

# *The Effect of Sleep Plus Morphine on the Respiratory Response to Carbon Dioxide*

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Respiratory response curves were obtained in 4 subjects while awake, asleep, awake after morphine, and asleep after morphine. Sleep plus morphine produced a decrease in slope and a displacement to the right of the carbon dioxide response curve. A substantial effect of sleep plus morphine on the depression of respiration was demonstrated.

PREVIOUS studies have demonstrated changes in respiratory response to carbon dioxide during sleep<sup>1, 2</sup> and after injection of morphine sulfate.<sup>3, 4</sup> Both sleep and the administration of morphine sulfate are accompanied by respiratory depression as measured by stimulus-response curves, consisting of plots of ventilation versus a carbon dioxide stimulus. In a study on the respiratory effects of phenazocine (Prinadol)<sup>5</sup> we noted a further shift of the response curve to the right in a subject who had received 3 mg. phenazocine and became drowsy during a rebreathing study. Therefore, to study the implied interaction of sleep and narcotic effect, we have studied the combined and separate effects of sleep and morphine sulfate to evaluate their respiratory depressant effects as measured by the respiratory response to carbon dioxide.

## **Method**

A respiratory carbon dioxide response curve computer, specifically designed to record alveolar ventilation versus end-expiratory CO<sub>2</sub><sup>6</sup> was used in conjunction with a rebreathing system to collect data for the study. The rebreathing

system is comprised of a flexible 15-liter reservoir in a circle apparatus which can be vented to room air or closed for rebreathing. When the system is vented to room air, the reservoir remains filled with 12 liters of oxygen. Each subject is fitted with a rubber metabolic mouthpiece and nose clip, and breathes into a Warren Collins J-2 low resistance one-way flutter valve. A pneumotachograph head with incorporated thermistor is mounted on the exhalation side of this valve. Large bore breathing tubes carry the gases through the 15-liter reservoir which is interposed between large three-way stopcocks that may be used to vent the system to room air. When not vented, the system permits rebreathing. A small polyethylene catheter is inserted through the Warren Collins J-2 valve so that the tip terminates at the level of the lips. A constant flow (800 ml./minute) of gas is drawn through the catheter to an infrared carbon dioxide analyzer, and then is returned to the rebreathing system.

The pneumotachograph strain gauge, thermistor, and the carbon dioxide analyzer act as inputs to the special purpose analog computer. Corrections are made for barometric pressure, temperature, water vapor, and physiologic dead space, so that the alveolar ventilation may be expressed in liters per minute (VT<sub>PS</sub>) and plotted on the Y axis of the XY plotter. The highest concentration of carbon dioxide for each exhalation is taken as the end-expiratory carbon dioxide and plotted on the X axis of the XY plotter. Before and after each run, the instrument was calibrated. The electroencephalogram was recorded from frontocentral disc electrodes on an Offner type R recorder and viewed on a Tektronix 561 oscilloscope. Depth of sleep was

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TABLE 1. Displacement of Respiratory Response Curve (mm. of mercury  $P_{CO_2}$ )

Subject	Control	After* Morphine	With Sleep	Sleep plus Morphine
1		6.2	9.9	24.2
2		1.3	4.5	22.2
3		3.8	4.1	17.9
4		3.3	7.9	12.9

Slope of Respiratory Response Curve in l./min./mm. Hg $P_{CO_2}$				
1	0.77	0.65	0.80	0.47
2	1.06	0.76	0.98	0.40
3	1.31	1.01	0.67	0.43
4	1.16	1.01		0.59

\* All subjects received 10 mg. morphine except subject 3 who received 12 mg.

evaluated according to the criteria described by Loomis *et al.*<sup>7,8</sup>

The study was carried out on 4 healthy adult male volunteers. Response curves were recorded while the subjects were awake, asleep, asleep after receiving morphine, and awake after receiving morphine. To obtain these observations, the sessions usually commenced at 2:00 A.M. The subjects were instructed to refrain from sleep, drugs, coffee,

and alcohol during the previous 16 to 20 hours. With the subject in a semirecumbent position (15 degrees from horizontal) an awake respiratory response curve was obtained. Following this the room was darkened and the subject was allowed to sleep while breathing through the mouthpiece and flutter valve with the system vented to room air. When a sleep record was observed on the oscilloscope both three-way valves were closed, establishing a circle system, and the electroencephalographic recording as well as the carbon dioxide response curve recording were commenced. Rebreathing and recording continued until arousal. This occurred in a variable period of time usually within eight minutes, during which time the electroencephalogram showed a light sleep pattern until arousal. The subject then received an intramuscular injection of morphine sulfate and was kept awake for the next half hour. At this time the room was again darkened and the subject allowed to sleep with the mouthpiece in place. When a sleep record was observed on the oscilloscope, the recording procedure was repeated. The fourth and final response curve determination was obtained immediately following the third after the subject had awakened but before there could be any appreciable change in pharmacologic effect of

