Obesity Hypoventilation Syndrome

D Naim, J Wallace

Citation

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Abstract

Obesity Hypoventilation Syndrome (OHS) refers to a state of chronic daytime hypoventilation associated with obesity. Criteria for the diagnosis include persistently elevated PaCO2 > 45 mmHg, a body mass index > 30 kg/m^2 and no other cause for hypoventilation. The exact pathophysiology has not been clearly defined, but the syndrome has been attributed to a combination of abnormal respiratory mechanics resulting in increased work of breathing, depressed central ventilatory control, and neurohormonal effects. Most patients with OHS have obstructive sleep apnea (OSA) and respond to CPAP therapy with significant improvement in daytime oxygenation and reduction in PaCO2. Those without OSA or who do not respond appropriately to CPAP, may require BIPAP therapy. Some OHS patients who initially require BIPAP can be switched to CPAP at a later time. Alternative methods of positive airway pressure treatment, such as average volume-assured pressure support or surgical interventions such as bariatic surgery or tracheostomy can be offered to patients who are refractory to CPAP or BIPAP.

INTRODUCTION

Obesity Hypoventilation Syndrome (OHS) refers to a state of chronic daytime hypoventilation associated with obesity that is usually extreme (body mass index (BMI) ≥ 40 kg/m^2). The disorder has also been known as the Pickwickian Syndrome after Burwell's 1956 case report (1) of an obese patient with hypercapnia, hypersomnolence and cor pulmonale noted the similarity to a character described by Charles Dickens in the Posthumous Papers of the Pickwick Club. The criteria for diagnosis of OHS include persistent elevation of arterial carbon dioxide tension (PaCO2) greater than 45 mmHg, a BMI that exceeds 30 kg/m^2 (in some patient series, 35 kg/m^2), and no other identifiable cause of hypoventilation (Table 1).

The term simple obesity (SO) is used to describe obese individuals without OHS or OSA. For those with sleep-disordered breathing, there is a strong association between OHS and OSA (Figure 1). About 90% of patients with OHS who have polysomnography are found to have OSA (2). Conversely, the prevalence of OHS in patients with OSA has been in the 10-20% range in most series (3,4). Overlap syndrome, OSA in patients with chronic obstructive pulmonary disease, is another hypercapnic sleep disorder. Hypercapnia may develop at a lower BMI in patients with Overlap Syndrome, but many of these patients are overweight or meet obesity criteria. OHS and Overlap Syndrome are each considered to be distinct clinical conditions.

The prevalence of OHS in the general population is not known, but has been estimated at approximately 0.5% for women and 1% for men (5). It seems to be a common, but under-recognized problem for persons with extreme obesity. Nowbar et al (6) found that 31% of a group of hospitalized patients with a BMI greater than 35 kg/m^2, and 48% with a BMI greater than 50 kg/m^2, had a P_aCO2 greater than 43 mmHg and no other reason for hypercapnia. It has been suggested that the widespread use of pulse oximetry without consideration of the possibility of hypercapnia may contribute to the under-recognition of chronic hypoventilation in obese hospitalized patients (7).

CLINICAL FEATURES

The clinical presentation of OHS is similar to that of OSA: disturbed sleep, snoring, excessive daytime sleepiness, morning headaches, depression and cognitive difficulties. But in addition, patients with OHS often develop sequelae of chronic hypoxia: polycythemia, pulmonary hypertension and cor pulmonale.

Untreated, OHS has been associated with substantial morbidity and early mortality. Affected patients are at risk for acute or subacute decompensation that usually requires hospitalization, often in an intensive care unit. Acute hypercapnic respiratory failure in patients with OHS is characterized by severe hypoxia and uncompensated

hypercapnia with cor pulmonale, and sometimes, massive edema and altered mental status. In the series of hospitalized patients reported by Nowbar (6), the 18 month mortality rate for those with OHS, 13% of whom were treated, was 23% compared to 9% for those with SO. In another report (8), 47% of hospitalized OHS patients who refused long-term positive pressure treatment died within 12 months.

