Instability of Ventilatory Control in Patients with Obstructive Sleep Apnea

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Because of the oscillatory pattern of upper airway resistance and breathing during sleep in patients with obstructive sleep apnea (OSA), we hypothesized that OSA patients have an underlying instability of ventilatory drive to inspiratory muscles. To assess the stability of ventilatory drive in OSA patients and controls, we used the pseudorandom binary stimulation (PRBS) test and examined the closed- and open-loop responses to hyperoxic hypercapnia. The closed-loop response is produced by interactions of dynamic gain in controller, plant, and ventilatory feedback. The open-loop response reflects controller dynamic gain or frequency-dependent chemosensitivity. As compared with 16 non-apneic, nonobese control subjects, a group of nine obese OSA patients had a higher peak response and a more rapid and irregular recovery phase of the closed-loop CO₂ response in the PRBS test. The two groups had similar open-loop responses in the PRBS test, suggesting that central dynamic CO₂ chemosensitivity was not abnormal in OSA. We conclude that the differences between OSA patients and controls in the closed-loop response in the PRBS test are not due to differences in dynamic controller gain, but are related to differences in dynamic plant gain and/or negative ventilatory feedback. In addition to OSA, obesity may affect these variables and may have been responsible for our findings. Hudgel DW, Gordon EA, Thanakitcharu S, Bruce EN. Instability of ventilatory control in patients with obstructive sleep apnea.

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During sleep, patients with obstructive sleep apnea (OSA) have periodic fluctuations in upper airway muscle activity, upper airway resistance, and ventilation (1, 2). The etiology of this disordered pattern of breathing has not been clarified, but some studies have addressed this issue. Modeling ventilatory control leads to the conclusion that an unstable, high-gain control system would predispose individuals to irregular or periodic breathing, especially during some stages of sleep (3-5). With such an unstable control system, small changes in arterial blood gases, if they occurred at a frequency to which the ventilatory mechanical system could respond, would produce larger than expected changes in inspiratory muscle activity and ventilation, which in turn would result in exaggerated changes in arterial blood gases, further exacerbating the problem. Greater than expected ventilatory stimulation would alternate with exaggerated ventilatory suppression. In addition to the amplitude of the response, the frequency of the oscillatory behavior of the system would also be dictated by the instability of dynamic ventilatory control. These response dynamics would be a primary factor in determining the pattern of the ventilatory response to a transient ventilatory stimulus.

Fluctuations in arterial blood gases, due to unstable ventilatory control, also would be expected to result in oscillations in upper airway mechanics (3). In addition to changes in tho-

racic pump muscle activity induced by oscillations in ventilatory control, the changes in upper airway mechanics would affect ventilation output. To assess the ventilatory mechanical response to an oscillating control system, artificially induced fluctuations in arterial blood gases were produced in Stage 2 non-rapid-eye-movement (NREM) sleep in healthy, nonapneic individuals (6). Obstructive apneas resulted from the fluctuations in ventilatory control in normally nonapneic individuals (6). Thus, if the dynamic ventilatory control system is unstable, irregular or oscillatory changes may occur in upper airway resistance and breathing.

Tests of dynamic ventilatory control offer certain advantages over standard, progressive or steady-state tests of ventilatory control that assess controller direct-current (DC) gain or chemosensitivity only. First, dynamic testing assesses the response dynamics of the system, as well as the magnitude of the response to a chemical stimulus to breathing. Second, testing of the dynamic control of breathing allows inferences to be made about the role of the different components of the dynamic ventilatory response, such as controller, plant, and negative ventilatory feedback. Abnormalities in any of these factors may contribute to variability in ventilation and periodic breathing. These aspects of dynamic ventilatory control can be determined with the pseudorandom binary stimulation (PRBS) test, during which a single breath, low-level chemical stimulus is repetitively applied in a random manner (7-9). In the study reported here, we utilized the CO₂ response in the PRBS test not only to examine the stability of dynamic ventilatory control in OSA, but also to identify specific differences in system components in subjects with OSA and control subjects during wakefulness.

