Postevent ventilation as a function of CO₂ load during respiratory events in obstructive sleep apnea

KENNETH I. BERGER, INDU AYAPPA, I. BARRY SORKIN, ROBERT G. NORMAN, DAVID M. RAPOPORT, AND ROBERTA M. GOLDRING

Division of Pulmonary and Critical Care Medicine and Bellevue Hospital Chest Service, Department of Medicine, New York University School of Medicine, New York, New York 10016

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Postevent ventilation as a function of CO₂ load during respiratory events in obstructive sleep apnea. J Appl Physiol 93: 917–924, 2002. First published June 14, 2002; 10.1152/japplphysiol.01082.2001.—Maintenance of eucapnia during sleep in obstructive sleep apnea (OSA) requires a balance between CO₂ loading during apnea and CO₂ elimination. This study examines individual respiratory events and relates magnitude of postevent ventilation to CO₂ load during the preceding respiratory event in 14 patients with OSA (arterial PCO₂ 42–56 Torr). Ventilation and expiratory CO₂ and O₂ fractions were measured on a breath-by-breath basis during daytime sleep. Calculations included CO₂ load during each event (metabolic CO₂ production – exhaled CO₂) and postevent ventilation in the 10 s after an event. In 12 of 14 patients, a direct relationship existed between postevent ventilation and CO₂ load during the preceding event (P < 0.05); the slope of this relationship varied across subjects. Thus the postevent ventilation is tightly linked to CO₂ loading during each respiratory event and may be an important mechanism that defends against development of chronic hypercapnia in OSA. An inverse relationship was noted between this postevent ventilatory response slope and the chronic awake arterial PCO₂ (r = 0.90, P < 0.001), suggesting that this mechanism is impaired in patients with chronic hypercapnia. The link between development of acute hypercapnia during respiratory events asleep and maintenance of chronic awake hypercapnia in OSA remains to be further investigated.

carbon dioxide; hypercapnia; hypoventilation; sleep apnea syndromes; Pickwickian syndrome

MAINTENANCE OF EUCAPNIA DURING sleep in patients with obstructive sleep apnea requires a balance between CO₂ loading during apneic/hypopneic events and CO₂ elimination. The majority of patients with obstructive sleep apnea are eucapnic, indicating that they are able to maintain this balance. Moreover, our laboratory has previously shown through direct measurements that this balance is maintained on an event-by-event basis because the majority of event-interevent cycles have near complete elimination of the CO₂ loaded during the preceding event (1). This observation suggests that interevent ventilation is responsive to CO₂ kinetics during each respiratory event. However, assessment of respiratory control by using the awake rebreathing CO₂ response has revealed no relationship to the cumulative CO₂ balance for the sleep period (1). These findings prompt the present investigation of the ventilatory-CO₂ control system during individual event-interevent cycles.

Prior data from this laboratory in eucapnic patients indicated that the size of the first breath after apnea was related to the duration of the preceding apnea (5). Because CO₂ load is a function of apnea duration, these data suggested that the size of the first breath after apnea might be related to the CO₂ load that accumulated during the preceding event. Other studies suggested that chronic hypercapnia may modify this response by noting absence of a big breath after apnea in some patients with chronic hypercapnia (4, 12, 16, 17); this finding was attributed to observed depressed ventilatory CO₂ responsiveness in these patients (4). These observations support an important role for CO₂ control mechanisms in establishing ventilatory compensation for the CO₂ loading of apnea/hypopnea.

We hypothesize that the interevent ventilation in obstructive sleep apnea is driven predominately by a measure of the acute increase in body CO₂ stores as a result of the preceding event. Alternatively, the interevent ventilation may be driven substantially by factors other than the acute change in CO₂, such as but not limited to acute hypoxic response, tonic wakefulness drive, or arousal. A test of our hypothesis is that the total ventilation in the first 10 s of the interevent period should increase with increasing CO₂ load. We further hypothesize that the presence of daytime hypercapnia would be associated with a blunting of this interevent ventilatory response to CO₂ load. A test of this hypothesis is that the interevent ventilatory response to the CO₂ load during the preceding event will decrease with increasing chronic hypercapnia.