PATHOPHYSIOLOGY OF OHS

Although the exact pathophysiology has not been clearly defined, OHS has been attributed to a combination of: 1) abnormal respiratory mechanics resulting in increased work of breathing; 2) depressed central ventilatory control; and 3) neurohormonal effects. More recent observations have led to the concept that sleep disordered breathing has an important causative role.

RESPIRATORY MECHANICS IN OBESITY

Obesity is associated with changes in respiratory mechanics that are particularly pronounced in persons with OHS. Sharp and co-workers found that total respiratory system compliance (chest wall + lung) was decreased to 80% of control values in volunteer subjects with SO and significantly reduced to 44% in patients with OHS (9). The reduction in chest wall compliance is a threshold type that requires greater negative pleural pressure to start airflow at the beginning of inspiration (10). Decreased lung compliance is likely due to increased blood volume and dependent airway closure.

Total respiratory resistance is also markedly increased in morbidly obese individuals, mostly due to lung volume reduction, especially functional residual capacity (FRC) (11). Although FEV1 and FVC are often low and expiratory flow rates are significantly reduced, the FEV1/FVC ratio is usually normal. Total respiratory resistance in obese persons is higher in the supine than the upright position (12), probably due to further drop in FRC causing smaller airway diameter and increased upper airway resistance. Lin et al (13) found that whereas eucapneic OSA patients had greater upper airway resistance than non-obese subjects only in the supine position, OHS patients had higher upper airway resistance in both the supine and sitting positions.

The alterations of respiratory mechanics in morbid obesity and OHS result in substantially greater work of breathing, averaging 3 times that of non-obese subjects (9). Compared to non-obese controls, extremely obese patients require significantly greater oxygen consumption for respiratory work during quiet breathing (14). Permissive hypoventilation might be a means of accommodation to the higher oxygen demand and risk for respiratory muscle fatigue, however, the physiology appears to be more complex, since many extremely obese individuals don't develop OHS and there is evidence that other mechanisms play a role.

CENTRAL VENTILATORY CONTROL IN OBESITY AND OHS

In addition to impairment in respiratory mechanics, patients with OHS have depressed central ventilatory drive. This is apparent because OHS patients can normalize arterial PaCO2 by voluntary hyperventilation (15).

In individuals with SO, increased ventilatory drive compensates for the impaired respiratory mechanics (16). Compared to SO subjects, OHS patients have decreased ventilatory drive when they inhale increasing concentrations of CO2 according to measurements that are independent of respiratory muscle function or mechanics (16). The ventilatory response to hypoxemia is also normal to enhanced in simple obesity, but reduced in OHS patients (17).

NEUROHORMONE PROFILES IN OBESITY AND OHS

Leptin is a hormone secreted by adipocytes that acts on hypothalamic receptors to signal satiety and regulate body weight. Leptin also acts on central respiratory centers to stimulate ventilation. Leptin-deficient mice have an attenuated ventilatory response to hypercapnia prior to developing obesity and significant hypercapnia once obesity is established (18). Leptin replacement reverses hypoventilation in these mutant mice.

In humans, obesity is associated with high serum leptin levels, suggesting the possibility of leptin resistance. Elevated leptin levels could provide a mechanism of compensation, conferring an augmented ventilatory drive to offset the effect of impaired respiratory mechanics. The ratio of CSF:serum leptin is lower in obese than non-obese individuals, despite significantly higher serum levels (19), suggesting impaired CNS transport. OHS patients have higher serum leptin levels than eucapneic OSA patients, and the levels are a better predictor of hypercapnia than BMI (20). Regular CPAP use in patients with OHS and OSA is associated with reduced serum leptin levels without change in BMI (21, 22). Explanations for this finding remains speculative and include reversal of leptin resistance,

reduction in sympathetic activity due to fewer obstructive events or better sleep quality that may allow release of substances like growth hormone that inhibit leptin secretion..

