The obesity hypoventilation syndrome

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ABSTRACT: The obesity hypoventilation syndrome, which is defined as a combination of obesity and chronic hypoventilation, ultimately results in pulmonary hypertension, cor pulmonale, and probable early mortality. Since the classical description of this syndrome nearly fifty years ago, research has led to a better understanding of the pathophysiologic mechanisms involved in this disease process, and to the development of effective treatment options. However, recent data indicate the obesity hypoventilation syndrome is under-recognized, and under-treated. Because obesity has become a national epidemic, it is critical that physicians are able to recognize and treat obesity-associated diseases. This article reviews current definitions of the obesity hypoventilation syndrome, clinical presentation and diagnosis, present understanding of the pathophysiology, and treatment options.

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Obesity hypoventilation syndrome is commonly defined as a combination of obesity (body mass index of >30 kg/m²) and awake arterial hypercapnia (PaCO₂ >45 mm Hg) in the absence of other known causes of hypoventilation.1-3 Clinically, patients may present with symptoms such as excessive daytime sleepiness, fatigue, or morning headaches, which are similar to symptoms seen in obstructive sleep apnea-hypopnea syndrome.4 However, patients with obesity hypoventilation syndrome have daytime hypercapnia and hypoxemia, which is associated with pulmonary hypertension and right-sided congestive heart failure (cor pulmonale).1 If untreated, recent studies indicate this syndrome results in substantial morbidity and probable early mortality.5,6 Although the precise pathophysiology remains unknown, physiologic consequences of obesity seem important.7 In a society in which approximately one third of adults are obese and the prevalence is expected to increase,8 recognition of this syndrome is essential because effective treatment options exist.9

History and definitions

Obesity hypoventilation syndrome was classically described as “Pickwickian syndrome” in a 1956 case report by Burwell.10 This patient resembled a character depicted by Dickens in his story, The Posthumous Papers of the Pickwick Club, because both were obese with excessive hypersomnia. Further, Burwell’s patient had hypoventilation during wakefulness, with hypoxemia-induced erythrocytosis, pulmonary hypertension, and cor pulmonale.

Subsequent investigation of patients with Pickwickian syndrome found nocturnal respiratory abnormalities, such as multiple “respiratory pauses” (apneas),11 which led to further study of these sleep-induced events. Research in eucapnic patients revealed that occasional apneas (as the result of sleep-induced
upper airway obstruction) were common and often asymptomatic, whereas frequent complete or partial apneas could cause sleep fragmentation resulting in a range of clinical symptoms including hypersomnolence. This syndrome is termed “obstructive sleep apnea-hypopnea syndrome.”

Additional investigations found daytime hypercapnia in approximately 10% to 15% of patients with obstructive sleep apnea-hypopnea syndrome. Other studies reported that although the majority (~90%) of patients with obesity and daytime hypercapnia had concurrent obstructive sleep apnea-hypopnea syndrome, a small minority of patients with obesity hypoventilation syndrome had no evidence of significant apnea-hypopnea events during sleep. Instead, these patients had sustained periods of hypoventilation, particularly during rapid eye movement sleep, which has been termed “sleep hypoventilation syndrome.”

In 1999, the American Academy of Sleep Medicine published recommendations to standardize definitions, eliminate confusion, and facilitate comparability of studies for research purposes. By these definitions, patients with obesity hypoventilation syndrome may have obstructive sleep apnea-hypopnea syndrome with hypercapnia, sleep hypoventilation syndrome, or a combination of sleep-related breathing disorders (Table 1).

### The scope of the problem

#### Epidemiology

Although the prevalence of obesity hypoventilation syndrome is unknown, a recent study of severely obese (body mass index ≥35 kg/m²) hospitalized patients found that 31% had daytime hypercapnia unexplained by other disorders. Although weight alone did not predict the presence of hypoventilation, almost half of the patients with a body mass index 50 kg/m² or greater had chronic daytime hypoventilation. Although data have shown men to be at higher risk for obstructive sleep apnea-hypopnea syndrome, the same has not been demonstrated for obesity hypoventilation syndrome.
Morbidity and mortality

Evidence suggests this syndrome is associated with significant mortality and morbidity. Two older case series, published before treatment options became available and before the routine use of in-hospital heparin prophylaxis, reported high in-hospital mortality rates principally related to progressive respiratory failure or acute pulmonary embolism.25,26 A recent study found hospitalized patients had a higher 18-month mortality rate of 23% compared with 9% among patients with simple obesity. Notably, although health care providers were informed of the obesity-associated hypoventilation, only 13% of patients were discharged with therapies known to be effective.6

