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During Physiologic Sleep in Normal Subjects**

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ALVEOLAR GAS TENSIONS, PULMONARY VENTILATION AND BLOOD pH DURING PHYSIOLOGIC SLEEP IN NORMAL SUBJECTS¹

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An increase in alveolar CO₂ tension has been reported to accompany normal sleep (1, 2). The study of gas tensions during sleep has, however, been limited by two factors:

1) No accurate method of breath-to-breath analysis has been available, so that only spot checks of alveolar CO₂ tensions have been used to compare waking with sleeping levels.

2) Procedures for obtaining alveolar or arterial samples have been disturbing to the subjects. It has not been possible, therefore, to study deep sleep by these methods.

The use of a rapid acting infrared CO₂ spectrophotometer has circumvented both of these limitations and permitted an accurate and continuous study of the alveolar CO₂ changes that occur during sleep.

This paper will deal with the magnitude and mechanism of CO₂ retention during sleep, and with the changes that occur in pulmonary ventilation, respiratory gas exchange, mechanics of breathing and blood pH.

METHODS

Each subject reported to the laboratory late in the evening without special preparation. A comfortable bed in a dark environment was provided. The necessary manipulations for a control series of measurements (see below) were carried out. The subject was then allowed to fall asleep. No sedative drugs were used. All observations were made with the subject in approximately the same body position. During the course of each study, the depth of sleep as judged by degree of consciousness, amount of motion and response to stimuli was frequently recorded.

A tight-fitting face mask was used for the administration and collection of gas. The mask was attached to a

low resistance valve with a small dead space. The arrangement was comfortable enough so that most subjects were able to sleep with the mask in place. During collection periods the system was frequently checked for leaks.

Expired air was collected in Douglas bags and the volume measured in a Tissot spirometer.

Alveolar CO₂ tensions were measured with a rapid acting infrared CO₂ analyzer. It has been shown by Collier, Affeldt and Farr (3) and verified by our group that in subjects without pulmonary disease, the peak end tidal CO₂ tension measured by this apparatus is equal (plus or minus 2 mm. Hg) to arterial CO₂ tension. This technique provided a breath-to-breath measurement of alveolar CO₂ tension without distraction or discomfort to the subject. CO₂ concentrations in expired air were measured by the same apparatus.

The oxygen concentrations in expired air samples were measured with a Pauling oxygen analyzer.

The volume of alveolar ventilation was calculated by the Bohr equation (4). Oxygen consumption, CO₂ production, alveolar oxygen tension, and the expiratory exchange ratio were calculated by standard methods (5, 6).

The ventilatory response to CO₂ was tested by the administration of CO₂ mixtures. Each mixture was administered for at least fifteen minutes before expired air was collected. The response to CO₂ was expressed as the ratio of the increment in alveolar ventilation to the increment in alveolar CO₂.

Appropriate vessels were intubated with No. 18 polyvinyl catheters for the collection of blood. The catheter was filled with sodium-heparin solution diluted 1 to 10 with normal saline. Between periods of blood withdrawal, a sterile cap was placed on the catheter. In this manner blood could be obtained without disturbing or waking the subjects.

Blood pH was measured by means of a Beckman pH meter. Readings were made at room temperature and converted to body temperature by the Rosenthal correction factor (7).

The oxygen content and saturation of arterial blood were determined by the technique of Van Slyke and Neill (8).

The mechanics of breathing during the waking and sleeping states were studied by measurements of pulmonary compliance and mean airway resistance.² These

² These measurements were made by Dr. Roe E. Wells.