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METHODS

Fourteen patients with severe obstructive sleep apnea were studied. Patients were recruited from the Sleep Disorders Center at the New York University/Bellevue Medical Center on the basis of complaints of severe sleepiness and nocturnal polysomnography revealing obstructive sleep apnea [apnea-hypopnea index (AHI) >30]. Patients were studied before any treatment of their obstructive sleep apnea. Exclusion criteria were as follows: clinical evidence for chronic lung disease, ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) <70%, cardiac failure other than cor pulmonale, left ventricular ejection fraction <50% or clinical evidence for left ventricular dysfunction, hypothyroidism (elevated serum thyroid-stimulating hormone level), current usage of respiratory depressants (including chronic methadone maintenance), or neuromuscular disease. The study was approved by the institutional review boards of New York University Medical Center and the Health and Hospitals Corporation of New York City. All patients signed informed consent before entering the study.

Each patient was studied in a fasting state. The protocol consisted of a daytime study during which sleep, ventilation, and CO2 load during respiratory events were monitored. Electrodes were attached for polysomnography (central and occipital electroencephalogram, electrooculogram, and submental electromyogram). With the patient resting in the supine position, an arterial blood-gas sample was withdrawn. A tight-fitting full face mask was applied to the patient to obtain continuous measurements of minute ventilation, CO2 excretion, O2 consumption, and respiratory exchange ratio. To obtain a steady-state baseline, data were collected during an awake period lasting 5–30 min. The lights were then turned off, and the patient was allowed to fall asleep. Data were then collected during a period of sleep that varied from 37 to 152 min.

Sleep was scored in 30-s epochs by using Rechtschaffen and Kales criteria (15). Ventilation was measured continuously with the face mask connected to a nonbreathing valve (series 1400, Hana Rudolph, Kansas City, MO). The inspiratory limb was connected to a pneumotachograph. Tidal volume was calculated by integrating airflow over inspiration after linearization of the inspiratory flow signal. Frequency was derived from the duration of each breathing cycle. To measure O2 consumption and CO2 excretion, the expiratory limb of the circuit was connected to a 5.1-liter mixing chamber containing a fan. The exhaled gas was analyzed for O2 and CO2 concentrations by using paramagnetic and infrared analyzers, respectively (Fitco Max-1, Physiodyne, Farmingdale, NY). O2 consumption and CO2 excretion were calculated by using standard equations. All signals were digitized and recorded on a breath-by-breath basis on an IBM-compatible computer for off-line analysis (Fitco Max-1, Physiodyne). O2 saturation was assessed by pulse oximetry with use of a finger probe (FasTrac, SensorMedics, Yorba Linda, CA).

CO2 load during respiratory events. The amount of CO2 loaded was calculated during each respiratory event by using a previously validated technique (1). Respiratory events were defined as either apneas (absence of airflow or tidal volumes <50 ml for >10 s) or hypopneas (tidal volumes <300 ml for >10 s). CO2 load during a respiratory event was calculated as the difference between metabolic CO2 production and CO2 excretion. CO2 excretion was directly measured on a breath-by-breath basis and was assumed equal to zero during apnea. However, metabolic CO2 production could not be directly measured because of the non-steady-state condition inherent to periodic breathing. Because there are minimal O2 stores, the average O2 consumption calculated from exhaled gas measurements over time would equal the metabolic O2 consumption. Therefore, an average rate for metabolic CO2 production was calculated for the entire sleep period equal to the average O2 consumption during the sleep period times the respiratory exchange ratio determined during the awake steady-state period. The metabolic CO2 production during a respiratory event was then calculated by multiplying the rate of metabolic CO2 production during sleep times the duration of the respiratory event (1).

