Obesity Hypoventilation Syndrome in the Critically Ill

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INTRODUCTION

Obesity hypoventilation syndrome (OHS) is characterized as obesity and daytime hypoventilation in the absence of other causes of hypoventilation such as pulmonary disease, neuromuscular weakness, or chest wall disorders. A common presentation of OHS is in the critically ill patient who presents for acute on chronic hypercapnic respiratory failure. As the proportion of obese and morbidly obese individuals increases, intensive care unit (ICU) providers need heightened awareness of OHS and its complications, prognosis, and treatment modalities. An understanding of the how obesity affects pulmonary function and control of ventilation is needed. Continuous positive airway pressure (PAP) (continuous PAP and noninvasive ventilation including bilevel PAP and more advanced modes) can successfully treat respiratory failure. Weight loss is critical in the management of obesity hypoventilation syndrome. Obesity hypoventilation is associated with significant morbidity and mortality.

KEYWORDS

- Obesity hypoventilation syndrome
- Critically ill
- Hypercapnic respiratory failure
- Continuous positive airway pressure

KEY POINTS

- Obesity hypoventilation syndrome is a common but underrecognized cause of acute on chronic hypercapnic respiratory failure in the intensive care unit.
- The development of the obesity hypoventilation syndrome is multifactorial and is due to impairments in pulmonary function, ventilatory drive, sleep-disordered breathing, and hormonal regulation.
- Obesity, an awake Paco₂ greater than 45 mm Hg, and a serum bicarbonate level higher than 27 mEq/L are key diagnostic indicators of the disease.
- Positive airway pressure (PAP) (continuous PAP and noninvasive ventilation including bilevel PAP and more advanced modes) can successfully treat respiratory failure.
- Weight loss is critical in the management of obesity hypoventilation syndrome.
- Obesity hypoventilation is associated with significant morbidity and mortality.
airway pressure (CPAP), bilevel positive airway pressure (BPAP), and average volume-assured pressure support (AVAPS) are modes of noninvasive ventilation (NIV) used to manage respiratory failure in this population. Long-term strategies to address weight loss are important in the chronic management of the patient with OHS, and pharmacologic therapy plays a significant role in respiratory stimulation. OHS is associated with significant negative outcomes, particularly in the critically ill. This review serves to increase knowledge of the epidemiology, diagnosis, pathophysiology, treatment, and outcomes in patients with OHS.

**EPIDEMIOLOGY**

The exact prevalence of patients with OHS is unknown. Most studies examining the prevalence of OHS were conducted in sleep laboratories and clinics, estimating that 10% to 20% of patients with obstructive sleep apnea (OSA) have OHS.\(^1\) According to data from the National Health and Nutrition Examination Survey in 2009-2010, 35.7% of United States adults are obese, with rates of obesity climbing fastest among the aging and men.\(^2\) Rates of morbid obesity in the United States are increasing, with 5% of Americans having a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared, ie, kg/m\(^2\)) greater than 40.\(^3\) It can be assumed that rates of OHS will increase as the population of obese patients increases. An estimate of the prevalence of OHS in the general adult population of the United States is 1 in 300 to 1 in 600 adults.\(^4\) The prevalence of OHS in hospitalized patients, and particularly the critically ill, is less known. In single study of consecutive adult hospitalized patients with a BMI of 35 or higher, OHS was present in 31%.\(^5\) In the ICU, obese patients represent up to 50% of all patients,\(^6\) and 8% of ICU admissions met criteria for OHS in a study at a single center.\(^7\) However, the underdiagnosis and underreporting of OHS likely underestimates the true prevalence. Ethnic and geographic factors also affect OHS prevalence. For example, the prevalence of OHS was 2.3% among Japanese patients with OSA.\(^8\) However, in a study conducted at a tertiary health care facility in Turkey, 3.4% of patients who underwent arterial blood gas analysis had evidence of hypoventilation, and OHS accounted for 24% of these subjects.\(^9\)

**PATHOPHYSIOLOGY**

The progression from obesity to OHS is variable and multifactorial.\(^10,11\) The prevalence of OHS correlates with the degree of obesity, severity of sleep-disordered breathing, and restrictive mechanics on lung function tests.\(^12,14\)

**Lung Mechanics**

With obesity there is reduction in the functional residual capacity (FRC) and expiratory reserve volume (ERV).\(^15\) These lung volumes are further reduced with OHS.\(^16\) The fat distribution can affect lung volumes. A central pattern of obesity is seen with morbid obesity, with higher waist to hip ratio and larger neck circumference.\(^16\) The central adiposity has been shown to correlate with lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV\(_1\)) independent of the BMI.\(^17\)