SLEEP-DISORDERED BREATHING AND OHS

Although the phenomenon of recurrent sleep apneas in a patient with Pickwickian syndrome was reported as early as 1966 (23), the potential role of sleep disordered breathing in causing daytime hypoventilation was not considered until the 1980's. Virtually all OHS patients have sleep disordered breathing. The majority (90%) have OSA, and the remaining 10% have sleep hypoventilation defined as a rise in p_aCO2 > 10mmHg or consistent O2 desaturation not associated with apneas or hypopneas (2,4). Furthermore, many OHS patients demonstrate improvement of daytime hypercapnia and hypoxia as early as 1 month after initiation of continuous positive airway pressure (CPAP) or bi-level airway pressure (BIPAP) (8, 24,25, 26), as well as improved ventilatory drive to resistive loads, hypoxia and hypercapnia (25, 26, 27,28).

The mechanisms by which OSA can lead to daytime hypoventilation have not been definitively elucidated, although several have been postulated. The augmented respiratory drive that occurs during recovery from an apneic event in eucapneic OSA patients is blunted in OHS patients (29). One hypothesis is that this depressed ventilatory response is actually the result of a protective adaptation to chronic hypoxia and hypercapnia to avoid the disturbances that result from recurrent obstructive events during sleep (30). Thus, depressed chemoresponsiveness and ventilatory hypoventilation as well as increased arousal thresholds may allow stable hypoventilation instead of recurrent apneas, hypopneas and PaO2 fluctuation. Combining this phenomenon with mechanical limitations, increased respiratory muscle oxygen consumption and fatigue could result in significant continuous nocturnal hypoventilation that eventually extends to the daytime.

Another hypothesis is supported by the observation that patients with severe OSA have acute CO2 retention when the inter-event time is short relative to the duration of events (31). A computer model that simulates OSA with varying event and inter-event durations has suggested that compensatory renal HCO3 retention in response to the CO2 accumulation due to this type of repeated obstructive events could be a mechanism for the development of chronic daytime hypercapnia in OSA (32)

DIAGNOSTIC EVALUATION FOR OHS

The possibility of OHS should be entertained in obese patients if the daytime serum bicarbonate level is 27 meq/L or greater (8). Polysomnography plays an important role in the evaluation of OHS, not only for diagnosing OSA or obstructive hypoventilation, but also for planning and individualizing treatment. During polysomnography, findings that suggest OHS include obstructive hypoventilation with severe hypoxia, or for patients with OSA, periods of hypoxia after obstructive events have resolved during CPAP titration (33). In such cases, an arterial blood gas determination should be performed to confirm that the PaCO2 is greater than 45 mmHg. If hypercapnia is documented, further evaluation should be undertaken to exclude other potential causative or contributory conditions (Table 2).

TREATMENT OF OHS

POSITIVE AIRWAY PRESSURE THERAPY

Of a wide variety of treatment options that have been tried, positive airway pressure (PAP), usually CPAP or bi-level positive airway pressure (BIPAP), has been the most successful.

Several studies (8, 24-28) have confirmed that most OHS patients have improvement in daytime hypercapnia and hypoxia as early as 1 month after PAP is initiated. Mokhlesi and colleagues found that adherence to CPAP or BIPAP therapy was the most important predictor of improvement. They calculated that the PaCO2 dropped 1.84 mmHg per hour of adherence, reaching a plateau when used an average of 7 hours per night (24). Nevertheless, 8 of 23 patients who used PAP at least 4 ½ hours per night did not have significant reduction of daytime PaCO2 and for 11, the value remained greater than 45 mmHg. Short-term nocturnal noninvasive positive pressure ventilation using a volume cycled ventilator has been shown to reverse daytime hypoxia and hypercapnia in OHS patients who were not initially responsive to CPAP (34). Most of these patients could be subsequently managed with CPAP.

CPAP VS BIPAP

How to identify OHS patients that require BIPAP versus those for whom CPAP is sufficient has been a subject of continued interest (Figure 2). BIPAP is generally recommended for patients with OHS for whom overnight polysomnography does not document OSA (35). Most patients with OHS and OSA can be treated effectively with CPAP, although some, especially those with a higher BMI,

more severe baseline hypoxemia, and more residual obstructive events while on CPAP, may have refractory nocturnal hypoxemia despite CPAP treatment. A recent randomized trial of CPAP versus BIPAP therapy in OHS patients who did not exhibit severe hypoxemia (SaO2 <80% for >10 minutes) has suggested that, in most cases, CPAP is sufficient since both modes were equally effective in improving daytime hypercapnia over a 3 month period (36).