Cost

Little is known about health care use and cost for patients with obesity hypoventilation syndrome. A recent Canadian study found that during the 5 years before the diagnosis of this syndrome, patients had more physician visits, generated higher fees, and were more likely to be hospitalized than patients with simple obesity. Two years after the diagnosis was made and treatment was initiated, patients had a significant reduction in physician fees and days hospitalized.5

Clinical presentation and diagnosis

Patients with obesity hypoventilation may present with unexplained hypoxemia or a broad spectrum of symptoms ranging from hypersomnolence or dyspnea to signs of right-sided congestive heart failure. Because these patients have a concurrent sleep-related breathing disorder with sleep-induced exaggeration of hypercapnia and hypoxemia and frequent arousals from sleep, presenting symptoms may include fatigue, hypersomnolence, mood disorders, and nocturnal or morning headaches.27 In patients with apneic or hypopneic events, symptoms may include loud snoring, choking, gagging, and resuscitative snorting. Untreated patients may develop secondary erythrocytosis and will ultimately develop pulmonary hypertension and cor pulmonale.28

Data suggest that obesity hypoventilation syndrome is under-recognized and under-treated.6 We believe the diagnosis is frequently missed because pulse oximetry is used to detect oxyhemoglobin desaturation without consideration for the presence of hypercapnia. As a result, patients may be inappropriately treated with supplemental oxygen alone, which does not reverse hypoventilation. In our opinion, arterial blood gas analysis should be obtained in any patient with morbid obesity and unexplained hypoxemia or signs of cor pulmonale.

Arterial blood gas testing is required to confirm the presence of daytime hypercapnia, and usually reveals compensated respiratory acidosis and hypoxemia. An elevated serum bicarbonate level may suggest that chronic hypercapnia is present, because hospitalized patients with this syndrome have higher serum bicarbonate levels when compared with patients with simple obesity (30 ± 4 mEq/L vs 24 ± 5 mEq/L, P = .01).6

Other conditions that cause chronic hypoventilation should be considered during the evaluation. The history and physical examination may reveal mechanical limitations (underlying lung disease, kyphoscoliosis, or myopathy), neuropathic conditions (diaphragmatic paralysis or neuropathy), or central control abnormalities (severe hypothyroidism, cerebrovascular accident, or central nervous system disease) suggesting a diagnosis other than obesity hypoventilation syndrome.27,29

Laboratory testing should include a complete blood count (to determine the existence of erythrocytosis), serum electrolytes, including phosphorus and creatinine phosphokinase (to determine additional factors that may be contributing to respiratory muscle weakness), and thyroid-stimulating hormone.27 Thyroid function testing should be performed because severe hypothyroidism has been shown to cause alveolar hypoventilation in the absence of severely impaired lung function.29,30 If hypoxemia-induced erythrocytosis is identified, recommendations state phlebotomy should only be performed if the hematocrit is greater than 65% with symptoms of hyperviscosity.31

Pulmonary function testing should include spirometry, lung volumes, a bronchodilator response, maximal inspiratory and expiratory pressures, and supine vital capacity (if diaphragmatic paralysis is suspected).27,29 These studies may support a diagnosis of chronic obstructive pulmonary disease (COPD). Like obesity hypoventilation syndrome, COPD can cause chronic hypoventilation. However, hypoventilation and hypercapnia are not common in COPD unless the forced expiratory volume in 1 second is less than 1 liter. Flanley described the concurrent conditions of COPD and obstructive sleep apnea-hypopnea syndrome, which he termed the “overlap syndrome.”32 In these patients with COPD, forced expiratory volume in 1 second that exceeded 1 liter, and chronic hypoventilation, apneas and hypopneas were prominent features on night-time polysomnography. If these patients are treated with supplemental oxygen alone, symptoms do not improve and nocturnal hypercapnia may worsen.33

Conditions that aggravate chronic hypoventilation should be identified and treated. The history may reveal the use of excessive alcohol, sedative-hypnotics, or narcotics, which have been shown to be respiratory depressants and should be avoided if possible.30

Finally, patients should be referred for night-time polysomnography testing to identify the underlying sleep disorder and to individualize treatment with either continuous positive airway pressure or noninvasive mechanical ventilation.24,28 In patients with evidence of impending respiratory failure (such as an uncompensated respiratory acidosis, significant hypoxemia, or mental status changes), immediate hospitalization is indicated. These patients require immediate ventilatory support.25,26
**Pathophysiology**

**Overview**

Despite significant research, the exact pathophysiologic mechanisms leading to obesity hypoventilation syndrome have not been clearly defined. The syndrome may result from complex interactions among impaired respiratory mechanics, abnormal central ventilatory control, possible sleep-disordered breathing, and neurohormonal aberrancies (Figure 1).7,28

**Respiratory system mechanics**

Significant impairment in respiratory system mechanics is present when individuals with obesity hypoventilation syndrome are compared with similarly obese patients without daytime hypercapnia. Reductions in total lung capacity, vital capacity, functional residual capacity, and increases in residual volume have been shown.7 Patients with more upper body fat distribution tend to have more severe derangements in lung volumes, suggesting that fat distribution may contribute to the pathogenesis.28
Because of decreased respiratory system compliance and increased resistance, these patients must maintain an increased work and oxygen cost of breathing. This may result in respiratory muscle fatigue. Maximal voluntary ventilation, a measure of ventilatory endurance, is reduced in simple obesity and further reduced in obesity hypoventilation syndrome.