BAROMETRIC PRESSURE 756 mm Hg

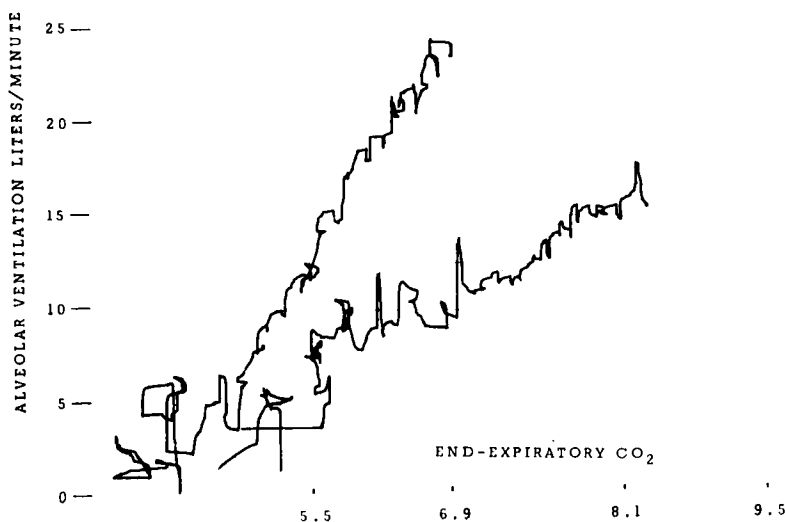


FIG. 1. Respiratory response curves obtained in subject 3 awake and asleep following 12 mg. morphine. Alveolar ventilation (liters/minute) is plotted against end-expiratory  $CO_2$ . Calibration of X axis with 5.5, 6.9, 8.1 and 9.5 per cent  $CO_2$  in oxygen corresponding to partial pressures of carbon dioxide of 39.0, 48.9, 57.4, and 67.4 mm. of mercury is shown. The marked change in slope and displacement observed during the sleep plus morphine determination is evident.

morphine sulfate, *i.e.*, between one and one and one-half hours after morphine administration.

### Results

The results are summarized in table 1. They represent four successful experiments in eleven attempts in 6 subjects. One subject had marked periodic breathing during sleep so that it was impossible to determine a meaningful respiratory response curve. Another subject consistently snored during sleep and the sound vibrations interfered with the measurement of air flow by the sensitive pneumotachograph. Other experiments were unsuccessful owing to technical reasons or to the inability of the subject to sleep at the appropriate time.

The displacement in the response curve measured at an alveolar ventilation of 20 liters/minute was comparable to that observed in previous studies with light sleep<sup>1,2</sup> or morphine.<sup>3,4</sup> The displacement noted in a subject who had received morphine and was asleep is substantially larger than that observed with sleep or morphine alone. Similarly, the small decrease in slope of the response curve after morphine is similar to that reported by Seed *et al.*<sup>7</sup> With sleep alone, Robin and associates<sup>1</sup> noted a decrease in response curve slope, but in our study the sleeping subject who had received morphine had a decrease in response curve slope that was very substantial.

In figure 1, some representative respiratory response curves from subject 3 are shown.

### Discussion

Alveolar ventilation-alveolar  $P_{CO_2}$  response curves are a good means for measuring the effects of drugs and sleep on respiration. Bellville and Seed have discussed the significance of these response curves as an index of the threshold and sensitivity of the respiratory center.<sup>2</sup> Parallel displacement of the response curve to the right and left of the control connotes a decreased or increased threshold respectively of the respiratory center to carbon dioxide. A change in the slope of the response curve is interpreted as a change in sensitivity of the respiratory center to carbon dioxide.

The data indicate that there is both a shift to the right (increased threshold) and a change in slope (decreased sensitivity). As previously pointed out<sup>9</sup> if there is both a shift in the response curve to the right and a decrease in slope interpretation of the data becomes more difficult. It is apparent that some of the displacement of the response curve measured at a ventilation of 20 liters/minute in the sleeping subject who has received morphine is due to a marked decrease in slope of the response curve. This cannot be corrected by extrapolation of the response curve to zero ventilation because of the large inherent errors attendant upon extrapolation. Robin and associates<sup>1</sup> reported a respiratory response curve slope of 1.4 liters/minute/mm. of mercury  $P_{CO_2}$  in the awake subject but only 0.35 liter/minute/mm. of mercury  $P_{CO_2}$  in the sleeping subject. It may be that the lower slope they reported in sleeping subjects is related to the method of determining slope. In the presence of respiratory depression the lower portion (below an alveolar ventilation of 10 liters/minute) of the respiratory response curve is nonlinear. Therefore it is essential to define a continuous response curve so that slope determinations can be made on the upper linear portion of the response curve.

Bülow recently discussed respiratory response curve changes during sleep in some detail.<sup>10</sup> They, as we, found only a moderate decrease in response curve slope. When they classified their subjects as having *stable* or *unstable* respiratory control they noted a larger decrease in response curve slope among the unstable group. Since we used a special purpose analog computer to pilot our data, we eliminated from this study subjects with periodic breathing during sleep, subjects that would be classified as having unstable respiratory control by Bülow. Therefore, our subjects probably represent only those who might be classified as having stable respiratory control and the average decrease in slope observed with sleep would be slightly less than might be found in a more representative sample of the population.

