Obesity Hypoventilation Syndrome as a Spectrum of Respiratory Disturbances During Sleep*

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Objective: To identify the spectrum of respiratory disturbances during sleep in patients with obesity hypoventilation syndrome (OHS) and to examine the response of hypercapnia to treatment of the specific ventilatory sleep disturbances.

Designs and methods: Twenty-three patients with chronic awake hypercapnia (mean $[\pm SD]$ PaCO$_2$, $55 \pm 6$ mm Hg) and a respiratory sleep disorder were retrospectively identified. Nocturnal polysomnography testing was performed, and flow limitation (FL) was identified from the inspiratory flow-time contour. Obstructive hypoventilation was inferred from sustained FL coupled with O$_2$ desaturation that was corrected with treatment of the upper airway obstruction. Central hypoventilation was inferred from sustained O$_2$ desaturation that persisted after the correction of the upper airway obstruction. Treatment was initiated, and follow-up awake PaCO$_2$ measurements were obtained (follow-up range, 4 days to 7 years).

Results: A variable number of obstructive sleep apneas/hypopneas (ie, obstructive sleep apnea-hypopnea syndrome [OSAHS]) were noted (range, 9 to 167 events per hour of sleep). Of 23 patients, 11 demonstrated upper airway obstruction alone (apnea-hypopnea/FL) and 12 demonstrated central sleep hypoventilation syndrome (SHVS) in addition to a variable number of OSAHS. Treatment aimed at correcting the specific ventilatory abnormalities resulted in correction of the chronic hypercapnia in all compliant patients (compliant patients: pretreatment, $57 \pm 6$ mm Hg vs post-treatment, $41 \pm 4$ mm Hg [$p < 0.001$]; noncompliant patients: pretreatment, $52 \pm 6$ mm Hg vs post-treatment, $51 \pm 3$ mm Hg; [difference not significant]).

Conclusions: This study demonstrates that OHS encompasses a variety of distinct pathophysiologic disturbances that cannot be distinguished clinically at presentation. Sustained obstructive hypoventilation due to partial upper airway obstruction was demonstrated as an additional mechanism for OHS that is not easily classified as SHVS or OSAHS.

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Key words: blood; carbon dioxide; hypercapnia; physiopathology; respiration; sleep apnea syndromes

Abbreviations: AASM = American Academy of Sleep Medicine; AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; FL = flow limitation; NPSG = nocturnal polysomnography; OHS = obesity hypoventilation syndrome; OSAHS = obstructive sleep apnea-hypopnea syndrome; SHVS = sleep hypoventilation syndrome

Recently, there has been an increased awareness of the cardiovascular and pulmonary consequences of obesity as a major source of morbidity and mortality. This study retrospectively investigates a subgroup of obese patients who present in the general medical setting with unexplained cardiopulmonary failure and chronic hypercapnia. These patients may be misdiagnosed as having either intrinsic heart disease or COPD, and, therefore, medical management may be inappropriate.

Approximately 45 years ago, Burwell et al described the obesity hypoventilation syndrome (OHS) in patients with morbid obesity, hypersonsomnolence, plethora, and edema. The pathophysiologic mechanisms underlying this syndrome are still poorly understood. The primary ventilatory abnormality was...
identified as sustained hypoventilation leading to hypercapnia, hypoxemia, and cardiopulmonary failure, and the term “pickwickian syndrome” was coined to describe these patients.1,2 More recently, this syndrome was termed the sleep hypoventilation syndrome (SHVS).3 Subsequently, Guilleminault et al4 described the presence of obstructive sleep apnea-hypopnea syndrome (OSAHS) in many of these patients. The relative importance of sustained hypoventilation vs obstructive apnea in the development of the hypercapnia in patients with OHS has not been clarified.5

The presence of obstructive sleep apnea-hypopnea in some patients with OHS and the correction of hypercapnia with the treatment of upper airway obstruction suggest that the hypercapnia can be dependent on the presence of the apnea-hypopnea phenomenon itself.6–9 In contrast, the relative absence of obstructive sleep apnea-hypopnea in other patients and the failure to correct the hypercapnia with treatment of the apnea-hypopnea indicates the importance of sustained hypoventilation.7 Thus, while daytime arterial Pco2 levels may normalize in some patients with continuous positive airway pressure (CPAP) therapy alone, other individuals may require the addition of positive-pressure ventilation, suggesting that there are multiple pathophysiologic mechanisms that may lead to OHS. These considerations suggest that in a given patient with OHS, the development of chronic hypercapnia may be dependent on the relative balance between the severity of apnea-hypopnea and the amount of nonapneic sustained hypoventilation.

