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SLEEP RELATED BREATHING DISORDERS (T LEE-CHIONG, SECTION EDITOR)

Obesity Hypoventilation Syndrome

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Abstract As the prevalence of obesity continues to rise, morbidity associated with obesity becomes more and more endemic. Of particular interest to pulmonary and sleep medicine physicians is the entity of obesity hypoventilation syndrome (OHS), formerly known as Pickwickian syndrome. Most patients with OHS also will be found to present with obstructive sleep apnea (OSA), which appears to play a major role in the pathogenesis of OHS. With or without OSA, the etiology of OHS may also be related to the extreme mechanical limitations imposed by obesity on the ventilatory apparatus. Treatment of OHS has been profoundly changed by the advent of non-invasive positive pressure therapies, including continuous positive airway pressure, bilevel positive airway pressure, and average volume-assured pressure support. Despite these advances, morbidity and mortality remain elevated in these individuals unless substantial weight loss can be achieved.

Keywords Obesity hypoventilation syndrome · Pickwickian syndrome · Obstructive sleep apnea · Control of breathing · Leptin · Pathogenesis of hypoventilation

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Introduction

Obesity-hypoventilation syndrome (OHS) is conventionally defined as hypercapnia during wakefulness in an individual with at least World Health Organization (WHO) Class I obesity [1] and in whom there is no alternate explanation for hypoventilation [2]. An awake arterial pCO_2 ($PaCO_2$) >45 Torr and body mass index (BMI) >30 kg/m^2 (in adults) establishes the suspicion for OHS; history, physical examination, and appropriate laboratory testing must exclude other reasons for hypercapnia such as obstructive airway disease, restrictive pulmonary or chest wall disorders (including neuromuscular disease affecting ventilatory function), licit or illicit use of respiratory depressant drugs, or congenital central hypoventilation syndrome. The "Pickwickian syndrome," a term coined by Burwell et al. in a case report that was published in 1956, is often used as a synonym for OHS [3]. However, it is not entirely clear whether that appellation, derived from the character "Joe the Fat Boy" described in Charles Dickens' novel "The Posthumous Papers of the Pickwick Club," is entirely appropriate considering more recent knowledge [4]. Competing diagnoses from which Joe might have suffered include obstructive sleep apnea (OSA) without OHS, OHS without OSA, Prader-Willi syndrome, Klein-Levin syndrome, or even narcolepsy. Moreover, the medical literature contains earlier reports that may well have described individuals with OHS that predate Dickens' description. For instance, in 1781, Fothergill reported two obese individuals complaining of somnolence whose symptoms remitted following substantial weight loss [5]. Had that case series received more widespread attention, I might now be writing a paper on "Fothergill syndrome."

The Oxford English Dictionary defines "syndrome" as "a concurrence of several symptoms in a disease; a set of such concurrent symptoms," making the point that there is not

necessarily a one-to-one correspondence between a group of symptoms and a single disease [6]. The heterogeneity of disorders associated with obesity, alveolar hypoventilation, and hypersomnia was recognized as early as 1972 in a paper by Douglas Carroll [7], and current thinking divides OHS into categories of OHS with OSA that remits after effective treatment of OSA, OHS with OSA that persists despite adequate treatment of OSA, and OHS without significant OSA [8]. The symptoms and signs of each of these OHS entities are not particularly different from those described by Fothergill and Dickens: excessive sleepiness and obesity, frequently accompanied by plethora (polycythemia) and *cor pulmonale* (Dickens referred to Joe as "young dropsy," dropsy being an archaic term for edema) [4]. To that may be added hypoventilation, as well as pulmonary hypertension without *cor pulmonale* and headache or nausea upon awakening (resulting from hypercapnia-induced cerebral vasodilation) [9].