Figure 1 schematically illustrates the primary end-point data obtained in the present study. During the events (apnea/hypopnea), CO2 excretion decreases. The resultant CO2 load (shaded areas) is calculated by integrating the difference between breath-by-breath CO2 excretion and average metabolic CO2 production during the event. The spirometry tracing illustrates a postevent increase in ventilation to levels above control periods with stable ventilation. The immediate postevent ventilation was assessed by summing the tidal volumes for all breaths initiated within the first 10 s of the intervention period. The analysis was limited to 10 s because chemical stimulus is maximal at the beginning of the interevent interval. In addition, the 10 s is less than the recirculation time, preventing a change in mixed venous PCO2 that may influence the postevent ventilation. Finally, an interevent interval of 10 s is shared by over 90% of event-inter-event cycles in all patients. In general, the 10-s postevent ventilation consisted of the first two to three breaths after the termination of the preceding event. The 10-s postevent ventilation was related to the CO2 load during the preceding respiratory event for each event in each subject. This assessment provides a measure of CO2 responsiveness after an event and does not require or imply full unloading during the interevent interval.

In addition to the above data, a continuous tracing of O2 saturation was obtained and recorded from the pulse oximeter in 13 of 14 patients. This tracing was analyzed to determine the nadir O2 saturation that occurred after each respiratory event.

Spirometry and ventilatory response to CO2 were obtained within 2 wk before the daytime study. The ventilatory response to CO2 was performed by a rebreathing technique (14). Ventilation was measured as the subject rebreathed from a closed system containing increasing CO2 in a hyperoxic gas mixture. CO2 was monitored by end-tidal level and was allowed to rise above the initial mixed venous level over 4 min. Fully automated custom software was utilized to perform this test and to acquire the ventilatory and gas signals for calculation of the slope of the relationship between minute ventilation and PCO2. Spirometry and ventilatory response to CO2 were determined before treatment of the underlying respiratory sleep disorder.

Data analysis. For each event in each subject, the CO2 load during the event, the total ventilation in the first 10 s after the termination of the event, and the nadir O2 saturation after the event were determined. The mean values for each of these variables were determined for all events in each subject.

For each patient, multivariate linear regression analysis was performed relating the 10-s postevent ventilation as the dependent variable to the amount of CO2 loaded during the preceding respiratory event and to the nadir O2 saturation after the event as two independent variables. This analysis included investigation for a possible interaction between CO2 load and nadir O2 saturation by including a multiplicative interaction term as a third factor in the multivariate analysis. For this analysis, data from individual events with the largest CO2 load (>200 ml/event) were excluded because, in
three subjects, the postevent tidal volume approached the previously measured inspiratory capacity, suggesting a mechanical limitation.

Data are presented as means ± SD. For all of the above analyses, a value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics for all 14 patients are illustrated in Table 1. All patients were obese [body mass index (BMI) 30.5–73.9 kg/m$^2$] with severe obstructive sleep apnea (AHI > 30 during diagnostic polysomnogram; AHI > 40 during data collection). Arterial $\text{PCO}_2$ ($\text{PaCO}_2$) varied across subjects (42–56 Torr). Nine patients had preexisting chronic hypercapnia with values for $\text{PaCO}_2$ ≥ 45 Torr and an elevated serum bicarbonate. The awake ventilatory response to $\text{CO}_2$ varied from values as low as 0.1 l/min/Torr, indicating a nearly absent response, to values as high as 5.0 l/min/Torr, indicating a vigorous response. There was no clinical evidence of intrinsic pulmonary disease. FEV$_1$/FVC ranged from 71 to 91% and was normal ($≥ 78\%$) in the nine patients with an elevated $\text{PaCO}_2$. FVC ranged from 68 to 117% of predicted. The observed reductions in FVC were due to a reduced expiratory reserve volume with a preserved inspiratory capacity, compatible with obesity.

The $\text{CO}_2$ load during respiratory events varied both within and between patients. Table 2 illustrates sum-