This study retrospectively identifies the spectrum of respiratory disturbances during sleep in patients with OHS and examines the responses of patients with chronic hypercapnia to treatment determined by an algorithm that allows the identification of the specific ventilatory sleep disturbances.

Materials and Methods

Patients included in the study were identified by reviewing the records of the Bellevue Hospital Pulmonary Function Laboratory and the New York University Sleep Disorders Center from 1991 to 2000. Forty-nine obese patients with excessive daytime somnolence and both chronic hypercapnia and a respiratory sleep disorder were identified. Chronic hypercapnia was defined as an awake Pco2 level of 45 mm Hg. A respiratory sleep disorder was defined as either an apnea-hypopnea index (AHI) of >15 events per hour of sleep or evidence for sustained hypoventilation during sleep (see below). Patients were not excluded for the presence of coexisting pulmonary diseases. These 49 patients were contacted by telephone and were asked to return to the sleep center for follow-up evaluations. Twenty-three patients returned for follow-up. These patients were interviewed to assess their compliance with treatment, and arterial blood gas analyses were performed while they were awake. The study group presented in this article includes these 23 patients in whom awake arterial blood gas analyses were available at two points in time (ie, the time of diagnosis and after the initiation of nocturnal therapy). These 23 patients did not differ from the patients in whom follow-up could not be obtained in any baseline characteristic (including age, degree of hypercapnia, pulmonary function, or AHI) except that they demonstrated a greater degree of obesity and hypoxia (mean weight, 326 vs 277 lb, respectively [p < 0.05]; and mean Pao2, 57 vs 71 mm Hg, respectively [p < 0.05]).

All patients underwent at least one nocturnal polysomnography (NPSG) session in the sleep laboratory to evaluate their complaint of daytime sleepiness. Recordings of central and occipital EEG, electrooculogram, and submental electromyogram were used to monitor sleep. A unipolar ECG was used for cardiac monitoring. O2 saturation was monitored with a pulse oximeter. Chest wall and abdominal movement were monitored with piezoelectric strain gauges. All patients had airflow monitoring that included analyses of the inspiratory flow-time waveform either from the CPAP generator10 or from a nasal cannula connected to a 2-cm H2O pressure transducer.11 Flow-time waveform analysis was adopted uniformly in our laboratory prior to our publication of this technique in 1994. One patient was seen in 1983 and is included in the study since the results of his initial studies revealed no O2 desaturation while he was being treated with optimal CPAP (see protocol below) and because subsequent polysomnography was performed with flow-time waveform analysis, confirming the initial data. Follow-up sleep studies to evaluate the adequacy of treatment were performed by recording pulse oximetry, mask pressure, and airflow.

Diagnostic/Treatment Algorithm

We utilized a diagnostic/treatment algorithm to identify the variety of respiratory sleep disturbances that were observed during the NPSG testing. Because multiple types of respiratory abnormalities may coexist in a given patient, the algorithm is designed to sequentially eliminate the different disorders in order to uncover the full spectrum of abnormality. The stepwise elimination of disorders is accomplished by the application of therapy. Currently, the selection of a treatment modality cannot be titrated directly to Pco2 because the monitoring of Pao2 levels during NPSG testing is invasive and because surrogates for Pao2, such as end-tidal Pco2 monitoring and transcutaneous capnography, are variably accurate.3 Therefore, the algorithm utilizes O2 desaturation as a marker for hypoventilation, which is in accordance with the American Academy of Sleep Medicine (AASM) guidelines.3 Flow limitation (FL) was utilized, in addition to apnea and hypopnea, as a marker of increased upper airway resistance.10–13

