Overlooking Obesity Hypoventilation Syndrome: The Need for Obesity Hypoventilation Syndrome Staging and Risk Stratification

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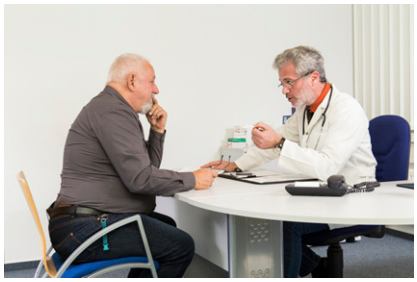
Numerous publications in recent years have documented that obesity affects one-quarter to one-third of the population not only in developed countries but also in developing ones. The increasing prevalence of obesity in children and adolescents and its impact on pulmonary function is a problem of today and, even more so, tomorrow (1). The obesity hypoventilation syndrome (OHS) is one piece of the puzzle describing the health impact of being overweight (2). Currently, large population-based studies of OHS relying on objective parameters of hypercapnia are missing; the actual prevalence of the disease is still unclear. However, data from specific groups, characterized by important risk factors, suggest prevalence rates of greater than 50%. These high rates may sensitize specialists and stimulate them to screen their patients, identify disease, and prevent serious complications. This is an important aspect of the study of Tran and colleagues (pp. 1279–1288) in this issue of *AnnalsATS* (3). The authors analyzed a large population of patients admitted for bariatric surgery to determine the prevalence of OHS, its predictors, and its associations with hypoxic load and metabolic derangements. They found that age, sex, hypoxia during sleep, and glucose metabolism may be important factors that could guide clinicians to stratify the risk of patients with obesity before administering potentially dangerous interventions. Importantly, they used the European Respiratory Society classification of OHS, which discriminates four stages from sleep hypoventilation up to complicated advanced stages of the disease.

OHS often remains undiagnosed in clinical practice, resulting in an incalculable impact on the outcomes of affected patients and downstream costs of care. Kreivi and colleagues recently analyzed treatment, comorbidities, and outcomes of their OHS patients over a 10-year period. Compared with patients with obstructive sleep apnea (OSA), patients with OHS presented with older age and higher body mass index (BMI) and were more often female. In addition, hypertension and diabetes were more prevalent in the OHS group. At 5 and 10 years follow-up, significantly more patients with OHS had died compared with patients with OSA, independent of anthropometric parameters (4).

One reason for the underdiagnosis of OHS is the lack of specific symptoms. Tran and colleagues underlined that standard history and questionnaires do not easily allow one to diagnosis or exclude OHS (3). Patro and colleagues retrospectively analyzed patients referred for polysomnography, examined the prevalence of OHS, and determined predictors of the disease. Almost 16% of the population met criteria for OHS. Predictors of the disease were nocturnal oxygen saturation as measured by pulse oximetry $<60\%$, forced vital capacity $<74.5\%$ predicted, and BMI >30.9 kg/m^2 (5).

Another reason the prevalence of OHS both in clinical practice and in the literature is underestimated is due to the specific requirements for its diagnosis in the current definition of the International Classification of Sleep Disorders (6). Diagnosing OHS requires a daytime elevation of carbon dioxide (CO_2) and does not allow for early diagnosis of the disease or its precursors (6). The European Respiratory Society (ERS) Task Force on Central Sleep Apnea focused on several pathophysiological and clinical components to determine earlier



stages of the disease (7). Before awake hypoventilation, indicated by daytime hypercapnia, latent impairment of ventilation manifests in specific situations of stress. These include exercise because of the increased metabolic activity and sleep because of the physiological reduction of minute ventilation in rapid eye movement and non–rapid eye movement sleep. The analyses of multiple blood gas samples or long-term transcutaneous CO_2 measurements during the night may show different patterns and allow for deeper insights into the spectrum of the disease. Patients may present with a rapid increase of CO_2 level after sleep onset without normalization throughout the night. Other individuals show intermittent periods of hypoventilation with or without normalization of the CO_2 level after awakening (7). In addition, bicarbonate levels during wakefulness reflect the CO_2 load during the night. The ERS Task Force proposed to use these parameters—hypercapnia during sleep, hypercapnia during wakefulness, and serum bicarbonate level—to differentiate the four stages of obesity-associated hypoventilation (7). Sivam and colleagues found that in a group of persons with severe obesity (BMI $>$ 40 kg/m^2), sleep hypoventilation (ERS stages I and II) was present in 19% of individuals, awake hypoventilation without comorbidities (III) in 17%, and awake hypoventilation with comorbidities (IV) in 3% (8). Predictors for

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sleep hypoventilation were awake oxygen saturation of ⩽93% and a partial pressure of CO_2 ⩾ 45 mm Hg measured in the supine position. Goyal and colleagues followed the ERS classification system to analyze the OHS prevalence in India (9). Though 5.9% of the population fulfilled OHS according to the *International Classification of Sleep Disorders–Third Edition* classification, 17.8% were diagnosed according to the ERS criteria. In patients with pure nocturnal hypoventilation, continuous positive airway pressure was sufficient to restore normal breathing in the majority of patients who presented with OSA without awake or asleep hypoventilation (ERS "at risk"), but it failed in the majority of patients with intermittent nocturnal (ERS stages I and II) or daytime hypoventilation (III, IV). Parameters of breathing disturbances, hypoxic load, and daytime sleepiness were continuously impaired with increasing ERS stages. This implies the continuum of the disease, the relevance of the earlier stages of OHS, and the need for treatment.

In their examination of presurgical bariatric patients, a group at high risk for OHS, Tran and colleagues confirmed the ability of the classification to not only identify OHS but also to correlate with apnea–hypopnea index, arterial oxygen saturation <90%, and BMI. This identifies on several important pathophysiological aspects of OHS.

- Severe obesity is associated with male sex and postmenopausal females through an increased mechanical load to the upper airways. This increases the work of breathing (10) and may impair ventilatory muscles.
- In addition, severe OSA is associated with a high hypoxic burden as confirmed by the increased time with arterial oxygen saturation <90%.
- The high BMI also elevates the metabolic rate, as shown by Javaheri and colleagues (11). Again, the data of Tran and colleagues on hemoglobin A1C and diabetes confirm the metabolic imbalance in patients with OHS versus those without OHS.

Unfortunately, these data do not answer another important pathophysiological question: Why do some patients develop hypoventilation disorders while others do not? Several studies suggest that hypercapnic ventilatory response, i.e., the increase of ventilation to a given level of hypercapnia, can discriminate patients with OHS from those with nonhypercapnic OSA (11). It is unknown whether the reduced hypercapnic ventilatory response is caused by a reduced sensitivity of the chemoreceptors, a blunted brain stem reaction, or an impairment of the executive muscles. However, the diminished response to hypercapnia suggests that the metabolic burden of obesity and its mechanical load on the upper airways are prerequisites of OHS, but hypercapnic ventilatory response is responsible for differences between patients with obesity with and without OHS.

Recent data suggest that continuous positive airway pressure reduces the mechanical load of the upper airways and reduces work of breathing, thus allowing for sufficient treatment of patients with severe obesity and OHS. If it fails, noninvasive ventilation is available to overcome hypoventilation (12–17). These options highlight a need for systematic screening of early stages of OHS, aiming to resolve symptoms and avoiding complications in our patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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