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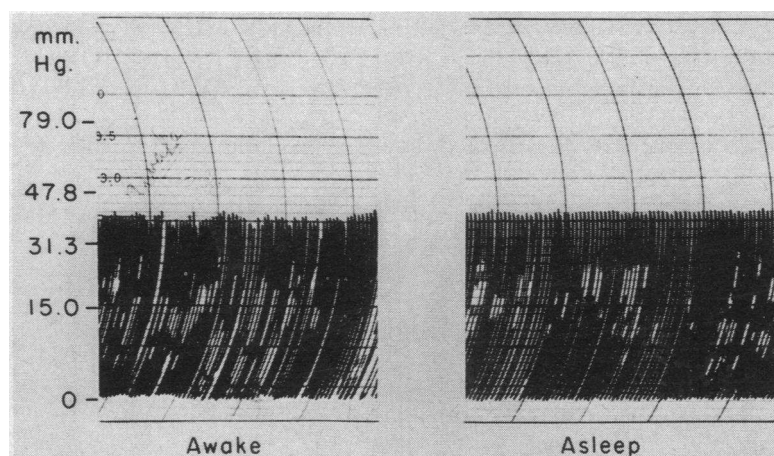


FIG. 1. A COMPARISON OF THE BREATH-TO-BREATH VARIATION OF ALVEOLAR CARBON DIOXIDE TENSION DURING THE WAKING AND SLEEPING STATES

measurements were made by the technique of Mead and Whittenberger (9). An intraesophageal balloon was used for the measurement of intrathoracic pressure. These studies were performed with the subject in the right lateral decubitus position awake and asleep.

Using these methods, breath-to-breath alveolar CO_2 tensions were obtained before and during sleep in 14 normal males. For comparison, 6 normal males were kept fully awake during the night and hourly alveolar CO_2 tensions were determined.

The ventilatory response to CO_2 , awake and asleep, was tested in 10 subjects.

In three subjects arterial blood pH was determined and in two of these subjects venous pH was determined simultaneously. A consistent difference between arterial and venous pH was observed in the sixteen samples studied in this way. Therefore, the pH studies made on four additional subjects were carried out on venous blood only to obviate the necessity of an indwelling arterial

catheter. Arterial oxygen saturations were determined in two subjects.

Pulmonary compliance and mean airway resistance studies were carried out in three subjects.

RESULTS

The changes that occurred with sleep may be considered under the following categories:

- 1) The breath-to-breath *variation* of alveolar CO_2 .
- 2) The *level* of alveolar CO_2 tension.
- 3) *Alveolar oxygen tension* and *arterial oxygen saturation*.
- 4) *Total ventilation, alveolar ventilation, oxygen consumption, CO_2 production* and *respiratory exchange ratio*.
- 5) *Ventilatory response* to CO_2 .
- 6) *Blood pH*.
- 7) *Mechanics* of breathing.
- 8) *Rhythm* of respiration.

Changes in breath-to-breath variation of alveolar CO_2 tension

An analysis of variance (10) was performed on the breath-to-breath variation of alveolar CO_2 tension in four representative subjects comparing a two minute period during the waking state with a similar period during the sleeping state.

During the waking state there was a mean breath-to-breath variation of alveolar CO_2 tension of 0.8 mm. Hg. Such variation reflects changes in both metabolism and in the control of ventilation.

TABLE I

A comparison of alveolar carbon dioxide tension awake and one hour after the onset of sleep

Subject	Alveolar carbon dioxide tension mm. Hg	
	Awake	Asleep
R. W.	41	44
A. G.	37	41
J. M.	41	47
J. S.	38	40
J. A.	42	46
R. C.	43	45
R. W.	40	41
R. R.	40	45
L. S.	42	45
O. B.	43	47
E. R.	44	49
Mean	41.0	44.6
	$p < 0.001$	