The algorithm (Fig 1) addresses the treatment of upper airway obstruction by increasing CPAP to obliterate the upper airway and the hypopnea. Persistent FL prompted further increases in CPAP. If O2 saturation was maintained at >90% with CPAP therapy, treatment was prescribed at the pressure determined by the algorithm. If persistent O2 desaturation was noted despite treatment for upper airway obstruction, nocturnal ventilation was initiated. The expiratory airway pressure was set equal to the CPAP required for the treatment of the upper airway obstruction, and the inspiratory airway pressure was increased until the O2 saturation was >90%. In three patients, O2 saturation could not be maintained at >90% despite the addition of ventilation, therefore, O2 was added to the ventilatory circuit. Five patients could not tolerate the use either of a nasal mask or a full face mask. Tracheostomy was offered to these patients for the treatment of the upper airway obstruction, with or without the addition of volume ventilation for residual O2 desaturation.

Apneas were defined as a decrease in airflow to <10% of the baseline for at least 10 s. Hypopneas were defined as a decrease in airflow to <50% of the baseline for at least 10 s without regard for
O₂ desaturation. FL was inferred from the presence of a plateau on the inspiratory flow-time contour.10–13 FL events were defined as two or more breaths (generally >10 s in duration) with a flattened inspiratory flow-time contour followed by an abrupt return to a normal sinusoidal contour. Although changes in peak airflow may have occurred during FL events, they were insufficient (i.e., <50% of baseline) for classification as hypopnea. Sustained FL was defined as FL that lasted for >2 min.

Additional data that were collected included spirometry for the assessment of FVC, FEV₁, and FEV₁/FVC ratio. In addition, 18 of 23 patients underwent assessment for ventilatory response to CO₂ by the rebreathing technique.14,15 The ventilatory response to CO₂ was obtained prior to the initiation of therapy for the ventilatory sleep disorder.

Data Analysis
The effectiveness of therapy was assessed by comparing the follow-up awake PaCO₂ and serum bicarbonate measurements to the corresponding values prior to the initiation of therapy. For this analysis, the paired t test was utilized, and p < 0.05 was considered to be statistically significant. Data are presented as the mean ± SD. Compliance with therapy was assessed through patient interview since a retrospective study does not allow for objective measures of compliance. Noncompliance was defined by the use of nocturnal therapy for >25 h per week.

Results
Patient characteristics are illustrated in Table 1. The study included 23 patients with an average age of 54 years. All patients were hypercapnic with an average PaCO₂ of 55 mm Hg and an average serum HCO₃ of 33 mEq/L. The ventilatory response to CO₂ was uniformly low (<1.2 L/min/mm Hg) with
the exception of one patient. The average FEV₁/FVC ratio was 74%, and eight patients had significant obstruction with a ratio of <70%. Nine of 15 patients without obstruction demonstrated a significantly reduced vital capacity (<70%). In these patients, the observed reduction in vital capacity was mostly due to a reduction in expiratory reserve volume that was compatible with obesity. The number of apneas and hypopneas identified during NPSG testing varied among the patients. Although the average AHI was 62, some patients demonstrated as few as nine apnea-hypopnea events per hour of sleep.

Table 1—Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>54 ± 13</td>
<td>28–73</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>56 ± 15</td>
<td>26–88*</td>
</tr>
<tr>
<td>AHI</td>
<td>62 ± 42</td>
<td>9–167</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>57 ± 21</td>
<td>26–98</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>63 ± 19</td>
<td>28–98</td>
</tr>
<tr>
<td>FEV₁/FVC ratio, %</td>
<td>74 ± 12</td>
<td>36–90</td>
</tr>
<tr>
<td>CO₂ response, L/min/mm Hg</td>
<td>0.8 ± 0.6</td>
<td>0.1–2.9</td>
</tr>
<tr>
<td>Initial PaO₂, mm Hg</td>
<td>57 ± 14</td>
<td>34–80</td>
</tr>
<tr>
<td>Initial PaCO₂, mm Hg</td>
<td>55 ± 6</td>
<td>47–68</td>
</tr>
<tr>
<td>Initial HCO₃, mEq/L</td>
<td>33 ± 3</td>
<td>29–44</td>
</tr>
</tbody>
</table>

*One subject with an apparently normal BMI was obese (height, 58 inches; weight, 123 lb).