Data from anesthetized morbidly obese patients undergoing surgery suggests they have high pleural pressures throughout the chest. There is reduction in respiratory system compliance, primarily from lung compliance rather than chest wall compliance.\(^18\) Compared with normal subjects, eucapnic obese individuals have a 20% lower respiratory system compliance, which drops further to almost 60% lower in OHS subjects\(^19\): high pleural pressures result in tidal breathing near their residual volume. Low lung volumes affect the respiratory mechanics unfavorably. At this point
the airways are more prone to closure and the lungs are less compliant. Resultant airway closure promotes air trapping and development of intrinsic positive end-expiratory pressure. A supine position compounds the adverse lung mechanics in these patients regarding FRC, compliance, and airflow limitation. Abdominal fat pushes against the diaphragm while supine, accounting for some of these changes. Overall the work of breathing is increased in OHS subjects and worsens while supine. Gas exchange is affected at low ERV and higher dead space, which occurs in obese subjects particularly in supine position. Of note, the higher waist to hip ratio, more so than the BMI, also correlates with reduction in partial pressure of oxygen (Pao₂) and alveolar-arterial oxygen difference. In addition, there is respiratory muscle fatigue in OHS in the face of increased work of breathing. The maximal voluntary ventilation is reduced in these subjects, and correlates with the level of hypercapnia. This inadequacy of compensatory mechanism is of unclear etiology, although overstretching of the diaphragm, thickening of the diaphragm, and chronic hypoxia with hypercapnia have been proposed as plausible mechanisms.

Sleep-Disordered Breathing

Most patients with OHS have OSA. However, approximately 10% of patients have sleep-related hypoventilation without OSA. The elevated apnea-hypopnea index (AHI) has been proposed as a mechanism for OHS development, but there are uncertainties with this hypothesis. In a meta-analysis the AHI was higher in patients with OSA who had hypercapnia when compared with eucapnic patients with OSA. However, the difference in AHI between the groups was only 12 events per hour. In a conflicting report, Sin and colleagues studied the modified hypercapnic ventilator response (cHCVR) in patients with and without OSA and did not find a correlation between the cHCVR and OSA, suggesting that sleep-disordered breathing did not lead to hypercapnia in patients with OSA. More recently, Macavei and colleagues did not find the AHI to be an independent predictor of OHS.

Nocturnal hypercapnia resulting from OSA seems to be related to daytime hypercapnia, particularly with prolonged apneic periods and reduced time between apneic episodes. This interval represents inadequate time for the minute ventilation to eliminate accumulated CO₂. The compensatory increase in serum bicarbonate must be unloaded during the nonsleep period to avoid blunting the effects on change in pH produced by change in partial pressure of CO₂ (PCO₂) on the brain chemoreceptors. Raurich and colleagues studied the CO₂ response in mechanically ventilated patients with OHS, and reported that patients with OHS with the highest serum bicarbonate had the most blunted CO₂ response. However, in patients who received acetazolamide, the serum bicarbonate was decreased and the CO₂ response improved. Sustained hypoxia during sleep-disordered breathing in these patients contributes to the pathogenesis of OHS. Mokhlesi and colleagues concluded from their meta-analysis that the time spent below 90% oxygen saturation at night was increased in subjects with OHS compared with eucapidacnic patients with OSA (56% vs 19%). This increase was reported to cause 24% variance in PCO₂ and more recently was also confirmed to be significant in causing daytime hypercapnia.

Ventilatory Drive

Obese subjects have been demonstrated to have higher oxygen consumption (VO₂) and carbon dioxide production (VCO₂) which, compared with nonobese subjects, result in a higher minute ventilation with a higher neural drive to breathe. Of note, the neural drive improves with weight loss in obese subjects. Unlike eucapnic obese patients, those with OHS are unable to increase their neural drive, permitting daytime
Patients with OHS have a blunted response to hypoxia and hypercapnia. Increased serum bicarbonate contributes to the blunted response, as already discussed. Increased suboptimal tidal volume adds to the inadequate ventilatory response. Furthermore, the ventilatory abnormalities in OHS are acquired and can be corrected over time with use of positive airway pressure (PAP) therapy, independent of weight loss.

Manuel and colleagues recently proposed an “early OHS” terminology based on their data whereby they identified a group of patients with obesity but without daytime hypercapnia who had elevated serum bicarbonate. Despite not having daytime hypercapnia, their hypoxic ventilatory response was similar to patients with OHS and significantly worse than normal obese individuals. The investigators speculate that these patients might develop OHS if there were further deterioration. Although this is a single-center study without a longitudinal follow-up, intriguingly it suggests that sustained hypoventilation rather than intermittent hypoxia might be more relevant.