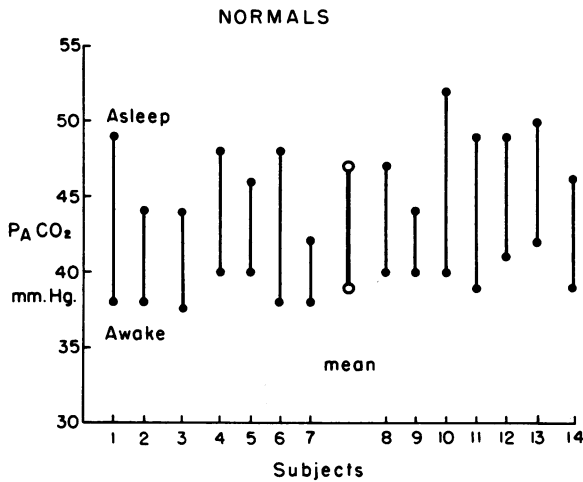


FIG. 2. PEAK ALVEOLAR CARBON DIOXIDE TENSIONS DURING SLEEP

During sleep these fluctuations virtually vanished. The mean breath-to-breath variation fell to 0.2 mm. Hg. An example of this stabilization of respiration is shown in Figure 1. The peak end tidal value of CO₂ during each breath is equal to alveolar CO₂ tension. The stability of alveolar CO₂ tension during sleep is obvious. The appearance of such stable respiration is a characteristic change that occurs with the onset of sleep. Its time of appearance correlates well with electroencephalographic changes indicating sleep (11).

Changes in the level of alveolar CO₂ tension

The infrared CO₂ analyzer provided about 7,000 measurements of alveolar CO₂ tension during each study. It is obviously not practical to report the complete data from each subject. To define the magnitude of the changes in alveolar CO₂ tension during sleep, three selected groups of data are presented:

a) A comparison of the average waking alveolar CO₂ tension with the average alveolar CO₂ tension after one hour of sleep. These data were obtained by averaging the breath-to-breath values of alveolar CO₂ tension during a two minute period while each subject was awake, and during a two minute period after the subject had been asleep for one hour. These data are shown in Table I. The mean increase in CO₂ tension after one hour of sleep is 3.6 mm. Hg. This is a highly significant change.

b) A comparison of the average waking alveolar CO₂ tension with the highest alveolar CO₂ tension attained and maintained for at least four consecutive breaths during sleep. The peak value obtained from four consecutive breaths insured that falsely high values produced by breath-holding would not be included. These data are shown in Figure 2, and it can be seen that the peak increase may be as high as 14 mm. Hg (Subject 10). The mean peak increase for the group is 9 mm. Hg which is a highly significant change.

c) Data illustrating the pattern of CO₂ increase during several hours of sleep. These data, obtained from three normal subjects, are shown in Figure 3. Alveolar CO₂ tensions are plotted along the ordinate and time in hours, along the abscissa. The straight lines connecting points indicate that continual CO₂ analysis was performed but only hourly measurements were charted. These data show considerable variation, apparently changing with the level of consciousness of the subject, but the values are higher during sleep than during waking. The peak rise in alveolar CO₂ tension tended to develop within the first one to two hours of sleep. This is consistent with the general belief that this period represents the time of deepest sleep (2).