Epidemiology

Although in the USA there are recent signs that obesity prevalence is climbing at a more modest rate than previously, the most current estimate remains high at about 35 % of the population aged ≥20 years [10]. Consequently, the medical consequences of obesity remain ubiquitous and that necessarily includes OHS. Not surprisingly, the difficulty in measuring arterial $PaCO_2$ in population surveys has precluded direct estimates of OHS prevalence. It appears that only Hashimoto et al. attempted this in a survey of a random sample of hospitals throughout Japan. Although it is unclear from the English abstract as to how the presence of OHS was established (even if I could have gotten the actual paper translated from the Japanese, an interlibrary loan request of participating institutions in the USA failed to obtain a copy), this report nonetheless estimated that 180 individuals had OHS nationwide, almost certainly far fewer than the actual number [11]. A variety of approaches have been taken to derive estimates less directly. One method arrives at an estimate by multiplying together the prevalence of obesity, prevalence of OSA in obesity, and prevalence of OHS in OSA using figures extracted from the literature. Using this method, Mokhlesi estimated the prevalence of OHS in the adult population with BMI ≥40 kg/m^2 to be in the range of 0.15 to 0.3 % [12]. The individual prevalence values used in his calculation were as follows: 3 % for the population prevalence of BMI ≥40 kg/m^2, 50 % for the prevalence of OSA in such a cohort, and 10–20 % for the prevalence of OHS in OSA patients with BMI ≥40 kg/m^2. The same group later published a revised calculation, using a higher prevalence of obesity (6 %) and consequently estimated OHS prevalence at 0.6 % in the BMI ≥40 kg/m^2 population [13]. There are obviously many uncertainties involved in such an estimate. While the prevalence of obesity in the USA is well-studied, the prevalence of OSA varies markedly by age and gender. For instance, Peppard et al recently updated OSA prevalence estimates from the well-regarded Wisconsin Sleep Cohort Study. They found that, for moderate to severe OSA with apnea-hypopnea index (AHI) ≥15/hour, prevalence values were as low as 0.18 % (for women aged <25 years with BMI between 30 and 49 kg/m^2) and as high as 56 % (for men aged ≥40 years with BMI 50–70 kg/m^2) [14]. Similarly, the prevalence of OHS varies considerably in patients with BMI >30 kg/m^2 plus OSA. Kaw et al. performed a systematic review and meta-analysis of 15 studies examining this relationship [15]. Six of the included studies were restricted to individuals with BMI >30 kg/m^2, all of whom had OSA and none with chronic obstructive pulmonary disease (COPD). The prevalence of OHS reported in these studies varied from a low of 15 % to a high of 50 %. Finally, the Mokhlesi calculation of OHS prevalence incorporated the non-standard value for BMI of ≥40 kg/m^2 rather than ≥30 kg/m^2 and, by definition, does not include individuals with OHS but without OSA. Ganesh et al. reported on a retrospective review of patients undergoing pulmonary function testing at an urban county hospital in Texas, although only an abstract was published [15]. Of 120 subjects with BMI ≥30 kg/m^2, 17.5 % met the criteria for OHS; presumably, this included both outpatients and inpatients. The highest prevalence was found in African-American women aged 51 to 60 years. Of note, there are previous reports confirming that OHS occurs more frequently in women than in men despite the higher male prevalence of OSA [12]. Perhaps of more value for the clinician are the predictors of OHS in the obese population. As well-demonstrated by Kaw et al., these include BMI, AHI, and forced vital capacity (FVC), with OHS prevalence increasing with the degree of obesity, severity of OSA, and degree of restrictive ventilatory impairment [16]. For clinicians practicing inpatient medicine, the findings from two studies are relevant. Nowbar et al. reported on patients undergoing pulmonary function testing at a large inner city hospital [17]. Out of 4332 admissions, 277 patients had BMI ≥35 kg/m^2; 127 were excluded due to comorbid lung disease, opioid treatment, or inability to consent and 75 declined participation. Of the remaining 150 subjects, 31 % had $PaCO_2$ ≥43 Torr and pH ≤7.42 and were identified as individuals with OHS. It is important to note two departures from the accepted criteria for OHS. First, the study was conducted in Denver, CO, at an altitude of 1400 m and the threshold value for $PaCO_2$ (≥43 Torr) was chosen to be >2 standard deviations (SD) above published mean reference values for $PaCO_2$ at that altitude [18]. Second, the pH criterion was justified as a means to eliminate patients with respiratory compensation for a primary metabolic alkalosis. A similar study from Turkey prospectively analyzed arterial blood gas (ABG) results from patients admitted to a tertiary care hospital [19]. Of 9480 samples, 3.4 % had $PaCO_2$ ≥45 Torr; after eliminating other