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METHODS

Subjects

Sixteen nonsnoring, nonapneic control subjects and nine OSA patients participated in the study, which was conducted in the Sleep Laboratory of the MetroHealth Medical Center in Cleveland, Ohio. All subjects had an overnight polysomnogram to establish the presence or degree of sleep-disordered breathing (SDB). The polysomnogram included vertex and occipital electroencephalograms (EEG), a chin electromyogram (EMG), recording of eye movements, oral and nasal airflow, thoracic and abdominal motion, and snoring, and monitoring of arterial oxygen saturation. OSA patients had a history of heavy snoring and excessive daytime sleepiness, characterized by somnolence during driving and/or job performance, or in sedentary activities such as during meetings, movies, and church services. OSA patients had more than 10 apneas and/or hypopneas per hour of sleep.

Terminology

For the purposes of the study, the controller was defined as the ventilatory response to changes in arterial CO_2 tension; the plant was the ventilatory mechanical and gas exchanging system that affects changes in arterial PCO_2 in response to changes in ventilation or in inspiratory CO_2 concentration; the negative ventilatory feedback loop was the actual change in ventilation that occurs in response to a chemical stimulus to breathing that leads to an alteration in arterial PCO_2 ; the closed loop was the integrated ventilatory response to a transient stimulus to breathing, as determined by the effects of a combination of the controller, plant, and negative ventilatory feedback; the open loop was the ventilatory response to transient changes in arterial PCO_2 , indicative of the dynamic controller response; the controller gain was the change in the ventilatory response to a progressive change in arterial PCO_2 (DC gain); the plant gain was the change in the arterial PCO_2 in response to a progressive change in inspired CO_2 concentration or a change in ventilation (DC gain); the dynamic gain was the frequency-dependent nature of the two gains mentioned previously, as determined with the PRBS test; and the closed- or open-loop gain was the dynamic gain of either the closed- or open-loop CO_2 ventilatory response in the PRBS test.

Techniques

The experimental techniques used for PRBS testing were similar to those used previously (9). Subjects were seated in a comfortable chair and breathed through a face mask that was connected to a pneumotachograph (Fleisch No. 2 with a Validyne transducer; Model MP45 $\pm$ 5 cm H_2O ; Validyne Corp., Northridge, CA) and a respiratory nonrebreathing valve. The CO_2 fraction at the airway opening was measured with an infrared analyzer (Hewlett-Packard, Waltham, MA). Airflow and the CO_2 fraction were digitized by an analog-to-digital converter at a rate of 90 Hz, and the digital data were entered into a microcomputer. Customized software displayed the flow and CO_2 fraction during on-line breath detection and measurement of breath-by-breath end-tidal CO_2 partial pressure and ventilation parameters. The inspiratory inlet of the nonrebreathing valve was switched between two Douglas bags containing the gas mixtures for inhalation (100% O_2 in one bag and 95% O_2 + 4% CO_2 in the other) by two computer-controlled pneumatic valves (Hans Rudolph, Kansas City, MO). Real-time software opened each valve on a random basis for a series of 63 breaths. The same 63-breath sequence of valve openings was repeated from three to six times, thus explaining the term "pseudorandom" for this method.

Protocol

Seated subjects breathed 100% O_2 for 5 min before the PRBS sequence was begun. The 63-breath sequence was repeated four to eight times (over a period of ~ 40 min) to complete a test on one individual. If in a given 63-breath sequence the subject coughed or swallowed excessively, the data of that particular sequence were not included in the data analysis. Throughout the study, a television or radio was used to maintain wakefulness. The solenoids controlling the gas-inspiratory valves were packed in foam rubber to eliminate the noise from these instruments.

