CHEST Recent Advances in Chest Medicine

Recent Advances in Obesity Hypoventilation Syndrome*

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Obesity hypoventilation syndrome (OHS) consists of a combination of obesity and chronic hypercapnia accompanied by sleep-disordered breathing. During the last 3 decades, the prevalence of extreme obesity has markedly increased in the United States and other countries. With a global epidemic of obesity, the prevalence of OHS is bound to increase. Patients with OHS have a lower quality of life with increased health-care expenses and are at a higher risk for the development of pulmonary hypertension and early mortality compared to eucapnic patients with sleep-disordered breathing. Despite the significant morbidity and mortality associated with this syndrome, it is often unrecognized and treatment is frequently delayed. Clinicians must maintain a high index of suspicion since early recognition and treatment reduces the high burden of morbidity and mortality associated with this syndrome. In this review, we will discuss the definition and clinical presentation of OHS, provide a summary of its prevalence, review the current understanding of the pathophysiology, and discuss the recent advances in the therapeutic options. ***(CHEST 2007; 132:1322–1336)***

Key words: bilevel positive airway pressure; continuous positive airway pressure; hypercapnia; hypoventilation; obesity hypoventilation syndrome; pickwickian syndrome; sleep apnea; sleep-disordered breathing

Abbreviations: AHI = apnea-hypopnea index; AVAPS = average volume-assured pressure support; BMI = body mass index; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; NIPPV = noninvasive positive-pressure ventilation; NREM = non-rapid eye movement; OHS = obesity hypoventilation syndrome; OSA = obstructive sleep apnea; PAP = positive airway pressure; REM = rapid eye movement

Before Burwell coined the term *Pickwickian syndrome*,[1] Auchincloss and colleagues[2] gave the first detailed description of a patient with obesity hypoventilation syndrome (OHS). Since then, our knowledge about the epidemiology, pathophysiology, treatment, and outcomes of OHS has improved significantly.

In the United States, a third of the adult population is obese, and the prevalence of extreme obesity (*ie*, body mass index [BMI] $\geq$ 40 kg/m^2) is increasing rapidly. From 1986 to 2000, the prevalence of BMI of $\geq$ 40 kg/m^2 has quadrupled, and that of BMI of $\geq$ 50 kg/m^2 has increased by fivefold.[3,4] The obesity epidemic is not only impacting adults in the United States, it is a global phenomenon affecting children and adolescents.[5–8] With such a global epidemic of obesity, the prevalence of OHS is likely to increase. In this review, we will discuss the definition and clinical presentation of OHS, provide a summary of its prevalence, attempt to give a cohesive and comprehensive review of its pathophysiology, and provide evidence that early recognition and treatment reduces the high burden of morbidity and mortality associated with this syndrome.

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The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Manuscript received January 4, 2007; revision accepted March 6, 2007.

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DOI: 10.1378/chest.07-0027

Definitions

OHS is defined as a combination of obesity (*ie*, BMI $\geq$ 30 kg/m^2) and awake chronic hypercapnia (*ie*, $Paco_2 \geq 45$ mm Hg) accompanied by sleep-disordered breathing.[9,10] It is important to recognize that OHS is a diagnosis of exclusion and should be distinguished from other conditions that are commonly associated with hypercapnia (Table 1). In approximately 90% of patients with OHS, the sleep-disordered breathing consists of obstructive sleep apnea (OSA).[11–13] Due to this association, the term *hypercapnic OSA* has been interchangeably used with OHS. The remaining 10% of patients with OHS have an apnea-hypopnea index (AHI) < 5.[11–13] The sleep-disordered breathing in this subset of patients has been labeled as *sleep hypoventilation* and is defined as an increase in $Paco_2$ during sleep by 10 mm Hg above wakefulness or a significant oxygen desaturation that is not explained by obstructive apneas or hypopneas.[9]

Overlap syndrome is the term used to describe the association of COPD and OSA. The prevalence of overlap syndrome among consecutive patients with OSA has been reported to be between 10% and 15%.[12,14,15] The prevalence of COPD in patients with OSA, however, is similar to its prevalence in the general population.[16] Patients with the overlap syndrome have an obstructive pattern on spirometry and, in comparison with patients with simple OSA, are more likely to have hypoxemia, hypercapnia, and pulmonary hypertension.[14,15,17] Hypercapnia develops in patients with the overlap syndrome at a lower BMI and AHI than that of patients with OHS without obstructive defects seen on spirometry and at a higher FEV_1 than hypercapnic patients with pure COPD. The breathing pattern and hypercapnic ventilatory response in these patients is, however, similar to those in patients with OHS.[11,18]

Congenital central hypoventilation syndrome is a disorder of ventilatory control that typically presents in newborns and results (in 90% of the cases) from a polyalanine repeat expansion mutation in the *PHOX2B* gene.[19] Symptomatic and asymptomatic children have survived to adulthood without ventilatory support.[20] These patients are heterozygous for the mildest of the *PHOX2B* polyalanine expansion mutations.[21,22]

Clinical Presentation and Diagnosis

In general, patients with OHS are middle-aged with a 2:1 male-to-female ratio. These patients tend to be extremely obese and experience significant sleep-disordered breathing. On presentation, the patients usually report the classic symptoms of OSA such as fatigue, hypersomnolence, loud habitual snoring, nocturnal choking episodes, and morning headaches. In contrast to patients with simple OSA, dyspnea, lower extremity edema, and low oxygen saturation measured by pulse oximetry during wakefulness are common. A restrictive defect seen on pulmonary function tests is common and is due to obesity. If left untreated, pulmonary hypertension and cor pulmonale can develop in patients with OHS.[23] Table 2 summarizes the clinical features of 631 patients with OHS reported in the literature.[11–13,17,24–34]

Patients with OHS have an elevated serum bicarbonate level due to the metabolic compensation for the chronic respiratory acidosis.[12,13,28,35] Therefore, serum bicarbonate level is a reasonable test to screen for hypercapnia because it is readily available, physiologically sensible, and less invasive than an arterial puncture to measure blood gas levels. It was recently shown[13] that the serum bicarbonate level combined with the severity of OSA can be used as clinical predictors of OHS in patients with morbid obesity and OSA (Fig 1). Accordingly, arterial blood gas measurements should be obtained to confirm the presence and severity of daytime hypercapnia in patients with obesity and sleep-disordered breathing who have hypoxemia on pulse oximetry during wakefulness or elevated serum bicarbonate levels.[10,13] If hypercapnia is present, pulmonary function testing and chest imaging can be useful in excluding other causes of hypercapnia. Laboratory testing should also include thyroid function tests to exclude severe hypothyroidism and a CBC count to rule out second-

Table 1—*Definition of OHS*

Required Conditions	Description
Obesity	BMI $\geq$ 30 kg/m^2
Chronic hypoventilation	Awake daytime hypercapnia ($Paco_2 \geq 45$ mm Hg)
Sleep-disordered breathing	OSA (AHI $\geq$ 5 with or without sleep hypoventilation) present in 90% of cases; sleep hypoventilation (AHI < 5) present in 10% of cases
Exclusion of other causes of hypercapnia	Severe obstructive airways disease; severe interstitial lung disease; severe chest wall disorders (*eg*, kyphoscoliosis); severe hypothyroidism; neuromuscular disease; and congenital central hypoventilation syndrome