explanations for hypoventilation, 23 % of individuals with BMI >30 kg/m were identified as suffering from OHS, a similar finding to that of the Denver study. Another source of important information consists of data from bariatric surgery programs, as management of severe obesity is increasingly being relegated to operative procedures that require careful preoperative evaluation in order to anticipate possible complications. In this regard, Chau et al. reviewed the literature on the prevalence of OHS in various patient groups and reported a prevalence of 8 % overall (range 7–22 %) in retrospective reports of patients being evaluated for bariatric surgery [20]. However, other authors have reported much higher rates of OHS in these patients. For instance, Domínguez-Cherit et al. found that 49 % of patients evaluated for bariatric surgery had OHS, with a mean BMI of 50 kg/m^2 [21].

Pathogenesis: "Can't Breathe" vs. "Won't Breathe"

Respiratory System Mechanics

Obesity, particularly morbid obesity, is known to exert profound effects on the mechanical properties of the respiratory pump. Consequently, the earliest theories of OHS pathogenesis were centered on these impairments and the adaptations that might be required of the organism to coexist with them. Respiratory system compliance is reduced, although it is somewhat controversial as to whether this is due to actual changes in the lung and/or chest wall elasticity or at least partially due to a decline in functional residual capacity (FRC). This reduction in FRC is attributable to "mass loading" of the chest and (particularly) the abdomen due to the weight of adipose tissue; as a consequence, tidal breathing takes place on a flatter portion of the pressure vs. volume curve, which translates into reduced compliance [22, 23]. This effect may be somewhat more marked in the supine position, but is profound even when upright. [24, 25] Also, regardless of posture, the mass of adipose tissue represents an increase in respiratory system inertance [26], which can be significant: in normal subjects, inertial loading elicits a compensatory increase in ventilatory drive [27]. Increased resistance to airflow has also been documented [25, 28–30], which in the older literature was postulated as possibly due to tissue resistance rather than airways obstruction. However, more recent investigations have implicated changes in airway resistance due to several factors: decreased FRC necessarily is accompanied by reduced airway caliber [31], and obesity is known to increase the prevalence of non-allergic asthma [32] associated with narrowing of the distal airways [33]. Consequently, work of breathing increases [34–36], requiring a greater degree of ventilatory drive in order to maintain eucapnia [37–39]; moreover, any increase in ventilation comes at the expense of a greater degree of ventilatory drive than in normal weight individuals [40]. Whether there is an intrinsic abnormality in diaphragmatic contractility due to obesity that leads to OHS has been of considerable interest. Animal studies utilizing the obese Zucker rat model have suggested that the diaphragm undergoes remodeling and that force generation is impaired; however, in vitro fatigue resistance and fiber oxidative capacity are maintained [41]. Even in patients with overt OHS, the ability to voluntarily increase minute ventilation (and achieve eucapnia) is preserved as long as significant airways obstruction is not present [42]. Reduced inspiratory force generation, as measured by maximal transdiaphragmatic pressure ($P_{di}max$) or maximal inspiratory mouth pressure ($P_I$max) has been demonstrated in obese subjects at rest [43–45]. Impaired diaphragmatic reserve strength in various conditions can be inferred when tension-time index (TTI) is increased above that of normal individuals, the assumption being that when TTI impinges on the maximum TTI capability of the inspiratory muscles, fatigue will ensue [46, 47]. Such an increase in TTI in obese subjects has been demonstrated at rest [43], during obstructive apneas [44], and during incremental exercise [45]. However, to my knowledge, actual evidence of inspiratory muscle fatigue in patients with OHS has not been reported.

