THE EFFECT OF SLEEP ON THE RESPIRATORY RESPONSE TO CARBON DIOXIDE

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During a study of the effects of noscapine and codeine [1] on the respiratory response to carbon dioxide inhalation, one of the subjects fell asleep during a control run, and there was a significant shift in the alveolar ventilation-alveolar P_{CO_2} response curve. This led us to investigate the effect of sleep on the respiratory response to carbon dioxide.

Methods

The equipment used to determine the respiratory response to carbon dioxide is shown in figure 1. The basic method and the equipment are the same as those used in previous studies [1-4] and is a modification of the technique described by Eckenhoff, Helrich and Hege.[5] With a nose clip in place each subject breathes through a rubber mouthpiece. The expired gases of the patient pass through a J-2 Warren Collins one-way flutter valve, to a Liston-Becker Model 16 infrared carbon dioxide gas analyzer. The volume of expired gas is measured by a dry flow Hospital Gas Meter (American Meter Co.), and its temperature is measured by a thermometer placed at the entrance to the gas meter. A photo cell is attached to the gas meter dial so that every 500 ml. of gas causes a blip to be recorded on one channel of a two-channel Sanborn recorder. On the other channel, the carbon dioxide concentration in the exhaled air is continuously recorded. By using two 3-way valves and a flexible oxygen reservoir, the patient can breathe either room air or rebreathe in a closed circle system of constant initial volume. With the valves closed the patient rebreathes his own expired gases, thus building up the concentration of carbon dioxide in the system.

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The resting normal alveolar carbon dioxide concentration was not measured, since at a low tidal volume the CO_2 concentration of end expiratory gas did not reflect the carbon dioxide concentration of alveolar gas. When the patient rebreathed in a closed system the end-expiratory carbon dioxide concentration was used as a measure of alveolar carbon dioxide concentration, since at high tidal volumes the former closely approaches the latter. The instrument was calibrated before and after each

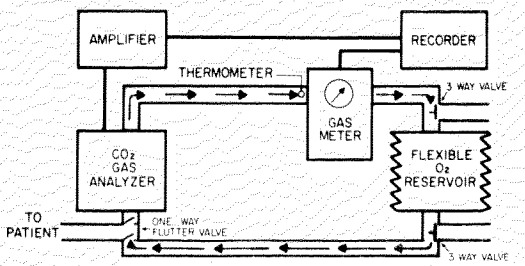

Fig. 1. Schematic diagram of equipment. (Reproduced by permission of The Williams & Wilkins Co., J. Pharmacol. & Exper. Therap. **121**: 71, 1957.)

run with CO_2-O_2 mixtures delivered from separate cylinders whose CO_2 content was assayed by the micro-Scholander method.* The barometric pressure was recorded and all gas volumes were corrected to BTPS. Alveolar ventilation was calculated by subtracting 180 ml. (The average dead space of the subjects calculated by the Bohr equation,[6] 140 ml. plus the valve volume, 40 ml.) from the corrected volume of each breath.

Oxygen concentration in the system was occasionally measured by an A. O. Beckman Model D oxygen analyzer at the beginning and end of a run. The oxygen content in the closed system was always between 40 and 30 per cent.

To verify the depth of sleep the electro-

* We are indebted to Miss Margaret Hood for performing these determinations.

encephalogram was continuously recorded during each run. Number 25 needle scalp electrodes were inserted in a fronto-central position over one hemisphere and all records were made on a Grass III D electroencephalograph at a paper speed on 30 mm. per second and calibrated at 50 μv. for 7 mm. deflection.

Observations to evaluate the respiratory effects of sleep were made in five healthy men. These tests were started late in the evening in a quiet room conducive to natural sleep. A control recording was first made while the subject was awake. Following this the subject was allowed to sleep while breathing through the system, *i.e.*, he slept with the nose clip on, with rubber metabolism mouthpiece in place and with needle electrodes in the scalp. The electroencephalogram was observed every five to thirty minutes, and if a sleep pattern was observed, tracings were obtained by stealthily and silently closing both three-way valves and letting the subject rebreathe in a closed system. Subjects usually awakened during rebreathing as the alveolar ventilation approached 10 liters per minute. A typical control recording is shown (fig. 2).

