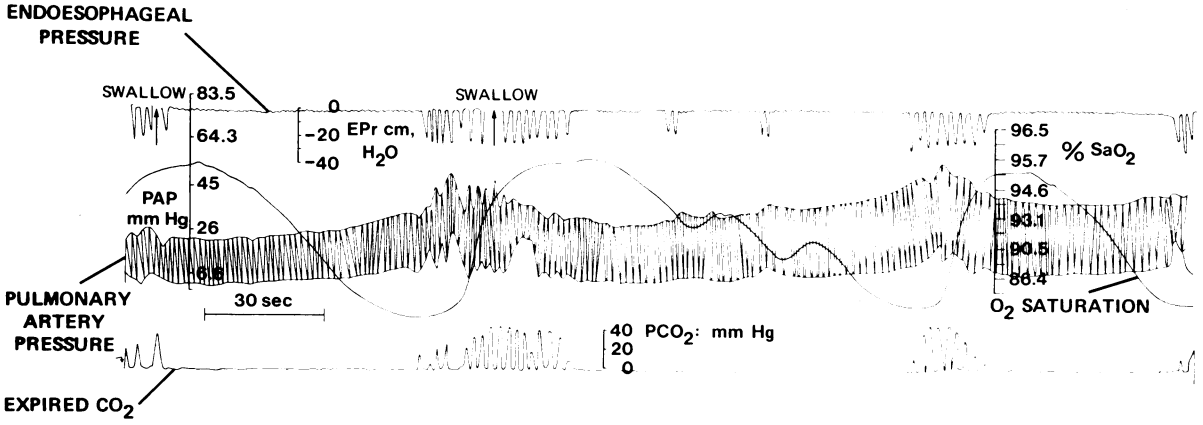

Figure 2.—Recording during sleep of a 54-year-old man who presents repetitive diaphragmatic apneic episodes. In each of the three episodes shown, pulmonary arterial pressure gradually increased during the episodes reaching a peak at the resumption of ventilation. These episodes occurred at the beginning of a series of repetitive apneic episodes; in less than ten minutes, the pulmonary arterial pressure reached values as high as 62 mm of mercury (systolic) and 45 mm of mercury (diastolic) at the end of a sleep apneic episode.

pulmonary arterial pressure than those with predominantly obstructive apnea.

The systolic and diastolic pulmonary arterial pressure usually began to increase after 15 to 20 seconds of apnea. In isolated apneic episodes, the pulmonary arterial pressure returned to the baseline level when normal respiration resumed. When several consecutive apneic episodes occurred, the systolic and diastolic pulmonary arterial pressure did not return to baseline levels between apneic episodes, but progressively rose to the highest values after five to ten minutes of repetitive apnea. When a normal breathing pattern was resumed or if the patient was awakened, the pulmonary arterial pressure returned to normal values in less than 100 seconds.

The highest systolic and diastolic pulmonary arterial values were always recorded at the resumption of respiration, between two consecutive apneic episodes. The systolic and diastolic pulmonary arterial pressure values were higher when associated with repetitive obstructive apneas than with diaphragmatic (central) apneas. This relationship was present even if the duration of the apnea was similar and even if the blood gas measurements showed a similar degree of hypoxemia, hypercapnia and acidosis.

Pulmonary studies during wakefulness. The waking pulmonary evaluations of the sleep apneic patients were compared to results obtained in the same laboratory on normals and patients with chronic lung diseases. Daytime pulmonary studies made both at rest and during exercise were within normal limits (see Table 2) in all sleep apneic patients. The waking oxygen saturation levels were also normal or slightly below normal in all patients (the lowest value was 94 percent oxygen saturation in one hypersomniac patient). The post-hyperventilation test was normal except for the 9-year-old child who showed considerably greater hypoventilation than his resting baseline level.

The CO_2 response curve was the only test for which results were below normal levels in two adults and the 9-year-old child. The two adults presented a slower rate of increase than normal (with 14 and 14.5 liters per minute for 48 mm of mercury compared with 21 to 23 liters per minute for controls) and reached a plateau with ventilation of 25 liters per minute at 50 mm of mercury. These results are borderline normal. In the 9-