†n = 18.

Nonapneic Ventilatory Disturbances

In addition to apnea and hypopnea, hypoventilation was identified by sustained O₂ desaturation that was not accompanied by periodic breathing. The protocol algorithm allowed the differentiation of two mechanisms for the sustained hypoventilation. Obstructive hypoventilation (ie, hypoventilation due to increased upper airway resistance) was inferred from the coexistence of FL with O₂ desaturation that is corrected with treatment of the upper airway obstruction (Fig 2). Central hypoventilation was inferred from the presence of O₂ desaturation that persists after the correction of FL (Fig 3). These hypventilatory disorders were identified during diagnostic polysomnography testing as well as during CPAP titration. These ventilatory disorders coexisted in individual patients, and multiple studies revealed marked variability in the number of each type of respiratory abnormality seen in a given patient, which precluded precise quantification.

Figure 2 illustrates the uncovering of obstructive hypoventilation during inadequate CPAP therapy. The illustrated data were obtained from a single patient at different times during one night of monitoring. The patient initially demonstrated severe repetitive obstructive apneas resulting in O₂ desaturation to approximately 80%. Increasing CPAP to levels of 8 cm H₂O obliterated the apnea but resulted in persistently low O₂ saturation of 80%. Further inspection of the tracings revealed a plateau on the inspiratory flow contour and a thoracoab-

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21968/ on 06/25/2017)
Abdominal paradox suggesting an obstructive hypoventilation. A further increase of CPAP to 10 cm H₂O resulted in normalization of the chest wall and abdominal movements, inspiratory flow contour, and O₂ saturation, providing further evidence that the hypoventilation was due to an obstructive etiology.

Figure 3 illustrates the uncovering of central hypoventilation during adequate CPAP therapy. The illustrated data were obtained in a single patient at different times during one night of monitoring. At low levels of CPAP, the patient demonstrated evidence for obstructive hypoventilation, as marked by decreased O₂ saturation at 80% and a flow-limited inspiratory flow contour. Increasing CPAP resulted in the correction of the FL, however, there was a decrease in airflow with persistently low O₂ saturation at 65%, suggesting central hypoventilation (middle). See text for details.

Of the 23 patients studied, 11 patients received diagnoses of obstructive upper airway abnormalities alone. These abnormalities included episodic FL events and prolonged periods of obstructive hypoventilation in addition to apnea-hypopnea. The remaining 12 patients received diagnoses of central sustained hypoventilation in addition to a variable number of obstructive upper airway abnormalities. There were no differences between patients with upper airway abnormalities alone and those with central sustained hypoventilation in age, gender, body mass index (BMI), degree of hypercapnia, ventilatory response to CO₂, AHI, or lung function.

Response to Treatment

Treatment was prescribed using the protocol algorithm. Of the 11 patients who demonstrated only obstructive abnormalities, 8 were treated with CPAP (mean CPAP, 13 cm H₂O; CPAP range, 10 to 16 cm H₂O) and 3 were treated with tracheostomy due to their inability to tolerate a nasal mask or face mask. Of the 12 patients who demonstrated central hypoventilation in addition to upper airway obstruction, 10 were treated with noninvasive bilevel ventilation (mean inspiratory pressure, 18 cm H₂O; inspiratory pressure range, 12 to 25 cm H₂O; mean expiratory pressure, 8 cm H₂O; expiratory pressure range, 3 to 14 cm H₂O), and 2 were treated with tracheostomy coupled with nocturnal volume ventilation.

The mean PaCO₂ was elevated prior to therapy (55 ± 6 mm Hg). The length of follow-up ranged from 4 days to 7 years, with an average value of 14 ± 19 months. After treatment was prescribed according to the protocol algorithm, there was a significant decrease in the PaCO₂ on follow-up examination (change on follow-up, 45 ± 6 mm Hg; p < 0.001), which was confirmed with an analysis of serum bicarbonate levels. Although this response of PaCO₂ and bicarbonate levels to treatment was significant for the group, the response in individual
patients was variable. Patients who responded to treatment (i.e., a > 4-mm Hg decrease in PaCO₂) did not differ from those without treatment responses in age, gender, initial BMI, AHI, length of follow-up, CO₂ responsiveness, or pulmonary function. Patients who demonstrated a treatment response had a decrease in body weight on follow-up examination that averaged 49 lb compared with a weight gain of 17 lb in patients without treatment responses (p < 0.05). Although the responders as a group demonstrated a decrease in weight, 7 of 15 patients (including 4 of 8 patients treated with CPAP alone) demonstrated a 10-lb weight change on follow-up examination.