From each such record multiple values of alveolar ventilation and corresponding alveolar P_{CO_2} were calculated and plotted (figs. 3 and 4) for control and sleep periods. From these graphs, the displacement in terms of P_{CO_2} at an alveolar ventilation of 10 liters per minute was

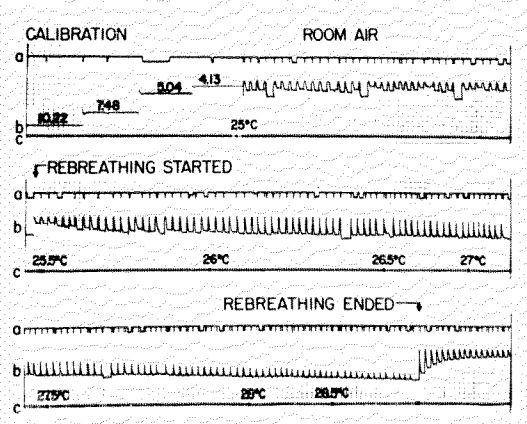

FIG. 2. Record of typical control run. Line (a) represents 500 ml. gas for each blip. Line (b) represents continuous plot of CO_2 concentration of exhaled air. Line (c) represents time base. (Reproduced by permission of The Williams & Wilkins Co., J. Pharmacol. & Exper. Therap. 121: 71, 1957.)

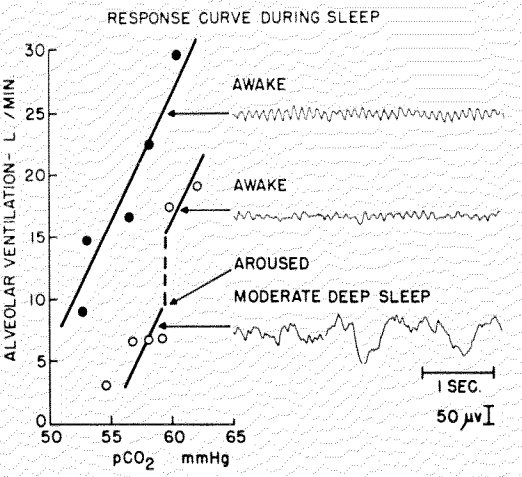

FIG. 3. Respiratory response curves and corresponding electroencephalograms of subject A.

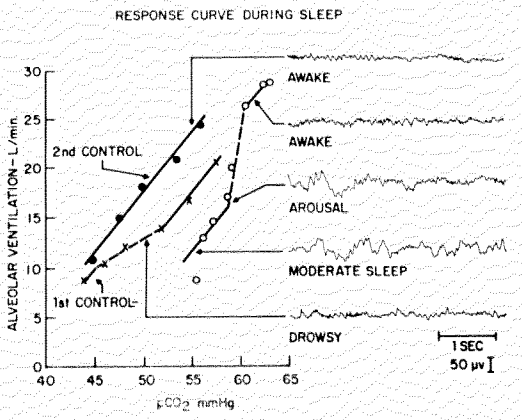

FIG. 4. Respiratory response curves and corresponding electroencephalograms of subject B.

determined for comparison with displacement produced by drugs and reported elsewhere [1-4] (table 1). Displacement to the right indicates respiratory depression. The electroencephalographic patterns corresponding to the control and sleep periods are also shown (figs. 3 and 4).

