

Obesity Hypoventilation Syndrome: A State-of-the-Art Review

Babak Mokhlesi MD MSc

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Summary

Obesity hypoventilation syndrome (OHS) is defined as the triad of obesity, daytime hypoventilation, and sleep-disordered breathing in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation. During the last 3 decades the prevalence of extreme obesity has markedly increased in the United States and other countries. With such a global epidemic of obesity, the prevalence of OHS is bound to increase. Patients with OHS have a lower quality of life, with increased healthcare expenses, and are at higher risk of developing pulmonary hypertension and early mortality, compared to eucapnic patients with sleep-disordered breathing. OHS often remains undiagnosed until late in the course of the disease. Early recognition is important, as these patients have significant morbidity and mortality. Effective treatment can lead to significant improvement in patient outcomes, underscoring the importance of early diagnosis. This review will include disease definition and epidemiology, clinical characteristics of the syndrome, pathophysiology, and morbidity and mortality associated with it. Lastly, treatment modalities will be discussed in detail. Key words: obesity hypoventilation syndrome; Pickwickian syndrome; hypercapnia; hypoventilation; sleep apnea; sleep-disordered breathing; CPAP; bi-level PAP. [Respir Care 2010; 55(10):1347–1362. © 2010 Daedalus Enterprises]

Babak Mokhlesi MD MSc is affiliated with the Section of Pulmonary and Critical Care Medicine, the Sleep Disorders Center, and the Sleep Medicine Fellowship, University of Chicago Pritzker School of Medicine, Chicago, Illinois.

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Correspondence: Babak Mokhlesi MD MSc, Section of Pulmonary and Critical Care Medicine, University of Chicago Pritzker School of Medicine, 5841 S Maryland Avenue, MC 0999, Room L11B, Chicago IL 60637. E-mail: bmokhles@medicine.bsd.uchicago.edu.

Historical Perspective

The association between obesity and hypersomnolence has long been recognized. Of historical interest, OHS was described well before OSA was recognized as a true clinical entity in 1969.^{1,2} The first published report of the association between obesity and hypersomnolence may have been as early as 1889.³ In fact, in 1909 after losing approximately 90 pounds, President Howard Taft stated, "I have lost that tendency to sleepiness which made me think of the fat boy in *Pickwick*. My color is very much better and my ability to work is greater."⁴ But it was not until 1955 that Auchincloss described in detail a case of obesity and hypersomnolence paired with alveolar hypoventilation.⁵ One year later, Burwell described a similar patient who finally sought treatment after his symptoms caused him to fall asleep during a hand of poker, despite having been dealt a full house of aces over kings.⁶ Although other clinicians had made the comparison some 50 years earlier,³ Burwell popularized the term "Pickwickian syndrome" in his case report by noting the similarities between his patient and the boy Joe (Fig. 1), Mr Wardle's servant in Charles Dickens's *The Posthumous Papers of the Pickwick Club*.⁷ Since then our knowledge about the epidemiology, pathophysiology, treatment, and outcomes of OHS has improved significantly.

Definition

OHS is defined as daytime hypercapnia and hypoxemia ($P_{aCO_2} > 45$ mm Hg and $P_{aO_2} < 70$ mm Hg at sea level) in an obese patient (body mass index [BMI] ≥ 30 kg/m²) with sleep-disordered breathing in the absence of any other cause of hypoventilation.⁸ 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). Hypercapnia is very unlikely to develop in OSA patients with BMI below 30 kg/m² (Fig. 2). In 90% of patients with OHS, the sleep-disordered breathing is simply OSA. The remaining 10% have sleep hypoventilation, which is defined as an increase in P_{aCO_2} of > 10 mm Hg above that of wakefulness or significant oxygen desaturations, neither of which is the result of obstructive apneas or hypopneas. Therefore, in these patients non-obstructive hypoventilation characterized by an apnea-hypopnea index (AHI) < 5 per hour is noted to be present. There is no accurate way to know into which category a patient with OHS will fall without performing an overnight polysomnogram.

Epidemiology

In the United States, a third of the adult population is obese, and the prevalence of extreme obesity (BMI ≥ 40 kg/



Fig. 1. Joe the "Fat Boy," the character in Dickens's *The Posthumous Papers of the Pickwick Club*, from which the term "Pickwickian syndrome" was derived. (From Reference 7.)

m²) has increased dramatically. From 1986 to 2005 the prevalence of BMI ≥ 40 kg/m² has increased by 5-fold, from affecting 1 in every 200 adults to 1 in every 33 adults. Similarly, the prevalence of BMI ≥ 50 kg/m² has increased by 10-fold, from affecting 1 in every 2,000 adults to 1 in every 230 adults.⁹ The obesity epidemic is not only impacting adults in the United States, it is a global phenomenon affecting children and adolescents.¹⁰⁻¹³ With such a global epidemic of obesity the prevalence of OHS is likely to increase.

Numerous studies have reported a prevalence of OHS between 10–20% in obese patients with OSA (Table 2).¹⁴⁻²⁰ The prevalence of OHS is higher in the subgroup of patients with OSA with extreme obesity (Fig. 3). A recent meta-analysis of 4,250 patients with obesity and OSA—who did not have COPD—reported a 19% prevalence of hypercapnia.²¹ The prevalence of OHS among hospitalized adult patients with BMI > 35 kg/m² has been reported at 31%.²²

Although the prevalence of OHS tends to be higher in men, the male predominance is not as clear as in OSA. In fact, 3 studies had a higher proportion of women with OHS.²²⁻²⁴ Similarly, there is no clear racial or ethnic pre-

Table 1. Definition of Obesity Hypoventilation Syndrome

Required Conditions	Description
Obesity	Body mass index ≥ 30 kg/m ²
Chronic hypoventilation	Awake daytime hypercapnia (P _{aCO₂} ≥ 45 mm Hg and P _{aO₂} < 70 mm Hg)
Sleep-disordered breathing	Obstructive sleep apnea (apnea-hypopnea index ≥ 5 events/h, with or without sleep hypoventilation) present in 90% of cases
	Non-obstructive sleep hypoventilation (apnea-hypopnea index < 5 events/h) 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 Congenital central hypoventilation syndrome

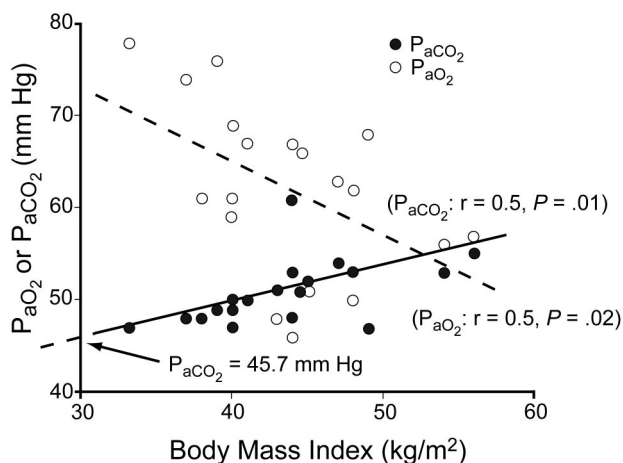


Fig. 2. Summary of 19 case series of patients with obesity hypoventilation syndrome, in which the authors reported the mean body mass index (BMI) and arterial blood gases. The mean P_{aCO₂} (in solid) and P_{aO₂} (in hollow) are plotted against the BMI. Although there were no patients with BMI below 30 kg/m² in these series, if the regression line for P_{aCO₂} is continued to a BMI of 30 kg/m² the P_{aCO₂} would be 45.7 mm Hg. Therefore, hypercapnia with OSA is unlikely to develop in patients with BMI < 30 kg/m².

dominance. However, due to higher prevalence of extreme obesity in African-Americans compared to other races, the prevalence of OHS might be higher in African Americans.^{25,26} Because of cephalometric differences, such as narrowing of the bony oropharynx and inferior displacement of the hyoid bone, OHS associated with OSA occurs at a lower BMI in Asians, compared to whites.^{19,27,28}

The prevalence of OHS in a community-based cohort is unknown, as it has not been studied, but its prevalence can be estimated among the general adult population in the United States. If approximately 3% of the general United States population has severe obesity (BMI ≥ 40 kg/m²)⁹ and half of patients with severe obesity have OSA,²⁹ and 10–20% of the severely obese patients with OSA have OHS, then a conservative estimated prevalence of OHS in the general adult population is anywhere between 0.15–0.3% (approximately 1 in 300 to 1 in 600 adults in the general population).³⁰ OHS may be more prevalent in the United States than in other nations because of its obesity epidemic.

Taken together, with such an epidemic of extreme obesity the prevalence of OHS is likely to increase and a high index of suspicion on the part of clinicians may lead to early recognition and treatment of this syndrome.

Clinical Presentation and Diagnosis

While most patients with OHS have had prior hospitalizations and have high healthcare resources utilization, the formal diagnosis of OHS is established late in the fifth or sixth decade of life. The 2 most common presentations are an acute-on-chronic exacerbation with acute respiratory acidosis leading to admission to an intensive care unit, or during a routine out-patient evaluation by a sleep specialist or a pulmonologist.^{16,22,31,32} Patients with OHS tend to be severely obese (defined as a BMI ≥ 40 kg/m²), have an AHI in the severe range, and are usually hypersomnolent. The vast majority of patients have the classic symptoms of OSA, including loud snoring, nocturnal choking episodes with witnessed apneas, excessive daytime sleepiness, and morning headaches. In contrast to eucapnic OSA, patients with stable OHS frequently complain of dyspnea and may have signs of cor pulmonale. Physical examination findings can include a plethoric obese patient with an enlarged neck circumference, crowded oropharynx, a prominent pulmonary component of the second heart sound on cardiac auscultation (this is often hard to hear, due to obesity), and lower extremity edema. Table 3 summarizes the clinical features of 757 patients with OHS reported in the literature.^{14-20,22,33-38}

Several laboratory findings are supportive of OHS, yet the definitive test for alveolar hypoventilation is an arterial blood gas performed on room air. Elevated serum bicarbonate level due to metabolic compensation of respiratory acidosis is common in patients with OHS and points toward the chronic nature of hypercapnia.^{22,35,39} Therefore, serum bicarbonate from venous blood could be used as a sensitive test to screen for chronic hypercapnia.²⁰ Figure 4 shows the prevalence of OHS in obese patients with OSA (BMI ≥ 30 kg/m² and AHI ≥ 5), using serum bicarbonate level combined with other readily available measures such

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Table 2. Prevalence of Obesity Hypoventilation Syndrome in Patients With Obstructive Sleep Apnea

First Author	N	Design	Country	Age* (mean)	BMI* (mean)	AHI* (mean)	OHS (%)
Verin ¹⁴	218	Retrospective	France	55	34	51	10
Laaban ¹⁵	1,141	Retrospective	France	56	34	55	11
Kessler ¹⁶	254	Prospective	France	54	33	76	13
Resta ¹⁷	219	Prospective	Italy	51	40	42	17
Golpe ¹⁸	175	Retrospective	Spain	ND	32	42	14
Akashiba ¹⁹	611	Retrospective	Japan	48	29	52	9
Mokhlesi ²⁰	359	Prospective	United States	48	43	62	20

* Age, body mass index (BMI), and apnea-hypopnea index (AHI) are mean values for all patients, calculated from the data provided by the authors in the article. ND = no data available. (Adapted from Reference 8.)

