Posthypoxic ventilatory decline during NREM sleep: influence of sleep apnea

Amal M. Omran, Salah E. Aboubakr, Loutfi S. Aboussouan, Lisa Pierchala, and M. Safwan Badr

Medical Service, John D. Dingell Veterans Affairs Medical Center, and Division of Pulmonary Critical Care Medicine, Department of Medicine, Wayne State University School of Medicine, Detroit, Michigan 48201

Submitted 15 October 2003; accepted in final form 19 February 2004

We wished to determine the severity of posthypoxic ventilatory decline in patients with sleep apnea relative to normal subjects during sleep. We studied 11 men with sleep apnea/hypopnea syndrome and 11 normal men during non-rapid eye movement sleep. We measured EEG, electrooculogram, arterial O2 saturation, and end-tidal PCO2. To maintain upper airway patency in patients with sleep apnea, nasal continuous positive pressure was applied at a level sufficient to eliminate apneas and hypopneas. We compared the prehypoxic control (C) with posthypoxic recovery breaths. Nadir minute ventilation in normal subjects was 6.3 ± 0.5 l/min (83.8 ± 5.7% of room air control) vs. 6.7 ± 0.9 l/min. 69.1 ± 8.5% of room air control in obstructive sleep apnea (OSA) patients; nadir minute ventilation (% of control) was lower in patients with OSA relative to normal subjects (P < 0.05). Nadir tidal volume was 0.55 ± 0.05 liter (80.0 ± 6.6% of room air control) in OSA patients vs. 0.42 ± 0.03 liter, 86.5 ± 5.2% of room air control in normal subjects. In addition, prolongation of expiratory time (TE) occurred in the recovery period.

Posthypoxic ventilatory decline (PHVD) relative to normal subjects.

METHODS

Subjects. The Human Investigation Committee of the Wayne State University School of Medicine and the Detroit Veterans Affairs Medical Center approved the experimental protocol. Informed, written consent was obtained from all subjects. We studied 11 normal men [apnea hypopnea index (AHI) = 1.1 ± 1.0 events per hour of sleep] and 11 men with sleep apnea/hypopnea syndrome (AHI = 27.0 ± 12.5) as determined by nocturnal polysomnography. Normal subjects were nonsnorers and were free of any cardiac, pulmonary, or sleep disorder. Sleep apnea patients were recently diagnosed and enrolled in the study while they were awaiting commencement of nasal continuous positive airway pressure (CPAP) therapy.

Breathing circuit. The subject was connected to the circuit with an airtight silicone rubber mask strapped and glued to the face to prevent leaks. The mask was connected to a Plateau Exhalation Valve (Respironics, Pittsburgh, PA) via a heated pneumotachometer. The total dead space of the circuit was 170 ml. There was no difference in the dead space between normal subjects and patients with sleep apnea.

The valve was connected to a Hans Rudolph four-way valve, so the inspiration was either from ambient air or from one of three cylinders containing the following gases: 100% N2, 8% O2, or 100% O2 connected to the inspiratory line. In patients with sleep apnea, a nasal CPAP machine (Quantum PSV, Healthdyne Technologies, Marietta, GA) was attached to the circuit upstream from the gas cylinders.

Measurements. Electroencephalograms (EEG), electrooculograms (EOG), and chin electromyograms were recorded using the international 10-20 system of electrode placement. (EEG: C3-A2 and C4-A1; EOG: F7-A2 and F8-A2). Inspiratory airflow was measured by a heated pneumotachometer (model 3700A, Hans Rudolph, Kansas City, MO), which was attached to pressure transducer (Validyne, Northridge, CA). The tidal volume (VT) was obtained from the electronic integration of the flow signal (model FV156 Integrator, Validyne, Northridge, CA). To ascertain the central etiology of apneas, upper airway pressure (supraglottic pressure) was measured with a pressure transducer (model TC-500XG, Millar Instruments, Houston, TX). The change (Δ) in end-tidal PCO2 concentration (PETCO2) was measured with air sampled continuously from the nasal mask by an infrared analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA). Arterial O2 saturation (SaO2) was estimated by a pulse oximeter with an ear probe (Biox 3700, Homed). The signals were

SLEEP-DISORDERED BREATHING is characterized by the occurrence of apnea/hypopnea alternating with hyperpnea. Sustained breathing instability is initiated by apnea or hypopnea leading to asphyxia, changes in the autonomic nervous system, and transient arousals from sleep (19, 20). It is postulated that the sum of these changes contributes to ventilatory overshoot, hypopcapnia, and hence apnea or hypopnea. Thus each apnea creates the conditions for the subsequent apnea and sustained breathing instability.