Data Analysis

The details of the methodology for data analysis are described elsewhere (9). Briefly, from the digitized flow and CO_2 signals, the on-line computer program calculated breath-by-breath values of inspiratory tidal volume (V_T), inspiratory and expiratory times (T_I and T_E , respectively), breath duration ($T_{\text{tot}} = T_I + T_E$), inspiratory minute ventilation ($V_I = V_T \times 60/T_{\text{tot}}$), inspired CO_2 fraction ($F_{I\text{CO}_2}$), and PET_{CO_2} . To obtain the response of V_I to single-breath inhalation of CO_2 in O_2 , we used a general system-identification technique known as the prediction-error method (PEM) of transfer function estimation (10). The PEM models the output of the linear system (e.g., V_I) as the sum of the response of the system to a deterministic (known, controllable) input (e.g., $F_{I\text{CO}_2}$) and random noise. Data from the first 63-breath sequence of the PRBS test were discarded, so that there would be no contamination of the data by breathing of ambient air.

Because our goal was to measure the dynamic response of the ventilatory control system, we removed the means of all input and output data in the data analyses. Therefore, our measured responses actually reflect changes from the mean level of ventilation. We calculated two types of responses: (1) the V_I response to a single-breath inhalation of CO_2 (reflecting the closed-loop dynamics of the respiratory CO_2 control system, including the ventilation feedback loop); and (2) the V_I response to a single-breath increase in PET_{CO_2} (reflecting the open-loop response of the central ventilatory controller).

Measured variables relating to dynamic ventilatory response are illustrated in Figure 1. To compare the characteristics of the closed-loop and open-loop impulse response in control and OSA subjects, we calculated the area under the curve (AUC) of the response, the peak magnitude of the response, the delay in ventilatory response (number of breaths to the beginning of the response to inspired CO_2), the rise time (time from 10% to 90% of the peak response), the time constant (65% of the time from the interpolated start time of the response to the peak response time), the duration of the response (the earliest time at which the integral of the ventilatory response reached and thereafter remained within $\pm 5\%$ of its final value), and the settling time (the time required for the response to decay from its peak value to 5% of the peak value and thereafter remain within $\pm 5\%$ of its final value).

To compare the characteristics of the response in the PRBS test in the frequency domain, we calculated the Fourier transformations of the real-time data for the open- and closed-loop responses. To normalize the data from the closed and open loops, we divided the ventilatory response of each subject by its zero-frequency value. The AUC of these data was calculated for the frequency range of 0.0 to 0.1 Hz, thereby providing the relative power over this frequency range. A less negative AUC indicates relatively more power over the frequency range analyzed.

Figure 1. Schematic diagram of the variables in the PRBS CO_2 response. Shaded area = AUC. a = Peak response; b = response delay; c = rise time; d = response duration; e = settling time.

All data analyses were performed with MATLAB software (Math Work, South Natick, MA). Group data were presented as mean $\pm$ SE. The independent *t* test was used to compare groups. Statistical significance was taken at $p \leq 0.05$.

RESULTS

Subjects

Subject characteristics are shown in Table 1. Proportionately more of the OSA group than the control group was male, and the OSA patients had a higher body mass index (BMI) than the controls. The apnea/hypopnea index (AHI) for the OSA patient group was 30 ± 5 (mean $\pm$ SEM) events per hour of sleep.

PRBS Responses

The closed-loop ventilatory responses to hyperoxic CO₂ single-breath stimuli in the control and OSA groups are shown in Figure 2. The AUC of this average ventilatory response was not different in the two groups, but the pattern of the response was distinctly different. The peak ventilatory response to hyperoxic CO₂ was higher in the OSA patients than in the control subjects, at 0.194 ± 0.030 L/min (mean $\pm$ SEM) and 0.101 ± 0.009 L/min, respectively ($p < 0.02$) (Table 2). In addition, the duration of the response was shorter in the OSA patients than in the control subjects, at 172 ± 35 s versus 348 ± 53 s, respectively ($p < 0.02$). The settling time was shorter in the OSA patients than in the controls, at 43 ± 10 s and 109 ± 26 s, respectively ($p < 0.03$). Thus, the closed-loop response of the OSA patients was characterized by a peak nearly twice as high and a recovery phase slightly more than half as long as was observed in the control subjects.