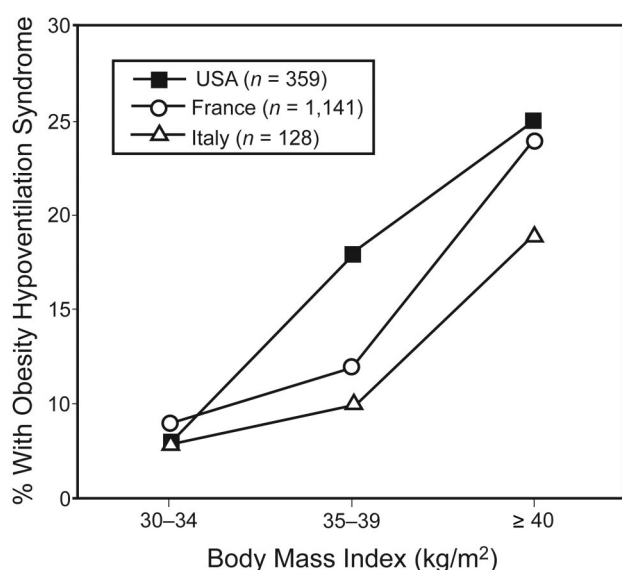


Fig. 3. Prevalence of obesity hypoventilation syndrome (OHS) in patients with obstructive sleep apnea (OSA), by categories of body mass index (BMI) in the United States,²⁰ France,¹⁵ and Italy. The data from Italy was provided by Professor Onofrio Resta from the University of Bari, Italy. In the study from the United States the mean BMI was 43 kg/m² and 60% of the subjects had a BMI above 40 kg/m². In contrast, the mean BMI in the French study was 34 kg/m² and 15% of the subjects had BMI above 40 kg/m². Consequently, OHS may be more prevalent in the United States, compared to other nations, because of its more exuberant obesity epidemic. (Adapted from Reference 8, with permission.)

as severity of obesity, and severity of OSA. 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 gases.

Additionally, hypoxemia during wakefulness is not common in patients with simple OSA. Therefore, abnormal arterial oxygen saturation detected via finger pulse oximetry (S_{pO₂}) during wakefulness should also lead clinicians to exclude OHS in patients with OSA.^{20,40} A useful tool

Table 3. Clinical Features of Patients With Obesity Hypoventilation Syndrome*

	Mean (range)
Age (y)	52 (42–61)
Male (%)	60 (49–90)
Body mass index (kg/m ²)	44 (35–56)
Neck circumference (cm)	46.5 (45–47)
pH	7.38 (7.34–7.40)
P _{aCO₂} (mm Hg)	53 (47–61)
P _{aO₂} (mm Hg)	56 (46–74)
Serum bicarbonate (mEq/L)	32 (31–33)
Hemoglobin (g/dL)	15 (ND)
Apnea-hypopnea index (events/h)	66 (20–100)
Oxygen nadir during sleep (%)	65 (59–76)
Percent time S _{pO₂} < 90%	50 (46–56)
FVC (% predicted)	68 (57–102)
FEV ₁ (% predicted)	64 (53–92)
FEV ₁ /FVC	0.77 (0.74–0.88)
Medical Research Council dyspnea class 3 or 4 (%)	69 (ND)
Epworth sleepiness scale score	14 (12–16)

* The studies included a total of 757 patients with obesity hypoventilation syndrome.^{14,20,22,24,33-38} ND = nonsufficient data available to calculate a range (Adapted from Reference 8.)

for a sleep physician interpreting the polysomnogram of a patient they have not seen in clinic may be the percent of total sleep time with S_{pO₂} spent below 90%.

In a recent meta-analysis, the mean difference of percent of total sleep time with S_{pO₂} spent below 90% was 37% (56% for hypercapnic OSA patients, 19% for eucapnic OSA patients), with very little overlap in the 95% confidence intervals (Table 4).²¹ In another study, Banerjee and colleagues prospectively compared sleep parameters in 23 patients with OHS (mean P_{aCO₂} 54 mm Hg) to 23 patients with eucapnic OSA, by performing overnight in-laboratory polysomnography.⁴¹ These 2 groups were

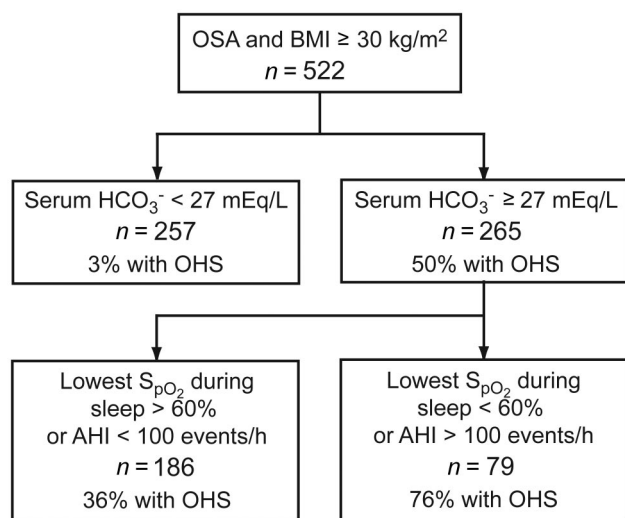


Fig. 4. Decision tree to screen for obesity hypoventilation syndrome (OHS) in 522 obese patients with obstructive sleep apnea (OSA) (body mass index [BMI] ≥ 30 kg/m² and apnea-hypopnea index (AHI) ≥ 5 events/h). Among those with a serum bicarbonate > 27 mEq/L, obesity hypoventilation syndrome (OHS) was present in 50% of the patients. Very severe OSA (AHI > 100 events/h or S_{pO_2} nadir during sleep less than 60%) increased the prevalence of OHS to 76%. (Data from Reference 20.)

matched for age (mean 45 y vs 43 y), BMI (58.7 kg/m² vs 59.9 kg/m²), AHI (49.6 events/h vs 39.4 events/h), and forced vital capacity (FVC) percentage of predicted (69% vs 74%). The only significant polysomnographic difference between these 2 well matched groups was the severity of nocturnal hypoxemia (Fig. 5).

If hypercapnia is present and confirmed with a measurement of arterial blood gases, pulmonary function testing and chest imaging should be performed to exclude other causes of hypercapnia. In patients with OHS, pulmonary function tests can be normal but typically reveal a mild to moderate restrictive defect due to body habitus, without significant evidence of airways obstruction (normal or near normal FEV₁/FVC). The expiratory reserve volume is significantly reduced in these patients with significant obesity. Patients with OHS may also have mild reductions in maximum expiratory and inspiratory pressures related to the combination of abnormal respiratory mechanics and relative weak respiratory muscles.⁴² In general, lung function is better preserved in OHS, compared to other chronic diseases in which patients develop hypercapnia (Fig. 6).⁴³ Other laboratory testing should include a complete blood count to rule out secondary erythrocytosis and severe hypothyroidism.

Morbidity and Mortality

The majority of patients with OHS are severely obese and have severe OSA.⁸ Severe obesity⁴⁴ and severe OSA

(defined as an AHI > 30 events/h),⁴⁵⁻⁴⁷ independent of hypercapnia, are known to negatively affect quality of life, morbidity, and mortality. OHS seems to present an additional burden on these patients above and beyond that of severe obesity and severe OSA.

Quality of Life

Hida et al matched patients with OHS to patients with eucapnic OSA by age, BMI, and lung function, and assessed quality of life with the Short Form-36 [36-item version of the Medical Outcomes Study Short-Form questionnaire].⁴⁸ There was no significant difference between the 2 groups, with the exception of social functioning, those with OHS being worse ($P < .01$). The authors hypothesized that this was because the patients with OHS were sleepier (Epworth sleepiness score 14.6 ± 4.9 vs 12.5 ± 4.6 , $P < .05$). Quality of life improved after 6 months of treatment with continuous positive airway pressure (CPAP) in both groups, but the authors did not examine whether the patients with OHS had a significantly greater improvement. Patients with OHS have a lower quality of life than those with other hypercapnic respiratory diseases, despite having a significantly lower P_{aCO_2} .⁴⁹ A confounding factor is that the patients with OHS were, predictably, more obese than those with other causes of hypercapnia.

Morbidity

It is also unclear whether patients with OHS experience higher morbidity than patients who are similarly obese and have OSA, as no studies have been performed to date. Berg et al performed a study where 26 patients with OHS were matched with patients of similar BMI, age, gender, and postal code (to control for socioeconomic factors).³⁶ The group with OHS was significantly more obese, although both groups were severely obese. The group with OHS was found to be more likely to carry a diagnosis of congestive heart failure (odds ratio 9, 95% CI 2.3-35), angina pectoris (odds ratio 9, 95% CI 1.4-57.1), and cor pulmonale (odds ratio 9, 95% CI 1.4-57.1). Pulmonary hypertension is more common (50% vs 15%) and more severe in patients with OHS than in patients with OSA.^{16,50-52} Patients with OHS were more likely to be hospitalized and more likely to be admitted to the intensive care unit. Rates of hospital admission decreased and were equivalent with the control group 2 years after treatment was instituted. In another prospective study, 47 patients with OHS had higher rates of admission to the intensive care unit (40% vs 6%) and need for invasive mechanical ventilation (6% vs 0%), when compared to 103 patients with similar degree of obesity but without hypoventilation.²²

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Table 4. Weighted Averages of Individual Determinants of Hypercapnia Between 788 Hypercapnic Obese Patients With OSA and 3,462 Eucapnic Obese Patients With OSA

	Weighted Mean (95% CI)		Mean Difference (95% CI)	P
	Hypercapnic	Eucapnic		
BMI (kg/m ²)	39 (34 to 44)	36 (31 to 41)	3 (2 to 4)	< .001
AHI (events/h)	64 (52 to 76)	51 (42 to 60)	12 (7 to 18)	< .001
FEV ₁ (% predicted)	71 (63 to 79)	82 (75 to 89)	-11 (-16 to 7)	< .001
FVC (% predicted)	85 (72 to 98)	93 (82 to 104)	-8 (11 to 5)	< .001
FEV ₁ /FVC	78 (74 to 83)	80 (77 to 84)	-2 (-5 to 1)	.02
Total lung capacity (% predicted)	77 (70 to 85)	84 (79 to 89)	-6 (10 to -3)	< .001
Percent total sleep time with S _{pO₂} < 90%	56 (42 to 70)	19 (-10 to 47)	37 (30 to 45)	< .001

OSA = obstructive sleep apnea
 BMI = body mass index
 AHI = apnea-hypopnea index
 FVC = forced vital capacity
 (Data from Reference 21.)

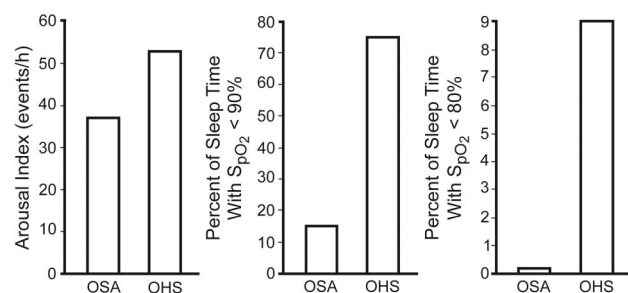


Fig. 5. Polysomnographic differences between patients with obesity hypoventilation syndrome (OHS) (*n* = 23) and patients with obstructive sleep apnea (OSA) (*n* = 23) matched for age, body mass index (BMI), apnea-hypopnea index, and lung function (forced vital capacity and FEV₁ percent of predicted). Patients with OHS have severe nocturnal hypoxemia and spend a significant percent of total sleep time with oxygen saturation (S_{pO₂}) below 90% and 80%. In fact, none of the patients with eucapnic OSA had a sustained oxygen saturation below 80%. Therefore, the severity of nocturnal hypoxemia is a useful tool for a sleep physician to suspect OHS when interpreting the polysomnogram of a patient for whom they have no other clinical background information. (Data from Reference 41.)