RESULTS

The results are summarized in table 1. The displacement of the respiratory response curve is shown at the different levels of sleep as determined electroencephalographically. For comparison the displacement obtained with 10 mg. of morphine sulfate intramuscularly is included. In general, the deeper the sleep the

TABLE 1

PARALLEL DISPLACEMENT OF RESPIRATORY RESPONSE CURVE DURING SLEEP AND AFTER MORPHINE
(Displacement of Response Curve From Control Curve in mm. Hg P_{CO_2})

Subject	Depth of Sleep (EEG Estimate)				Awake but 1 Hour After Morphine 10 mg. Intramuscularly
	Drowsy	Light	Moderate	Moderate Deep	
A	4.8	6.0	7.6		6.0
B	4.9		9.6		5.3
C		3.2	7.8		
D				9.0	6.4
E	6.5	8.3			9.0

more profound the respiratory depression. The respiratory response curves for subject A are shown in figure 3. In figure 4 are shown some of the respiratory response curves for subject B. There was a profound shift of the respiratory response curve to the right during moderately deep sleep, which was greater than that produced by 10 mg. of morphine sulfate given intramuscularly. Furthermore, even the drowsy subject exhibited a significant shift of the response curve to the right. When an individual awakened the response curve promptly shifted to the left: to the value observed during the drowsy state, and within a few minutes, as the subject became more alert, shifted even further to correspond to the wide awake curve.

DISCUSSION

Shifts in the alveolar ventilation-alveolar P_{CO_2} response curve may be used as an index of responsiveness of the respiratory center without making any assumption as to the mechanism of stimulation or depression. Respiratory depression can be defined either by displacement of the curve so that higher values of P_{CO_2} are required to produce the same ventilation, a decrease in responsiveness; or by a flattening of the slope so that an increase in P_{CO_2} produces a smaller increase in ventilation response, a decrease in sensitivity. In our experience two or three points may not define the actual response curve and unless a continuous plot is made or multiple points along the curve determined, estimates of slope may be unreliable. Indeed, we have found that at higher values of P_{CO_2} the control and after drug response curve tend to be parallel. Only at the lower values of P_{CO_2} are changes in slope apparent.[4] However, the value for slope depends on the value of P_{CO_2} at which it is measured and thus changes in slope are difficult to assess. We believe it more accurate to define respiratory depression in terms of a parallel shift in the response curve, a decrease in responsiveness.

Our data indicate that sleep as well as morphine depresses respiration. Either narcotics or sleep may depress the metabolic rate. Measurement of minute volume alone, while the subject is breathing room air, may not assess true respiratory effects, but rather a combination of respiratory and metabolic effects. Higgins and Means [7] pointed out that respiratory rate and minute volume may be subject to wide variation without any change in the sensitivity of the respiratory control mechanisms. Carbon dioxide excretion is proportional to the product of alveolar ventilation and alveolar P_{CO_2}. Any decrease in carbon dioxide production and hence, metabolism, at a constant P_{CO_2} will result in a decrease in alveolar ventilation. Thus, any effect that lowers CO_2 production or respiratory quotient will appear to cause respiratory depression if only ventilation is measured.

A question arises as to the meaning or significance of alveolar P_{CO_2} when it is obtained by the technique of rebreathing outlined. Neither the P_{CO_2} in the alveoli nor that in the arterial blood controls respiration, but instead it is probably the P_{CO_2} of brain tissue.[7–10] In plotting alveolar ventilation-P_{CO_2} response curves, the assumption is made that alveolar P_{CO_2} gives an index of brain tissue P_{CO_2}, and that brain tissue P_{CO_2} changes proportionally to alveolar P_{CO_2}. This is true only if one has approximate equilibrium conditions. This problem has been discussed at length [4] and although a true steady state equilibrium is never achieved during rebreathing as outlined, a dynamic balance or dynamic equilibrium does appear to be achieved. Evidence for a state of dynamic balance during rebreathing stems from the fact that: (1) in the present study a plot of alveolar ventilation versus P_{CO_2}, as in earlier studies, was a straight line after the first two minutes of rebreathing; (2) a

corresponding plot obtained by Nielsen under steady state conditions was also a straight line; [11] (3) extensions of the straight lines obtained from plots during the control runs of rebreathing data are close to the room air points. This would indicate that the differential between alveolar and brain tissue P_{CO_2} levels is close to that present during steady state conditions. Thus, the displacement of the alveolar ventilation-alveolar P_{CO_2} response curve can be taken as an index of the increase in brain tissue P_{CO_2} necessary to drive respiration.

