CO₂ homeostasis during periodic breathing in obstructive sleep apnea

KENNETH I. BERGER, INDU AYAPPA, I. BARRY SORKIN, ROBERT G. NORMAN, DAVID M. RAPOPORT, AND ROBERTA M. GOLDRING
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Berger, Kenneth I., Indu Ayappa, I. Barry Sorkin, Robert G. Norman, David M. Rapoport, and Roberta M. Goldring. CO₂ homeostasis during periodic breathing in obstructive sleep apnea. J. Appl. Physiol. 88: 257–264, 2000.—The contribution of apnea to chronic hypercapnia in obstructive sleep apnea (OSA) has not been clarified. Using a model (D. M. Rapoport, R. G. Norman, and R. M. Goldring. J. Appl. Physiol. 75: 2302–2309, 1993), we previously illustrated failure of CO₂ homeostasis during periodic breathing resulting from temporal dissociation between ventilation and perfusion ("temporal V˙/Q˙ mismatch"). This study measures acute kinetics of CO₂ during periodic breathing and addresses interapnea ventilatory compensation for maintenance of CO₂ homeostasis in 11 patients with OSA during daytime sleep (37–171 min). Ventilation and expiratory CO₂ and O₂ fractions were measured on a breath-by-breath basis by means of a tight-fitting full facemask. Calculations included CO₂ excretion, metabolic CO₂ production, and CO₂ balance (metabolic CO₂ production – exhaled CO₂). CO₂ balance was tabulated for each apnea/hypopnea event-interevent cycle and as a cumulative value during sleep. Cumulative CO₂ balance varied (~3.570 to +1.388 ml). Positive cumulative CO₂ balance occurred in the absence of overall hypoventilation during sleep. For each cycle, positive CO₂ balance occurred despite increased interevent ventilation to rates as high as 45 l/min. This failure of CO₂ homeostasis was dependent on the event-to-interevent duration ratio. The results demonstrate that 1) periodic breathing provides a mechanism for acute hypercapnia in OSA, 2) acute hypercapnia during periodic breathing may occur without a decrease in average minute ventilation, supporting the presence of temporal V˙/Q˙ mismatch, as predicted from our model, and 3) compensation for CO₂ accumulation during apnea/hypopnea may be limited by the duration of the interevent interval. The relationship of this acute hypercapnia to sustained chronic hypercapnia in OSA remains to be further explored.

carbon dioxide; blood; hypercapnia (physiopathology); respiration; sleep apnea syndromes (physiopathology); pulmonary gas exchange (physiology)

CHRONIC HYPERCAPNIA in association with obesity has been termed the obesity hypoventilation syndrome (2, 6). Mechanisms reported to contribute to the hypercapnia include central hypoventilation manifested by a decrease in minute ventilation during wakefulness and/or sleep (14, 22), increased work of breathing due to abnormal pulmonary mechanics and obesity (20), and ventilation-perfusion (V˙/Q˙) mismatch due to associated cardiopulmonary disease (5). Although the obesity hypoventilation syndrome is frequently associated with obstructive sleep apnea (OSA), the specific contribution of the apnea phenomenon to chronic hypercapnia has not been clarified (13). In OSA, comparison between hypercapneic and eucapneic patients may reveal equal numbers and duration of apneas, which suggests that apnea itself does not mediate the hypercapnia (8). On the other hand, treatment of apnea by nasal continuous positive airway pressure or tracheostomy may result in correction of the hypercapnia, suggesting an important contribution of the periodic breathing (14, 16, 23, 24).