Mortality

Patients with untreated OHS have a significant risk of death. A retrospective study reported that 7 out of 15 patients with OHS (46%) who refused long-term noninvasive positive airway pressure (PAP) therapy died during an average 50-month follow-up period.³⁵ A prospective study by Nowbar et al followed a group of 47 severely obese patients after hospital discharge.²² The 18-month mortality rate for patients with untreated OHS was higher than the control cohort of 103 patients with obesity alone (23% vs 9%), despite the fact that the groups were well

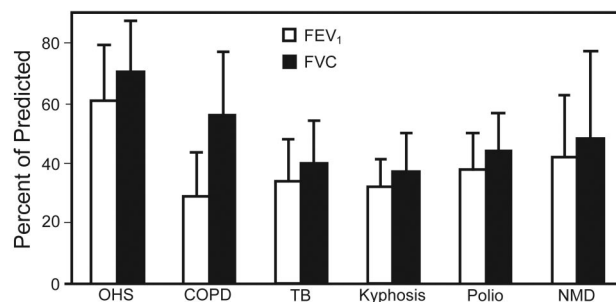


Fig. 6. Spirometric results from patients receiving chronic noninvasive ventilation at home for hypoventilation (*n* = 211). Lung function is better preserved in obesity hypoventilation syndrome (OHS), compared to other chronic diseases associated with hypercapnia. Data presented as mean and standard deviation. FVC = forced vital capacity. TB = post-tuberculosis. Kyphosis = kyphoscoliosis. NMD = neuromuscular disease. (Data from Reference 43.)

matched for BMI, age, and a number of comorbid conditions. When adjusted for age, sex, BMI, and renal function, the hazard ratio of death in the OHS group was 4.0 in the 18-month period. Only 13% of the 47 patients were treated for OHS after hospital discharge. The difference in survival was evident as early as 3 months after hospital discharge. Budweiser and colleagues conducted a retrospective analysis of 126 patients with OHS and found the 1, 2, and 5-year survival rates to be 97%, 92%, and 70%, respectively.³⁷

Together, these 2 studies suggest that adherence to PAP therapy may lower the short-term mortality of patients with OHS (Fig. 7).^{8,37} Accordingly, identifying patients with OHS in a timely manner is important. Treatment should be initiated without delay to avoid adverse outcomes such as readmission to the hospital, acute-on-chronic respiratory failure requiring intensive care monitoring, or

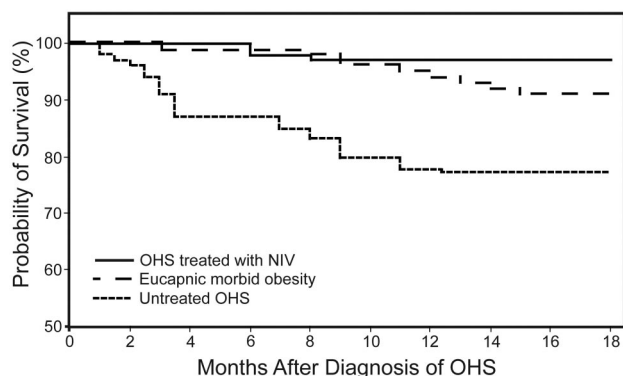


Fig. 7. Survival curves for patients with untreated obesity hypoventilation syndrome (OHS) ($n = 47$, mean age 55 ± 14 y, mean body mass index [BMI] 45 ± 9 kg/m², mean P_{aCO_2} 52 ± 7 mm Hg) and eucapnic morbidly obese patients ($n = 103$, mean age 53 ± 13 y, mean BMI 42 ± 8 kg/m²), as reported by Nowbar et al.,²² compared to patients with OHS treated with noninvasive ventilation (NIV) therapy ($n = 126$, mean age 55.6 ± 10.6 y, mean BMI 44.6 ± 7.8 kg/m², mean baseline P_{aCO_2} 55.5 ± 7.7 mm Hg, mean adherence to NIV of 6.5 ± 2.3 h/d). Data for OHS patients treated with NIV was provided courtesy of Dr Stephan Budweiser and colleagues from the University of Regensburg, Germany.³⁷ (Adapted from Reference 8, with permission.)

death. More importantly, adherence to therapy should be emphasized and monitored objectively.²⁴ It is also important to note that the data on morbidity and mortality are limited because they are driven by sleep-laboratory-derived cohorts, retrospective studies, and small sample sizes. Larger studies with community cohorts are needed to confirm these findings.

Pathophysiology

The P_{aCO_2} is determined by the balance between CO_2 production and elimination (minute ventilation and the fraction of dead-space ventilation). The hypercapnia in OHS is entirely due to hypoventilation, as short-term treatment with PAP improves hypercapnia without any significant changes in body weight, CO_2 production, or the volume of dead space.³⁹ However, the exact mechanisms that lead to hypoventilation in obese individuals are complex and probably multifactorial (Fig. 8). There have been a variety of physiologic differences between patients with OHS and those with obesity and/or OSA described to date: increased upper-airway resistance;⁵³ an excessive mechanical load imposed on the respiratory system by excess weight, ventilation-perfusion mismatching secondary to pulmonary edema,⁵⁴ or low lung volumes/atelectasis;⁵⁵ an impaired central response to hypoxemia and hypercapnia; the presence of sleep-disordered breathing; and impaired neuro-hormonal responses (leptin resistance). Although these are undoubtedly present, the most convincing evidence for the pathogenesis lies behind the universal presence of sleep-

disordered breathing and a blunted central response to hypercapnia and hypoxia. Recently, Norman and colleagues proposed a mathematical model that combines sleep-disordered breathing, central respiratory drive, and renal buffering to explain the development of this condition.⁵⁶

The Excessive Load on the Respiratory System

Upper-Airway Obstruction. Patient with OHS have a higher upper-airway resistance both in the sitting and supine position, when compared to patients with eucapnic OSA with similar degrees of obesity and control subjects.⁵³ However, it remains unclear if an increased upper-airway resistance plays a role in the development of daytime hypercapnia in this subset of patients.

Respiratory System Mechanics. In OHS there is an increase in the work of breathing in order to move the excess weight on the thoracic wall and abdomen during breathing.⁵⁷ However, it is unclear what contribution, if any, these altered mechanics have in the pathogenesis of OHS. The lung compliance of OHS patients is less than an equally obese control group (0.122 L/cm H₂O vs 0.157 L/cm H₂O). This can be explained by the lower functional residual capacity of the OHS group (1.71 L vs 2.20 L). There is an even greater difference in chest-wall compliance between the 2 groups (OHS 0.079 L/cm H₂O vs obese controls 0.196 L/cm H₂O).⁵⁷ Patients with OHS also have a 3-fold increase in lung resistance that has been attributed to a low functional residual capacity.^{57,58} The changes in lung mechanics are frequently demonstrated on spirometry by a low FVC and FEV₁ and a normal FEV₁/FVC ratio. The spirometric abnormalities may be related to the combination of abnormal respiratory mechanics and weak respiratory muscles.^{17,34,59,60} The changes in respiratory system mechanics in subjects with OHS impose a significant load on the respiratory muscles and lead to a 3-fold increase in the work of breathing.⁵⁷ As a result, morbidly obese patients dedicate 15% of their oxygen consumption to the work of breathing compared to 3% in non-obese individuals.⁶¹

Respiratory Muscles. The maximal inspiratory and expiratory pressures are normal in eucapnic morbidly obese patients but are reduced in patients with OHS.⁶²⁻⁶⁴ Patients with mild OHS, however, might have normal inspiratory and expiratory pressures.⁶⁵ A more accurate assessment of the diaphragmatic strength by cervical magnetic stimulation has not been performed in patients with obesity hypoventilation.⁶⁶ The role of diaphragmatic weakness in the pathogenesis of this disorder remains uncertain because patients with OHS can generate similar transdiaphragmatic pressures at any level of diaphragmatic activation, compared to eucapnic obese subjects.⁶³

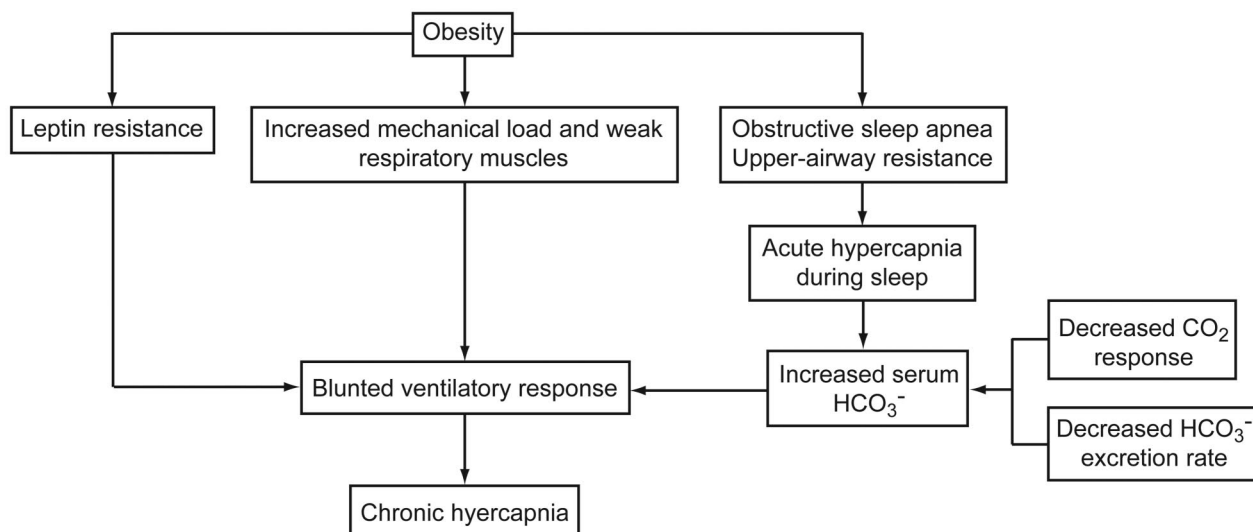


Fig. 8. Mechanisms by which obesity can lead to chronic daytime hypercapnia.

In a study by Sampson, patients with OHS were able to generate transdiaphragmatic pressure equivalent to that of eucapnic obese patients during hypercapnia-induced hyperventilation, suggesting that respiratory muscle weakness may not play a role in the development of OHS. In addition, the OHS group showed no evidence of acute diaphragmatic fatigue (or neuromuscular uncoupling) throughout the hypercapnic trial when measured by the ratio of peak electrical activity of the diaphragm to peak transdiaphragmatic pressure, which should theoretically eliminate the variable of inadequate patient cooperation.⁶³ Hypercapnia is also known to have deleterious effects on diaphragmatic function, so it will be difficult to determine whether respiratory muscle fatigue is a cause of or an effect of OHS.⁶⁷

Taken together, the data suggest that obesity imposes a significant load on the respiratory system in patients with OHS. Obesity is not, however, the only determinant of hypoventilation, since less than a third of morbidly obese individuals develop hypercapnia.^{15,20,59}

Blunted Central Respiratory Drive

Patients with OHS are able to voluntarily hyperventilate to eucapnia.⁶⁸ This is probably the simplest evidence for a defective central respiratory drive, although there is plenty of additional evidence. Patients with OHS do not hyperventilate to the same degree as morbidly obese patients when rebreathing CO₂.^{60,63,65} This deficit corrects in most patients after therapy with PAP.^{65,69,70} In patients with severe OSA but without hypercapnia, the hypercapnic ventilatory response does not change with PAP therapy.⁷⁰ In addition, patients with OHS do not augment their minute ventilation to the same degree as when forced to breathe a

hypoxic gas mixture.^{65,70,71} This blunted hypoxic drive also corrects with PAP therapy.^{65,70} The reversibility of the blunted central drive suggests that they are secondary effects of the syndrome (and necessary for its persistence), but not the origin of it.