There is increasing evidence that patients with sleep apnea have an underlying central breathing instability. Weitzman et al. (30) observed periodic breathing with repetitive central apnea after tracheotomy for treatment of obstructive sleep apnea (OSA). Likewise, Önal and Lopata (22) showed persistence of periodic breathing after tracheostomy in a group of patients with OSA syndrome. Similar conclusions were reached by several investigators using specific tests of ventilatory control such as the pseudorandom binary stimulus test (13) or proportional-assist ventilation (32). However, previous studies used contrived interventions that do not occur in the course of breathing instability during sleep. Therefore, we sought to determine the effects of brief hypoxic exposure on breathing during non-rapid eye movement (NREM) sleep. We hypothesized that patients with sleep apnea demonstrate a more pronounced posthypoxic ventilatory decline (PHVD) relative to normal subjects.

Address for reprint requests and other correspondence: M. S. Badr, Harper Hospital, 3900 John R. 3-Hudson, R-3923, Detroit, MI 48201 (E-mail: sbadr@med.wayne.edu).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
displayed on a polygraph recorder (model 7-D, Grass, West Warwick, RI) and stored digitally on videotape (Vetter) for further analysis.

Protocol. Every subject breathed room air for 5 min (control period) followed by 3 min of hypoxia. Several hypoxic runs were performed in each subject; the minimum interval between hypoxic trials was 5 min. A total of 76 trials were conducted in OSA, and 70 trials were conducted in normal subjects. Hypoxia was abruptly terminated with one breath of 100% inspired O2 fraction (FICO2) followed by room air breathing. Changes in chemical stimuli were delayed by the breathing circuit as well as the lung-chemoreceptors circulation time. This delay was determined from the elapsed time between initiation of 100% FICO2 and the change in oxyhemoglobin saturation. The total delay was 13.5 ± 3.2 and 12.3 ± 4.5 s for normal subjects and OSA patients, respectively. There was no statistically significant difference in the delay time between the two groups of subjects (P > 0.05).

Data analysis. Wakefulness or sleep stage was scored according to standardized criteria (24) by an independent observer. The subjects were in stable stage 2 or stage 3 sleep during the hypoxic exposures and data collection periods. Inspired VT, expiration time (Te), total time, breathing frequency (f), and SaO2 were calculated breath by breath during stable sleep during the first normoxic period (last 5–10 breaths during control period), hypoxic period (last 10 breaths), and recovery period (first 10 breaths from the point of 100% FICO2 initiation). However, analysis of VT, minute ventilation (V̇I), and respiratory rate was limited to the first six recovery breaths as these values were returning back to control values by recovery breath 6. Nadir breath was identified as the breath with the lowest VT. Breaths for analysis were selected by an independent observer during a period of stable sleep with no evidence of an arousal (26). All the data were normalized to the control period data for comparison. Each subject was represented by the average of all trials.

Hypoxic chemoresponsiveness was computed in each subject to ensure that differences between the two groups were not due to differences in chemoresponsiveness. The hypoxic ventilatory response (HVR) was defined as the amount of change in VT between the mean room air and hypoxia VT divided by the change in SaO2 between room air and hypoxia (∆VT/∆SaO2, l·min⁻¹·%SaO2⁻¹). Statistical analysis. The dependent outcome variables of interest (VT, V̇I, Te, and f) were all expressed as percentage of control values. A two-way repeated-measures ANOVA was used to assess the effect of hypoxia and of the subjects’ group (OSA vs. controls) on the outcome variables. A two-way repeated-measures ANOVA was also used to assess the effect of recovery from hypoxia (from recovery breath 1 through recovery breath 6) and of the subjects’ group (OSA vs. controls) on the outcome variables.

To ensure that the assumptions underlying the two-way repeated-measures ANOVA were met, a Levene’s test was used to assess the homogeneity of variances in outcome measures between the OSA and control groups, and the Mauchly test of sphericity was used to assess the homogeneity of variances of the differences in outcome measures between each pair of recovery breaths.