The apnea phenomenon per se may contribute to acute hypercapnia in two ways. Because of the apneas themselves, a decrease in the average ventilation may occur during periodic breathing (14). In this setting, the average level of ventilation can only be maintained at the awake steady-state level when there is a compensatory increase in ventilation in the interapnea period. In addition, we have utilized computer modeling of CO₂ homeostasis during periodic breathing to predict an alternative mechanism for hypercapnia that occurs despite maintenance of ventilation (15). The proposed mechanism for this hypercapnia can be considered a V˙/Q˙ mismatch resulting from temporal dissociation between ventilation and perfusion ("temporal V˙/Q˙ mismatch"). As with traditional V˙/Q˙ mismatch (27), CO₂ homeostasis in the presence of temporal V˙/Q˙ mismatch requires that interapnea ventilation be increased above that required for maintenance of steady-state ventilation (15).

The present study measures the acute kinetics of CO₂ accumulation and CO₂ elimination during sleep in patients with ventilatory sleep disorders and addresses the interapnea ventilatory compensation for maintenance of CO₂ homeostasis during periodic breathing.

METHODS

Eleven patients with severe OSA 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 OSA (apnea-hypopnea index >30). Patients were studied before any treatment of their OSA. Exclusion

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criteria were as follows: clinical evidence of chronic lung disease, ratio of forced expired ventilation in 1 s to forced vital capacity <70%, cardiac failure other than cor pulmonale, left ventricular ejection fraction <50%, hypothyroidism (elevated serum thyroid-stimulating hormone level), current use 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.

Patients were studied in a fasting state. The protocol consisted of a daytime study, during which sleep and CO2 balance were monitored. Electrodes were attached for polysomnography (central and occipital electroencephalogram (EEG), electrooculogram, and submental electromyogram). With the patient resting in the supine position, an arterial blood gas sample was withdrawn and mixed venous PCO2 was measured with a rebreathing technique (1, 11). 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 throughout the protocol, during wakefulness and sleep. To obtain a steady-state baseline, data were collected during a period of wakefulness lasting 5–30 min. The lights were then turned off, and the patient was allowed to fall asleep. Data collection during sleep lasted for 37–171 min. Immediately after the patient's final awakening, mixed venous PCO2 was measured again. Additional measurements, obtained within 2 wk of the daytime study, included spirometry and ventilatory response to CO2 (17, 29).

Mixed venous PCO2 was measured as previously described (11). PCO2 was measured at the mouth while patients rebreathed from a reservoir until a constant PCO2 was achieved indicating an equilibration between alveolar and mixed venous PCO2. Reservoir volume and starting PCO2 were adjusted to achieve an equilibration of PCO2 lasting at least two breaths and occurring within one circulation time (15 s). If an equilibration could not be achieved, then mixed venous PCO2 was estimated using an exponential extrapolation technique (1). Figure 1 is a Bland-Altman plot of repeated measurements of mixed venous PCO2 in individual patients; using this methodology, we have calculated that repeated measurements of mixed venous PCO2 have an intradass correlation coefficient of 0.99.

Sleep was scored in 30-s epochs by the criteria of Rechtshaffen and Kales (18). Ventilation was measured continuously with the face mask connected to a nonrebreathing valve (series 1400, Hans 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 breath. To measure O2 consumption and CO2 excretion, the expiratory limb of the circuit was connected to a 5.1-liter active mixing chamber. The exhaled gas was analyzed for O2 and CO2 concentrations with paramagnetic and infrared analyzers, respectively (Fitco Max-1, Physiodyne, Farmington, NY). O2 consumption and CO2 excretion were calculated using standard equations. All signals were digitized and recorded on a breath-by-breath basis on an IBM-compatible computer for off-line analysis.

CO2 balance was calculated in two ways: 1) as a cumulative value for the entire sleep period and 2) as a value for each cycle consisting of an apnea/hypopnea (event) and its subsequent interevent period. Respiratory events were defined as apneas (absence of airflow or tidal volumes <50 ml for >10 s) or hypopneas (tidal volumes <300 ml for >10 s).