There are a few hypotheses as to the origin of these defects. Obesity, genetic predisposition, sleep-disordered breathing, and leptin resistance have been proposed as mechanisms for the blunted response to hypercapnia. The weight load was suggested as a mechanism behind the blunted respiratory drive, because weight loss improves P_{aCO₂} level in patients with OHS. But this is unlikely to be related directly to weight, because, if anything, weight loss blunts the response of eucapnic morbidly obese subjects to hypercapnia.⁷² The blunted respiratory response to hypercapnia is also unlikely to be familial, because the ventilatory response to hypercapnia is similar between first-degree relatives of patients with OHS and control subjects.⁷³

Treatment of sleep-disordered breathing with PAP therapy might improve the response to hypercapnia.^{65,69,70} The airway-occlusion pressure 0.1 s after the start of inspiratory flow (P_{0,1}) response to hypercapnia improves as early as 2 weeks and reaches normal levels after 6 weeks of therapy with PAP in patients with mild OHS (P_{aCO₂} between 46–50 mm Hg). The response of minute ventilation to hypercapnia improves by the sixth week of therapy, but does not normalize.⁶⁵ These findings, however, are not universal.^{39,69,74}

Leptin. Leptin, a satiety hormone produced by adipocytes, stimulates ventilation.^{75–78} Obesity leads to an increase in the CO₂ production and load.⁷⁵ Therefore, with increasing obesity the excess adipose tissue leads to increasing levels of leptin in order to increase ventilation to

compensate for the additional CO₂ load. This is the reason as to why the vast majority of severely obese individuals do not develop hypercapnia. Patients with OHS and OSA have significantly higher leptin levels, compared to lean or BMI matched subjects without OSA. Although the independent contribution of OSA or OHS to leptin production remains unclear, the data suggest that excess adiposity is a much more significant contributor to elevated serum leptin levels than OSA or OHS.⁷⁹⁻⁸² Patients with OHS, however, have a higher serum leptin level than eucapnic subjects with OSA matched for percent body fat and AHI, and their serum leptin level drops after treatment with PAP.^{81,83,84} These observations suggest that patients with OHS might be resistant to leptin. For leptin to affect the respiratory center and increase minute ventilation it has to penetrate into the cerebrospinal fluid. The leptin cerebrospinal fluid-to-serum ratio is 4-fold higher in lean individuals, compared to obese subjects (0.045 ± 0.01 vs 0.011 ± 0.002 , $P < .05$).⁸⁵ Individual differences in leptin cerebrospinal fluid penetration may explain why some obese patients with severe OSA develop OHS and others do not.

Sleep-Disordered Breathing. Sleep-disordered breathing is considered necessary for the diagnosis of OHS and can take 2 forms. The first and by far the most common type is OSA, and the second is central hypoventilation. OSA is well established in the pathophysiology of OHS by the resolution of hypercapnia in most (but not all) patients by treatment with either tracheostomy or PAP therapy.^{23,24,33,35,65,86,87} Norman and colleagues have proposed an elegant mathematical model that explains the transition from acute hypercapnia during sleep-disordered breathing to chronic daytime hypercapnia.⁵⁶ In most patients with OSA, the hyperventilation after an apnea eliminates all CO₂ accumulated during the apnea.⁸⁸ But if the inter-apnea hyperventilation is inadequate or the ventilatory response to the accumulated CO₂ is blunted, it could lead to an increase in P_{aCO₂} during sleep (Fig. 9).⁸⁹ Even in this acute setting during sleep the kidneys can retain small amounts of bicarbonate to buffer the decrease in pH. If the time constant for the excretion of the small amount of accumulated bicarbonate is slow, then the patient will have a net gain of bicarbonate and will retain some CO₂ during wakefulness to compensate for the retained bicarbonate.⁵⁶ Therefore, the combination of a decreased response to CO₂ and a slow rate of bicarbonate excretion rate will lead to a blunted respiratory drive for the next sleep cycle.

Predictors of Hypercapnia in Obese Patients With OSA

Many studies have tried to find risk factors or predictors of hypercapnia (OHS) in cohorts of patients with OSA, but

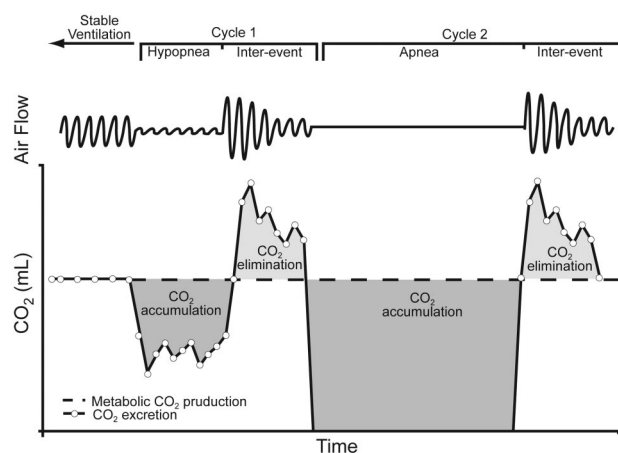


Fig. 9. Schematic demonstrating how CO₂ excretion is dependent upon inter-event hyperventilation. In the first cycle, the inter-event hyperventilation is sufficient to excrete the CO₂ accumulated during the hypopnea. In the second cycle, much more CO₂ is accumulated during the apnea than is excreted after the event. Repetitive cycles of inability to eliminate CO₂ accumulation during the apneic period leads to CO₂ retention and increase in P_{aCO₂} level. (Adapted from Reference 89, with permission.)

the results have been mixed.^{14-20,34,90} In a recent large meta-analysis from 15 studies of obese patients with OSA—but without COPD—Kaw et al were able to identify 3 significant predictors of chronic hypercapnia: severity of obesity, as measured by the BMI; severity of OSA, measured by either AHI or hypoxia during sleep; and degree of restrictive chest physiology. The mean AHI in the hypercapnic group was 64 events/h (95% CI 52–76 events/h) versus 51 events/h in the eucapnic group (95% CI 42–60 events/h, difference between groups $P < .001$).²¹ In 2 studies the authors found the prevalence of OHS in patients with an AHI > 60 events/h to be 25–30%.^{30,90} Likewise, Kaw found the mean BMI in the hypercapnic group to be 39 kg/m² (95% CI 34–44 kg/m²) versus 36 kg/m² (95% CI 31–41 kg/m², difference between groups $P < .001$) (see Table 4).²¹

Treatment

Although there are no established guidelines on treatment of OHS, treatment modalities are each based on different perspectives of the underlying pathophysiology of the condition: reversal of sleep-disordered-breathing, weight reduction, and pharmacotherapy.

Treatment of Sleep-Disordered Breathing

Positive Airway Pressure Therapy. PAP (in the form of CPAP therapy) was first described in the treatment of OHS in 1982.⁸⁶ Although subsequent studies confirmed its

efficacy, failure of CPAP in some cases has led to uncertainty whether CPAP should be attempted initially or if bi-level PAP therapy (more commonly known as noninvasive ventilation [NIV]) is a better modality.^{15,24,39,86,91} In a recent prospective study of ambulatory patients with severe OHS—based on the severity of obesity, OSA and the degree of hypercapnia—57% of patients were titrated successfully with CPAP alone, and the mean pressure required was 13.9 cm H₂O.⁴¹ The remaining 43% of patients with OHS failed CPAP titration because of persistent hypoxemia at therapeutic or near therapeutic pressures. In these patients the oxygen saturation remained below 90% for more than 20% of total sleep time. However, these patients who “failed CPAP” had a residual AHI of 25 events/h, which suggests that in some patients a therapeutic pressure was not achieved. Although both groups were extremely obese, the CPAP-failure group was more obese (mean \pm SEM BMI 61.6 \pm 1.7 kg/m² vs 56.5 \pm 1.2 kg/m², $P = .02$). Since this was a single-night titration study, the question of whether residual hypoxemia would resolve with long-term treatment was left unanswered.⁹²

A recent prospective randomized study performed by Piper et al⁹³ compared the long-term efficacy of bi-level PAP versus CPAP. In this study 45 consecutive patients with OHS underwent a full night of CPAP titration. Nine patients (20%) were excluded because of persistent hypoxemia—arbitrarily defined as 10 continuous minutes of $S_{pO_2} < 80\%$ without frank apneas—during the CPAP titration. The remaining 36 patients who had a successful CPAP titration night were subsequently randomized to either CPAP ($n = 18$) or bi-level PAP ($n = 18$). Those randomized to bi-level PAP underwent an additional titration night to establish the effective inspiratory and expiratory pressures. Supplemental oxygen administration was necessary in 3 patients in the CPAP group and 4 in the bi-level PAP group. After 3 months, there was no significant difference between the groups in adherence to PAP therapy or in improvement in daytime sleepiness, hypoxemia, or hypercapnia. This study confirms that the majority of patients with OHS (80%) can be successfully titrated with CPAP. These findings also suggest that, as long as OSA and nocturnal hypoxemia are effectively treated with CPAP, it makes no significant difference at 3 months if patients are given bi-level PAP or CPAP therapy. Therefore, bi-level PAP is not superior to CPAP a priori; rather, treatment should be individualized to each patient.

Bi-level PAP should be instituted if the patient is intolerant of higher CPAP pressure (> 15 cm H₂O) that may be required to resolve apneas and hypopneas or if hypoxemia is persistent despite adequate resolution of obstructive respiratory events during the titration study.⁹⁴ During bi-level PAP titration, the inspiratory PAP (IPAP) should be at least 8 to 10 cm H₂O above the expiratory PAP (EPAP)

in order to effectively increase ventilation.^{33,35,95,96} In the minority of patients with OHS who do not have OSA, EPAP can be set at 5 cm H₂O and IPAP can be titrated to improve ventilation.^{95,96} Bi-level PAP should also be considered if the P_{aCO_2} does not normalize after 3 months of therapy with CPAP.

Adherence to PAP Therapy. Adherence to PAP therapy, measured as average hours of daily use in the last 30 days, is directly correlated with improvement in daytime arterial blood gas values. In a retrospective study of 75 out-patients with stable OHS, the P_{aCO_2} decreased by 1.8 mm Hg and the P_{aO_2} increased by 3 mm Hg per hour of daily CPAP or bi-level PAP use during the last 30 days before a repeated measurement of arterial blood gases. Patients who used PAP therapy for > 4.5 h/d had a considerably greater improvement in blood gases than less adherent patients (ΔP_{aCO_2} 7.7 \pm 5 mm Hg vs 2.4 \pm 4 mm Hg, $P < .001$; ΔP_{aO_2} 9.2 \pm 11 mm Hg vs 1.8 \pm 9 mm Hg, $P < .001$). In addition, the need for daytime oxygen therapy decreased from 30% of patients to 6%.²⁴ There was no significant difference in improvement of hypercapnia and hypoxemia between patients on CPAP ($n = 48$) and patients on bi-level PAP therapy ($n = 27$). Improvement in blood gas values may be seen as early as one month after the institution of PAP therapy.^{24,65,97}

The impact of long-term NIV on vital capacity and lung volumes is contradictory. Several studies have reported no change in lung volumes or FVC after successful treatment of OHS with bi-level PAP.^{23,35,74} In contrast, 2 studies of patients with OHS reported significant improvements in vital capacity and expiratory reserve volume after 12 months of NIV, without any significant changes in BMI or in FEV₁/FVC ratio.^{96,98}

Lack of Improvement in Hypercapnia With PAP Therapy. The most common reason for persistent hypercapnia in patients with OHS is lack of adherence to PAP therapy. However, if there is documented evidence of adequate adherence by objective monitoring of PAP devices, other possibilities need to be entertained, such as inadequate PAP titration, CPAP failure, other causes of hypercapnia such as COPD, or metabolic alkalosis due to high doses of loop diuretics.