Gas Exchange

Obesity is known to affect several aspects of gas exchange that may further stress ventilatory capacity. In common with other causes of restrictive ventilatory impairment, obese individuals adopt a more rapid, shallow breathing pattern potentially increasing the dead space to tidal volume ratio (V_d/V_t), making each breath less efficient in terms of CO_2 clearance [48, 49]. Despite this, obese subjects do not have significantly elevated dead space ventilation under normal, resting conditions [50••, 51]. Interestingly, administration of oxygen has been found to increase dead space in several studies of patients with OHS and is associated with worsening hypercapnia [52•, 53]. In contrast to the literature on dead space, distribution of ventilation is adversely impacted by obesity, with reduced ventilation to dependent lung zones [54, 55, 56•]. The dominant mechanism for this appears to be the reduction in FRC attendant to obesity, which may decline to below closing capacity (CC) [57, 58]. Closing capacity represents the lung volume at which small airways in the dependent lung zones become compressed due to the effects of gravity. Part of each tidal breath then takes place below CC, impairing ventilation to areas of the lungs that remain perfused (effectively a shunt). This is manifested as hypoxemia and an increased alveolar-arterial pO_2 gradient ($P_{(A\text{-}a)}O_2$) [57, 58].

Unfortunately, the manner in which these changes in respiratory system mechanics and gas exchange might translate into the ventilatory failure of OHS remains obscure. Physiologists and clinicians dating back to the 1950s have sought to explain OHS as an adaptation to the excessive work of

breathing imposed by obesity, wherein ventilatory drive is moderated in such a way so as to accept higher levels of $PaCO_2$ in exchange for a lessening of work of breathing. This line of reasoning has been supported circumstantially by the finding that OHS patients generally exhibit greater degrees of restrictive ventilatory impairment than those of similar weight who are eucapnic [16, 50••]. However, these cross-sectional studies demonstrate association, not causality, and no actual mechanism for this has ever been demonstrated. Other theories held that diaphragmatic fatigue or dysfunction is etiologic, but as has been detailed above, evidence for these mechanisms is lacking as well. Consequently, much attention has devolved onto abnormalities in ventilatory control ("won't breathe) as the underlying basis for OHS in the majority of cases. As far back as 1983, Sampson and Grassino demonstrated depressed respiratory drive in response to hypercapnia in obese patients who had recovered from OHS compared to those who never experienced ventilatory failure; the latter group exhibited an augmented response compared to normals [39]. This finding raises the question as to whether patients with OHS have a pre-existing defect in ventilatory control that leads to overt OHS as they gain weight. However, there are no prospective studies available to bolster this contention and attempts to demonstrate the existence of inherited defects in ventilatory control by testing close relatives of OHS patients have not been supported the theory of an inherited control of breathing defect [59, 60].

OHS and OSA

In contrast to theories involving work of breathing, an association between OHS and what we now recognize as OSA was reported 50 years ago by Gastaut [61], and in Carroll's nosology of the Pickwickian syndrome, this entity was described as "Pickwickian syndrome, Gastaut's type." [7] The majority of OHS patients are found to also have OSA, with only a distinct minority exhibiting AHI of <5 [13], and treatment of OSA results in resolution of OHS in most individuals [62]. Thirty years of ensuing research by Berger, Ayappa, Sorkin, Norman, Rapoport, and Goldring built a case for the cumulative effect of impaired nocturnal CO_2 clearance as the mechanism for OHS pathogenesis in patients with OSA [63–68]. To summarize, inadequate compensatory ventilation between obstructive respiratory events leads to persistently high levels of $PaCO_2$ during any given night. As a result, renal reabsorption and generation of bicarbonate occurs during the night, and reversal of this process is too slow to be accomplished on the following day. The accumulation of CO_2 during each night results from the interplay between the length of each obstructive event compared to the inter-event interval, the magnitude of ventilation during the inter-event interval, a temporal mismatch between the timing of CO_2 presentation to the alveolar-capillary interface and alveolar ventilation, and the increase in CO_2 production known to occur in obesity [50••]. The higher steady-state level of serum bicarbonate that results acts to blunt respiratory drive (particularly that which is normally augmented in response to hypercapnia) and maintains awake hypoventilation. Of course, this still does not explain the existence of the small number of patients with OHS not associated with OSA or who do not attain eucapnia when any degree of OSA that might be present is effectively treated. Rapoport et al. have suggested that these individuals be designated as the "true Pickwickians," also described by Carroll way back in 1972 as "Pickwickian syndrome, Auchincloss's type." [7] The pathogenesis for this variety of OHS remains obscure.