Changes in the alveolar ventilation-alveolar P_{CO_2} response curve may be produced by phenomena that have no direct relation to the respiratory center or reflex control of respiration. For instance, a change in dead space, in cerebral blood flow or in the mechanical behavior of the respiratory apparatus may influence the alveolar ventilation-alveolar P_{CO_2} response curve.

The magnitude of the errors introduced by these variables can be ascertained from the following considerations. A decrease in physiological dead space might be misinterpreted. For instance, a 50 ml. decrease in dead space not taken into account in the calculation of alveolar ventilation, will cause an apparent respiratory stimulation—that is an apparent parallel displacement of response curve toward lower values of P_{CO_2}. If the subject breathed 15 times per minute the calculated alveolar ventilation will be in error by + 750 ml. and if the slope of the response curve for this individual is 1.5 l./minute/mm. of mercury P_{CO_2}, then at the measured P_{CO_2} the actual curve should be 0.5 mm. to the left of the plotted curve. Thus, the contribution of a change in dead space during sleep would be negligible in comparison to the magnitude of the shifts observed in this study.

Similarly, it might be argued that an increase in cerebral circulation could cause apparent respiratory depression. Mangold, Sokoloff, Conner, Leinerman, Therman and Kety [12] reported a 10 per cent increase in cerebral blood flow during sleep. This would, in effect, cause an apparent respiratory depression—that is, a parallel displacement of the response curve of 0.7 to 1.4 mm. of mercury towards higher values of P_{CO_2} in normal man. The basis for this calculation is as follows: The carbon dioxide production by the brain remains constant. We are using alveolar P_{CO_2} as an index of brain tissue P_{CO_2}. At constant cerebral blood flow venous internal jugular vein P_{CO_2} is higher than arterial P_{CO_2} by a constant amount and brain tissue P_{CO_2} is proportional to some function of arterial and venous P_{CO_2}. Since under conditions of constant cerebral blood flow the relation between arterial and venous P_{CO_2} is fixed, it does not matter which one is used to estimate brain tissue P_{CO_2}. If cerebral blood flow increases, the venous CO_2 content must fall and with it the venous P_{CO_2}. From the article of Mangold *et al.*[12] the normal differential between arterial and internal jugular vein blood CO_2 content is 5.8 volumes per cent. An increase in cerebral blood flow from 59 ml./minute/100 Gm. to 65 ml./minute/100 Gm. of brain tissue means a decrease of 0.54 volumes per cent in the CO_2 content of the internal jugular vein blood. This decrease in CO_2 content would be accompanied by a decrease in venous blood P_{CO_2} of 1.4 mm. of mercury at a hemoglobin oxygen saturation of 70 per cent.[13] If the mean brain tissue P_{CO_2} is equal to the mean of the P_{CO_2} of the arterial and venous blood entering and leaving the brain capillaries × a diffusion constant as proposed by Kety [14] then a shift of 1.4 mm. of mercury Pv_{CO_2} will result in only 0.7 mm. of mercury changes in brain tissue P_{CO_2}. This means a decrease in ventilation or apparent respiratory depression in terms of an alveolar ventilation-alveolar P_{CO_2} response curve. On the other hand, if blood flow in the brain is through alternately opening and closing capillaries, the brain tissue P_{CO_2} will be more nearly reflected by the venous P_{CO_2} and the effect of a change in cerebral blood flow from 50 to 65 ml./min./100 Gm. tissue will be to produce an apparent shift in the response curve corresponding to approximately 1.4 mm. of mercury P_{CO_2}. The apparent respiratory depression due to a change in cerebral circulation is insignificant when compared to displacements observed in this study.