Cumulative CO2 balance for the sleep period. After the awake steady-state collection period, sleep associated with the onset of periodic breathing was identified by EEG criteria. CO2 balance during this non-steady-state condition is represented by the difference between metabolic CO2 production and CO2 excretion. CO2 excretion was directly measured on a breath-by-breath basis. However, metabolic CO2 production during sleep could not be directly measured because of the instability of ventilation. In contrast, because there are minimal O2 stores, the cumulative breath-by-breath O2 consumption during periodic breathing would equal the metabolic O2 consumption. Therefore, the metabolic CO2 production during sleep was estimated by multiplying the breath-by-breath O2 consumption during sleep by the respiratory exchange ratio determined during the awake steady-state period. The cumulative CO2 balance for the entire sleep period was determined by summing breath-by-breath values for CO2 balance.

To validate the calculations utilized for determination of CO2 balance, we compared our breath-by-breath method with a method that accumulated all exhaled gas over time. To collect the exhaled gas, the exhaust from the mixing chamber was collected in a 120-liter spirometer (Tissot gasometer, Collins, Braintree, MA). A normal volunteer was used for measurements under three different conditions: 1) steady-state ventilation, 2) step changes in ventilation, and 3) simulated repetitive apneas. For each of the test conditions, the calculated cumulative CO2 excretion and O2 consumption from our system deviated by <25 ml (during a 10-min collection) from the cumulative CO2 excretion and O2 consumption derived from the Tissot spirometer.

Cycle CO2 balance during sleep. CO2 balance was also calculated for each respiratory cycle as the difference between the CO2 accumulated during a respiratory event and the CO2 eliminated during the subsequent interevent period. During apnea, CO2 accumulation cannot be calculated with a breath-by-breath technique. Therefore, an average (rather than a breath-by-breath) rate for metabolic CO2 production was utilized 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.

Figure 2 schematically illustrates the calculation of cycle CO2 balance. During the events (apnea/hypopnea), CO2 excretion decreases. The resultant accumulation of CO2 is calcu-
lated by integrating the difference between breath-by-breath CO₂ excretion and average metabolic CO₂ production during the event. During the interevent periods, the elimination of CO₂ is calculated by integrating the difference between CO₂ excretion and metabolic CO₂ production during the interevent period. The difference between the accumulation of CO₂ during the event and the elimination of CO₂ during the subsequent interevent period determines the CO₂ balance for the event-interevent cycle.

To validate the calculations utilized for determination of cycle CO₂ balance, we compared this method using the average metabolic CO₂ production with the method using the breath-by-breath CO₂ production described above. For all patients, the sum of the cycle CO₂ balances equaled the cumulative breath-by-breath CO₂ balance for the same time period.

**RESULTS**

Characteristics for all patients are illustrated in Table 1. All patients were obese (body surface area >2 m², body mass index 32.8–73.9 kg/m²) with severe OSA (apnea-hypopnea index >40 during data collection). Seven patients had preexisting chronic hypercapnia with arterial PA CO₂ (PaCO₂) ≥45 Torr and an elevated serum bicarbonate. There was no clinical evidence of intrinsic pulmonary disease. The ratio of forced expiratory volume in 1 s to forced vital capacity ranged from 71 to 90% and was normal (78%) in the seven patients with an elevated PaCO₂. The 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.

Cumulative CO₂ balance during sleep. Figure 3 illustrates the cumulative CO₂ balance over the period of study as obtained from breath-by-breath analysis (see METHODS). During the initial portion of the study while patients were awake (10–36 min, as confirmed by EEG analysis), CO₂ balance was stable, consistent with

Table 1. Patient characteristics

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BSA, body surface area; BMI, body mass index; AH1, apnea-hypopnea index, calculated as number of apneas plus hypopneas per hour of sleep; PCO₂, mixed venous PCO₂, measured before sleep period. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume; Ve, minute ventilation.
steady-state conditions. The duration of sleep ranged from 37 to 171 min. For the entire sleep period, CO₂ balance varied from \(-3,570\) ml, indicating a decrease in body CO₂ stores, to \(+1,388\) ml, indicating an increase in body CO₂ stores.