These data from sleeping subjects may be com-

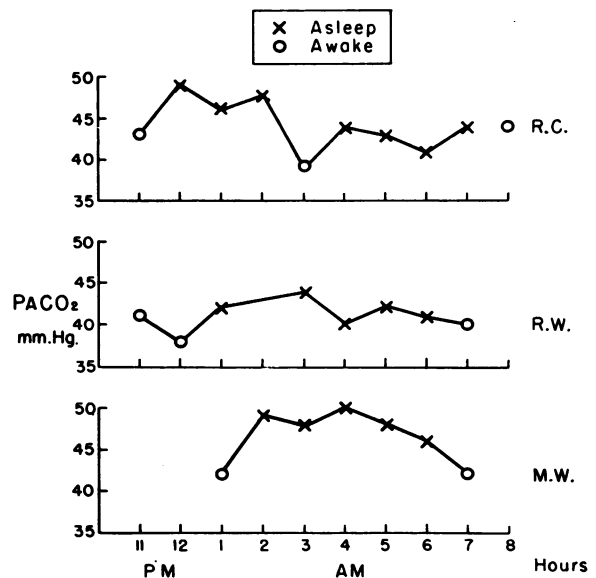


FIG. 3. HOURLY CHANGES IN ALVEOLAR CARBON DIOXIDE TENSION IN THREE NORMAL SUBJECTS

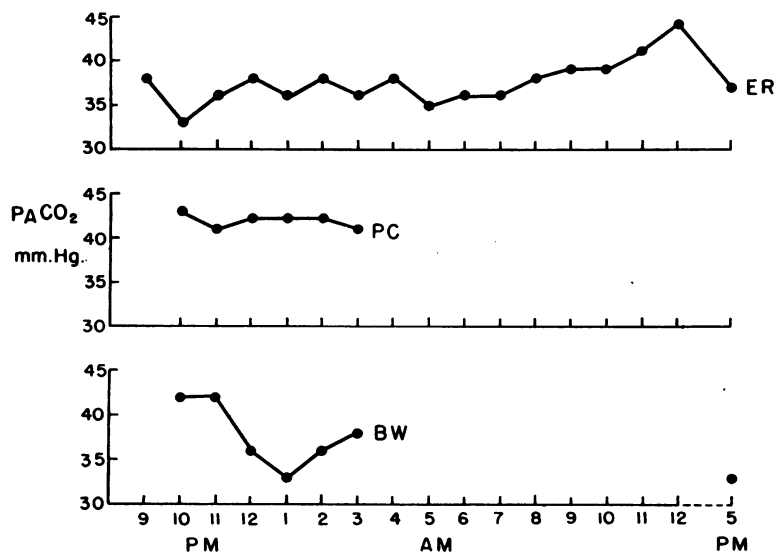


FIG. 4. HOURLY CHANGES IN ALVEOLAR CARBON DIOXIDE TENSION IN WAKING NORMALS AT NIGHT

pared with those shown in Figure 4. These data are taken from three normal subjects, awake and fully conscious during a given night of study. It can be seen that alveolar CO_2 tension in the non-sleeping subjects does not increase consistently during the night. This finding indicates that there is no normal diurnal cycle of alveolar CO_2 tension independent of sleep.

Changes in alveolar oxygen tension and arterial oxygen saturation

The data in Table II demonstrate a mean decrease in alveolar oxygen tension of 3 mm. Hg during sleep. This decrease is not statistically

TABLE II

A comparison of alveolar oxygen tension awake and asleep

Subject	Alveolar oxygen tension mm. Hg	
	Awake	Asleep
A. G.	101	106
J. S.	109	109
J. A.	107	104
R. C.	106	106
R. W.	113	111
R. R.	122	111
L. S.	105	100
O. B.	105	92
Mean	108.4	104.9
	$p > 0.20$	

significant.³ The arterial oxygen saturations during sleep, shown in Table III, confirm the absence of arterial unsaturation during sleep.

Changes in total ventilation, alveolar ventilation, oxygen consumption, CO_2 production and respiratory exchange ratio

Changes in total and alveolar ventilation, oxygen consumption, CO_2 production and respiratory exchange ratio during sleep are shown in Table

³ Theoretically an increase in alveolar CO_2 tension without a change in the respiratory exchange ratio will result in a fall in alveolar oxygen tension. Alveolar oxygen tensions were calculated from experimentally obtained alveolar CO_2 tensions, expired CO_2 concentration and inspired and expired oxygen concentrations. The failure to demonstrate a significant decrease in alveolar oxygen tension in the face of an increased alveolar CO_2 tension probably is related to methodological problems. Oxygen analysis was performed by means of a Pauling oxygen analyzer which has an accuracy at best of plus or minus 1 per cent. Small errors in the determination of inspired and expired oxygen concentration will produce large errors in the calculation of respiratory exchange ratio. (This problem presumably accounts for the fact that a number of the respiratory exchange ratios shown in Table IV are greater than 1.00.) Since four separate experimental observations were necessary to calculate each alveolar oxygen tension, the inherent experimental error is obviously greater than would be expected if only a single measurement was required, as in the case of alveolar CO_2 tension.

IV. There is a mean decrease of 2.15 L. per minute in total ventilation and a mean decrease of 1.66 L. per minute in alveolar ventilation. These changes are statistically significant. There is a mean decrease in oxygen consumption of 57 ml. per minute and a mean decrease in CO₂ production of 79 ml. per minute during sleep.⁴ These changes are also statistically significant. The respiratory exchange ratio is not significantly different during sleep.