Banerjee et al (33) found that 43% of patients with extreme obesity, OSA and OHS continued to spend >20% of total sleep time (TST) with SaO2 <90% during CPAP titration. Those authors suggested that the percentage of TST with SaO2 <90% despite elimination of obstructive events may be a useful indicator for identifying patients who require BIPAP therapy. A switch to BIPAP therapy has also been recommended for patients who do not achieve an acceptable daytime PaCO2 after 1-2 months of CPAP therapy (37). Many patients initially started on BIPAP can later be converted to CPAP once there is resolution of the hypercapnia (8,34)

Patients presenting with OHS and acute respiratory failure have been successfully treated with BIPAP or volume-cycled non invasive positive pressure ventilation that was initiated during hospitalization and continued as nocturnal therapy after discharge (8). Although only 3 of 54 could be treated initially with CPAP, once the patients stabilized and a second sleep study was performed, 16 could be maintained on CPAP therapy over a mean period of 50 months.

A PAP titration algorithm (37) has been proposed (Figure 3) in which titration with CPAP is taken to a level where there is resolution of obstructive events. If SaO2 is persistently lower than 90%, the mode is changed to BIPAP by adding IPAP at least 8 cmH20 above the final CPAP level.

SUPPLEMENTAL OXYGEN THERAPY

Supplemental nocturnal oxygen is required in 20 – 50% of OHS patients with the initiation of CPAP or BIPAP treatment (8,24,35,36). A smaller proportion require oxygen therapy during the day (8,24). In many cases, both daytime and nocturnal oxygen supplementation can be with withdrawn over a period of months if the patient is adherent with PAP therapy (24,35,36)

AVERAGE VOLUME-ASSURED PRESSURE SUPPORT

In cases of failed CPAP therapy in the treatment of OHS, a newer mode of noninvasive ventilation, average volume-assured pressure support (AVAPS) has been shown to improve daytime hypercapnia compared to BIPAP alone (38). The AVAPS device provides a targeted tidal volume by automatically adjusting inspiratory positive airway pressure within a preset range. In the study, compared to BIPAP alone, AVAPS added to BIPAP resulted in significant improvement of transcutaneous CO2 after 6 weeks of therapy; however there was no significant difference between sleep quality and quality of life.

TRACHEOSTOMY

Prior to the availability of PAP therapy, tracheostomy was the most effective treatment for OSA, providing long-term symptomatic improvement as long as the stoma remained open (39). Patients with OHS have also experienced improvement of hypersomnolence and cor pulmonale after tracheostomy, however some remained hypercapneic (40, 41). A study by Kim and collegues found that compared to eucapneic OSA patients, tracheotomy was less effective in eliminating apneic events and normalizing daytime gas exchange in patients with OHS although most showed improvement in AHI, as well as daytime hypercapnia and hypoxia (41). Those authors suggested that continued sleep disordered breathing after tracheotomy in OHS patients may be attributed to obstruction of the tracheotomy stoma by fatty tissue or the appearance of central apneic events.

WEIGHT REDUCTION

Although there has been mention of cases for which dietary weight reduction has resulted in substantial improvement in OHS (1,8), the medical literature provides no evidence that it is a feasible long-term solution for any significant proportion of affected patients.

Bariatric surgery, including the most current laparoscopic approaches for gastric bypass and gastric banding, is effective in providing substantial weight loss for most patients, as well as reduction in OSA symptoms and AHI (42). Weight loss tends to be greater after the bypass procedures than with gastric banding. The mortality (0.1-2.0%) and complication (13%) risks associated with bariatric surgery are significant, but lower with the laparoscopic methods (42,43). Sugerman and colleagues reported improvement in 38 OHS patients after bariatric gastric surgery over an average of 4 ½ years, with a mean increase of PaO2 from 54 to 68 mm Hg, a mean decrease in PaCO2 from 53 to 47 mm Hg and reduction in pulmonary hypertension (44). For patients with OSA, despite

improvement in AHI and daytime somnolence, significant OSA often persists after bariatric surgery even when considerable weight loss is achieved (45). The persistence of OSA is particularly evident in patients with very high AHI (>100 events/hr), who continue to have severe OSA despite large reductions in obstructive events. Furthermore, during the 10 year period after bariatric surgery, recurrence or worsening of OSA with or without weight gain can occur (44, 46, 47). Thus, although OHS patients, especially those refractory to PAP, may benefit from bariatric surgery, many will continue to require PAP therapy during subsequent years.