### Table 1. Patient characteristics

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M, male; F, female; BSA, body surface area; BMI, body mass index; AHI, apnea/hypopnea index calculated as the number of apneas plus hypopneas per hour sleep; $\text{PaCO}_2$, arterial $\text{PCO}_2$; $\text{PaO}_2$, arterial $\text{PO}_2$; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume.
mary data for event CO₂ load, immediate postevent ventilation, and nadir O₂ saturation during sleep. The data represent the average values (± SD) for all events in each subject. Ninety-seven percent of all events in all subjects occurred during stage 2 sleep. The mean CO₂ load during respiratory events varied between patients and ranged from 38 to 151 ml. The average CO₂ load during an event tended to be higher in patients with higher awake PaCO₂ (r = 0.65, P = 0.01). The mean postevent ventilation varied between patients and ranged from 2,197 to 6,448 ml/10 s. All patients demonstrated augmented postevent ventilation above control steady-state levels (mean increase 190%), and extrapolation of the 10-s data to 1 min reveals postevent ventilatory rates as high as 59 l/min (650% increase compared with control). In addition, the postevent ventilation exceeded 1,667 ml/10 s (10 l/min by extrapolation) in >97% of events in all patients, including those with preexisting chronic awake hypercapnia. The average 10-s postevent ventilation tended to be higher in patients with higher awake PaCO₂, although this trend failed to reach statistical significance (r = 0.38, P = 0.19).

The relationship between the 10-s postevent ventilation and the CO₂ load during the preceding event is evaluated in each patient in Fig. 2. The 10-s postevent ventilation was directly related to the amount of CO₂ loaded during the preceding respiratory event in 12 of 14 patients (r = 0.32–0.87; P < 0.005). This relationship between postevent ventilation and CO₂ load did not differ for hypopneas compared with apneas. The slope of this relationship defines the ventilatory response to endogenous CO₂ loading during a respiratory event; this slope varied across patients and averaged 30.3 ml·10 s⁻¹·ml CO₂ load⁻¹ (range 13.3–49.5 ml·10 s⁻¹·ml CO₂ load⁻¹).

Figure 3 illustrates the relationship between the 10-s postevent ventilation and the nadir O₂ saturation in the 13 patients in whom data for O₂ saturation were obtained. A significant inverse relationship between 10-s postevent ventilation and nadir O₂ saturation was observed in only 6 of 13 patients. For these six patients, multivariate linear regression analysis was performed to investigate whether nadir O₂ saturation was associated with postevent ventilation independently of the effect of CO₂ load during the event. A significant independent association between nadir O₂ saturation and 10-s postevent ventilation was observed in only one of six patients. In this one patient, the effect of the nadir O₂ saturation on the postevent ventilation was relatively small compared with the effect of the event CO₂ load on postevent ventilation (ratio of standardized β-coefficients 0.43) and the r² for the regression improved by only 0.04. In addition, the multivariate analysis revealed that the relationship between the interaction term for nadir O₂ saturation times event CO₂ load and postevent ventilation was not statistically significant.

Figure 4 illustrates the relationship between the postevent ventilatory response slope (shown in Fig. 3) and the degree of preexisting hypercapnia. The postevent ventilatory response slope was defined as the slope of the relationship between the 10-s postevent ventilation and the CO₂ load during the preceding event. The postevent ventilatory response slope was tightly coupled to the degree of preexisting hypercapnia as assessed by either the chronic awake PaCO₂ (r = 0.90, P < 0.001) or serum bicarbonate (r = 0.84, P < 0.001). Patients with preexisting chronic awake hypercapnia demonstrated a lower postevent ventilatory response slope compared with eucapnic patients. Multivariate analysis revealed that this relationship between the postevent ventilatory response and the chronic awake PaCO₂ was not improved by addition of either BMI, FVC, FEV₁/FVC, or apnea duration as independent variables (r² change < 0.06 and P > 0.05 for each factor analyzed as a separate model).

Figure 5 illustrates the relationship between the ventilatory response to CO₂ measured during wakefulness and the postevent ventilatory response measured during sleep. The postevent ventilatory response slope correlated poorly with the awake rebreathing ventilatory response slope.