Changes in the ventilatory response to CO₂

The data relating to change in the ventilatory response to CO₂ are shown in Table V. During sleep there is a mean decrease of 1.05 L. per minute of alveolar ventilation per mm. Hg of alveolar CO₂ tension. This is a highly significant decrease. The magnitude of this change is illustrated in Figure 5, where waking and sleeping response curves from three representative studies are shown.

This depression of the ventilatory response to CO₂ sets in rapidly when sleep develops and is rapidly reversed when waking occurs. This is demonstrated by the following qualitative observation. While asleep, breathing mixtures containing 4 to 6 per cent CO₂ led to only moderate augmentation of ventilation. Subjects who awoke

⁴ CO₂ production was measured in all 14 experimental subjects. Oxygen consumption was measured in 8 subjects.

TABLE III

A comparison of arterial oxygen saturation awake and asleep in two normal subjects

Subject	Arterial oxygen saturation %	
	Awake	Asleep
R. R.	94	94
L. S.	96	95

while breathing these mixtures showed a marked hyperventilation almost *immediately* after waking. Subjects remaining awake under these circumstances continued to hyperventilate profoundly. Subjects drifting back to sleep showed a subsidence of total ventilation to the previous sleeping level.

Changes in blood pH

The changes in pH during sleep were measured by taking samples of blood each hour since no method of continuous measurement of blood pH in humans is available. The mean value for waking and sleeping pH in each subject was obtained by averaging the values found during each state. These data are shown in Table VI and show a mean decrease of 0.03 pH unit during sleep, a statistically significant change.

Data illustrating the pattern of pH changes during sleep are shown in Figure 6. Blood pH is

TABLE IV

A comparison of total ventilation, alveolar ventilation, oxygen consumption, carbon dioxide production and respiratory exchange ratio during the waking and sleeping states

Subject	Total ventilation		Alveolar ventilation		O ₂ consumption		CO ₂ production		Respiratory exchange ratio	
	Awake	Asleep	Awake	Asleep	Awake	Asleep	Awake	Asleep	Awake	Asleep
	<i>l./min. B.T.P.S.</i>		<i>l./min. B.T.P.S.</i>		<i>ml./min. S.T.P.D.</i>		<i>ml./min. S.T.P.D.</i>			
R. W.	7.69	5.45	5.08	2.72			233	146		
A. G.	6.20	4.20	3.68	2.14	232	120	154	99	0.66	0.82
J. M.	8.64	5.17	6.42	3.33			399	174		
J. S.	7.99	4.97	4.80	3.30	204	163	204	157	1.00	0.96
J. A.	6.31	6.04	3.72	3.87	190	197	174	197	0.92	1.00
R. C.	8.10	6.06	5.09	3.76	258	202	242	198	0.94	0.98
R. W.	11.60	7.13	7.47	4.17	303	182	337	193	1.04	1.06
R. R.	6.23	4.80	4.47	2.91	183	122	192	144	1.05	1.18
L. S.	7.72	8.41	5.63	5.29	256	300	246	279	0.96	0.93
O. B.	9.89	8.32	6.67	5.30	342	351	359	276	1.05	0.79
E. R.	6.12	3.87	4.25	2.28			244	147		
C. C.	8.65	5.41			319	202	311	184	0.97	0.91
R. W.	7.99	5.32			314	192	296	176	0.94	0.92
Mean	7.93	5.78	5.21	3.55	260	203	261	182	0.95	0.96
p	<0.001		<0.001		<0.025 >0.01		<0.05 >0.005		not sig.	

TABLE V

A comparison of the ventilatory response to carbon dioxide during the waking and sleeping states

Subject	Δ Alveolar ventilation	
	Awake	Asleep
	<i>L./min./mm. Hg CO₂ tension</i>	
R. W.	3.30	0.13
A. G.	1.32	0.57
J. M.	2.03	0.43
J. S.	0.65	0.22
J. A.	0.94	0.46
R. C.	1.09	0.72
R. R.	0.79	0.45
L. S.	1.30	0.33
O. B.	0.75	0.04
E. R.	1.88	0.12
Mean	1.40	0.35
p	<0.001	

plotted along the ordinate and time in hours, along the abscissa. It can be seen that blood pH tends to fall during sleep. The decrease in pH, however, is not present as consistently as is the rise in alveolar CO₂ tension.