Figure 4 relates the CO₂ balance to the change in measured mixed venous P CO₂ during sleep in 9 of 11 patients. The cumulative CO₂ balance was directly related to the change in mixed venous P CO₂ (r = 0.80, P = 0.01). When the cumulative CO₂ balance was close to zero, there was essentially no change in mixed venous P CO₂. The presence of a positive or negative CO₂ balance was associated with changes in mixed venous P CO₂ during sleep, providing independent confirmation of the direction of change in CO₂ balance during sleep. In addition, when the CO₂ balance was positive, the change in mixed venous P CO₂ fell within the published range of P CO₂ change during 30 min of CO₂ rebreathing with loads of comparable magnitude (9).

No consistent trend was seen between CO₂ balance (expressed as ml/h sleep) and the presence of chronic hypercapnia during wakefulness, nor was CO₂ balance (expressed as ml/h sleep) related to the measurement of ventilatory response to CO₂ during wakefulness (r = 0.03, P = 0.92).

Ventilation during sleep. Table 2 displays data used to compare the relationship of average minute ventilation to metabolic CO₂ production during the awake steady-state period and during sleep. Average minute ventilation was calculated as the sum of the tidal volumes divided by the total time. The data are the average values for the entire sleep period. Minute ventilation was maintained during sleep compared with wakefulness, despite the presence of apneas. The change in the ratio of minute ventilation to metabolic CO₂ production during sleep compared with wakefulness varied between patients. The two patients who demonstrated a negative CO₂ balance during sleep demonstrated an increase in the ratio of minute ventilation to metabolic CO₂ production consistent with overall hyperventilation. In contrast, the two patients with the largest positive CO₂ balance during sleep demonstrated essentially no change in the ratio of minute ventilation to metabolic CO₂ production. Thus positive CO₂ balance occurred in the absence of hypoventilation, as marked by a constant relationship between minute ventilation and metabolic rate.

Cycle CO₂ balance during sleep. The observation that the average minute ventilation during the entire sleep period was maintained indicates that the interevent ventilation must have increased above the value during wakefulness to compensate for absent or low ventilation during apnea and hypopnea. For all cycles, the interevent tidal volume was \(1,175 \pm 376\) ml and the interevent ventilation was \(21.2 \pm 7.7\) (SD) l/min. Figure 5 illustrates the relationship between the CO₂ balance for each cycle and the level of its tidal volume and interevent ventilation (extrapolated to l/min). No relationship was seen between the CO₂ balance for each cycle and its interevent tidal volume or interevent ventilation. Positive CO₂ balance was not associated with a low interevent ventilation and occurred despite increased interevent ventilation to rates as high as 45 l/min.

Although the interevent ventilation reached a maximum rate of 45 l/min, the duration of the interevent periods varied. Figure 6A plots the interevent ventilation as a function of the periodicity expressed as the event-to-interevent duration ratio. The event-to-interevent duration ratio ranged up to 9:1, and high ratios were associated with increasing event durations. As the relative duration of the event increased (increasing ratios), there was a progressive increase in the interevent ventilation to a plateau at ratios \(>3:1\). This plateau occurred at an interevent ventilation that was 450% of the awake steady-state value and reflects the
maximum ventilation achieved by any patient during the interevent periods.

Figure 6B examines the effects of the event-to-interevent duration ratio on cycle CO₂ balance. When the event duration was short relative to the interevent duration (<3:1), the cycle CO₂ balance varied around zero and averaged ~4 ml. In contrast, when the event duration was long relative to the interevent duration (>3:1), there was an obligate positive cycle CO₂ balance (P < 0.001 compared with <3:1). Further analysis revealed that, for patients with a positive cumulative CO₂ balance during sleep, cycles with ratios >3:1 accounted for 80% of the total positive CO₂ balance during the period of sleep.