Figure 4 divides patients into two groups, based on the self-reported compliance with therapy, and illustrates the response of PaCO₂ to treatment. At baseline, the degree of hypercapnia was similar in the compliant patients compared with that of the non-compliant patients (57 ± 6 vs 52 ± 6 mm Hg, respectively; difference not significant). For noncompliant patients, there was no change in the mean PaCO₂ level on follow-up examination (51 ± 3 mm Hg; difference not significant). In contrast, PaCO₂ was corrected to near-normal values in patients who complied with therapy (41 ± 4 mm Hg; p < 0.001). The observed changes in PaCO₂ level were confirmed by an analysis of serum bicarbonate levels.

Figure 5 subdivides the compliant patients into those who were treated for upper airway obstruction alone (CPAP, five patients; tracheostomy, three patients) and those who required the addition of nocturnal ventilation (bilevel ventilation, five patients; tracheostomy plus volume ventilation, two patients). The left panel illustrates that treatment of upper airway obstruction alone with CPAP or tracheostomy corrected the chronic hypercapnia.
(Paco₂, 56 ± 7 vs 41 ± 5 mm Hg, respectively; p < 0.01). Of note, this effect of CPAP was also apparent for three patients who had underlying obstructive lung disease (open symbols). The right panel illustrates the data for patients treated with nocturnal ventilation. Since Paco₂ could not be reliably measured during the study, nocturnal ventilation was titrated to eliminate O₂ desaturation. Nocturnal ventilation corrected the chronic hypercapnia (Paco₂ prior to nocturnal ventilation, 58 ± 4 mm Hg; Paco₂ after nocturnal ventilation, 42 ± 4 mm Hg; p < 0.01).

**DISCUSSION**

The present study identifies a variety of ventilatory sleep disorders that occur in chronically hypercapnic patients with OHS. Four disorders were identified through the use of a NPSG protocol. These disorders include SHVS, OSAHS, prolonged obstructive hypoventilation due to partial upper airway obstruction, and the overlap of associated pulmonary disease with a ventilatory sleep disturbance. Although a retrospective analysis does not allow the delineation of the specific contribution of each ventilatory disorder toward the development of chronic hypercapnia, treatment aimed at correcting the specific ventilatory abnormalities resulted in the correction of chronic hypercapnia in all compliant patients. In addition, it is clear that nocturnal ventilation was not necessary for all patients to correct their chronic hypercapnia since CPAP alone was sufficient for some. These observations suggest a relationship between the nocturnal ventilatory disorders, which are mechanisms for acute hypercapnia, and the development of chronic daytime hypercapnia in these patients.

The presence of coincidental underlying functional lung abnormalities was noted in a significant number of patients in the present study (obesity and/or COPD). Coincidental functional lung abnormalities can contribute to hypercapnia either by directly causing hypoventilation or by impairing the compensation for coexistent apnea-hypopnea or hypoventilation. Of note, these patients did not necessarily require nocturnal ventilation, as was seen in three of the six patients with the overlap syndrome (ie, sleep apnea with obstructive lung disease) despite severe mechanical ventilatory impairment. For these patients whose awake Paco₂ levels were normalized following CPAP therapy alone, it is clear that the underlying obstructive lung disease was not the primary etiology of the chronic awake hypercapnia.