The improvement in chronic daytime hypercapnia in patients who are adherent to PAP therapy is neither universal nor complete. In 2 studies,^{24,93} the P_{aCO_2} did not improve significantly in approximately a quarter of patients who had undergone successful PAP titration in the laboratory and were highly adherent (> 6 h/night) to either CPAP or bi-level PAP therapy. In one study, 8 patients (23%) among the 34 patients who used PAP for at least 4.5 h/d, did not have a significant improvement in their P_{aCO_2} —decrease in P_{aCO_2} of less than 4 mm Hg. These

non-responders had lower AHI, compared to responders (44 ± 45 events/h vs 86 ± 47 events/h, $P = .03$). Mean adherence to PAP therapy was 7.2 ± 2.1 h/d for non-responders versus 6.0 ± 1.7 h/d for responders ($P = .1$).²⁴

This lack of response to PAP therapy, combined with reports of persistent hypoventilation after tracheostomy,³³ suggests that in a subset of patients with OHS, factors other than sleep-disordered breathing are the driving force behind the pathogenesis of hypoventilation. These patients will most likely need more aggressive nocturnal mechanical ventilation, with or without respiratory stimulants (see below).

Average Volume-Assured Pressure-Support Ventilation.

Average volume-assured pressure-support ventilation is a hybrid mode of pressure-support and volume-controlled ventilation that delivers a more consistent tidal volume with the comfort of pressure-support ventilation. Average volume-assured pressure-support ventilation ensures a preset tidal volume during bi-level-S/T mode, and the expiratory tidal volume is estimated based on pneumotachographic inspiratory and expiratory flows. The IPAP support is then titrated in steps of 1 cm H₂O/min in order to achieve the preset tidal volume. As a result, the IPAP is variable. The EPAP on the other hand is set between 4–8 cm H₂O and the respiratory backup rate can be set at 12–18 breaths/min with an inspiratory/expiratory ratio of 1:2. The role of a backup rate remains unclear, since patients with OHS are typically tachypneic during sleep, with respiratory rates ranging between 15–30 breaths/min. However, it is conceivable that during titration central apneas could develop with pressure-support ventilation, and in those instances a backup rate would be useful.⁹⁹ Although more costly than CPAP or bi-level PAP therapy, it has been shown effective in a randomized controlled study of OHS patients with milder degrees of hypercapnia.¹⁰⁰

Oxygen Therapy. In up to 50% of patients with OHS, oxygen therapy (in addition to PAP therapy) is necessary to keep $S_{pO_2} > 90\%$ in the absence of hypopneas and apneas.⁴¹ The need for nocturnal oxygen may abate with regular PAP usage. One retrospective cohort study found the need for daytime supplemental oxygen decreased from 30% to 6% in patients who were adherent to PAP therapy.²⁴ Therefore, patients should be reassessed for both diurnal and nocturnal oxygen requirements a few weeks to months after PAP therapy is instituted, since oxygen therapy is costly.

Phlebotomy. Phlebotomy has not been systematically studied in patients with OHS who develop secondary erythrocytosis. Secondary erythrocytosis is a physiological response to tissue hypoxia in order to enhance oxygen car-

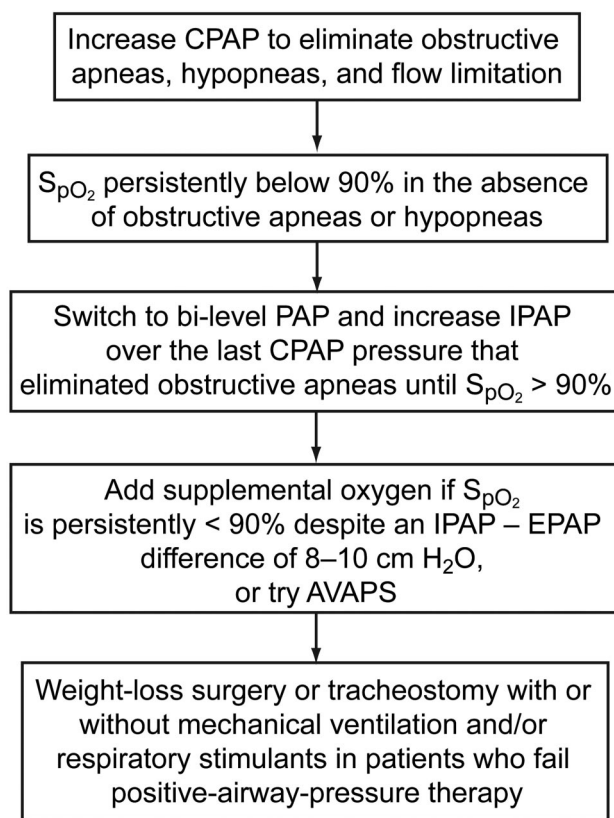


Fig. 10. Suggested therapeutic algorithm during continuous positive airway pressure (CPAP) titration in patients with obesity hypoventilation syndrome. IPAP = inspiratory positive airway pressure. EPAP = expiratory positive airway pressure. AVAPS = average volume-assured pressure-support ventilation.

rying capacity. However, hyperviscosity impairs oxygen delivery and can counteract the beneficial effects of erythrocytosis. In adult patients with congenital cyanotic heart disease, phlebotomy has been recommended if the hematocrit is above 65% only if symptoms of hyperviscosity are present.¹⁰¹ However, it is difficult to extrapolate this recommendation to patients with OHS, because many symptoms of hyperviscosity are similar to the symptoms of OHS. Reversing hypoventilation and hypoxemia with PAP therapy eventually improves secondary erythrocytosis, and phlebotomy is rarely needed in patients with OHS.⁹⁸

In-Laboratory PAP and Oxygen Titration. Figure 10 provides a therapeutic algorithm during polysomnography in order to address the variety of respiratory events observed in patients with OHS.³³ Even though auto-adjusting PAP technology can be used in patients with simple OSA to bypass laboratory-based titration studies, this technology cannot be recommended in patients with OHS, because it does not have the ability to recognize hypoventilation and hypoxemia. As a result, patients with OHS require a laboratory-based PAP and oxygen titration.

Taken together, the data suggest that CPAP is effective in the majority of patients with stable OHS, particularly in the subgroup that have severe OSA. Bi-level PAP should be strongly considered in patients who fail CPAP, patients with OHS who experience acute-on-chronic respiratory failure, and in patients who have OHS without OSA. Whether average volume-assured pressure-support ventilation has long-term benefits over bi-level PAP remains uncertain.

Treatment of OHS with PAP improves blood gases, morning headaches, excessive daytime sleepiness and vigilance, dyspnea, pulmonary hypertension, and leg edema.^{23,35,74} Improvement in symptoms and blood gases is directly related to adherence to therapy, and maximum improvement in blood gases can be achieved as early as 2 to 4 weeks. Therefore, early follow-up is imperative and should include repeat measurement of arterial blood gases and objective assessment of adherence to PAP, as patients frequently overestimate adherence.¹⁰²⁻¹⁰⁴ Changes in serum bicarbonate level and pulse oximetry could be used as a less invasive measure of ventilation if the patient is reluctant to undergo a repeated measurement of arterial blood gases. Discontinuing oxygen therapy when no longer indicated can decrease the cost of therapy in patients with OHS.

Surgical Interventions

Weight-Reduction Surgery. Bariatric surgery has variable long-term efficacy in treating OSA. One study of patients undergoing Roux-en-Y showed that those with severe OSA had a reduction in AHI of 80 events/h to 20 events/h an average of 11 months after surgery.¹⁰⁵ Although this drastic reduction in sleep-disordered breathing would probably be enough to normalize daytime blood gases, some of these patients still have moderate OSA and would benefit from continued PAP therapy. In another study, approximately half of the patients who had mild OSA after bariatric surgery had developed severe OSA 7 years postoperatively, despite no significant change in their weight.¹⁰⁶ A recently published meta-analysis that included 12 studies with 342 patients who underwent polysomnography before bariatric surgery and after maximum weight loss reported that there was a 71% reduction in the AHI, with a reduction from baseline of 55 events/h (95% CI 49–60 events/h) to 16 events/h (95% CI 13–19 events/h). Only 38% achieved cure, defined as AHI < 5 events/h. In contrast, 62% of patients had residual disease, with the mean residual AHI of 16 events/h. Many of these patients had persistent moderate OSA, defined as AHI ≥ 15 events/h.¹⁰⁷ It is also known that in the 6–8 years after weight-reduction surgery, patients experience 7% weight gain.¹⁰⁸ Therefore, patients with OHS who undergo bariatric sur-

gery should be monitored closely for recurrence of sleep-disordered breathing.

Only one study has examined the impact of bariatric surgery on OHS. Initially, blood gases improved. In 31 patients, preoperative P_{aO_2} increased from 53 mm Hg to 73 mm Hg one year after surgery, and P_{aCO_2} decreased from 53 mm Hg to 44 mm Hg. In the 12 patients from whom arterial blood gas measurements were available 5 years after surgery, values had worsened, with the mean P_{aO_2} dropping to 68 mm Hg and P_{aCO_2} increasing to 47 mm Hg.¹⁰⁹ In these 12 patients, BMI had hardly increased from 1 to 5 years postoperatively (38 kg/m² to 40 kg/m²). The worsening in daytime blood gases is probably from the redevelopment of sleep-disordered breathing.

Bariatric surgery is associated with significant risk. The perioperative mortality is between 0.5% and 1.5%. OSA and OHS may be associated with higher operative mortality.^{110,111} The independent risk factors associated with mortality are intestinal leak, pulmonary embolism, preoperative weight, and hypertension. Depending on the type of the surgery, intestinal leak occurs in 2–4% of patients and pulmonary embolism occurs in 1% of patients.¹¹¹ Ideally, patients with OHS should be treated with PAP therapy—or tracheostomy in cases of PAP failure—before undergoing surgical intervention, in order to decrease perioperative morbidity and mortality. Moreover, PAP therapy should be initiated immediately after extubation to avoid postoperative respiratory failure,¹¹²⁻¹¹⁴ particularly in that there is no evidence that PAP therapy initiated postoperatively leads to anastomotic disruption or leakage.^{113,115}

Tracheostomy. Tracheostomy was the first therapy described for the treatment of OHS.¹¹⁶ In a retrospective study of 13 patients with OHS, tracheostomy was associated with significant improvement in OSA. With the tracheostomy closed, the mean non-rapid-eye-movement (non-REM) AHI and REM AHI were 64 events/h and 46 events/h, respectively; with the tracheostomy open, the non-REM AHI and REM AHI decreased to 31 events/h and 39 events/h, respectively. In 7 patients the AHI remained above 20 events/h. These residual respiratory events were associated with persistent respiratory effort, suggesting that disordered breathing was caused by hypoventilation through an open tracheostomy, rather than central apneas. However, the overall improvement in the severity of sleep-disordered breathing after tracheostomy led to the resolution of hypercapnia in the majority of the patients.¹¹⁷ Today tracheostomy is generally reserved for patients who are intolerant of, or not adherent to, PAP therapy. It is also an option for that minority of patients who do not have a significant improvement in daytime blood gases despite adherence to PAP therapy, especially those patients who have signs or symptoms of cor pulmonale. Patients with

tracheostomy may require nocturnal ventilation, as it does not treat any central hypoventilation that may be present.¹¹⁸ A polysomnogram with the tracheostomy open is necessary to determine whether nocturnal ventilation is required.³³

Pharmacologic Respiratory Stimulation

Respiratory stimulants can theoretically increase respiratory drive and improve daytime hypercapnia, but the data are extremely limited.