**DISCUSSION**

The present study examined the postevent ventilation and related it to the volume of CO₂ loaded during the preceding respiratory event in eucapnic and hypercapnic patients with obstructive sleep apnea. The results demonstrate that 1) there is a direct relationship between the 10-s postevent ventilation and the volume of CO₂ loaded during the preceding respiratory event, 2) the slope of this relationship between postevent ventilation and CO₂ load varies across patients, and 3) an inverse relationship exists (r = 0.90) between this postevent ventilatory response slope and the chronic awake PaCO₂. These observations suggest that the chemical stimulus resulting from the CO₂ loaded during respiratory events is a major factor controlling the magnitude of the postevent ventilation.
A model of CO₂ kinetics during periodic breathing has previously been used to demonstrate that most of the CO₂ loaded during a respiratory event is eliminated in the first few breaths after termination of the event (13). In the present study, the magnitude of the ventilation during the first 10 s after a respiratory event averaged 190% above control levels and was as high as 650% above control, even in patients with preexisting chronic hypercapnia. In eucapnic patients, the size of the first breath after apnea has been related to the duration and, by implication, CO₂ load of the preceding event (5). In contrast, in chronic hypercapnia, prior studies (4, 12, 16, 17) have demonstrated failure to increase tidal volume in the first breath after apnea; however, in one of these studies tidal volume did increase in the patient with the longest apnea duration, implying high CO₂ load (4). The present study extends these observations by demonstrating that the postevent ventilation is directly related to the volume of CO₂ loaded during the preceding respiratory event. Hypercapnic patients also demonstrated high postevent ventilation; however, this high postevent ventilation was lower for a given amount of CO₂ load (lower postevent ventilatory response slope) compared with eucapnia. This reduced postevent ventilatory response slope seen in chronic hypercapnia would result in a decreased interevent elimination of CO₂ compared with eucapnia at a given blood PCO₂; however, the

Fig. 2. Relationship between 10-s postevent ventilation and CO₂ load during the preceding event in each subject. Each graph represents data for all events in a given patient. ○, Apneas; ●, hypopneas. The 10-s postevent ventilation was directly related to the amount of CO₂ loaded during the preceding respiratory event in 12 of 14 patients (\( r = 0.32-0.87; \ P < 0.005 \)). NS, not significant.
increased gradient for CO₂ elimination in the hypercapnic state counterbalances this effect, allowing for stability of PaCO₂, albeit at an elevated value.

Potential mechanisms that may contribute to the reduction of the postevent ventilatory response slope seen with increasing chronic awake PaCO₂ include mass loading from obesity, underlying pulmonary disease such as chronic obstructive disease, elevation of serum bicarbonate, and/or altered whole body CO₂ storage capacity. In the present study, the postevent ventilation was increased in all patients regardless of the chronic awake PaCO₂, suggesting that mechanical limitation did not play a role. Moreover, multivariate analysis failed to demonstrate a relationship between the postevent ventilatory response and either BMI, FVC, or FVC/FEV₁. A likely mechanism for the reduced postevent ventilatory response slope seen in patients with chronic hypercapnia relates to gradual adaptation of chemoreceptors (9) that may occur as a consequence of elevated serum bicarbonate and/or alterations in whole body CO₂ storage capacity. The relative contribution of all of these factors may differ in other patient populations.

Theoretical considerations (13), confirmed in human studies (1), have delineated the ventilatory requirements necessary to fully unload the CO₂ loaded during the preceding respiratory event. During periodic breathing, maintenance of the average rate of ventilation at the steady-state level requires a compensatory increase in interevent ventilation to compensate for

Fig. 3. Relationship between 10-s postevent ventilation and nadir O₂ saturation in 13 patients in whom adequate data for O₂ saturation were obtained. Each graph represents data for all events in a given patient. A significant inverse relationship between 10-s postevent ventilation and nadir O₂ saturation was observed in only 6 of 13 patients.
apnea. Moreover, maintenance of PCO₂ at the steady-state level requires a further increase in interventive ventilation to overcome temporal dissociation between ventilation and perfusion (“temporal V/Q mismatch”). The latter increase in ventilation is required because periodic patterns of breathing imply a temporal dissociation between ventilation and perfusion (1, 13). As with other forms of V/Q mismatch, maintenance of eucapnia in the setting of temporal V/Q mismatch requires that interventive ventilation be increased above that required for maintenance of steady-state ventilation. Because of these requirements, the high 10-s postevent ventilatory rates seen in the present study do not necessarily imply full unloading of the CO₂ load during the prior respiratory event. Prior observations from this laboratory have, in fact, demonstrated that temporal V/Q mismatch may lead to acute hypercapnia despite markedly increased interventive ventilation when intervent duration is short (1).