**Ventilatory control**

Data suggest that abnormalities in ventilatory control are also involved in the pathogenesis of this syndrome. Patients with obesity hypoventilation syndrome can achieve eucapnia (or even hypocapnia) during voluntarily hyperventilation, implying that impairments in respiratory system mechanics alone do not explain the hypoventilation. Moreover, investigators have identified abnormalities in both hypercapnic and hypoxemic ventilatory responses, which are measurements of ventilatory control.

The ratio of change in the diaphragmatic electromyogram response to increasing concentrations of inhaled carbon dioxide ($\Delta$EMG/$\Delta$PCO$_2$) is thought to be a direct measure of central ventilatory drive. Patients with simple obesity have an augmented ventilatory response, whereas patients with obesity hypoventilation syndrome have a response similar to that of nonobese patients. These findings imply that eucapnic obese patients have an increased central ventilatory drive that is needed to compensate for the mechanical restrictions of obesity, whereas patients with obesity hypoventilation seem to lack this compensatory increased drive.

**Obstructive sleep apnea-hypopnea syndrome and decreased ventilatory response**

There is a significant relationship between obstructive sleep apnea-hypopnea syndrome and obesity hypoventilation syndrome. Although it is not clear why only 10% to 15% of patients with obstructive sleep apnea-hypopnea develop hypoventilation, it has been postulated that obstructive sleep apnea-hypopnea syndrome may lead to a depressed ventilatory response and hypoventilation.

Chronic exposure to hypoxia and sleep fragmentation attenuate central ventilatory drive. Patients with cyanotic congestive heart disease have a reduced hypoxic ventilatory response, which is reversed when the shunt hypoxemia is corrected. Healthy subjects with chronic exposure to hypoxia of altitude have a reduction in both the hypoxic and hypercapnic ventilatory response. In addition, sleep deprivation in healthy volunteers decreases the hypercapnic ventilatory response.

In obstructive sleep apnea-hypopnea syndrome, apneic events result in sleep hypoxemia, hypercapnia, and increased ventilatory effort. This causes arousals, which improve upper airway patency and normalize blood gas tensions. However, frequent apneas with arousals lead to sleep fragmentation. In patients with obstructive sleep apnea-hypopnea syndrome, this chronic exposure to hypoxemia and sleep fragmentation may, in susceptible individuals, lead to a diminished ventilatory drive and resultant hypoventilation.

Patients with these concurrent syndromes may be caught in a “vicious cycle” (Figure 2). Apnea-induced hypoxemia and sleep fragmentation may diminish the ventilatory response. This decreased ventilatory response, combined with deranged lung mechanics, may prevent restoration of post-apnea eucapnia, which leads to more severe exposure to hypoxemia and hypercapnia and further attenuation of the ventilatory response.

There is evidence supporting this theory. Patients with obstructive sleep apnea-hypopnea syndrome (and daytime eucapnia) demonstrated an augmented ventilatory drive with large tidal volume breaths after an apnea, whereas patients with obesity hypoventilation syndrome did not have a compensatory ventilatory response after apneas. Furthermore, the severity of hypercapnia has been correlated with the severity of sleep-induced respiratory abnormalities, the mechanical impairment of the respiratory system, and the degree of daytime hypoxemia.

**Leptin and the ventilatory response**

Recent evidence suggests that the protein leptin may be involved in the pathogenesis of obesity hypoventilation syndrome. Leptin is produced by adipose tissue and acts on receptors in the hypothalamus to suppress appetite. A mutation in the gene that encodes the leptin protein causes obesity in mice and in humans. In addition, leptin acts on the central respiratory centers to stimulate ventilation, whereas leptin deficiency has been associated with hypoventilation.

Leptin-deficient mice hypoventilate, and leptin replacement results in increased ventilation. In wild-type mice with diet-induced obesity, leptin levels increase more than 10-fold and are associated with an increase in ventilation. These findings suggest leptin may be involved in maintaining an adequate level of ventilation for a given degree of obesity.