Medroxyprogesterone. Medroxyprogesterone acts as a respiratory stimulant at the hypothalamic level.¹¹⁹ The results of treatment in patients with OHS have been contradictory. In a series of 10 men with OHS treated with high doses of oral medroxyprogesterone (60 mg/d) for one month, the P_{aCO_2} decreased from 51 mm Hg to 38 mm Hg and the P_{aO_2} increased from 49 mm Hg to 62 mm Hg.¹²⁰ All these patients were able to normalize their P_{aCO_2} with 1–2 min of voluntary hyperventilation, suggesting that there was no limitation to ventilation. Of note, polysomnographic data were not available for these 10 men with OHS, so it remains unclear whether they had concomitant OSA as well. In contrast, medroxyprogesterone did not improve P_{aCO_2} , minute ventilation, or ventilatory response to hypercapnia in 3 OHS patients who remained hypercapnic after tracheostomy.³⁹ Administration of a medication that may increase the risk of venous thromboembolism to a population whose mobility is limited may be unwise.^{121,122} In addition, high doses of medroxyprogesterone can lead to breakthrough uterine bleeding in women and to decreased libido and erectile dysfunction in men.

Most but not all patients with OHS can normalize their P_{aCO_2} with voluntary hyperventilation.⁶⁸ The inability to eliminate CO_2 with voluntary hyperventilation may be due to mechanical impairment. In one study, the ability to drop the P_{aCO_2} by at least 5 mm Hg with voluntary hyperventilation was the main predictor of a favorable response to medroxyprogesterone.¹²³ Therefore, a respiratory stimulant in patients who cannot normalize their P_{aCO_2} with voluntary hyperventilation—due to limited ventilation and/or mechanical impairment—can lead to an increase in dyspnea or even worsening of acidosis with acetazolamide.

Acetazolamide. Acetazolamide induces metabolic acidosis through carbonic anhydrase inhibition, which increases minute ventilation in normal subjects. There is only one published case report describing normalization of blood gases after tracheostomy,³⁹ although, interestingly, the agent reduces the AHI in patients with moderate to severe OSA.^{124,125}

In summary, the treatment options other than PAP are poorly studied. PAP therapy is the mainstay of treatment,

but the best approach for those who do not respond to this modality is unknown and may include a combination of PAP therapy and pharmacotherapy with respiratory stimulants or tracheostomy, with or without nocturnal ventilation.

Summary

With such a global epidemic of obesity, the prevalence of OHS is likely to increase. Despite the significant morbidity and mortality associated with the syndrome, it is often unrecognized and treatment is frequently delayed. A high index of suspicion can lead to early recognition of the syndrome and initiation of appropriate therapy. The treatment options other than PAP have been poorly studied, and further research is needed to better understand the long-term treatment outcomes of patients with OHS. For the time being, clinicians should encourage adherence to PAP therapy in order to prevent the serious adverse outcomes of untreated OHS. Weight-reduction surgery or tracheostomy, with or without pharmacotherapy with respiratory stimulants, should be considered in cases of PAP failure. Further research is needed to better understand the pathophysiology, discover newer PAP modalities, explore non-PAP treatment options, and improve long-term treatment outcomes of patients with OHS.

REFERENCES

1. Lugaresi E, Coccagna G, Tassinari CA, Ambrosetto C. [Particularités cliniques et polygraphiques du syndrome d'impairance des membres inférieurs]. *Rev Neurol* 1965;115:545. *Article in French.*
2. Gastaut H, Tassinari CA, Duron B. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. *Brain Res* 1966;1(2):167-186.
3. Lavie P. Who was the first to use the term Pickwickian in connection with sleepy patients? History of sleep apnoea syndrome. *Sleep Med Rev* 2008;12(1):5-17.
4. Sotos JG. Taft and Pickwick: sleep apnea in the White House. *Chest* 2003;124(3):1133-1142.
5. Auchincloss JH Jr, Cook E, Renzetti AD. Clinical and physiological aspects of a case of obesity, polycythemia and alveolar hypoventilation. *J Clin Invest* 1955;34(10):1537-1545.
6. Burwell CS, Robin ED, Whaley RD, Bickelmann AG. Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome. *Am J Med* 1956;21(5):811-818.
7. Dickens, C. The posthumous papers of the Pickwick club. Boston: Ticknor and Fields; 1867.
8. Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. *Proc Am Thorac Soc* 2008;5(2):218-225.
9. Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health* 2007;121(7):492-496.
10. Prentice A, Webb F. Obesity amidst poverty. *Int J Epidemiol* 2006; 35(1):24-30.
11. Skidmore PM, Yarnell JW. The obesity epidemic: prospects for prevention. *QJM* 2004;97(12):817-825.
12. Spritzer DA. Obesity epidemic migrates east. *CMAJ* 2004;171(10): 1159.

13. Miech RA, Kumanyika SK, Stettler N, Link BG, Phelan JC, Chang VW. Trends in the association of poverty with overweight among US adolescents, 1971-2004. *JAMA* 2006;295(20):2385-2393.
14. Verin E, Tardif C, Pasquis P. Prevalence of daytime hypercapnia or hypoxia in patients with OSAS and normal lung function. *Respir Med* 2001;95(8):693-696.
15. Laaban JP, Chailleux E. Daytime hypercapnia in adult patients with obstructive sleep apnea syndrome in France, before initiating nocturnal nasal continuous positive airway pressure therapy. *Chest* 2005;127(3):710-715.
16. Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest* 2001;120(2):369-376.
17. Resta O, Foschino Barbaro MP, Bonfitto P, Talamo S, Mastrosimone V, Stefano A, et al. Hypercapnia in obstructive sleep apnoea syndrome. *Neth J Med* 2000;56(6):215-222.
18. Golpe R, Jimenez A, Carpizo R. Diurnal hypercapnia in patients with obstructive sleep apnea syndrome. *Chest* 2002;122(3):1100-1101.
19. Akashiba T, Akahoshi T, Kawahara S, Uematsu A, Katsura K, Sakurai S, et al. Clinical characteristics of obesity-hypoventilation syndrome in Japan: a multi-center study. *Intern Med* 2006;45(20):1121-1125.
20. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. *Sleep Breath* 2007;11(2):117-124.
21. Kaw R, Hernandez AV, Walker E, Aboussouan L, Mokhlesi B. Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review and meta-analysis of cohort studies. *Chest* 2009;136(3):787-796.
22. Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004;116(1):1-7.
23. Masa JF, Celli BR, Riesco JA, Hernandez M, Sanchez De Cos J, Disdier C. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. *Chest* 2001;119(4):1102-1107.
24. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani A, Hassaballa HA, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. *J Clin Sleep Med* 2006;2(1):57-62.
25. Freedman DS, Khan LK, Serdula MK, Galuska DA, Dietz WH. Trends and correlates of class 3 obesity in the United States from 1990 through 2000. *JAMA* 2002;288(14):1758-1761.
26. McTigue K, Larson JC, Valoski A, Burke G, Kotchen J, Lewis CE, et al. Mortality and cardiac and vascular outcomes in extremely obese women. *JAMA* 2006;296(1):79-86.
27. Sakakibara H, Tong M, Matsushita K, Hirata M, Konishi Y, Suet-sugu S. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. *Eur Respir J* 1999;13(2):403-410.
28. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest* 2003;124(1):212-218.
29. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: a population-based perspective. *Expert Rev Respir Med* 2008;2(3):349-364.
30. Littleton SW, Mokhlesi B. The Pickwickian syndrome: obesity hypoventilation syndrome. *Clin Chest Med* 2009;30(3):467-478.
31. Lee WY, Mokhlesi B. Diagnosis and management of obesity hypoventilation syndrome in the ICU. *Crit Care Clin* 2008;24(3):533-549.
32. Quint JK, Ward L, Davison AG. Previously undiagnosed obesity hypoventilation syndrome. *Thorax* 2007;62(5):462-463.
33. Berger KI, Ayappa I, Chatr-Amontri B, Marfatia A, Sorkin IB, Rapoport DM, et al. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. *Chest* 2001;120(4):1231-1238.
34. Leech JA, Onal E, Baer P, Lopata M. Determinants of hypercapnia in occlusive sleep apnea syndrome. *Chest* 1987;92(5):807-813.
35. Perez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez Caruncho M, Caballero Muinelos O, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Chest* 2005;128(2):587-594.
36. Berg G, Delaive K, Manfreda J, Walld R, Kryger MH. The use of health-care resources in obesity-hypoventilation syndrome. *Chest* 2001;120(2):377-383.
37. Budweiser S, Riedl SG, Jorres RA, Heinemann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007;261(4):375-383.
38. Resta O, Foschino-Barbaro MP, Bonfitto P, Talamo S, Legari G, De Pergola G, et al. Prevalence and mechanisms of diurnal hypercapnia in a sample of morbidly obese subjects with obstructive sleep apnoea. *Respir Med* 2000;94(3):240-246.
39. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome: a reevaluation of the Pickwickian syndrome. *Chest* 1986;89(5):627-635.
40. Olson AL, Zwillich C. The obesity hypoventilation syndrome. *Am J Med* 2005;118(9):948-956.
41. Banerjee D, Yee BJ, Piper AJ, Zwillich CW, Grunstein RR. Obesity hypoventilation syndrome: hypoxemia during continuous positive airway pressure. *Chest* 2007;131(6):1678-1684.
42. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci* 2001;321(4):249-279.
43. Janssens JP, Derivaz S, Breitenstein E, De Muralt B, Fitting JW, Chevrolet JC, et al. Changing patterns in long-term noninvasive ventilation: a 7-year prospective study in the Geneva Lake area. *Chest* 2003;123(1):67-79.
44. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293(15):1861-1867.
45. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin Sleep Cohort. *Sleep* 2008;31(8):1071-1078.
46. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;6(8):e1000132.
47. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365(9464):1046-1053.
48. Hida W. Quality of life in obesity hypoventilation syndrome. *Sleep Breath* 2003;7(1):1-2.
49. Budweiser S, Hitzl AP, Jörres RA, Schmidbauer K, Heinemann F, Pfeifer M. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. *Respir Res* 2007;8:92.
50. Atwood CW Jr, McCrory D, Garcia JG, Abman SH, Ahearn GS. Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126(1 Suppl):72S-77S.