There is one additional chapter currently being written in the search for the pathogenesis of OHS, involving the adipokine leptin. Leptin is synthesized in adipose tissue, and consequently, plasma levels reflect the degree of obesity in any given individual. In a rodent model, leptin exerts activity in the hypothalamus that inhibits appetite [69], and the fact that obese individuals tend to remain so suggests that human obesity is a leptin-resistant condition. Leptin has also been found to have respiratory stimulant properties [70], and patients with OHS have leptin levels even higher than in weight-matched eucapnic obese subjects [71]. Consequently, many have concluded that leptin resistance in breathing control centers may also be involved in OHS pathogenesis [72, 73].

Diagnosis

At its simplest, the diagnosis of OHS lies in a measurement of height and weight that calculates to a BMI >30 kg/m^2 plus an arterial blood gas determination yielding a $PaCO_2$ >45 Torr. However, it is also necessary to eliminate other possible causes of hypercapnia, which usually entails pulmonary function testing and chest radiography to exclude respiratory disorders that could contribute to ventilatory impairment. Since a restrictive ventilatory impairment is usually apparent, the possibilities of chest wall anatomical disorders (e.g., kyphoscoliosis and ankylosing spondylitis) and neuromuscular disorders (e.g., muscular dystrophies, myasthenia gravis, amyotrophic lateral sclerosis, and other congenital and acquired neuromuscular diseases) must be considered. The possibility of these disorders may prompt measurement of maximal inspiratory and expiratory mouth pressure ($P_i$max and $P_e$max) and electromyography/nerve conduction studies. If obstructive ventilatory impairment is found (e.g., from COPD), a judgment must ensue as to whether the degree of obstruction is sufficient to explain the presence of ventilatory insufficiency. Evidence should also be sought with respect to licit and illicit use of ventilatory depressant drugs, specifically opioids. In addition, due to the importance of OSA in the pathogenesis of most OHS, nocturnal

polysomnography (NPSG) is essential and if OSA is present, additional titration with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (bilevel PAP) is indicated (see below).

In lieu of arterial blood gas determination, some have advocated non-invasive measurement of $PaCO_2$ by means of end-tidal gas sampling [74•]. This might be contemplated when arterial blood gas determination cannot be accomplished, or perhaps as a screening tool; however, such a measurement must be interpreted with due consideration for its inherent inaccuracies, particularly in the presence of concomitant airways obstruction [75]. Generally speaking, assessment for hypoxemia in the awake patient using pulse oximetry has not been a popular approach due to the relative insensitivity of oxyhemoglobin saturation as a reflection of hypercapnia. However, Mandal et al. have combined awake pulse oximetry with measurement of FVC as a means to screen for OHS. In a group of patients with BMI >30 kg/m^2, no spirometric evidence of airways obstruction, and probable sleep disordered breathing on overnight oximetry, an FVC <3.5 L plus oxyhemoglobin saturation by pulse oximetry (SpO_2) <95 % in men and FVC <2.3 L plus SpO_2 <93 % in women, had fairly high sensitivity for identifying those with chronic ventilatory failure [76•]. Another approach consists of using serum bicarbonate values from samples of venous blood; not surprisingly, this parameter is almost always increased in patients with OHS [20, 50••, 77, 78]. Mokhlesi has suggested using serum bicarbonate as a screening test to eliminate the possibility of OHS, finding that values <27 mEq/L correctly identified 97 % of his sample of obese OSA subjects as not having OHS [77]. Conversely, serum bicarbonate values ≥27 mEq/L identified only 50 % of the subjects who had proven OHS, making this metric of little use as a positive predictor. Finally, in an attempt to identify obese patients at risk for OHS but who do not yet exhibit frank awake hypercapnia, Manuel et al. studied individuals with BMI >30 kg/m^2 who were eucapnic but whose measured base excess (BE) was on average about 3 mmol/L [79••]. This group was compared to obese eucapnic subjects with BE averaging about 0 mmol/L and obese hypercapnic subjects with mean BE of about 3.8 mmol/L. Interestingly, the eucapnic subjects with elevated BE exhibited hypoxic and hypercapnic responses that were more similar to the hypercapnic obese than to the eucapnic obese with normal BE. Consequently, the possibility exists that a group of obese patients could be identified before they transition to frank OHS, allowing for early intervention to prevent the progression of disease. Obviously, diuretic or corticosteroid therapy must be excluded before interpretation of an elevated bicarbonate level is attempted in the context of potential OHS.