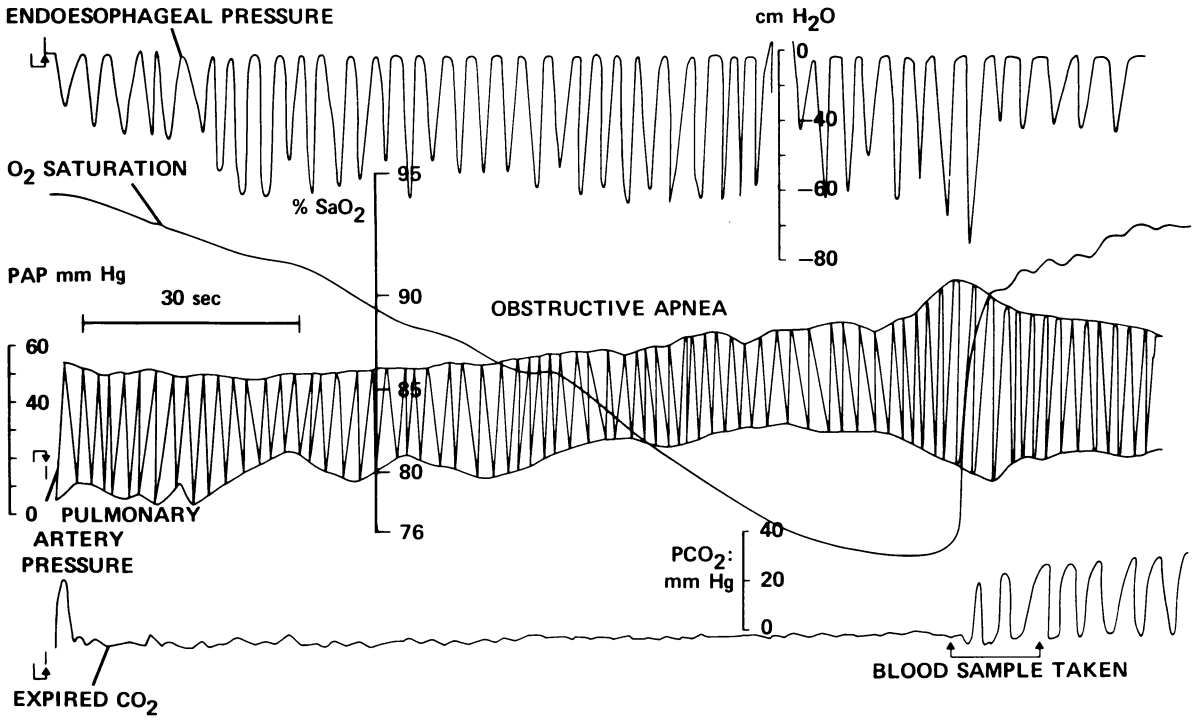

Figure 3.—Recording of an obstructive sleep apneic episode of 165 seconds duration in a 48-year-old man. The pulmonary arterial pressure progressively increased and was 75 mm of mercury (systolic) and 25 mm of mercury (diastolic) at the end of the episode when respiration resumed through the upper airway (airway PCO_2). When the blood sample was drawn, the following values were obtained: pH = 7.28; arterial carbon dioxide partial pressure ($PaCO_2$) = 47 mm of mercury; arterial oxygen partial pressure (PaO_2) = 46 mm of mercury; arterial oxygen saturation (SaO_2) = 71.5 percent.

year-old boy the CO_2 response curve was significantly lower than normal value.

Rhinolaryngologic examination during wakefulness. Laryngologic examination of patients with predominantly obstructive sleep apnea failed to show any defect responsible for the functional obstruction during sleep.

Follow-up and treatment. Four hypersomniac patients (two adults and two children) with predominantly obstructive sleep apnea syndromes were monitored for one night with a rigid hypopharyngeal tube positioned through the nostril. For three patients this procedure did not decrease the number of obstructive apneas during sleep compared with results of previous recordings. In the fourth case there was a 10 percent decrease from baseline. One adult hypersomniac patient had nasal reconstruction, but the number of apneic episodes remained unchanged.

During the follow-up period the sleep disorder increasingly impaired the daily lives of the 12- and 15-year-old children. In the 12-year-old child, an adenoidectomy and a tonsillectomy were done during the follow-up period with no improvement of the apnea syndrome. In both children, a borderline but progressive hypertension developed (blood pressure = 150/100 and 160/105 mm of mercury). No specific cause could be found to explain the development of this symptom in spite of an extensive evaluation. A chronic tracheostomy was then carried out on both children. Within 15 hours after the procedure the systemic hyperten-

TABLE 2.—*Results of Daytime Pulmonary Studies in a Patient with Predominant Central Apneic Episodes (Patient 1) and in a Patient with Mixed and Obstructive Apnea (Patient 2)*