The marked decrease in respiratory response curve slope in the sleeping individual who has received morphine is worthy of further discussion. Usually the response curve slope

is taken as an indication of respiratory center sensitivity. Thus in an open loop system if  $R$  is the input and  $C$  the output it would be equal to  $C/R$  or the gain  $G$ , ( $C = RG$ ). However, in a closed loop system the situation is entirely different since the output,  $C$ , is equal to  $RG/(1 + G)$ . If we compare the effect of a change in  $G$  on the output of a system without feedback it can be seen that the control system with feedback is less affected by a change in gain than the system without feedback. Therefore, in terms of control of respiration we may say that a change in respiratory center sensitivity will produce little change in respiratory response curve slope—or going one step further—if there is a large change in respiratory response curve slope there must be a huge change in respiratory center sensitivity since this is a system that contains multiple feedback loops. An alternative explanation would be that during sleep plus morphine some of the feedback loops normally associated with respiratory control are not functioning. It is known that making feedback loops nonoperative will profoundly affect a regulating mechanism's performance and thus could be an alternative explanation to the large change in response curve slope observed. This probability is given credence by the observation of Bülow who observed that there was an increased responsiveness to  $\text{CO}_2$  during the hypoxemic state (breathing 14 per cent oxygen) while awake but not during the sleeping state.<sup>10</sup> His study in a few subjects suggests that the feedback loop from the chemoreceptors is not as operative during sleep.

It has been shown that respiratory depression increases with increased depth of sleep.<sup>2, 10</sup> To rule out the possibility that a deeper level of sleep might be associated with the post-drug response curve the electroencephalogram was monitored continuously and observed to be indicative of light sleep. Subsequently upon reviewing the electroencephalographic recordings, it appears that during three of the postdrug response curve determinations there are occasional artifacts that may represent rapid eye movements as well as low voltage fast activity. This suggests that following morphine we may have produced paradoxical sleep.<sup>11</sup> Paradoxical, or the rapid eye move-

ment stage of sleep, is characterized by an electroencephalogram that normally might be thought to represent a light stage of sleep. However, during this stage of sleep arousal is difficult and response to stimuli is markedly depressed. Bülow performed electro-oculography on 12 subjects during sleep and concluded that the response curve during rapid eye movement sleep is about the same as that observed during light sleep, although the marked instability in respiration during rapid eye movement sleep usually makes evaluation of the ventilatory response to  $\text{CO}_2$  difficult.<sup>10</sup> Thus it appears unlikely that the results are due to morphine inducing a deeper level of sleep as measured by the electroencephalogram. It may be that there is a dissociation between electroencephalographic and other criteria of depth of sleep, such as arousal threshold, and certainly respiratory response to carbon dioxide, that indicate a deeper stage of sleep. In either event sleep in the presence of morphine is accompanied by profound respiratory depression.

Thus we have demonstrated a substantial effect of sleep plus morphine on depression of respiration. If we think in terms of the dose-effect curve for morphine and plot displacement of response curve versus dose of morphine, it appears that there must a discontinuity in the curve when sleep supervenes. That is, respiratory depression normally associated with a dose of morphine abruptly becomes much greater as soon as consciousness is lost. Does the same phenomenon apply to other drugs such as the anesthetics? If so, how much of the very substantial respiratory depression seen during anesthesia is related to the altered state of consciousness and how much is due to the drug *per se*?

The results presented in this study would substantiate the teaching that narcotics be used cautiously in the patient with cerebral depression. These data help to explain why a poor risk patient might tolerate a therapeutic dose of morphine well at one time but experience severe respiratory depression following the same dose subsequently if he were to fall asleep.

Certainly this study poses many problems concerning the interaction of sleep, altered states of consciousness and drug effects. It

is hoped that as our methods for studying these effects improve we may understand these interactions more fully.

### Summary

Respiratory response curves were obtained in 4 subjects in the awake state, asleep, after morphine and asleep after morphine. Sleep plus morphine produced substantial displacement of the response curve as well as a change in slope.

The authors are grateful to Dr. William C. Dement for reviewing the electroencephalograms and for his helpful suggestions.

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**INTRACTABLE PAIN** Results of vagotomies performed on 74 patients in a Japanese hospital for relief of intractable abdominal pain are presented. Causes of pain in these individuals were listed as malignancy (46 cases), undetermined (15), chronic pancreatitis (4), peptic ulcer (3), and "others" (6). Excellent results were obtained in 36 instances, good in 24 and poor in 14. Side effects of the operations were adjudged not serious enough to contraindicate the procedure where applicable. The rationale of the pain relief is not clear but is believed to be through alteration of autonomic nerve function rather than interruption of afferent or efferent somatic impulses. (*Oi, M., and Kobayashi, K.: Vagotomy as a Surgical Procedure for Relief of Pain, Amer. J. Surg.* 106: 49 (July) 1963.) (ABTRACTOR'S NOTE: The evidence presented is inconclusive to support either the assumption that the surgery *per se* relieved the pain in these patients or that any relief obtained was related to alteration of autonomic function.)