Figure 7 illustrates data from one patient who demonstrated a positive cumulative CO₂ balance plotted on a background of predictions from the computer model of CO₂ homeostasis during periodic breathing (15). The axes are the same as in Fig. 6A. The data points from all cycles in this patient are subdivided into cycles with positive CO₂ balance (open symbols) or zero/negative balance (closed symbols). When the event duration was short relative to the interevent duration (<3:1), the open symbols were displaced downward, indicating that positive cycle CO₂ balance occurred as a result of a failure to sufficiently increase the interevent ventilation. In contrast, when the event duration was long relative to the interevent duration (>3:1), positive CO₂ balance occurred in this patient, despite markedly increased interevent ventilation.

The data in Fig. 7 are superimposed on a background of two lines that indicate the calculated interevent ventilatory rate required 1) to maintain average ventilation constant during periodic breathing and 2) to maintain PaCO₂ constant, as derived from the computer model of CO₂ homeostasis. Examination of the data against this background reveals that positive cycle CO₂ balance was associated with interevent ventilatory rates that were below the ventilatory rate required for maintenance of a constant PaCO₂. At high ratios, the interevent ventilatory rate was at the maximal level that this patient achieved, yet positive CO₂ balance still occurred, suggesting that failure to extend the duration of the interevent period contributed to observed cycle CO₂ retention.

DISCUSSION

The present study measures ventilation and its relationship to CO₂ kinetics during periodic breathing in OSA. The results demonstrate that 1) periodic breath-
ing provides a mechanism for acute hypercapnia in OSA, 2) acute hypercapnia during periodic breathing may occur without a decrease in average minute ventilation, in accord with the presence of temporal V/Q mismatch, as predicted by our computer model, and 3) compensation for CO₂ accumulation during apnea/hypopnea may be limited by the duration of the interevent interval as well as by the magnitude of the interevent ventilation.

Prior studies have suggested that chronic hypercapnia is associated with failure to augment ventilation during the interapnea periods (8, 14, 21, 25). An implication of this finding is that the average ventilation during periods containing repetitive apneas is decreased below the awake steady-state level (14). In contrast, the results of the present study reveal that acute hypercapnia may occur, despite markedly augmented interapnea ventilation and preservation of average ventilation during the sleep period at the awake steady-state level. The observation that CO₂ loading occurred without a decrease in average minute ventilation suggests the presence of V˙/Q˙ mismatch.

V˙/Q˙ mismatch in lung disease is traditionally conceptualized as a spatial mismatch, so that ventilation is nonuniform with respect to perfusion. We have described an alternate conceptualization of V˙/Q˙ mismatch based on the fact that periodic patterns of breathing can be associated with a temporal dissociation between ventilation and perfusion in the normal lung (15). During periods of apnea/hypopnea there may be continued perfusion with limited ventilation (analogous to low spatial V˙/Q˙ mismatch), and during interevent periods there may be an increased ventilation relative to blood flow (analogous to high spatial V˙/Q˙ mismatch). Using a mathematical model of CO₂ homeostasis, we demonstrated that this temporal V˙/Q˙ mismatch may lead to hypercapnia, despite maintenance of average minute ventilation. These considerations indicate that temporal V˙/Q˙ mismatch provides a mechanism for acute CO₂ retention during periodic breathing in the absence of underlying lung disease.

In the present study, support for the presence of temporal V˙/Q˙ mismatch stems from the observed CO₂ retention that occurred without an associated decrease in average ventilation during periodic breathing. Although traditional spatial V˙/Q˙ mismatch and increased physiological dead space of lung disease may contribute to CO₂ retention in OSA, the magnitude of the contribution was probably minimal in these patients. V˙/Q˙ mismatch may occur in obesity because of abnormalities in pulmonary mechanics and airway closure (12, 19). However, in the present study there was no clinical evidence of underlying lung disease. In addition, any traditional spatial V˙/Q˙ mismatch that may have been present was likely minimized by the large tidal volumes (up to 2,600 ml) during the interevent ventilatory periods.
The addition of traditional V/Q mismatch and increased physiological dead space to the temporal V/Q mismatch of periodic breathing would impose a requirement for even greater interevent ventilation to maintain CO₂ homeostasis. Thus, although temporal V/Q mismatch may provide an independent mechanism leading to hypercapnia, its effect would be accentuated on the background of lung disease. These considerations may help explain the observation that chronic hypercapnia in patients with OSA is frequently associated with relatively mild degrees of underlying obstructive airways disease (5).