Hypoxia is a known stimulant of ventilation that may have contributed to the ventilatory drive present at the termination of a respiratory event. Prior studies have demonstrated that O₂ therapy applied to prevent arterial O₂ desaturation during apnea attenuates the size of the first breath after the apnea (4). In our data, the 10-s postevent ventilation was less well correlated to nadir O₂ saturation than to CO₂ load, but the relationship was statistically significant in six patients. However, an independent relationship between postevent ventilation and O₂ saturation could only be demonstrated in one patient, an effect of hypoxia through interaction with the CO₂ load response may have been present.

Additional factors that influence the postevent ventilation include the ventilatory response to arousal per se, the increased ventilation that results from mech-anoreceptor activation and changes in upper airway resistance that occur on awakening, and the sleep stage during which the respiratory event occurs. Previous studies have demonstrated that arousal from sleep results in an augmented ventilation even in the absence of apnea/hypopnea (2). This increase in ventilation after arousal from sleep has been attributed to state-related changes in neural drive and state-related changes in upper airway resistance (2, 3, 7, 11). However, in these studies, the magnitude of the increased ventilation due to arousal per se was relatively small (20–50%) compared with the average 190% increase in ventilation observed in the present study. In addition, modeling studies based on data obtained from human subjects have indicated that the contribution of the arousal response would be further minimized in the presence of high chemical drive as occurs after apnea as a result of CO₂ accumulation and hypoxia (10, 11). Lastly, it is possible that the ventilatory response in the partially aroused state in the intervent period depends on the sleep state from which it evolved and may differ significantly for rapid eye movement (REM) sleep. The findings of the present study pertain to daytime non-REM sleep, and the role of nighttime and REM sleep in the control of the postevent ventilatory response to CO₂ load has not been examined.

The postevent ventilatory response examined in the present study likely reflects the output of an integrated CO₂ control system. However, the postevent ventilatory response to CO₂ load during repetitive events correlated poorly with the traditional ventilatory response to CO₂ measured by the rebreathing technique during wakefulness. This dissociation reflects additional inputs to the ventilatory control system that are present during the periodic pattern of breathing inherent to obstructive apnea. First, during wakefulness, the ventilatory response to CO₂ was measured during hypoxia, reflecting central chemoreceptor activity, whereas the postevent ventilatory response to CO₂ was measured under variable hypoxia, resulting in a potential contribution from peripheral chemoreceptors. Second, although it was previously assumed that the
arousal from sleep after a respiratory event represents a return to the wakefulness state, more recent data suggest that a distinct transiently aroused state may exist. This state is characterized by enhanced cardiorespiratory activation compared with wakefulness. Although the enhanced respiratory activity after arousal is not fully accounted for by CO₂ chemosensitivity as tested awake, it may have augmented the postevent ventilatory response to CO₂ (6, 8). Third, the increase in blood CO₂ content during the event and/or cardio- dynamic changes that occur on arousal have the net effect of increasing CO₂ flow in a manner analogous to that invoked at the onset of exercise (“cardiodynamic hyperpnea”) (18). These three mechanisms may contribute to the magnitude of the postevent ventilatory response to CO₂ observed in the present study. These considerations highlight the possibility that the traditional CO₂ rebreathing response measured during wakefulness may not be an appropriate measure of the CO₂ control system during periodic breathing in sleep.

In summary, investigation of ventilatory control mechanisms during the periodic breathing of obstructive sleep apnea requires consideration of duration of events and/or CO₂ loading. The postevent ventilation is tightly linked to CO₂ kinetics during periodic breathing and appears to be an important mechanism that defends against development of acute hypercapnia in patients with obstructive sleep apnea. The inverse relationship noted between the postevent ventilatory response slope and the chronic awake PaCO₂ suggests that this mechanism is impaired in patients with chronic hypercapnia. The link between development of acute hypercapnia during respiratory events asleep and maintenance of chronic awake hypercapnia in obesity hypoventilation syndrome remains to be further investigated.

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REFERENCES