When examined in the frequency domain, the AUC of the normalized closed-loop response between 0 and 0.1 Hz of the OSA patients was greater than that of the control subjects, at -260 ± 93 L/min/0.01 L CO₂ and -617 ± 140 L/min/0.01 L CO₂, respectively ($p < 0.05$) (Figure 3). This result indicates that the power of the ventilatory response in the PRBS test was higher at the frequencies measured in OSA patients.

Open-loop responses of the two groups to hyperoxic CO₂ stimuli are shown in Figure 4. The AUC was not different for the two groups, but the peak response to hyperoxic CO₂ stimulation was greater in the OSA patients than in the control group, at 0.088 ± 0.008 L/min and 0.062 ± 0.007 L/min, respectively ($p < 0.03$) (Table 3). There were no differences in any other of the parameters assessed. The normalized AUC of the open-loop frequency response was not different in the two groups. These data show that there were only minor differences in the open-loop ventilatory response to hyperoxic CO₂ in the two study groups.

DISCUSSION

The results of this study show that there is a difference in the pattern of the response of obese OSA patients and nonobese, nonapneic control subjects to a single breath of hyperoxic CO₂

Figure 2. Closed-loop PRBS response to hyperoxic CO₂ in OSA patients and control subjects (solid line = mean response; dashed lines = 95% confidence limits). (A) OSA. (B) Control. The OSA patients had a higher peak response and shorter settling and response duration times.

during wakefulness, as measured with the PRBS technique. This difference was observed primarily in the closed-loop response. The closed-loop response reflects the interactions of the gains in the components of the ventilatory control system and their response dynamics for one or more of the three subsystems within this system: the controller, the plant, and the negative ventilatory feedback loop. In the closed-loop response to CO₂ in the PRBS test, OSA patients had a higher peak amplitude and a faster and more irregular recovery than was seen in the control subjects. Since the CO₂ was administered under conditions of hyperoxia, these results probably illustrate differences between these two groups in the central dynamic control of breathing. In general, the open-loop response—the arterial PCO₂–ventilation response—which reflects the dynamic gain of the controller and thereby relates to chemosensitivity, was similar in the two groups, with the only difference observed being in the peak amplitude of the response.

Technical Considerations

The PRBS test allows the examination of variables contributing to the ventilatory response to transient ventilatory stimuli. By applying a stimulus in a random manner, the frequency of stimulation is approximately flat, and therefore does not induce a response biased toward any response frequency. Because few data are collected during normocapnic hyperoxia, the PRBS test is likely to underestimate the low-frequency gain, which is represented by the length of the tail of the recovery phase of the closed-loop response. Because the control subject group in our study had a longer such tail, we may have underestimated the difference between the two groups in this range of the response. However, we were primarily interested in the response in the higher frequency range, a range in which most periodic breathing or OSA occurs, of from 0.01 to 0.05 Hz.

A potential limitation of the present study was that it was done during wakefulness and not during sleep. Because of the irregular breathing pattern in OSA patients during sleep, it would not have been possible to use low levels of CO₂ stimulation during sleep in these subjects and obtain a response that was detectable in distinction from the underlying variability in ventilation. Our finding of a difference in dynamic ventilatory

TABLE 1
SUBJECT CHARACTERISTICS*

Characteristics	OSA (n = 9)	Control (n = 16)	p Value
Sex, M:F	8:1	10:6	—
Age, yr	44.3 $\pm$ 6.2	39.7 $\pm$ 4.5	0.535
BMI, kg/m ²	38.8 $\pm$ 2.3	25.8 $\pm$ 1.4	< 0.001

Definition of abbreviation: BMI = body mass index.

* Values are mean $\pm$ SEM.