Treatment

Positive Airway Pressure

The use of tracheotomy as a means to eliminate obstructive sleep disordered breathing and reverse OHS has been reported for more than 40 years, while the use of CPAP for this purpose emerged from a report by Sullivan et al. and the work of Rapoport and coworkers in the 1980s [62, 80]. Non-invasive application of positive airway pressure has since become the treatment of choice for patients with OHS with or without OSA, although the latter group usually requires bilevel PAP. This latter point was the conclusion reached in a study by Ojeda Castillejo et al., which compared outcomes for OHS patients with or without OSA (AHI >5/h) managed with bilevel PAP-S/T at home [81••]. Efficacy was demonstrated in terms of reduced 1- and 5-year mortality and improved spirometric variables, $PaCO_2$, and PaO_2, with similar results for those without, as well as with OSA. Much has been written in the recent past concerning the optimum choice of PAP modality for treatment of OHS. The various modalities that have been studied include CPAP, bilevel PAP in spontaneous mode (bilevel PAP-S), bilevel PAP in spontaneous/timed mode (bilevel PAP-S/T) with and without high backup rates, and average volume-assured pressure support (AVAPS). At the outset, it should be noted that several technologies are currently not recommended for treatment of OHS: auto-titrating CPAP, auto-titrating bilevel PAP, and adaptive servo-ventilation (ASV). The first two modalities are designed to eliminate obstructive apneas and hypopneas, but their titration algorithms do not guarantee an adequate degree of ventilation; the last modality targets the patient's own recent minute ventilation or peak inspiratory flow (depending on the manufacturer), both of which are presumed to be inadequate to begin with given the diagnosis of OHS. Piper recently reviewed the extant randomized controlled trials (RCTs) comparing various treatment modalities for OHS [82••]. Two studies incorporated comparisons of lifestyle modifications with PAP: one that included CPAP [83••] and one with bilevel PAP-S/T [84•]. Not surprisingly, both reported significant improvements in hypercapnia for treatment with PAP compared to the control groups. Three investigations incorporated treatment with CPAP vs. various bilevel PAP modalities: one using bilevel PAP-S [85], one using bilevel PAP-S/T [86], and one testing an AVAPS mode [83••]. Two studies indicated that there were modest advantages to the non-invasive ventilation modes, although improvements in hypercapnia were similar; one reported better subjective sleep quality [85] and one indicated that 6-min walk distance, health-related quality-of-life, and spirometric variables were better for those receiving ventilatory assistance [83••]. There are four reports incorporating both bilevel PAP-S/T and AVAPS, all of which failed to demonstrate much in the way of an advantage to using AVAPS

[83••, 87••, 88, 89], although two studies reported AVAPS producing lower values of transcutaneous pCO_2 during sleep [88, 89] and one indicated that sleep quality was better using bilevel-S/T [88]. One study is unique in comparing bilevel PAP-S/T at different backup rates with bilevel PAP-S; the latter mode resulted in a greater number of residual respiratory events (central and mixed) and more frequent oxyhemoglobin desaturation [90•]. One is left with the impression that, for most patients, CPAP will be sufficient over the long term; however, it is difficult to argue against implementing a bilevel PAP mode in patients with more severe degrees of hypercapnia or who are beginning treatment after an admission for an acute exacerbation of chronic ventilatory failure from OHS (the so-called critical care syndrome of "near-miss death" described by Fletcher [91] or the "malignant obesity hypoventilation syndrome" of Marik [92]. Clearly, the lesson from the study by Masa et al. is that overnight titration with the proposed mode of PAP is important in terms of demonstrating optimal resolution of respiratory events in patients with sleep disordered breathing [90•].