Figure 1

Table 1: Obesity Hypoventilation Syndrome Diagnostic Criteria

1) **BMI > 30 kg/m^2**
2) **$PaCO_2$ > 45 mmHg**
3) **Associated sleep breathing disorder (OSA , obstructive or central hypoventilation or all)**
4) **No other cause of hypoventilation**

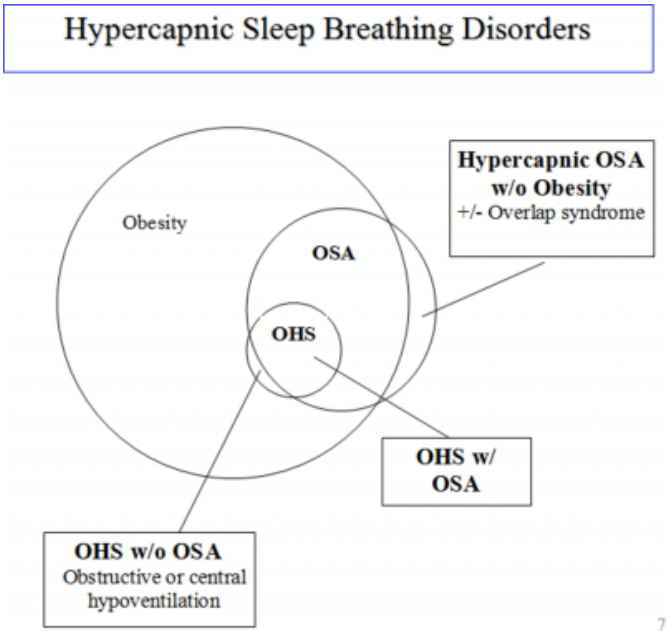
Figure 2

Table 2: Causes of Chronic Hypoventilation Other Than Obesity Hypoventilation Syndrome

1) **Primary pulmonary disease**
    a. **COPD/Overlap Syndrome**
    b. **Advanced pulmonary parenchymal disease (eg interstitial lung disease)**
    c. **Severe upper airway obstruction (eg tracheal stenosis)**
2) **Chest wall disorders**
    a. **Kyphoscoliosis**
    b. **Thoracoplasty**
3) **Neuromuscular disorders**
    a. **Myopathies**
    b. **Muscular dystrophies**
    c. **Bilateral diaphragmatic paralysis**
    d. **Guillain-Barret Syndrome**
    e. **Amyotrophic lateral sclerosis**
    f. **Myasthenia Gravis**
    g. **Cervical spine injury**
4) **Primary CNS disorders**
    a. **Primary central hypoventilation syndromes**
    b. **Brain stem infarction or tumor**
5) **Myxedema**
6) **Drugs (narcotics, sedatives)**
7) **Metabolic abnormalities (hypokalemia, hypophosphatemia, hypomagnesemia, metabolic alkalosis)**