A χ² test and a Fisher’s exact test were used to compare OSA and normal subjects in the proportion of trials in which the prolongation of Te met physiological criteria for central apneas. P values <0.05 were considered to indicate statistical significance. All analyses were performed using SPSS version 11.5 (SPSS, Chicago, IL).

RESULTS

Figure 1A is a representative polygraph record of one hypoxic run in a normal subject. Termination of hypoxia resulted in a modest reduction in VT and flow but no apnea. In contrast, termination of hypoxia in the patient with sleep apnea resulted in a central apnea followed by several cycles of unstable breathing (Fig. 1B).

Exposure to hypoxia resulted in oxyhemoglobin desaturation of similar magnitude between the two groups; oxyhemoglobin saturation reached a nadir of 86.3 ± 4.4% in normal subjects and 84.3 ± 1.4% in patients with OSA (P > 0.05). There was no difference in HVR between the normal subjects (0.17 ± 0.1 l·min⁻¹·%SaO2⁻¹, 13.5% of room air control) and OSA patients (0.25 ± 0.1 l·min⁻¹·%SaO2⁻¹, 11% of room air control) (P > 0.05). Similarly, there was no difference in HVR by repeated testing from the first to the last hypoxic trial in either group.

Likewise, there was no significant difference in the magnitude of hypocapnia between the two groups: PetCO2 during hypoxia was reduced by −2.4 ± 0.8 Torr in normal subjects and −2.2 ± 0.2 Torr in OSA patients (P > 0.05).

The effect of hypoxia and posthypoxic recovery is shown in Fig. 2. Hypoxia resulted in increased V̇I, VT, and f in both groups (P < 0.05). Termination of hypoxia resulted in PHVD once changes in chemical stimuli reached the peripheral chemoreceptors. Thus hypoxia reached the peripheral chemoreceptors between breaths 3 and 4 for OSA patients (Fig. 2, arrow) and between breaths 4 and 5 for normal subjects (double arrow). The magnitude of PHVD was more pronounced in patients with sleep apnea relative to normal subjects (Table 1 and Fig. 2). During the posthypoxic recovery, nadir VT in normal subjects was 83.8 ± 5.7% of room air control vs. 69.1 ± 8.5% of control in OSA patients (P < 0.05). Nadir V̇I was 86.5 ± 5.2% of control in normal subjects vs. 80.0 ± 6.6% of control in OSA patients vs. 86.5 ± 5.2% of control in normal subjects (P < 0.05). Similarly, prolongation of Te was more pronounced in OSA patients relative to normal subjects because longest Te in OSA patients was 5.6 ± 1.5 s, 292 ± 127.6% of control, and longest Te in normal subjects was 2.61 ± 0.3 s, 120 ± 11.2% of control (P < 0.01, Fig. 2). Moreover, the number of trials with prolongation of Te meeting an a priori cutoff duration for central apneas (Peak Te > 200% of control) was higher in OSA patients (49 apneas, 65% of all trials) compared with normal subjects (13 apneas, 19% of all trials, P < 0.001). Similarly, the percentage of normal subjects having at least one trial with Te > 200% was 45.4% (5 of 11) in the normal subjects compared with 100% (11 of 11) of subjects with OSA (Fisher’s exact test P = 0.01).

DISCUSSION

Summary of findings. The major findings of our study were 1) PHVD manifested as decreased V̇I and prolongation of Te, and 2) PHVD was more pronounced in patients with sleep apnea relative to normal subjects.

Methodological considerations. We considered several conditions that may influence the interpretation of our data. First, our study is dependent on stability of sleep state between hypoxia and recovery. We gave scrupulous attention to identifying and excluding trials with transient change in sleep state. In this regard, we modified the American Sleep Disorders Association definition of arousals (26) by decreasing the minimum time to 2 s. An observer identified all arousals independently of changes in ventilation. Thus we are confident that changes noted in our study were not due to changes in sleep state in either group.

Second, comparisons between changes in ventilation on transitions between different gas mixtures require similarity in
the experimental apparatus. Specifically, the circulatory delay time required for the change in $P_O_2$ to reach the peripheral chemoreceptors, estimated at 6–8 s (1, 11, 16), should be similar in the two groups. In our study, the total delay time (circuit and the circulatory delay times) was similar in the two groups. Likewise, the circuit dead space was also similar in both groups. Finally, the location of the sampling prongs inside the nose also ensured an accurate $P_TCO_2$, measurement because it was not affected by the high flow in the nasal CPAP mask. Thus the noted changes between the two groups were not due to differences in the breathing circuit.