51. Kessler R, Chaouat A, Weitzenblum E, Oswald M, Ehrhart M, Apprill M, et al. Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. *Eur Respir J* 1996;9(4):787-794.
52. Sugeran HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg* 1988;207(5):604-613.
53. Lin CC, Wu KM, Chou CS, Liaw SF. Oral airway resistance during wakefulness in eucapnic and hypercapnic sleep apnea syndrome. *Respir Physiol Neurobiol* 2004;139(2):215-224.
54. Kaltman AJ, Goldring RM. Role of circulatory congestion in the cardiorespiratory failure of obesity. *Am J Med* 1976;60(5):645-653.
55. Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss and respiratory function. *J Appl Physiol* 2010;101(1):199-205.
56. Norman RG, Goldring RM, Clain JM, Oppenheimer BW, Charney AN, Rapoport DM, et al. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. *J Appl Physiol* 2006;100(5):1733-1741.
57. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. The total work of breathing in normal and obese men. *J Clin Invest* 1964;43:728-739.
58. Rubinstein I, Zamel N, DuBarry L, Hoffstein V. Airflow limitation in morbidly obese nonsmoking men. *Ann Intern Med* 1990;112(11):828-832.
59. Javaheri S, Colangelo G, Lacey W, Gartside PS. Chronic hypercapnia in obstructive sleep apnea-hypopnea syndrome. *Sleep* 1994;17(5):416-423.
60. Lopata M, Freilich RA, Onal E, Pearle J, Lourenco RV. Ventilatory control and the obesity hypoventilation syndrome. *Am Rev Respir Dis* 1979;119(2 Pt 2):165-168.
61. Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing ($VO_{2\text{RESP}}$) at rest. *Am J Respir Crit Care Med* 1999;160(3):883-886.
62. Kelly TM, Jensen RL, Elliott CG, Crapo RO. Maximum respiratory pressures in morbidly obese subjects. *Respiration* 1988;54(2):73-77.
63. Sampson MG, Grassino K. Neuromechanical properties in obese patients during carbon dioxide rebreathing. *Am J Med* 1983;75(1):81-90.
64. Becker HF, Piper AJ, Flynn WE, McNamara SG, Grunstein RR, Peter JH, et al. Breathing during sleep in patients with nocturnal desaturation. *Am J Respir Crit Care Med* 1999;159(1):112-118.
65. Han F, Chen E, Wei H, He Q, Ding D, Strohl KP. Treatment effects on carbon dioxide retention in patients with obstructive sleep apnea-hypopnea syndrome. *Chest* 2001;119(6):1814-1819.
66. American Thoracic Society, European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med* 2002;166(4):518-624.
67. Laffey J, Kavanagh B. Permissive hypercapnia. In: Tobin MJ, editor. *Principles and practice of mechanical ventilation*. New York: McGraw-Hill Professional; 2006:379.
68. Leech J, Onal E, Aronson R, Lopata M. Voluntary hyperventilation in obesity hypoventilation. *Chest* 1991;100(5):1334-1338.
69. Berthon-Jones M, Sullivan CE. Time course of change in ventilatory response to CO_2 with long-term CPAP therapy for obstructive sleep apnea. *Am Rev Respir Dis* 1987;135(1):144-147.
70. Lin CC. Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep apnoea syndrome. *Eur Respir J* 1994;7(11):2005-2010.
71. Zwillich CW, Sutton FD, Pierson DJ, Greagh EM, Weil JV. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. *Am J Med* 1975;59(3):343-348.
72. Emirgil C, Sobol BJ. The effects of weight reduction on pulmonary function and the sensitivity of the respiratory center in obesity. *Am Rev Respir Dis* 1973;108(4):831-842.
73. Jokic R, Zintel T, Sridhar G, Gallagher CG, Fitzpatrick MF. Ventilatory responses to hypercapnia and hypoxia in relatives of patients with the obesity hypoventilation syndrome. *Thorax* 2000;55(11):940-945.
74. Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P, Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. *Chest* 2007;131(1):148-155.
75. Kalra SP. Central leptin insufficiency syndrome: an interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions. *Peptides* 2008;29(1):127-138.
76. Tankersley C, Kleeberger S, Russ B, Schwartz A, Smith P. Modified control of breathing in genetically obese (ob/ob) mice. *J Appl Physiol* 1996;81(2):716-723.
77. Tankersley CG, O'Donnell C, Daoud MJ, Watchko JF, Mitzner W, Schwartz A, et al. Leptin attenuates respiratory complications associated with the obese phenotype. *J Appl Physiol* 1998;85(6):2261-2269.
78. Considine RV, Sinha MK, Heimann ML, Kriaucinas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334(5):292-295.
79. Ip MS, Lam KS, Ho C, Tsang KW, Lam W. Serum leptin and vascular risk factors in obstructive sleep apnea. *Chest* 2000;118(3):580-586.
80. Barcelo A, Barbe F, Llompert E, de la Pena M, Duran-Cantolla J, Lalaria A, et al. Neuropeptide Y and leptin in patients with obstructive sleep apnea syndrome: role of obesity. *Am J Respir Crit Care Med* 2005;171(2):183-187.
81. Shimura R, Tatsumi K, Nakamura A, Kasahara Y, Tanabe N, Takiguchi Y, et al. Fat accumulation, leptin, and hypercapnia in obstructive sleep apnea-hypopnea syndrome. *Chest* 2005;127(2):543-549.
82. Makinodan K, Yoshikawa M, Fukuoka A, Tamaki S, Koyama N, Yamauchi M, et al. Effect of serum leptin levels on hypercapnic ventilatory response in obstructive sleep apnea. *Respiration* 2008;75(3):257-264.
83. Phipps PR, Starritt E, Catterson I, Grunstein RR. Association of serum leptin with hypoventilation in human obesity. *Thorax* 2002;57(1):75-76.
84. Yee BJ, Cheung J, Phipps P, Banerjee D, Piper AJ, Grunstein RR. Treatment of obesity hypoventilation syndrome and serum leptin. *Respiration* 2006;73(2):209-212.
85. Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, et al. Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet* 1996;348(9021):159-161.
86. Rapoport DM, Sorkin B, Garay SM, Goldring RM. Reversal of the Pickwickian syndrome by long-term use of nocturnal nasal-airway pressure. *N Engl J Med* 1982;307(15):931-933.
87. Leech JA, Onal E, Lopata M. Nasal CPAP continues to improve sleep-disordered breathing and daytime oxygenation over long-term follow-up of occlusive sleep apnea syndrome. *Chest* 1992;102(6):1651-1655.
88. Ayappa I, Berger KI, Norman RG, Oppenheimer BW, Rapoport DM, Goldring RM. Hypercapnia and ventilatory periodicity in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2002;166(8):1112-1115.
89. Berger KI, Ayappa I, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. CO_2 homeostasis during periodic breathing in obstructive sleep apnea. *J Appl Physiol* 2000;88(1):257-264.

90. Kawata N, Tatsumi K, Terada J, Tada Y, Tanabe N, Takiguchi Y, et al. Daytime hypercapnia in obstructive sleep apnea syndrome. *Chest* 2007;132(6):1832-1838.
91. Schafer H, Ewig S, Hasper E, Luderitz B. Failure of CPAP therapy in obstructive sleep apnoea syndrome: predictive factors and treatment with bilevel-positive airway pressure. *Respir Med* 1998;92(2):208-215.
92. Mokhlesi B. Positive airway pressure titration in obesity hypoventilation syndrome: continuous positive airway pressure or bilevel positive airway pressure. *Chest* 2007;131(6):1624-1626.
93. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008;63(5):395-401.
94. Kushida CA, Chediak A, Berry RB, Brown LK, Gozal D, Iber C, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. *J Clin Sleep Med* 2008;4(2):157-171.
95. Redolfi S, Corda L, La Piana G, Spandrio S, Prometti P, Tantucci C. Long-term non-invasive ventilation increases chemosensitivity and leptin in obesity-hypoventilation syndrome. *Respir Med* 2007;101(6):1191-1195.
96. de Lucas-Ramos P, de Miguel-Diez J, Santacruz-Siminiani A, Gonzalez-Moro JM, Buendia-Garcia MJ, Izquierdo-Alonso JL. Benefits at 1 year of nocturnal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. *Respir Med* 2004;98(10):961-967.
97. Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. *Chest* 1994;105(2):434-440.
98. Heinemann F, Budweiser S, Dobroschke J, Pfeifer M. Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. *Respir Med* 2007;101(6):1229-1235.
99. Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. *Intensive Care Med* 2009;35(2):306-313.
100. Storre JH, Seuthe B, Fiechter R, Milioglou S, Dreher M, Sorichter S, et al. Average volume-assured pressure support in obesity hypoventilation: a randomized crossover trial. *Chest* 2006;130(3):815-821.
101. Thorne SA. Management of polycythaemia in adults with cyanotic congenital heart disease. *Heart* 1998;79(4):315-316.
102. Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. *Am J Respir Crit Care Med* 1994;149(1):149-154.
103. Rauscher H, Formanek D, Popp W, Zwick H. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. *Chest* 1993;103(6):1675-1680.
104. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147(4):887-895.
105. Haines KL, Nelson LG, Gonzalez R, Torrella T, Martin T, Kandil A, et al. Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea. *Surgery* 2007;141(3):354-358.
106. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. *Chest* 1994;106(6):1702-1704.
107. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *Am J Med* 2009;122(6):535-542.
108. Sjoström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351(26):2683-2693.
109. Sugeran HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr* 1992;55(2 Suppl):597S-601S.
110. Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361(5):445-454.
111. Fernandez AZ, Jr., Demaria EJ, Tichansky DS, Kellum JM, Wolfe LG, Meador J, et al. Multivariate analysis of risk factors for death following gastric bypass for treatment of morbid obesity. *Ann Surg* 2004;239(5):698-702.
112. Squadrone V, Coxa M, Cerutti E, Schellino MM, Biolino P, Occella P, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA* 2005;293(5):589-595.
113. Ebeo CT, Benotti PN, Byrd RP, Jr., Elmaghraby Z, Lui J. The effect of bi-level positive airway pressure on postoperative pulmonary function following gastric surgery for obesity. *Respir Med* 2002;96(9):672-676.
114. El-Sohl AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. *Eur Respir J* 2006;28(3):588-595.
115. Huerta S, DeShields S, Shpiner R, Li Z, Liu C, Sawicki M, et al. Safety and efficacy of postoperative continuous positive airway pressure to prevent pulmonary complications after Roux-en-Y gastric bypass. *J Gastrointest Surg* 2002;6(3):354-358.
116. Hensley MJ, Read DJ. Intermittent obstruction of the upper airway during sleep causing profound hypoxaemia. A neglected mechanism exacerbating chronic respiratory failure. *Aust N Z J Med* 1976;6(5):481-486.
117. Kim SH, Eisele DW, Smith PL, Schneider H, Schwartz AR. Evaluation of patients with sleep apnea after tracheotomy. *Arch Otolaryngol Head Neck Surg* 1998;124(9):996-1000.
118. Mokhlesi B, Tulaimat A. Recent advances in obesity hypoventilation syndrome. *Chest* 2007;132(4):1322-1336.
119. Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. *J Appl Physiol* 1992;73(2):393-404.
120. Sutton FD Jr, Zwillich CW, Creagh CE, Pierson DJ, Weil JV. Progesterone for outpatient treatment of Pickwickian syndrome. *Ann Intern Med* 1975;83(4):476-479.
121. Poulter NR, Chang CL, Farley TM, Meirik O. Risk of cardiovascular diseases associated with oral progestagen preparations with therapeutic indications. *Lancet* 1999;354(9190):1610.
122. Douketis JD, Julian JA, Kearon C, Anderson DR, Crowther MA, Bates SM, et al. Does the type of hormone replacement therapy influence the risk of deep vein thrombosis? A prospective case-control study. *J Thromb Haemost* 2005;3(5):943-948.
123. Skatrud JB, Dempsey JA, Bhansali P, Irvin C. Determinants of chronic carbon dioxide retention and its correction in humans. *J Clin Invest* 1980;65(4):813-821.
124. Tojima H, Kunitomo F, Kimura H, Tatsumi K, Kuriyama T, Honda Y. Effects of acetazolamide in patients with the sleep apnoea syndrome. *Thorax* 1988;43(2):113-119.
125. Whyte KF, Gould GA, Airlie MA, Shapiro CM, Douglas NJ. Role of protriptyline and acetazolamide in the sleep apnea/hypopnea syndrome. *Sleep* 1988;11(5):463-472.