Mechanics of breathing

The effect of sleep on pulmonary compliance and mean airway resistance is shown in Table VII. There are small and probably insignificant changes in pulmonary compliance while airway resistance showed a small but consistent decrease during sleep. The number of subjects studied is not large enough to permit statistical analysis for significance. However, these data indicate that sleep

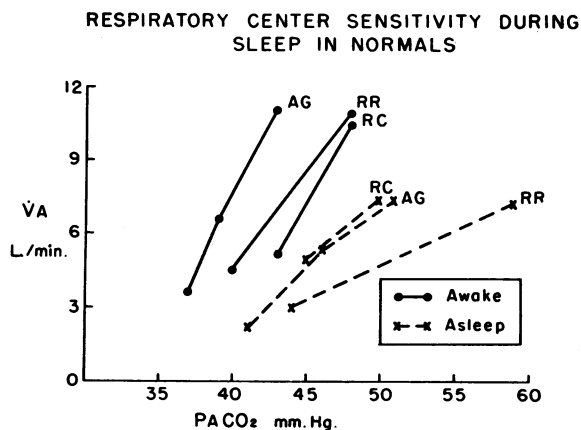


FIG. 5. WAKING AND SLEEPING VENTILATORY RESPONSE TO CARBON DIOXIDE IN THREE NORMAL SUBJECTS

TABLE VI

A comparison of blood pH during the waking and sleeping states

Subject	Source	Average blood pH	
		Awake	Asleep
L. T.	Artery	7.43	7.42
M. W.	Artery	7.40	7.37
M. P.	Artery	7.45	7.41
P. N.	Vein	7.44	7.41
T. A.	Vein	7.46	7.41
M. P.	Vein	7.41	7.37
R. R.	Vein	7.42	7.40
Mean		7.43	7.40
	p < 0.001		

does not produce an increase in airway resistance or a decrease in pulmonary compliance. Thus the work of breathing, if anything, is less during sleep than in the waking state.

Rhythm of respiration

Six of 14 normal subjects showed cyclic breathing of the Cheyne-Stokes variety during sleep. These variations in the rhythm of breathing differed from true Cheyne-Stokes breathing in that

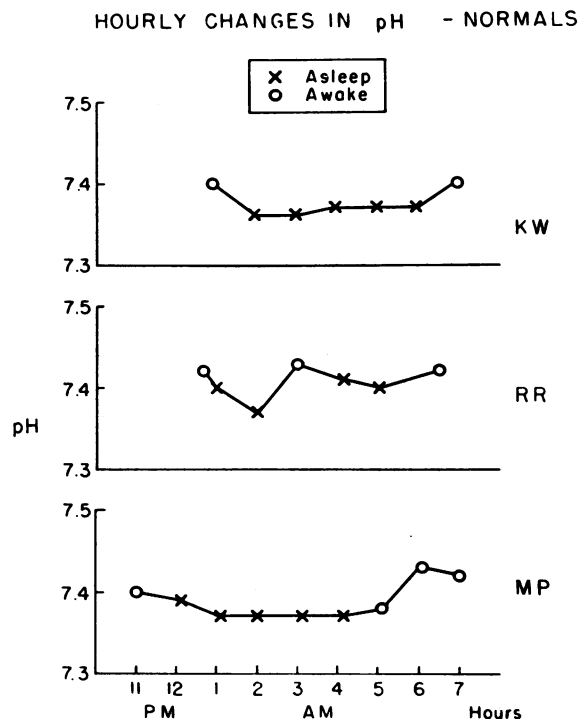


FIG. 6. HOURLY CHANGES IN BLOOD pH IN THREE NORMAL SUBJECTS

periods of hyperventilation alternated with hypopnea rather than with apnea. In normal subjects periodic breathing was only found transiently. No subject demonstrated this variety of breathing longer than one hour during a night of sleep. An example of this phenomenon is shown in Figure 7.