TABLE 2
CLOSED-LOOP DATA*

Variables	OSA (n = 9)	Control (n = 16)	p Value
AUC, L/min/s	1.623 ± 0.296	1.567 ± 0.313	0.907
Peak, L/min/s	0.194 ± 0.030 [†]	0.101 ± 0.009 [†]	0.017
Response delay, s	7.538 ± 1.314	8.567 ± 0.653	0.439
Rise time, s	7.013 ± 1.029	8.537 ± 1.311	0.491
Time constant, s	8.047 ± 1.115	8.480 ± 1.423	0.837
Response duration, s	172.28 ± 34.96 [†]	348.38 ± 53.41 [†]	0.011
Settling time, s	42.62 ± 9.59 [†]	109.01 ± 26.38 [†]	0.029
Normalized AUC, L/min/0.01 L CO ₂ [†]	-259.82 ± 93.42 [†]	-617.46 ± 139.65 [†]	0.044

Definition of abbreviation: AUC = area under the curve.

* Values are mean ± SEM.

[†] p < 0.05.

[†] Normalized AUC and AUC of the magnitude of the frequency response.

control of obese OSA patients and control subjects in wakefulness suggests that the former have an underlying abnormality of dynamic ventilatory control that may at least in part contribute to their unstable, oscillatory changes in upper airway caliber and breathing during sleep. The cause of this abnormality in ventilatory control was beyond the scope of our study, but speculations can be made about it on the basis of our results (*see the following discussion*).

Another potential problem in relating these findings to sleep is the effect of body position. We conducted the CO₂ challenges in the PRBS test with our subjects in the sitting instead of in the supine position, in order to maintain wakefulness. Some differences in control of breathing responsiveness may exist in these two body positions (11), but in the study by Xie and colleagues (11), the hypercapnic response was affected less than the hypoxic response. In the present study, both control subjects and OSA patients were studied in the sitting position.

Other factors, such as cardiovascular function and gender, affect the results of PRBS testing. Now that a difference in PRBS test responses of OSA patients and control subjects has been demonstrated, the etiology of this difference will need to be explored. The effects of gender and body size should be considered in this evaluation.

Possible Mechanism(s) of Observed Changes

From the open- and closed-loop responses in the PRBS test, we can begin to identify specific differences within the dynamic ventilatory control system in OSA patients and control subjects. There arises the question of the cause of the higher peak and shorter recovery time observed in the closed-loop response of the OSA patients. Because the open-loop response demonstrates that the controller dynamic gain in the OSA patients was not substantially different from that in the normal subjects, the differences seen in the closed-loop responses of the two groups are not likely to have been due to differences in controller function, but are more likely to have been due to differences in the dynamic gains of the plant or ventilatory feedback loop (9). Because the peak of the closed-loop response is proportional to the product of the controller and plant dynamic gains, and because the controller dynamic gain in the OSA patients was not substantially different from normal, we conclude that the difference between the two groups in the peak of the closed-loop response was primarily due to a difference in plant dynamic gain, with this gain being higher in the OSA patients. This finding is consistent with the expectation that the plant dynamic gain would have been higher in the obese subjects in the study, with or without OSA, who would have had a smaller lung volume than the normal

subjects (3). This smaller lung volume would result in larger changes in arterial CO₂ tension per unit of ventilation because of less buffering capacity of lung CO₂ stores, which are smaller with a smaller lung volume.

The settling time and the duration of the response to stimulation are affected by the controller response to the washout of CO₂ from central chemoreceptors, and by negative ventilatory feedback. The stronger the negative ventilatory feedback, the shorter and more undamped the settling and response times will be (9). Because the controller responses were similar in our two groups of subjects, we conclude that the primary factor producing the shorter settling and response times in OSA was a stronger negative ventilatory feedback. Because of the small lungs in obesity, we would expect a greater reduction in arterial PCO₂ per unit increase in ventilation, and subsequently a greater suppression of ventilation because of the resultant relative hypocapnia. These changes would lead to a more rapid recovery of ventilation toward baseline after an initial stimulation, and therefore to the shorter settling and response times seen in our OSA patients.