Third, the use of hypoxia as a method of inducing hyperventilation has substantial physiological appeal. However, there is intrasubject and intersubject variability in the magnitude of ventilatory change and hence the magnitude of ensuing hypocapnia. Therefore, we are unable to construct a plot of ventilation vs. $P_TCO_2$, or to determine the actual apneic threshold in our subjects. Such determination requires the use of mechanical ventilation, which allows for precise control of $V_T$ during hyperventilation trials.

Fourth, our study was aimed at investigating how hypoxia may influence subsequent ventilation. Specifically, abnormal respiratory events produce a myriad of physiological perturbations including arousals, increased sympathetic nervous system activity, changes in intrathoracic pressures, and increased blood pressure (14, 20, 23). Therefore, our protocol does not faithfully mimic the chemical, neurological, or mechanical perturbations resulting from apnea.

Finally, our study participants were all men. Although there is no gender difference in PHVD during wakefulness (16) or NREM sleep (28), extrapolation of findings to women requires caution given the gender differences in the prevalence of sleep apnea (4). Although we had set out to investigate both genders, we were unable to identify women with sleep apnea within the broad parameters of the study, including absence of comorbid conditions and similarity in age and anthropometric parameters.
Mechanisms of posthyperventilation ventilatory decline. The development of central apnea or hypopnea in the aftermath of hyperventilation is mostly due to hypcapnia. However, the manifestations of hypcapnia after brief hypoxia are delayed and mitigated by the development of short-term potentiation (STP), which leads to a gradual decay of ventilation (1, 9, 11). We noted that ventilation reached a nadir immediately on termination of hypoxia at the level of the peripheral chemoreceptors, indicative of lack of STP (1). Our previous work demonstrating no evidence of STP on termination hypoxia of 5 min (1) but clear evidence of STP after 1 min of hypoxia. Thus 3 min of hypoxic exposure abolished, or greatly attenuated, STP in normal men and those with sleep apnea syndrome.

Posthyperventilation ventilatory decline manifests as changes in depth or frequency of respiration, depending on the model of hyperventilation. We found that PHVD manifested as changes in depth or frequency of respiration, depending on the model of hyperventilation. We noted that hyperventilation reached a nadir immediately on termination of hypoxia at the level of the peripheral chemoreceptors, indicative of lack of STP (1). Our findings corroborate our laboratory’s previous work demonstrating no evidence of STP on termination hypoxia of 5 min (1) but clear evidence of STP after 1 min of hypoxia. Thus 3 min of hypoxic exposure abolished, or greatly attenuated, STP in normal men and those with sleep apnea syndrome.

Posthyperventilation ventilatory decline manifests as changes in depth or frequency of respiration, depending on the model of hyperventilation. We found that PHVD manifested as changes in depth or frequency of respiration, depending on the model of hyperventilation. We noted that hyperventilation reached a nadir immediately on termination of hypoxia at the level of the peripheral chemoreceptors, indicative of lack of STP (1). Our findings corroborate our laboratory’s previous work demonstrating no evidence of STP on termination hypoxia of 5 min (1) but clear evidence of STP after 1 min of hypoxia. Thus 3 min of hypoxic exposure abolished, or greatly attenuated, STP in normal men and those with sleep apnea syndrome.

Ventilatory control instability in sleep apnea. The use of nasal CPAP to ensure upper airway patency in sleep apnea patients allowed us to conclude that noted PHVD was due to central breathing instability rather than upper airway obstruction. In addition, we noted that the number and proportion of central apneas in the recovery period after hypoxic stimulation was higher in OSA patients relative to normal subjects, suggesting that patients with sleep apnea are more susceptible than normal subjects to central breathing instability for a given perturbation. Our findings corroborate previous studies demonstrating instability of the ventilatory control system in patients with sleep apnea. Ónal and Lopata (22) showed persistence of periodic breathing after tracheotomy in a group of patients with OSA, indicative of a central breathing instability. Similarly, Hudgel et al. (13) demonstrated instability of the ventilatory control system in patients with sleep apnea relative to normal subjects during wakefulness by using the pseudorandom binary stimulation test with a single breath of CO2. Finally, Younes et al. (32) used proportional-assist ventilation during sleep in patients with mild and severe sleep apnea and demonstrated that the ventilatory control system is more unstable in patients with severe relative to mild sleep apnea; however, no comparison was made with normal subjects. The available studies all concur that sleep apnea is associated with central breathing instability.