Discussion

Kuna: What is the definition of OHS? Is it a clinical subset of OSA, or is it an entity unto itself? You said that there are people with OSA and hypercapnia, and when you treat them with CPAP and bring them back, their CO₂ retention is gone. Do those people have OHS?

Mokhlesi: I think the only way you can classify these patients is by doing an intervention, either a tracheostomy or PAP therapy, because many times we don't know in which category they fall when they present in the clinic. So the majority of patients with OHS have very severe OSA, and in approximately 75% when you successfully treat the OSA, the hypercapnia gets better. You can label them as one spectrum of disease: hypercapnic OSA.

But within that hypercapnic OSA patient (and I showed you data not only from our group but from the Australian group) 25% of them who have AHIs in the 40s and 50s still remain hypercapnic despite adequate adherence to therapy and adequate PAP titration. So there is a spectrum within OHS.

On one end there are patients with severe OSA and hypercapnia, and they are the vast majority of OHS patients. In that group, treatment of OSA with PAP therapy (CPAP or BPAP) can completely resolve daytime and nocturnal hypoventilation. Therefore, in this group OSA is the major contributor to hypoventilation because nocturnal CPAP therapy normalizes P_{aCO₂} without any substantial change in body mass index or fraction of dead-space ventilation.

Then there is the middle spectrum in which OSA is a contributor but perhaps not the main cause of hypoventilation. These are the patients who, despite adherence to PAP therapy, after a successful titration the hypercapnia improves minimally. One could hypothesize that in these PAP non-responders the cause of hypercapnia

is more complex and multifactorial and not solely related to OSA. In these patients decreased central chemore-sponsiveness may be the main cause of their hypercapnia, which does not improve after resolution of OSA, with either PAP therapy or tracheostomy. Luckily, they represent only 25% of the hypercapnic OSA patients.

The other end of the spectrum is the true hypoventilators, the classic Pickwickian, in which they really don't have any OSA. These are the patients in whom CPAP would be inappropriate and they need NIV with BPAP or other modalities. Since they do not have OSA, they typically need a very low EPAP, and ideally need a high IPAP to augment tidal volume and improve ventilation. In this subgroup tracheostomy does not change minute ventilation or the hypercapnic ventilatory response. They remain hypercapnic and they require nocturnal mechanical ventilation, either noninvasively or through a tracheostomy.

So there's a spectrum, and I'm lumping all 3 conditions of the spectrum into one large category of OHS. The only way to know in which category the patient falls is by performing a polysomnogram and PAP titration and assessing response to therapy in a few weeks.

Kuna: So can you diagnose OHS in an untreated patient with OSA?

Mokhlesi: You can certainly label an obese patient as OHS if they have untreated OSA and other causes of hypercapnia have been excluded. However, as I said, you won't know where on the OHS spectrum the patient falls: responder, partial responder, or non-responder to CPAP (a pure hypoventilator). There's no way to distinguish them ahead of time without an overnight polysomnogram, except for a small minority who really have no OSA on the sleep study, and that's less than 10% of all OHS: the pure hypoventilators. And these are not pa-

tients who have central apneas: if anything they're tachypneic.

The use of backup rate doesn't make sense, because in patients with OHS the respiratory rate during sleep doesn't typically go below 18 breaths per minute. Our patients' respiratory rates were closer to 25 to 30 breaths per minute while asleep, so a backup rate won't kick in. In the average volume-assured pressure-support mode a backup rate is a nice feature, but it never or rarely kicks in, and backup-rate capability or timed mode adds to the expense of the PAP device.

Kapur: I was interested in the data you presented from the study of CPAP responders who were randomized to CPAP or BPAP.¹ The conclusion was that there wasn't any difference between the two, but all the trends seemed to be in favor of the BPAP, including the Epworth Sleepiness Score and sleep quality. I'm wondering if they have a large enough sample size to really answer the question of which is the better therapy.

1. Piper AJ, Wang D, Yee BJ, Barnes DJ, Grunstein RR. Randomised trial of CPAP vs bi-level support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. *Thorax* 2008; 63(5):395-401.

Mokhlesi: That's a good point, because there were 18 patients in each group, so it was a small study. The primary outcome for which the study was powered was change in CO₂, and the degree of improvement expected was obtained from their prior studies. So the study was not powered to answer other outcomes, such as quality-of-life measures and Epworth Sleepiness Score. There was a statistically significant improvement in the Pittsburgh Sleep Quality Index questionnaire, but the difference in quality of life measured with the Short Form-36 [36-item version of the Medical Outcomes Study Short-Form questionnaire] was not statistically different. But you're right, it was not powered for the other outcomes, and even when

they put P_{aCO_2} as their primary outcome, the trend was in favor of BPAP.

Gay: I want to address some of these more difficult patients to ventilate with the failure of the CO_2 to fall. I've spent the last couple years trying to convince CMS [Centers for Medicare and Medicaid Services] to recognize that these are a different breed of patients, who need more sophisticated equipment, and I'm interested in how many times you've walked that road, trying to get more horsepower delivered to these people without tracheostomizing them, so that you can get a portable home ventilator?

Mokhlesi: Without tracheostomy I have not been successful. I have not been able to get patients on a more sophisticated ventilator at home through an NIV method. My limited experience with 5 to 10 patients has been that the insurance companies will not reimburse for these more sophisticated units without a tracheostomy.

Gay: That's the irony of this whole system right now, and our sponsors here are all very enthusiastic about these portable ventilators now, because en face, with a stroke of a pen, by calling it hypercapnic respiratory failure I can get a device. Getting a more sophisticated BPAP device requires jumping through many more hoops, so I'm very hopeful that soon there'll be some more sanity with this and better coverage for new technology. We'll have more opportunities to use this equipment that I think these people aren't getting because of these quirky certification necessities.

Malhotra: Do you know why with these newer devices the backup rate is not kicking in? I ask because some of these patients who have a CO_2 of 80 mm Hg and a bicarbonate of 40 mEq/L, and you start blowing them down, they get a very severe post-hypercapnic metabolic alkalosis. I don't know what their breathing looks like

at that stage; I don't know if they still have the high drive we're used to seeing in these patients.

Mokhlesi: I'm also concerned. You can override them if you give them a high enough backup respiratory rate. When you look at data not only from OHS but from any type of respiratory failure, patient-ventilator or patient-device dyssynchrony and asynchrony get more and more significant with ineffective breaths at higher IPAP; that is, the higher the IPAP, the higher the risk of dyssynchrony. So you could argue that with a very high IPAP or high backup respiratory rate you can override them, but you will have increased discomfort and dyssynchrony, and these can lead to increased frequency of ineffective breaths or sometimes even auto-triggering.

There's concern about alkalosis in patients with OHS. The German group had a large cohort of OHS and they looked at predictors of mortality in that group, one of which was alkalosis.¹ However, alkalosis at baseline, and not after NIV, was associated with higher mortality.

One could argue that aggressive ventilation at night with NIV does not necessarily increase mortality, but ultimately it's a tradeoff as well. Higher IPAP or a high backup rate to override the patients' respiratory rate could be more difficult to tolerate for some patients and can lead to reduced adherence or complete discontinuation of PAP therapy.

1. Budweiser S, Riedl SG, Jorres RA, Heine mann F, Pfeifer M. Mortality and prognostic factors in patients with obesity-hypoventilation syndrome undergoing noninvasive ventilation. *J Intern Med* 2007; 261(4):375-383.

Malhotra: I understand. It just makes me nervous if I get a blood gas in the middle of the night and see a pH more than 7.5. I don't know what their drive is like. Another question I have is based on some anecdotes and on a few of these patients during bronchoscopy. Some had airway occlusion,

which opened only when I blew air through the suction port. How much of the OHS pathogenesis is central versus airway?

Mokhlesi: I think the majority of them have an important upper-airway component, which we're typically able to resolve with PAP titration. But I've had a handful of patients whom I put in the lab and to my surprise the airway is open: they're just tachypneic and they're tidal volumes are shallow, but the upper airway is patent throughout the night: they just desaturate and their transcutaneous CO_2 goes up, but the airway is patent for the whole night in the supine position. And these are people with BMIs in the 50s. I think those are the true hypoventilators.

Malhotra: I think about different diseases or different phenotypes. They're different patients aren't they?

Mokhlesi: I think they are.

Pierson:* You've nicely illustrated that this is a disease with very high morbidity and increased mortality, and it's increasing in prevalence as our obesity epidemic continues. As you pointed out, most often it is first recognized when the patient presents in the ICU with acute-on-chronic respiratory failure; that's certainly been my experience at a hospital with a population similar to yours. Yet often these patients have not actually been out of the medical system. In many cases they've been followed by somebody and misdiagnosed as having COPD or CHF [congestive heart failure]. You'll see a fair number of them who've had echocardiograms that the problems are on the right side but who have continued to be managed as having CHF. It seems like this is an area in which

* David J Pierson MD FAARC, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Harborview Medical Center, University of Washington, Seattle, Washington.

there is a tremendous educational need for clinicians who are not sleep specialists, because they are the people who are following these patients and not recognizing what they have on their hands.

Mokhlesi: I agree.

Parthasarathy: Studies in the ICU of morbidly obese individuals found expiratory flow limitation, using negative-expiratory-pressure techniques. I'm just curious if the 25% are still retaining CO₂?

Mokhlesi: Yes. I hadn't considered that thus far.

Parthasarathy: The other anecdotal evidence, going along with what Atul [Malhotra] was pointing out, in terms of these people being hypercapnic and then you're giving them all this IPAP and ventilating them. Have you noticed that some of these people, when they flip over to the supine position, they start going into central apneas? You're ventilating them at a high level of BPAP, so it seems like there is a need for servo ventilation in these patients.

Malhotra: I agree.

Parthasarathy: We published a study in *Intensive Care Medicine* in which we found that the supine sleep deficiency seems to be correlated with central apneas.¹ Maybe it would be nice to do a comparison study.

1. Ambrogio C, Lowman X, Kuo M, Malo J, Prasad AR, Parthasarathy S. Sleep and non-invasive ventilation in patients with chronic respiratory insufficiency. *Intensive Care Med* 2009;35(2):306-313.

Kuna: What do you think is protecting the morbidly obese person who doesn't have hypercapnia from developing hypercapnia?

Mokhlesi: There are several things we can think about hypothetically. One is that their response to leptin is adequate. Leptin works at the hypothalamus and increases ventilation to meet the demand for that extra ventilatory load that they have because of severe obesity. In other words, they don't have leptin resistance.

Another possibility is to look not just at the BMI, but how the fat is distributed: if the fat is distributed such that it leads to restrictive physiology—the “apple” shape versus the “pear” shape, for example.

The other possibility would be whether they have OSA, because not all of these patients develop OSA, and even if they do develop OSA, then we get into the realm of that mathematical modeling that Norman and colleagues have proposed that tries to explain how the acute hypercapnia during obstructive respiratory events while asleep leads to chronic daytime hypercapnia.¹ But we have to remember that the mathematical model is just a model, and it hasn't been shown in humans. The model proposes that the patient with severe OSA who has a reduced response to CO₂ combined with a decreased bicarbonate excretion rate—the 2-hit phenomenon—is at higher risk of CO₂ retention.

But I think chronic hypercapnia in severely obese patients is multifactorial, we can't just blame it on one factor or another; that's why the pathophysiology of OHS is fascinating and is still not fully elucidated.

1. Norman RG, Goldring RM, Clain JM, Openheimer BW, Charney AN, Rapoport DM, et al. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. *J Appl Physiol* 2006;100(5):1733-1741.