The higher amplitude of the closed-loop ventilatory response in the frequency domain indicates that more power existed in the OSA group at the frequencies that we examined.

Figure 3. Closed-loop PRBS response in the frequency domain (solid line = mean response; dashed lines = 95% confidence limits). (A) OSA. (B) Control. OSA patients had a higher gain at all frequencies analyzed (normalized magnitude, ventilatory response/ventilatory response at 0 Hz frequency).

Figure 4. Open-loop PRBS response to hyperoxic CO₂ in OSA patients and control subjects (solid line = mean response; dashed lines = 95% confidence limits). (A) OSA. (B) Control. The responses differed only in amplitude, which was higher in the OSA patients.

Most importantly, there was more power in the frequency range of 0.01 to 0.05 Hz, which represents an oscillatory breathing pattern of one cycle every 20 to 100 s, resembling the frequency of the oscillations of apnea seen in OSA during sleep. This higher power in the frequency domain indicates that the amplitudes of ventilation at the frequencies found in the response were greater in the OSA patients. This finding is consistent with the existence of a more oscillatory and thereby more unstable closed-loop response in the OSA patients. Because the open-loop responses of the OSA patients and control subjects were similar in the frequency domain, we believe that the major differences between the two groups were due to differences in plant dynamic gain and negative ventilatory feedback.

Our study was done under conditions of hyperoxia during wakefulness. To apply to OSA the concepts of dynamic ventilatory control discussed here, one has to consider the effects of different levels of oxygen concentration and the effects of sleep on the CO₂ response in the PRBS test. As reported by Lai and Bruce (12), the dynamic gain of the closed-loop response to CO₂ stimulation in the PRBS test was greater in normoxia than in hyperoxia. The peripheral chemoreceptors

would be expected to potentiate the ventilatory response to CO₂ in normoxia as compared with hyperoxia, because of the depressed peripheral chemoreceptor activity that exists in hyperoxia. Extending this logic, we would anticipate that during hypoxemia, because of the greater activity of the peripheral chemoreceptors, the input of the peripheral chemoreceptors to the dynamic ventilatory response to CO₂ would increase even further. In fact, the peripheral chemoreceptors would not only influence the magnitude of the response, but also its frequency dynamics. The time constant of the peripheral chemoreceptor is much shorter than the time constant of the central chemoreceptor; and we would therefore anticipate a more rapid response the more activated the peripheral chemoreceptor (13, 14). A smaller time constant would shorten the rise and recovery (settling) times of the CO₂ response in the PRBS test, an effect that would be all the more destabilizing to the dynamic control of breathing. Therefore, had we made these measurements in normoxia or hypoxemia, we would most likely have observed an exaggeration of the pattern seen in our OSA patients. In addition, we would probably have found higher power in the frequency domain during normoxia or hypoxia, as was found by Lai and Bruce (12). These effects of normoxia or hypoxia would probably decrease the dynamic stability of the ventilatory muscle control system, potentially resulting in periodic fluctuations of upper airway caliber and irregular breathing. Interestingly, even during hyperoxia, we found a pattern of PRBS response in our OSA patients that might indicate an underlying susceptibility to unstable breathing. In hyperoxia, the peripheral chemoreceptors would contribute minimally to the response, indicating that factors other than the peripheral chemoreceptors may be responsible for the instability that we observed. If chemosensitivity in OSA patients and normal subjects is similar, the instability in ventilatory control that we observed is most likely not a consequence of central or peripheral controller function, but is more likely to be related to dynamic gains in plant and/or negative ventilatory feedback and/or to temporal dynamics.