	Patient 1—54-year-old man					*Patient 2—49-year-old man*			
		Exercise Sessions					*Exercise Sessions*		
	Supine Rest	*No. 1*	*No. 2*	*No. 3*	*No. 4*	*Supine Rest*	*No. 1*	*No. 2*	*No. 3*
Bicycle ergometer	0	300	600	900	1,100	..	300	600	900
Heart rate	53	58	95	135	170	86	106	134	172
Arterial PO_2 (mmHg)	97	98	100	93	97	95	94	90	93
Arterial PCO_2 (mmHg)	34	42	42	41	35	40	45	46	41
Arterial pH	7.44	7.35	7.35	7.33	7.30	7.35	7.33	7.30	7.26
Arterial HCO_3 (mEq/L)	22.5	22.5	22.5	21.0	16.7	21.5	23	21.9	17.8
Arterial O_2 sat. (percent)	97.2	97.5	97.2	96.0	96.0	94.6	95.6	95.3	95.2
Resp. rate (freq/min)	20.7	20.5	23.5	28.0	33.0	13.7	19.5	23	27.5
Tidal volume (ml)	632	1,167	1,660	2,130	2,574	474	968	1,393	1,708
Minute ventilation	13.1	23.9	39.0	59.6	84.9	6.5	18.9	32.0	47.0
Alveolar ventilation	8.36	15.6	28.8	40.8	63.2	4.6	12.5	23.1	38.9
Dead space ventilation	4.71	8.28	10.2	18.9	21.8	1.9	6.4	8.9	8.1
Dead space/tidal vol. (percent)	36.0	34.6	26.0	31.6	25.6	28.6	33.7	27.8	17.2
O_2 uptake (L/min)	0.34	0.92	1.55	2.19	2.73	.223	.787	1.432	1.956
O_2 uptake index	4.8	13.2	22.2	31.2	39	3.36	11.9	21.6	25.5
O_2 pulse max.	0.09	0.23	0.23	0.23	0.23	..	..	..	..
Alveolar PO_2 (mmHg)	115	110	104	104	112	107.5	96.3	96.8	105.7
Alveolar-arterial O_2 diff. (mmHg)	18	2	4	11	15	12.5	2.3	6.8	12.7
CO_2 production (L/min)	.329	.760	1.40	1.94	2.56	..	..	..	..
Resp. exchange ratio	.98	.82	.90	.88	.935	.97	.83	.86	.95
Vent. equiv. O_2 uptake	38.9	25.9	25.1	27.1	31.0	..	..	..	..

	Lung Volumes	*Predicted Normal*	*Lung Volumes*	*Predicted Normal*
Vital capacity (cc)	4774	4320	3434	3690
Insp. capacity (cc)	2980	2880	2203	2460
Exp. reserve vol. (cc)	1794	1440	1231	1230
FRC (cc)	4280	3408	2888	2796
Residual vol. (cc)	2486	1968	1657	1566
Total lung capacity (cc)	7260	6288	5091	5256
Helium wash-out (min)	20	Stabilized at 18	20	Stabilized at 10 and 19

Ventilatory Mechanics	*Pre-*	*Post-*	*Predicted Normal*	*Pre-*	*Post-*	*Predicted Normal*
Timed exp. capacity (cc)	4573	4396	4320	3173	3173	3690
in seconds	9	11	..	5.2	3.7	..
Max exp. flow rate, L/min.	360	281	223	423	466	262
Max. breathing cap., L/min.	154	176	142	134	156	131

Resp. = respiration
freq/min = frequency/minute
Vol. = volume
Max. = maximum
Vent. equiv = ventilatory equivalent
insp. = inspiratory
exp. = expiratory
FRC = functional respiratory capacity
Cap. = capacity
Sat. = saturated

sion was no longer present (blood pressure = 120/80 and 125/80 mm of mercury). Episodes of sleep apnea were also virtually eliminated after tracheostomy.

Comment

The occurrence of minor respiratory irregularities in normal adults during sleep is well known.[13-16] Sudden death during sleep has been reported in patients with neurological problems involving respiratory areas,[17,18] such as poliomyelitis and Ondine's Curse syndrome. The typical Pickwickian syndrome, where respiratory and cardiovascular dysfunctions during both sleep and wakefulness are associated with obesity, has been well documented.