Weight Loss

Substantial weight loss has been the most obvious treatment for OHS, dating back to the earliest descriptions of the entity [5]. Unfortunately, these early descriptions also document that weight loss is not only difficult to achieve by diet and exercise, but also difficult to sustain [5]. More recently, bariatric surgery has come into vogue particularly since patients with OHS can be considered to have a life-threatening condition. Case series starting in the early 1980s have reported improvement or resolution of OHS concomitant with substantial weight loss no matter which particular bariatric procedure is utilized, including open procedures and, more recently, laparoscopic procedures such as gastric banding [93–97]. However, patients with OHS undergoing bariatric procedures do experience higher complication rates than those without OHS [97]. Complications of bariatric surgery include post-operative respiratory disorders including, notably, pulmonary embolus as well as wound dehiscence, wound infection, and incisional hernia [97–99]. In general, fewer complications are experienced with laparoscopic procedures [98]. Common sense would dictate that OHS should be adequately treated with a positive airway pressure modality prior to contemplating bariatric surgery.

Respiratory Stimulants

Medroxyprogesterone and the carbonic anhydrase inhibitor acetazolamide have both been suggested as possible treatments for OHS in view of their properties as stimulants of central ventilatory drive. While medroxyprogesterone may be useful in OHS patients without OSA or as an adjunct to treatment of OHS with OSA after effective treatment for the latter has been established, there are few data to support long-term use [100, 101]. Since the advent of positive pressure modalities, there has been little impetus to use this drug in OHS particularly in view of potential side effects such as thromboembolic disease. Acetazolamide has the potential to counter the elevated bicarbonate levels that, as previously discussed, represent an important mechanism leading to OHS in patients with OSA. One study in intubated OHS patients after an admission to intensive care for acute ventilatory failure demonstrated a reduction in bicarbonate and improved hypercapnic ventilatory response after receiving this drug [102]. As with medroxyprogesterone, acetazolamide may find some use in the short term for patients with OHS, but in view of the success of positive pressure treatment, there should be few situations in which it is indicated. Also, as with medroxyprogesterone, side effects (electrolyte disturbance, lightheadedness, and paresthesias) may well be experienced.

Outcomes

Untreated, OHS carries with it the danger of elevated morbidity and mortality in comparison to individuals with only OSA. In one study, mortality in OHS was about twice that of individuals with OSA mainly due to cardiovascular causes [103••]. A study examining the Danish National Patient Registry found that diabetes, hypertension, atrial fibrillation, congestive heart failure, and obstructive airways disease (COPD and asthma) were highly prevalent in the 3 years prior to a diagnosis of OHS [104•]. Obesity hypoventilation syndrome is a major cause of type 3 pulmonary hypertension, which may not fully resolve after positive airway pressure treatment [105]. Although after effective treatment patients with OHS still carry the elevated risk of morbidity and mortality associated with remaining obese, there does exist a significant improvement in many outcomes. As previously noted, a long-term study of outcome in patients with OHS and OSA treated with bilevel PAP-S/T demonstrated mortality rates at multiple endpoints extending as long as 10 years; 5- and 10-year mortality was 71.9 and 60.1 %, respectively [81••].

Conclusions

Obesity is ubiquitous in our population, and therefore OHS will remain a challenge for pulmonary and sleep medicine physicians who must maintain a high index of suspicion when candidates for this disorder present themselves. While identifying patients with possible OHS is straightforward and effective treatments are now available, a high degree of clinical acumen is required both to exclude other causes of hypoventilation and to foster compliance with treatment. Major advances have been made in elucidating the pathogenesis

of OHS when it is accompanied by OSA, but when OSA is not present the mechanisms leading to ventilatory failure remain obscure. Until a "cure" for obesity is developed, OHS will remain a challenge for clinicians and a fascinating subject for research in control of breathing, respiratory physiology, and the practice of respiratory care.

Compliance with Ethical Standards

Conflict of Interest Lee K. Brown serves on the Polysomnography Practice Advisory Committee of the New Mexico Medical Board and chairs the New Mexico Respiratory Care Advisory Board. He has served on a focus group for Koninklijke Philips N.V/Philips Respironics and is a consultant for Considine and Associates, Inc. He co-edits the Sleep and Respiratory Neurobiology section of Current Opinion in Pulmonary Medicine and authored an online chapter on treatment of sleep disordered breathing for UpToDate.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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