Mechanisms Contributing to Ventilatory Instability in Sleep

That ventilatory instability in sleep is of paramount importance in the pathogenesis of OSA was demonstrated by Onal and Lopata (15), when they showed that tracheotomized OSA patients had persistent periodic breathing in sleep. Several mechanisms related to the control of breathing, and factors that affect the control of breathing, have been proposed as contributors to the unstable breathing in OSA. As discussed earlier, an increased loop gain, caused by high controller and/or plant gain(s), may lead to unstable ventilatory control (16).

TABLE 3
OPEN-LOOP DATA*

Variables	OSA (n = 9)	Control (n = 16)	p Value
AUC, L/min/s	0.710 ± 0.174	0.337 ± 0.79	0.077
Peak, L/min/s	0.088 ± 0.008 [†]	0.062 ± 0.007 [†]	0.028
Response delay, s	7.538 ± 1.314	8.567 ± 0.653	0.439
Rise time, s	2.898 ± 0.188	3.014 ± 0.126	0.601
Time constant, s	2.119 ± 0.138	2.204 ± 0.092	0.602
Response duration, s	171.34 ± 37.41	139.86 ± 41.30	0.617
Settling time, s	53.68 ± 12.13	47.78 ± 15.76	0.800
Normalized AUC, L/min/0.01 L CO ₂ [‡]	-373.74 ± 95.71	-285.68 ± 92.89	0.546

Definition of abbreviation: AUC = area under the curve.

* Values are mean ± SEM.

[†] p < 0.05.

[‡] Normalized AUC and AUC of the magnitude of the frequency response.

The role of an increased controller gain was demonstrated experimentally by Gleeson and colleagues (17) when they subjected healthy individuals to resistive respiratory loads during NREM sleep. Those subjects with high hypercapnic ventilatory drives during wakefulness developed oscillatory breathing after release of the load during NREM sleep. Chapman and colleagues (13) found that subjects who developed periodic breathing during NREM sleep when loop gain was increased with an external breathing circuit were those with increased responsiveness to hypercapnia during wakefulness. Webb (18) speculated that neurologic or circulatory delays in the feedback loop of ventilatory control that occur in sleep, especially with aging, may also contribute to periodic breathing in sleep. Cherniack (3) focused on the influence of the hyperbolic arterial P_{CO_2} -ventilation relationship on ventilatory stability after the stabilizing effects of environmental stimuli are removed as sleep begins. The importance of the level of arterial P_{CO_2} and the extent of body gas stores were stressed. During hypercapnia, a given increase in ventilation will result in a greater change in P_{CO_2} , which will have a greater tendency to induce an apnea than if hypercapnia were not present. Skatrud and Dempsey (19) also emphasized the importance of arterial P_{CO_2} in setting the ventilation pattern in NREM sleep. In a comprehensive modeling study, Khoo and coworkers (20) proposed that in addition to levels of controller and plant gains, rapidity of sleep onset, arousal threshold, and the tendency for upper airway collapse were important in the pathogenesis of OSA. Warner and associates (21) found that those individuals with a high degree of upper airway resistance during wakefulness had obstructive apneas in NREM sleep during hypoxic hypocapnia. The dynamics of changes in sleep state and upper airway mechanics were found to be most influential when controller gain was low.

NREM sleep is likely to reduce controller gain (9). In healthy, nonapneic subjects, the controller gain was found to decrease in Stage 2 NREM sleep as compared with wakefulness, but the closed-loop response did not change. Thereby, the low controller gain in NREM sleep will be accompanied by an increased dynamic plant gain and/or an increased negative ventilatory feedback. We speculate that obese OSA patients may experience an even greater increase in dynamic gains in plant or negative ventilatory feedback in NREM

sleep, because of a greater than normal decrease in lung volume and/or an increased arterial P_{CO_2} . This greater than normal increase in plant or negative ventilatory feedback gain would tend to destabilize the dynamic ventilatory control system in NREM sleep. Thus, several variables may influence breathing pattern in NREM sleep, and may predispose some individuals to OSA in NREM sleep. The relative importance of these variables has yet to be determined.