Figure 3

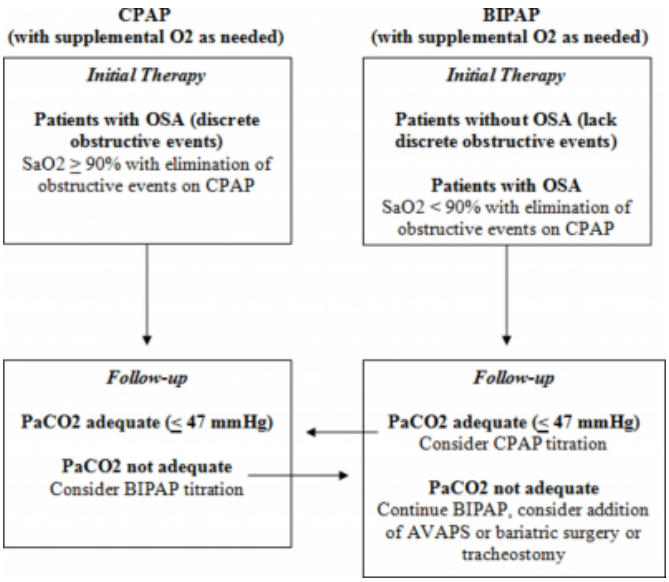
Figure 1



Legend: Three hypercapneic sleep breathing disorders: OHS has been documented in 10 - 20% of patients with OSA in most series (3,4). 85-90% of OHS patients have OSA, the remainder do not have classic discrete obstructive events during sleep but usually have obstructive or central hypoventilation. Hypercapnic OSA in patients with BMI <30 kg/m^2 is most frequently seen in patients with COPD and OSA (overlap syndrome), but has also been reported in patients of Asian descent (37).

Figure 4

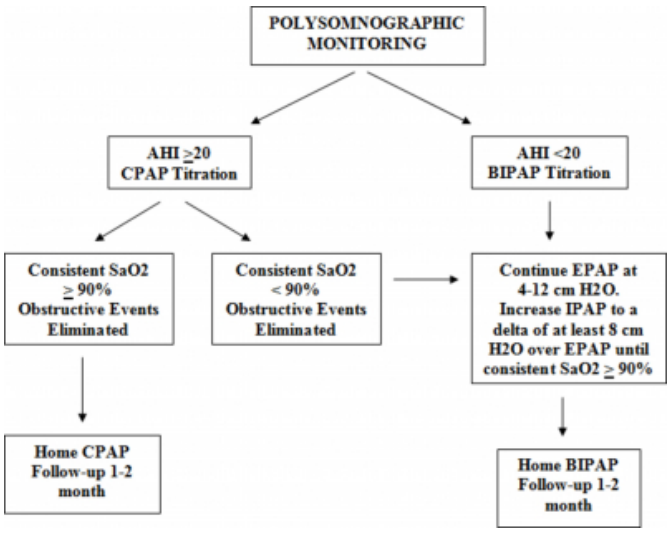
Figure 2: Obesity Hypoventilation Syndrome CPAP versus BIPAP



Legend: CPAP versus BIPAP Therapy in Patients with OHS. During the initial PSG, OHS patients without discrete obstructive events of OSA are titrated to BIPAP (35). Most patients with OHS and OSA respond to CPAP (24), although BIPAP has been recommended for those who continue to have SaO2 <90% with elimination of obstructive events (33). In addition to nocturnal CPAP or BIPAP, supplemental O2 may also be indicated initially. After 3 months of CPAP or BIPAP therapy, most who are compliant demonstrate reduction of daytime PaCO2 and, in many cases, supplemental O2 can be discontinued. Some who initially required BIPAP can eventually switch to CPAP (8,34). A small proportion initially treated with CPAP will not have adequate reduction in PaCO2 and may need to switch to BIPAP (37). Patients who do not respond appropriately to BIPAP may benefit from a trial of average volume-assured pressure support (AVAPS) (38) or weight-reduction surgery or tracheostomy.

Figure 5

Figure 3: Suggested Algorithm for CPAP or BIPAP Titration for Patient with Obesity Hypoventilation Syndrome (Adapted from Mokhlesi Chest 2007 (37)



Legend: Suggested algorithm for CPAP or BIPAP Titration in Patients with Obesity Hypoventilation Syndrome. Patients with discrete obstructive events can be titrated to CPAP and treated if SaO2 remains ≥ 90%. Patients with few or no obstructive events, and those who continue to have SaO2 < 90% once obstructive events are eliminated on CPAP should have BIPAP titration with the goal of SaO2 ≥ 90%. A delta of at least 8 cmH20 IPAP over EPAP has been required for successful long-term BIPAP therapy of OHS (37). Patients should be followed-up in 1-2 months to assess effectiveness of CPAP or BIPAP therapy.

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Author Information

Dan Naim, MD
Division of Pulmonary, Critical Care and Sleep Medicine, Olive View-UCLA Medical Center

Jeanne Wallace, MD, MPH
Division of Pulmonary, Critical Care and Sleep Medicine, Olive View-UCLA Medical Center