DISCUSSION

The increase in alveolar CO_2 tension during sleep is a consistent finding. Alveolar CO_2 tension may be increased by either of two mechanisms:

- 1) An increase in CO_2 production.
- 2) A decrease in alveolar ventilation.

Since the data show that sleep is accompanied by a decrease rather than an increase in CO_2 production, the CO_2 retention of sleep is to be explained by a decrease in alveolar ventilation. This decrease in alveolar ventilation is apparently related to a depression of respiratory center sensitivity to CO_2 . This is indicated by the marked decrease in the ventilatory response to CO_2 observed during sleep.

The ventilatory response to CO_2 may be accepted, with some reservations, as a quantitative expression of respiratory center sensitivity to CO_2 (12, 13). The reservations are as follows:

- 1) Inhaled CO_2 stimulates the peripheral chemoreceptors in the aortic and carotid bodies as well as the medullary chemoreceptors (14).

TABLE VII
Mechanics of breathing during sleep in three normal subjects

Subject	Pulmonary compliance		Mean airway resistance	
	Awake	Asleep	Awake	Asleep
	<i>L./cm. H₂O</i>		<i>cm. H₂O/L./sec.</i>	
E. R.	0.238	0.179	2.18	1.48
D. J.	0.164	0.203	2.03	1.09
D. T.	0.177	0.201	2.40	1.42

- 2) The CO_2 tension and pH of arterial blood and of the respiratory center are related but are not necessarily equal. At present, techniques for the measurement of intracellular pH and CO_2 are not available.

- 3) Any factor which modifies the volume of ventilation may modify the ventilatory response to CO_2 . It has been shown by Cherniack and Snidal (15) in normal subjects that the ventilatory response to CO_2 may be depressed by increasing airway resistance. Fritts, Fishman and Courmand (16) have suggested that the depressed ventilatory response to CO_2 in emphysema may be related to the increased work of breathing in this disorder.

Since pulmonary compliance is not decreased and mean airway resistance is not increased by sleep, it appears that the depression of the ventilatory response to CO_2 during sleep is not related to impairment of the mechanics of breathing.

It therefore seems probable that the changes in

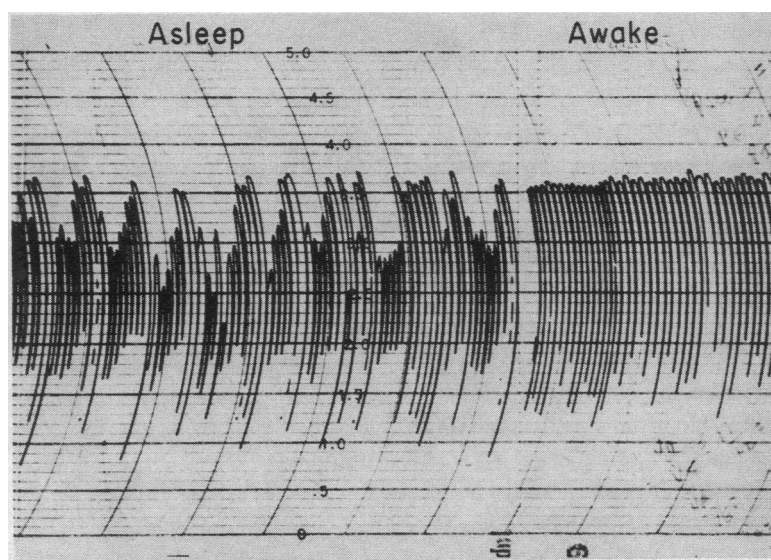


FIG. 7. PERIODIC BREATHING IN A NORMAL SUBJECT DURING SLEEP

the ventilatory response to CO_2 during sleep represent changes in respiratory center sensitivity to CO_2 . Since these changes take place within seconds, it seems probable that they are mediated neurogenically.