Modeling Projections

Data sets from two previous studies and the data from the current study, all generated with the same PRBS technique, allowed us to model the anticipated ventilatory response to a transient CO_2 stimulus in NREM sleep in OSA (7). The data sets used for this were: (1) the PRBS CO_2 responses in wakefulness and NREM sleep of nonapneic normal subjects (9); (2) the PRBS CO_2 responses during hyperoxia and normoxia of nonapneic controls (12); and (3) the data from the current study. Analysis of the experimental closed- and open-loop responses provided the parameters necessary for the closed- and open-loop controller models. Calculations from these two components allowed the establishment of the plant model. By applying to both the control and OSA group data of the current study the same differences in wakefulness versus sleep, and the same changes from hyperoxia to normoxia in PRBS responses, we found different ventilatory dynamics during the breathing of ambient air in NREM sleep, with the dynamics of OSA patients giving them a tendency toward ventilatory instability. Introduction of random fluctuations in venous CO_2 content into the model produced greater changes in arterial P_{CO_2} and ventilation in OSA patients than in controls (Figure 5). This result is consistent with the presence of an increased plant dynamic gain. In addition, modeling of the closed-loop PRBS CO_2 response in NREM sleep in OSA patients during normoxia also showed changes consistent with ventilatory instability, in the form of a greater peak response and shorter recovery time in OSA patients than in controls (Figure 6). In this modeling exercise, the same percentage change in the variables for the transition from wakefulness to NREM sleep was used for both groups. However, we would speculate that the increase in plant dynamic gain from wakefulness to sleep

Figure 5. Modeling of the arterial P_{CO_2} (A) and ventilation (B) responses to a single alteration in mixed venous P_{CO_2} , applied in a random order in OSA patients (solid line) and control (dashed line) subjects (see text for explanation). Greater fluctuation in both variables occurred in the OSA patients.

Figure 6. Simulation of average ventilatory response to a single alteration in venous P_{CO_2} during NREM sleep in OSA patients (solid line) and control subjects (dashed line). The OSA response is potentially destabilizing, with a higher peak and a more rapid recovery (see text).

would be greater in OSA patients, so that our modeling may underestimate the fluctuations in arterial P_{CO_2} and ventilation that occur with fluctuations in venous P_{CO_2} .

Role of Obesity

The increased dynamic gains in plant and negative ventilatory feedback discussed earlier may not be directly related to OSA, but may instead be related to obesity in our OSA patients. These two variables are linked, in that in adults there is a close relationship between the presence of OSA and obesity (22, 23) and it has been well documented that weight loss alleviates OSA (24, 25). With weight loss it is possible that dynamic gains in plant and negative ventilatory feedback would decrease because of an increase in lung volume and a decrease in arterial P_{CO_2} . Thus, it is reasonable to anticipate that ventilatory stability would improve with weight loss, and this improvement might in turn very well be a factor in improving the stability of upper airway caliber during sleep, thereby contributing to the alleviation of OSA seen with weight loss. Clearly, studies controlling for obesity will be necessary to evaluate the role of body weight in dynamic ventilatory control.

Mechanical Effects of Unstable Ventilatory Control

We would anticipate that unstable ventilatory control of breathing would affect the control of upper airway patency during sleep. With large swings in ventilatory control, there would be large swings in upper airway motoneuron activity that would be larger than the swings in chest-wall pump muscles, such as the diaphragm (6, 12, 26). This imbalance in the motor control activities of these two muscle groups could result in large fluctuations in upper airway caliber to the point of upper airway occlusion (3). Diminution of the swings in ventilatory control, induced by smoothing of the F_{ICO_2} fluctuations in OSA patients during sleep, was found to dramatically decrease the appearance of obstructive apneas (27). Therefore, we conclude that the pattern of the response to the transient CO_2 stimulus used in the present study may be indicative of unstable dy-

namic control of breathing, and may have contributed to the abnormal breathing pattern present during NREM sleep in the obese OSA patients that we studied.

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