Human obesity is also associated with elevated serum levels of leptin, which may explain a means by which eucapnia is maintained in most obese individuals. It has been speculated that in some individuals leptin resistance may lead to a reduction in ventilation, but further research is necessary to confirm this theory.

**Treatment**

**Weight loss**

The ideal treatment for obesity hypoventilation syndrome is weight loss, which improves most of the physiologic abnor-
malities thought to be involved in the pathogenesis and ultimately leads to the restoration of daytime eucapnia.7,18,38

Weight loss of at least 10 kg results in a significant improvement in vital capacity and maximum voluntary ventilation, and a significant reduction in daytime PaCO₂.38 Although data are limited, weight loss has also been shown to significantly increase central ventilatory drive as measured by the diaphragmatic electromyogram response to carbon dioxide inhalation.38 In patients with obesity hypoventilation syndrome and concurrent obstructive sleep-apnea hypopnea syndrome, weight loss reduced the number of sleep-disordered breathing events (apneas and hypopneas), decreased the severity of desaturation associated with any residual apneas, and led to the resolution of the daytime hypercapnia.63

The National Institutes of Health consensus statement addresses the issue of surgical treatment for obesity and

Figure 2 The vicious cycle of obesity hypoventilation syndrome (see text for further explanation). OHS, obesity hypoventilation syndrome; OSAHS, obstructive sleep apnea-hypopnea syndrome.
Continuous positive airway pressure and noninvasive mechanical ventilation

As previously stated, there are a variety of sleep-associated respiratory disturbances (apneas, hypoventilation, or both) that are found in obesity hypoventilation syndrome. Treatment that corrects the specific sleep-related breathing disorder results in the reversal of chronic daytime hypercapnia.66

In patients with concurrent obstructive sleep apnea-hypopnea syndrome, nocturnal continuous positive airway pressure therapy (applied by nasal mask) is usually effective. This therapy provides continuous positive pressure during the respiratory cycle, which maintains upper airway patency, eliminates apneas and hypopneas, and restores daytime eucapnia.67

A subset of patients with obstructive sleep apnea-hypopnea syndrome, however, will not respond to continuous positive airway pressure therapy, and may require noninvasive mechanical ventilation to alleviate daytime hypercapnia. Noninvasive mechanical ventilation may be achieved with a nasal mask and either a bilevel positive airway pressure device or a volume ventilator. Bilevel systems permit independent adjustment of inspiratory and expiratory positive airway pressure. Differences between these pressures assist with lung inflation during each respiratory cycle thereby supporting ventilation. The inspiratory and expiratory pressures, like continuous positive airway pressure, also maintain upper airway patency. Volume ventilation better ensures adequate alveolar ventilation and provides the advantage of allowing higher peak inspiratory pressures.16

Several factors have been identified that may explain why some patients with obesity hypoventilation syndrome and obstructive sleep apnea-hypopnea syndrome are not adequately treated with continuous positive airway pressure alone. In some patients, despite high continuous positive airway pressures, airway patency is not established. These patients may need higher peak inspiratory pressures, which only volume ventilation can provide. Other patients may have concurrent sleep hypoventilation syndrome, which necessitates noninvasive ventilatory support to augment ventilation.16 Finally, in some patients, intolerance to therapy may be a significant issue. Among patients who cannot tolerate any form of ventilatory support, a tracheostomy may be required.18,66

In patients with obesity hypoventilation syndrome whose underlying sleep disorder is hypoventilation alone, noninvasive mechanical ventilation is the mainstay of treatment. Hypoxia and hypercapnia develop as a consequence of hypoventilation. Treatment with supplemental oxygen alone is inadequate, and ventilatory support is required to correct the hypercapnia.24,66

In addition to evidence that treatment directed at the underlying sleep-associated respiratory disturbance alleviates daytime hypercapnia, there is emerging evidence that treatment also alleviates symptoms such as morning headaches, morning drowsiness, sleepiness, dyspnea, and leg edema.24

Progesterone

Medroxyprogesterone has been shown to increase hypercapnic chemosensitivity and improve ventilation in patients with obesity hypoventilation syndrome.68,69 However, it does not improve apnea frequency or symptoms of sleepiness,70 and there are limited data regarding adverse effects and outcomes of long-term use. As a result, experts do not currently recommend progesterone therapy.28

Conclusion

Because obesity has become a national epidemic, it is imperative that physicians are able to recognize and treat obesity-associated diseases. Evidence suggests that obesity hypoventilation syndrome is under-recognized, undertreated, and associated with a significant increase in mortality. These findings are particularly disturbing because effective treatment options exist. Further investigations are needed to completely understand the prevalence, pathophysiology, morbidity, and long-term treatment outcomes associated with this syndrome.

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References