The present study indicates that respiratory abnormalities, which previously had been emphasized only in populations with obvious central nervous system pathology or in notably obese populations, are also found rather commonly during the sleep of nonobese patients who have a chronic sleep disturbance. Indeed, the present case finding data from male sleep disorder patients suggest that the frequency of a sleep apnea syndrome among such patients may be as high as 25 to 30 percent. It should also be emphasized that with rare exceptions, absolutely no abnormality existed in the waking state. Thus examinations conducted during wakefulness would clearly fail to show any problem. This factor explains why the condition remained uniformly undiscovered at the time of referral in our case series, and further dictates that all male patients complaining of a sleep problem should routinely have respiratory evaluation during sleep. Although none of the patients was specifically aware of the respiratory problem, a history of heavy snoring, beginning before the development of the sleep disorder, was present in every case. Such a history should probably be regarded as an important diagnostic clue.

All of the patients in this study—insomniacs, REM narcoleptics and hypersomniacs—although nonobese, presented patterns during sleep similar to those seen in obese Pickwickian patients. The rate of respiratory pauses during sleep was the same as that occurring in the Pickwickian syndrome, and a similar degree of hypoxemia, hypercapnia and acidosis occurred repetitively throughout the night in association with these pauses. Changes in pulmonary arterial pressure during sleep were also similar to those reported by Coccagna and co-workers,[19] Lonsdorfer and co-workers,[20] Kurtz and co-workers[21] and Fruhman[17] in Pickwickian patients and in patients having a primary hypoventilation syndrome. However, unlike both the Pickwickian patients and the patients with primary hypoventilation syndromes (except for one child with an abnormal CO_2 response curve and an abnormal posthyperventilation test), the nonobese patients in the present study had normal pulmonary function during wakefulness.

What leads to a respiratory abnormality during sleep in these patients? Since no primary defect in the respiratory control mechanisms was detected during wakefulness, the abnormality in breathing would appear to be related to central nervous system structures involving both brain-stem respiratory neurons and neurons controlling sleep.

A second question is: Why do each of these apneic episodes end? The carotid chemoreceptors could be involved in the sudden resumption of respiration, particularly in diaphragmatic (central) apnea, but it is difficult to understand why the durations of apneic episodes have wide variations in individual patients. One would assume that, if hypoxemia, hypercapnia and acidosis played a major role in the resumption of respiration, an apneic episode would end when specific low values were reached. This was not the case; some apneic episodes were very short, the episode ending before significant changes occurred in the blood gas levels.

A relationship was found between the three different sleep disorders and the type of sleep induced respiratory abnormality; while all three types of apnea were observed, sleep apneic patients with insomnia presented a predominance of diaphragmatic (central) type apnea, and REM narcoleptics and hypersomniacs with sleep apnea had a majority of obstructive pauses. The sample sizes for these three categories of sleep disorders were small, but further experience with a larger number of sleep apneic insomniacs, REM narcoleptics and hypersomniacs has confirmed this relationship. One hypothesis suggested by this relationship is that the difference in the type of predominant apnea could account for the difference in the sleep symptomatology. Although these patients differed in both the type of sleep complaint and the type of predominant apnea, the pulmonary arterial changes during sleep and the frequency of systemic hypertension during wakefulness were similar in the two groups.

An "essential" hypertension was found in approximately half of the nonobese apneic patients

in this study. Can sleep apnea induce secondary, permanent cardiovascular changes? Although we were unable to continuously monitor the systemic arterial pressure during sleep before and after tracheostomy as did Coccagna and co-workers[22] in five similar cases, we would like to emphasize the medical history of the two children. After a tracheostomy, which bypassed the functional obstruction induced by sleep, the essential hypertension disappeared completely. It is difficult to determine exactly why systemic arterial pressure may be influenced by sleep apneic episodes. Our current hypothesis is that repetitive hypoxia, hypercapnia and acidosis are involved. We are currently testing this hypothesis using a more extensive cardiovascular protocol and a new series of sleep apneic patients.

A final issue is the possible interaction of certain drugs which depress the central nervous system control of respiration with the sleep apneic syndrome. At least two instances of barbiturate-induced crises have already been reported in patients with sleep apnea; one eventually led to death.[23] One of our obstructive sleep apneic patients had an acute respiratory episode with upper airway obstruction secondary to a supposed hypopharyngeal collapse. This episode was precipitated by 10 mg intramuscular injections of diazepam given twice at one-hour intervals as a premedication for surgical operation. Within 10 minutes after the second injection, the patient presented such a severe reaction that an emergency tracheostomy was considered. These reactions suggest that certain chemotherapies should be cautiously applied to patients who may have a sleep apnea syndrome, especially since physicians frequently prescribe barbiturates or benzodiazepines or both for insomniacs.