A unique feature of our NPSG algorithm is the analysis of the inspiratory flow-time contour as a measure of upper airway resistance in order to identify the full spectrum of underlying respiratory abnormalities and to determine a treatment prescription. Previous studies have demonstrated that CPAP therapy is beneficial in treating hypercapnia in patients with obstructive sleep apnea and that mechanical ventilation is beneficial in treating sustained central hypoventilation. This protocol extends these observations by defining an additional ventilatory sleep disorder characterized by sustained periods of hypoventilation due to partial upper airway obstruction, which can be identified from an analysis of the inspiratory flow-time contour. Increasing CPAP to obliterate the FL was successful in correcting the chronic hypercapnia. Although the necessity of this strategy was not proved in our study, this therapeutic approach is in accord with Henke et al who demonstrated that increases in upper airway resistance during sleep produce acute CO₂ retention, suggesting that a failure to identify obstructive hypoventilation may lead to the persistence of hypercapnia when CPAP therapy is titrated to eliminate only apnea and hypopnea. Moreover, even if sustained obstructive hypoventilation does not lead to hypercapnia, it may impede compensation for CO₂ accumulation during coexistent apnea-hypopnea events.

The polysomnography protocol used O₂ saturation as a noninvasive marker of hypoventilation. Other noninvasive markers of hypoventilation, such as transcutaneous PCO₂ and end-tidal PCO₂ levels are available. However, the transcutaneous PCO₂ level may not track the PaCO₂ level during sleep hypoventilation and end-tidal PCO₂ cannot be assessed during CPAP/bilevel therapy and may be inaccurate in the presence of shallow tidal volumes. Similarly, direct measures of ventilation may be unreliable. A pneumotachograph connected to a tight-fitting face mask is subject to error from mask leaks (especially while applying positive pressure), and respiratory inductive plethysmography is subject to inaccuracy with changes in body or chest/abdomen band position. Based on these considerations, a AASM taskforce has proposed O₂ desaturation as the best available noninvasive technique for assessing hypoventilation. It should be noted that O₂ desaturation also may occur because of altered lung volumes and/or changes in ventilation/perfusion relationships in the absence of hypoventilation. However, in the present study nocturnal ventilation was successful in correcting chronic hypercapnia when it was titrated to eliminate O₂ desaturation, despite the absence of PCO₂ and ventilation monitoring, in accord with the AASM recommendations.

Although chronic hypercapnia improved following treatment of nocturnal hypoventilation and/or apnea, additional factors may have contributed to the correction of daytime Paco₂ levels. In fact, CPAP may lead to the normalization of Paco₂ due to changes in...
respiratory drive that occur as a consequence of improved upper airway mechanics.\textsuperscript{19,20} Additional factors that may have contributed to the normalization of chronic hypercapnia include improved pulmonary mechanics by weight loss,\textsuperscript{21} improved gas exchange by diuresis, and/or correction of metabolic alkalosis.\textsuperscript{22} In this context, it is of interest that there was a loss of weight in some patients who demonstrated improved daytime \( \text{PaCO}_2 \) levels on follow-up examination. However, a loss of weight was not required for the correction of hypercapnia in all patients, as evidenced by the lack of weight loss in approximately half of the patients who had improved daytime \( \text{PaCO}_2 \) levels, including half of the patients treated with CPAP alone. For the subgroup that did lose weight, it is unclear whether weight loss \textit{per se} caused improved hypercapnia or whether nocturnal therapy facilitated diuresis by the relief of nocturnal hypoxia and hypercapnia, highlighting the interrelationship between the variety of factors leading to cardiorespiratory failure in these patients.

In summary, this study highlights that OHS encompasses a variety of distinct pathophysiologic disturbances that cannot be distinguished clinically at presentation. For the subgroup of these patients with OSAHS, hypercapnia was corrected by treatment of upper airway obstruction alone, indicating that acute hypercapnia resulting from respiratory events during sleep provided the basis for chronic awake hypercapnia. For the subgroup of OHS patients with SHVS, the treatment of nocturnal \( \text{O}_2 \) desaturation by ventilation resulted in the correction of chronic hypercapnia, despite the absence of \( \text{PCO}_2 \) monitoring during ventilator titration. In addition, this study demonstrated that sustained obstructive hypoventilation due to partial upper airway obstruction occurs in a subset of patients and may be an additional mechanism for OHS that is not easily classified as either SHVS or OSAHS. Last, although in some patients underlying lung disease coexisted with these disorders, its contribution to the development of OHS was variable.

\textbf{References}