A working hypothesis to explain the respiratory acidosis of sleep may be stated as follows: The sensitivity of the respiratory center to CO_2 is dependent on, among other factors, afferent impulses coming to it from numerous areas in the nervous system. During the waking state the number of afferent impulses is relatively large, producing a brisk alveolar ventilation and resulting in a normal waking alveolar CO_2 tension. During sleep, the number of impulses is decreased and the responsiveness of the respiratory center consequently decreases. The result is a decreased level of alveolar ventilation and a rise in alveolar CO_2 tension until a new steady state is achieved.

The elevated alveolar CO_2 tension during sleep reported here is in agreement with the findings of most previous studies (1, 2). Mills has reported that the elevation of alveolar CO_2 tension that takes place during the night occurs as a result of a normal diurnal cycle and is independent of whether or not the subject is sleeping (17). Our finding that normal subjects kept awake at night show no respiratory acidosis differs from the results reported by Mills. It should be pointed out that Mills studied only one subject (himself) during sleep. In addition, his technique of study consisted of utilizing a Haldane tube for the determination of alveolar CO_2 tensions. At various times during the night an alarm clock roused him from sleep so that a sample of expired air might be obtained. In view of the rapid changes in CO_2 tensions that we have observed in the transition from the sleeping to the waking state, it is doubtful that Mills' observations can be considered as representing alveolar CO_2 tensions *during sleep*.

Changes in the cerebral circulation have been investigated by workers in the field of sleep. It seems probable that the changes observed may be related to changes in alveolar gas tensions. Thus, the increase in cerebral blood flow and decrease in cerebral vascular resistance during sleep reported by Mangold and co-workers (18) may be accounted for by the increase in alveolar CO_2 tension.

Doust and Schneider (19) have proposed a

theory which ascribes sleep to cerebral hypoxia. Using the technique of ear oximetry these authors found that arterial oxygen saturation decreased progressively during the process of sleep, reaching its lowest levels during deep sleep.

In our own studies a mean decrease of 3 mm. Hg in alveolar oxygen tension was found during sleep, but this decrease was not statistically significant. The shape of the oxyhemoglobin dissociation curve is such that the saturation values for highly saturated blood fall on the flat portion of the curve. Under these circumstances, even subjects who showed the greatest decrease in alveolar oxygen tension did not have a decrease of sufficient magnitude to produce arterial oxygen unsaturation. In the subject whose hemoglobin is unsaturated in the waking state the findings may be different. Because of the shape of the oxyhemoglobin dissociation curve a small decrease in alveolar oxygen tension may produce a significant decrease in arterial oxygen saturation.

At any rate, no evidence of significant arterial oxygen unsaturation was found in our normal subjects during sleep, and thus the hypoxic theory of the genesis of sleep appears to be untenable. The possibility of a marked decrease in oxygen saturation during sleep in subjects who are moderately unsaturated while awake is under investigation.

The data reported here do not in any sense define the fundamental nature of the sleeping state. They lend themselves, however, to several generalizations:

1) The basic changes associated with sleep are rapidly reversible. The rapidity of these changes suggests that neurogenic mechanisms play a decisive role in the genesis and maintenance of normal sleep.

2) Sleep does not represent a static state. The sleeping subject shows changes in the depth of sleep, the number of bodily movements (2), alveolar gas tensions, electroencephalographic patterns (11) and blood pH.

3) Theories of the genesis of sleep based on changes in blood gas constituents are probably untenable.

SUMMARY

Physiologic sleep in the normal subject is associated with a significant fall in total and alveolar

ventilation, with a significant rise in alveolar CO₂ tension, with a fall in CO₂ production and oxygen consumption, with a fall in ventilatory response to CO₂, with a fall in blood pH, and with a considerable incidence of periodic breathing. Alveolar oxygen tension, arterial oxygen saturation, respiratory exchange ratio, and the mechanics of breathing are not significantly altered by sleep.

The CO₂ retention of sleep is related to a depression of respiratory center sensitivity. The speed of onset and reversal of this depression of respiratory center sensitivity suggests that it is mediated neurogenically.

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