After this report was submitted, we became aware of a paper by Sackner and co-workers[24] describing the existence of a typical sleep apnea syndrome in 12 adult patients presenting with daytime sleepiness. In their case material, only two patients fail to meet the 25 percent overweight criterion of obesity. Their data therefore suggest a need for increased awareness of the existence of these problems in the nonobese population.

REFERENCES

1. Burwell C, Robin E, Whaley R, et al: Extreme obesity associated with alveolar hypoventilation: A Pickwickian syndrome. Am J Med 21:811-818, 1956

2. Lugaresi E, Coccagna G, Mantovani M, et al: Impersonnie essenziali associate a respirazione periodica. Sist Nerv 21:18-27, 1969

3. Coccagna G, Mantovani M, Berti-Ceroni G, et al: Sindromi ipersonniche-ipoventilatore. Minn Med 61:1073-1084, 1970

4. Severinghaus J, Mitchell R: Ondine's curse—Failure of respiratory center automatically while awake. Clin Res 10:122, 1962

5. Guilleminault C, Eldridge F, Dement W: Narcolepsy, insomnia and sleep apneas. Bull Physiopathol Resp 8:1127-1138, 1972

6. Guilleminault C, Eldridge F, Dement W: Insomnia with sleep apnea—A new syndrome. Science 181:856-858, 1973

7. Rechtschaffen A, Kales A: Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. National Institutes of Health Publication No. 204. Washington, DC, Superintendent of Documents, Book 1-62, 1968

8. Bulow K, Ingvar D: Respiration and state of wakefulness in normals studied by spyrography, capnography and EEG. Acta Physiol Scand 51:230-238, 1961

9. Duron B, Tassinari C, Gastaut H: Analyse spirographique et electromyographique de la respiration au cours du sommeil controlé per l'EEG chez l'homme normal. Rev Neurol 115:562-574, 1966

10. Duron B: La fonction respiratoire pendant le sommeil physiologique. Bull Physiopathol Resp 8:1277-1288, 1972

11. Plum F, Brown H, Snoep E: Neurologic significance of post-hyperventilation apnea. JAMA 181:1050-1055, 1962

12. Aserinsky E: Physiological activity associated with segments of the rapid eye movement period, *In* Kety S, Evarts E, Williams H (Eds): Sleep and Altered States of Consciousness. Baltimore, Williams and Wilkins, 1967, pp 335-350

13. Tassinari C, Dalla Bernardina B, Cirignotta F: Apneic periods and the respiratory related arousal patterns during sleep in the Pickwickian syndrome: a polygraphic study. Bull Physiopathol Res 8:1087-1102, 1972

14. Weights, Height and Age of Adults—United States, 1960-1962. U.S. Public Health Service. Public Health Service Publication No. 1000, Series U-No. 14: Washington, DC, 1966

15. Snyder F, Hobson J, Morrison D, et al: Changes in respiration, heart rate and systolic blood pressure in human sleep. J Appl Physiol 19:417-422, 1964

16. Robin E, Whaley R, Crump C, et al: Alveolar gas tension, pulmonary ventilation and blood pH during physiologic sleep in normal subjects. J Clin Invest 37:981-989, 1958

17. Fruhman G: Hypersomnia with primary hypoventilation syndrome and following cor pulmonale. Bull Physiopathol Resp 8: 1173-1179, 1972

18. Plum F, Swanson A: Abnormalities in central regulation of respiration in acute and convalescent poliomyelitis. Arch Neurol and Psych 80:267-285, 1958

19. Coccagna G, Mantovani M, Brignami F, et al: Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. Bull Physiopathol Resp 8:1159-1172, 1972

20. Lonsdorfer J, Meunier-Carus J, Lampert-Benignus E, et al: Aspects hemodynamiques et respiratoires du syndrome Pickwickien. Bull Physiopathol Resp 8:1181-1192, 1972

21. Kurtz D, Bapst-Reiter J, Fletto R, et al: Les formes de transition du syndrome Pickwickien. Bull Physiopathol Resp 8: 1115-1125, 1972

22. Coccagna G, Mantovani M, Brignami F, et al: Tracheostomy in hypersomnia with periodic breathing. Bull Physiopathol Resp 8:1217-1227, 1972

23. Hishikawa Y, Furuya E, Wakamatsu H, et al: A polygraphic study of hypersomnia with periodic breathing and primary alveolar hypoventilation. Bull Physiopathol Resp 8:1139-1151, 1972

24. Sackner M, Landa J, Forrest T, et al: Periodic sleep apnea —Chronic sleep deprivation related to intermittent upper airway obstruction and central nervous system disturbance. Chest 67: 164-171, 1975