Compensation for CO₂ accumulation during apnea/hypopnea is a function of the magnitude of the interevent ventilation and the duration of the interevent interval. Because achievable interevent ventilation is limited by pulmonary mechanics, CO₂ loading must occur as the relative duration of the event lengthens and as the relative duration of the interevent interval shortens. For patients in the present study, the interevent ventilation increased to a plateau at values four to five times the baseline awake steady-state ventilation. This plateau occurred during cycles with longer events (high event-to-interevent duration ratios) when the required compensatory ventilation would be the greatest. Consequently, cycles with high event-to-interevent duration ratios universally demonstrated a positive CO₂ balance. Therefore, despite large compensatory interevent ventilation, failure to extend the duration of the interevent period appears to provide a critical mechanism for development of acute hypercapnia in OSA. These observations imply that, in OSA, severe sleepiness and the factors that control sleep latency may contribute to this failure to extend the interevent period and facilitate the generation and maintenance of CO₂ retention during sleep.

Several additional factors may have influenced the calculated CO₂ balance during sleep: changes in metabolic fuel utilization affecting the respiratory quotient (RQ), changes in cardiac output, and Haldane-Bohr chemistry. In our protocol, we assumed that RQ derived from the awake respiratory exchange ratio remained unchanged during sleep. Published data suggest that the changes in RQ during sleep are small (approximately ±0.02), but these have not been measured during periodic breathing (3, 28). To our knowledge, no data exist about changes in RQ in OSA, and factors such as sleep stage, intermittent hypoxia, circadian rhythms, and obesity may have influenced RQ in opposing directions (4, 7, 10, 26). For this reason, we utilized the change in mixed venous PCO₂ to independently confirm the direction of change in cumulative CO₂ balance and its magnitude. Fluctuations in cardiac output can influence temporal V/Q mismatch and CO₂ balance. Specifically, if cardiac output increases in relation to the postevent hyperventilation, the potential temporal V/Q mismatch and consequent CO₂ retention would be reduced. The extent of this effect was previously calculated by our computer model of CO₂ homeostasis (15). In the present study, the observed CO₂ loading indicates that any changes in cardiac output were insufficient to eliminate the temporal V/Q mismatch. Lastly, it is clear that the change in PCO₂ that occurs as a result of O₂ desaturation (Haldane effect) might influence CO₂ balance. Because our calculations are based on measurement of the exhaled CO₂ content, any change due to the Haldane effect will be included in our calculations. Theoretically, the influence of the Haldane effect on CO₂ balance would vary as the timing of the desaturation varies with respect to the interevent breathing period. On inspection of our data we have noted that, for any given patient, the desaturation occurs at different points in the event-interevent cycle. Therefore, it is unlikely that the Haldane effect provides an explanation for the cumulative CO₂ balance.

The results of the present study highlight the complexity of maintaining CO₂ homeostasis during periodic breathing. Because of the variety of factors that may lead to hypercapnia in OSA, it may be difficult to attribute hypercapnia to a single factor in a given patient. In our data, CO₂ loading during the sleep period did not relate to preexisting chronic hypercapnia or reduced CO₂ response. As predicted by our model, temporal V/Q mismatch provides an additional stress that, coupled with associated disorders, may lead to the development of acute hypercapnia, even when there is no decrease in average minute ventilation during sleep. The relationship of these observations on the generation of acute hypercapnia to the mechanisms for sustained chronic hypercapnia in OSA remains to be further explored.

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