The effect of a change in compliance or a change in airway resistance on the response curve may also be calculated.[4] Changes in compliance and changes in airway resistance

produce changes in slope and not parallel displacement. A 10 per cent decrease in compliance or a 400 per cent increase in airway resistance will produce a 10 per cent decrease in slope, and this is not of sufficient magnitude to explain the displacements of response curves observed in this study.

If the functional residual capacity (FRC) decreased with sleep, the alveolar ventilation-alveolar P_{CO_2} response curve would be displaced to the right. A decrease in FRC means that the P_{CO_2} within the alveoli will oscillate over a larger range than normal even though the mean alveolar P_{CO_2} remains the same. The arterial P_{CO_2} which is used as an estimate of brain tissue P_{CO_2} is equal to the mean alveolar P_{CO_2}. Since the end-expiratory P_{CO_2} is being used as an estimate of the mean alveolar P_{CO_2}, it is clear that a decrease in FRC will make it appear that the alveolar P_{CO_2} is higher than it actually is. An idea of the magnitude of the effect of a one liter decrease in the FRC on the response curve may be gained from the following considerations: Carbon dioxide production is proportional to the $P_{A_{CO_2}}$ at the end of inspiration $\times$ (FRC + TV) $-$ $P_{A_{CO_2}}$ at the end of expiration $\times$ (FRC) $=$ $V_{CO_2} \times P_B$, and this remains constant despite changes in FRC. Taking the data of DuBois, Britt, and Fenn,[15] we may calculate the effect of one liter decrease in FRC. At the end of inspiration $P_{A_{CO_2}} = 38.3$ mm. of mercury and $P_{A_{CO_2}}$ at the end of expiration $= 40.4$ mm. of mercury, FRC $= 6.0$ l., T.V. $= 0.6$ l., $V_{CO_2} \times P_B = (38.3)(6.6) - (40.4)(6) = 10.4$ mm. of mercury liters. Now let FRC $= 5$ liters. Then:

$$(38.3 - x)(5.6) - (40.4 + x)(5) = 10.4 \text{ and } x = 0.2 \text{ mm. Hg } P_{CO_2}$$

or the end-expiratory carbon dioxide concentration measured would be 0.2 mm. of mercury higher than that ordinarily used in the estimation of mean alveolar P_{CO_2}. Therefore, the actual P_{CO_2} response curve would be 0.2 mm. of mercury to the left of the response curve calculated.

The shift in the response curve might be due to a time delay in muscular response since the ventilation is not measured under steady state conditions. During sleep the end-expiratory P_{CO_2} of one of the subjects climbed at a rate of 6 mm. of mercury per minute. Thus a shift of 9 mm. of mercury P_{CO_2} would have meant a time delay of 90 seconds, beyond whatever time delays are involved in obtaining the awake response. While asleep this subject was switched from rebreathing to breathing room air. It required 24 seconds for the end-expiratory P_{CO_2} to return to normal. While awake the same subject rebreathed until the identical level of ventilation was achieved as that during sleep. The end-expiratory P_{CO_2} was lower at this ventilation level. The awake subject was then switched back to breathing room air and it required 20 seconds for the end-expiratory P_{CO_2} to return to normal. Thus, it required 4 seconds longer for the end-expiratory P_{CO_2} to return to normal during sleep. At the rate of climb of P_{CO_2} observed during this study, a 4-second delay would correspond to a shift in the alveolar ventilation-alveolar P_{CO_2} response curve of 0.4 mm. of mercury P_{CO_2} in the direction of respiratory depression. Admittedly, the foregoing analysis is semi-quantitative. A complete analysis of lag and its relation to the CO_2 "off transient" is complicated and would, of necessity, involve more precise data than is available and analysis of feedback components by means of complex plane plots. Nonetheless, the above analysis indicates that the order of magnitude of any delay effects is not sufficient to account for the displacements of the alveolar ventilation-P_{CO_2} response curve seen during this study.