Table 1. Effect of hypoxia and posthypoxic recovery in all subjects

<table>
<thead>
<tr>
<th></th>
<th>Vi, l/min</th>
<th>Vr, liters</th>
<th>f, breaths/min</th>
<th>Te, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.7±0.5</td>
<td>0.680±0.024</td>
<td>14.5±0.9</td>
<td>2.42±0.20</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>13.1±0.8†</td>
<td>0.828±0.034†</td>
<td>16.1±1.0</td>
<td>2.17±0.18</td>
</tr>
<tr>
<td>Nadir</td>
<td>6.7±0.9††</td>
<td>0.55±0.047††</td>
<td>12.3±1.4†*</td>
<td>5.60±1.54††</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7.7±0.6</td>
<td>0.501±0.041</td>
<td>15.9±0.6</td>
<td>2.20±0.12</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>9.0±1.0†</td>
<td>0.560±0.054†</td>
<td>16.2±0.7</td>
<td>2.12±0.14</td>
</tr>
<tr>
<td>Nadir</td>
<td>6.3±0.5†</td>
<td>0.420±0.027†</td>
<td>15.0±0.5</td>
<td>2.61±0.25†</td>
</tr>
</tbody>
</table>

Values are means ± SD. Vi, minute ventilation; Vr, tidal volume; f, breathing frequency; Te, expiratory time. *Statistically significant difference from normal subjects, P < 0.05. †Statistically significant difference from control, P < 0.05.
The precise picture of the underlying central “breathing instability” in sleep apnea remains unclear. However, several putative possibilities warrant discussion. First, we cannot attribute the development of central apnea and periodic breathing in sleep apnea patients to attenuation of STP because both groups demonstrated a similar pattern of decay in the recovery period. Second, patients with sleep apnea may be genetically susceptible to the development of posthyperventilation apnea, which may play a role in the pathogenesis of periodic breathing and upper airway obstruction. This possibility is buttressed by recent data demonstrating a possible genetic basis for sleep apnea (5). Finally, ventilatory control abnormalities can be due to the chronic central nervous system insult due to repetitive apneas, hypoxia, and sleep fragmentation. Using magnetic resonance spectroscopy, Kamba and coworkers (17, 18) revealed metabolic changes in normal appearing brain tissue in patients with sleep apnea. Likewise, Verbraecken et al. (29) showed a reduction of the slope of CO₂ drive after 1 yr of treatment with nasal CPAP, indicative of a reversible abnormality in ventilatory control. Accordingly, the PHVD may be amplified by the presence of sleep apnea and its associated abnormalities. Our data do not allow us to distinguish between genetic or acquired ventilatory control abnormalities; this would require a repeat study after monitored therapy with nasal CPAP.

Implications to the pathogenesis of sleep apnea. We found that central apnea and periodic breathing occurred on termination of brief hypoxia in patients with sleep apnea. Conversely, several investigators have found that induction of periodic breathing results in upper airway obstruction at the nadir of ventilatory drive (12, 21). Likewise, studies from our laboratory have shown that induction of hypopapnic central apnea is associated with complete upper airway obstruction in patients with documented OSA (3). These studies combined support the notion that obstructive and central apneas share a common pathogenesis, namely central breathing instability. Accordingly, the morphological differences reflect differences in anatomy and not pathogenesis. This would explain why a patient with obstructive apnea would continue to manifest central apnea after tracheostomy and the development of complete upper airway occlusion in a patient with central apnea.

The overlap in the pathogenesis of central and obstructive apnea may explain the reported effectiveness of nasal CPAP in the treatment of central sleep apnea (25, 31) and may provide the rationale for further exploration of pharmacological therapy in the treatment of sleep apnea syndrome. It is plausible that patients with OSA can benefit from mixed-modality therapy combining pharmacological therapy aimed at correction of central breathing instability with surgical correction of abnormal upper airway anatomy. The development and validation of such approach would be a major qualitative advance in the management of sleep apnea syndrome.

REFERENCES