The use here of the alveolar ventilation-P_{CO_2} response curves to analyze the effects of sleep does not necessarily imply that the major mechanism by which sleep causes respiratory depression is by depressing the response of the respiratory mechanism to the effects of carbon dioxide. There are other factors such as change in sensory stimuli arriving at the respiratory center, inhibition of reflex mechanisms and/or other causes that may be important in regulating the respiratory control mechanism. However, the alveolar ventilation-alveolar P_{CO_2} response curve represents a convenient index of the effects of sleep on respiratory response to CO_2 and permits comparison with changes observed following administration of drugs.

Doust and Schneider[16] have reported that the arterial blood oxygen saturation decreases during sleep and Nielsen and Smith[17] have

shown that hypoxia shifted the respiratory response curve to the left, or in the direction of respiratory stimulation. Thus, if arterial blood oxygen saturation were a factor in our studies it would negate any respiratory depressant effects of sleep. Therefore, hypoxia which might threaten an individual during sleep actually would act as a respiratory stimulant.

The effect of narcotics on the respiratory response to carbon dioxide does not necessarily parallel their effect on wakefulness. In fact, data obtained in other studies [1-4] following the administration of codeine and morphine to some of the subjects in this study indicates that the depression of respiration due to moderate sleep is much greater than that produced by 10 mg. of morphine intramuscularly. Although the narcotics and sleep both depress respiration, the narcotics do this without altering the state of wakefulness. For this reason it is essential when evaluating the effects of drugs on the respiratory response to carbon dioxide to maintain the subjects in an alert state to rule out the possibility that shifts in the response curve are due to the subject becoming drowsy. Fortunately this phenomena was appreciated early and in all our studies with drugs, subjects have been carefully observed and have been required to perform a task, such as reading, which would assure reasonable alertness.

Mills [18] has reported a diurnal variation in the alveolar carbon dioxide tension. Certainly one must consider whether this phenomenon is real or related to the subject becoming drowsy. The use of gas samples collected immediately on awakening to estimate alveolar P_{CO_2} is open to question since while monitoring the end expiratory CO_2 with the subject breathing room air we observed that a decrease in end expiratory CO_2 was coincident with or preceded awakening.

There is, in addition to the displacement of the alveolar ventilation-P_{CO_2} curve to the right during sleep, another phenomenon to be mentioned. Respiratory rhythm during sleep is irregular. There is a waxing and waning in depth and frequency of respiration. At levels of P_{CO_2} above 50 mm. of mercury this is less marked but it is still present. For this reason there is a wider scatter of points about the straight line response curve during sleep than during the control run—almost as if the control mechanism were oscillating about a control value. This phenomenon warrants further investigation.

Our findings agree with those of Robin, Whaley, Crump and Travis.[19] However, in addition we have shown that the depth of sleep influences the degree of respiratory depression. Although they too observed periodic breathing during sleep, the one discrepancy between their results and ours is that they observed the end-expiratory CO_2 to be more stable during sleep than during wakefulness. We found the end-expiratory P_{CO_2} to be more constant during wakefulness than during sleep.

Reed and Kellogg [20] have also recently assessed the effects of sleep on the ventilation-P_{CO_2} response curve. They observed a displacement of the response curve of approximately 7 mm. of mercury P_{CO_2} during sleep and this was the same at sea level as at high altitudes. Furthermore, they, too, found that sleep produced no significant change in slope.

Summary

The respiratory response to endogenously accumulated carbon dioxide has been measured in terms of the alveolar ventilation-alveolar P_{CO_2} response curve. Respiratory depression has been shown to exist during sleep and to be greater the more profound the depth of sleep. The level of sleep was verified by electroencephalographic recording and with increasing depth of sleep respiratory depression increased.

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