Until recently it was unclear whether moderate supplemental oxygen would affect patients with OHS in the same way as patients with chronic obstructive pulmonary disease (COPD). Hollier and colleagues compared the responses of 14 patients with OHS with matched, nonobese healthy controls to exposure to fractions of inspired oxygen (FiO2) of 0.28 and 0.5. In patients with OHS, hyperoxia (breathing at FiO2 of 0.5) led to hypoventilation, increased dead space/tidal volume ratio (VD/VT), and a reduced pH. Of note, the VD/VT was reduced in both groups but the normal group was compensated by an increase in minute ventilation above baseline. In OHS patients there was a marked hypoventilation for first 5 to 10 minutes followed by a partial recovery of minute ventilation, which was insufficient to overcome the increase in VD/VT, which primarily arose from a reduction in tidal volume. An earlier study indicated a more marked increase in PCO2 and reduction in minute ventilation in patients with an OHS breathing FiO2 of 1, indicating significant hyperoxia-induced respiratory depression.

**Adipokines and Obesity Hypoventilation Syndrome**

Adiposity can contribute to the pathogenesis of OHS via metabolic derangements. Leptin and adiponectin are adipokines released by adipose tissue. Leptin stimulates respiration, and leptin deficiency leads to hypoventilation. Obese subjects demonstrate high leptin levels suggestive of resistance. Leptin levels have been shown to be 50% higher in OHS than in controls. Campo and colleagues reported that hyperleptinemia in obese subjects reduces respiratory drive and hypercapnic response independent of the percentage of body fat. Similarly, serum leptin was found to be more strongly associated with hypercapnia than the degree of adiposity. Hypoxia has been shown to stimulate leptin secretion, suggesting that increased leptin levels may be related to hypoventilation in OHS. In fact, treatment of OHS with NIV did reduce leptin levels in a small group of patients. The role of leptin in ventilatory control is still being elucidated. Adiponectin released by adipokines have an antiatherogenic effect, and the levels are reduced in obesity. Hypoxia stimulates hypoxia-inducible factor 1α, thereby increasing leptin and reducing adiponectin levels. Reduced adiponectin levels have been found in patients with OHS.

**CLINICAL PRESENTATION AND DIAGNOSIS**

The initial presentation of OHS in critically ill patients is acute on chronic hypercapnic respiratory failure. Such patients tend to be severely obese, have severe OSA, and are usually drowsy. Cor pulmonale, facial plethora, enlarged neck circumference, rapid
shallow respirations, a loud P2 on cardiac examination, and elevated jugular venous distention are findings on physical examination. If the patient has had a sleep study, the mean oxygen nadir during sleep is lower and time spent with oxygen saturation less than 90% is increased. In a study of patients with OHS the mean oxygen nadir was 65%, with a mean 50% of time with oxygen saturation less than 90%. Approximately 90% of patients with OHS have concomitant OSA while the remainder has evidence of nonobstructive sleep hypoventilation, demonstrated by an increase in sleep partial pressure of CO₂ in arterial blood (PaCO₂) or oxygen saturation 88% or less in the absence of obstructive events. Pulmonary function testing reveals a mild to moderate restrictive ventilatory defect and a severely reduced ERV without evidence of airflow obstruction. An awake arterial blood gas while on room air with a PaCO₂ greater than 45 mm Hg is needed to confirm daytime hypoventilation. Daytime hypoxemia during wakefulness should also lead clinicians to suspect OHS.¹ It is important to recognize that OHS is a diagnosis of exclusion and exists in the absence of other causes of hypoventilation such as pulmonary disease, neuromuscular weakness, or chest wall disorders. The alveolar-arterial (A-a) gradient is usually normal and can differentiate pulmonary parenchymal disease as the cause of hypoventilation; however, owing to ventilation and perfusion mismatch in the lung bases of obese patients, it is not uncommon to have a modest elevation in A-a gradient.⁶⁵ Serum bicarbonate can be used as a screening test, with levels less than 27 mEq/L having a 97% negative predictive value.¹ A serum bicarbonate level of 27 mmol/L and higher gives sensitivity of 76.6% and specificity of 74.6%. A nadir oxygen saturation level (SpO₂) less than 80% is also an independent predictor of the diagnosis of OHS with a sensitivity of 82.8% and specificity of 5.5%.⁶⁶ Secondary erythrocytosis may be found on complete blood count. In the ICU, transcutaneous PₐCO₂ and end-tidal PₐCO₂ may also be useful in monitoring.⁶⁷

Unfortunately OHS is often underdiagnosed, incorrectly diagnosed, and undertreated. Although Nowbar and colleagues⁵ reported the prevalence of OHS among hospitalized patients with BMI of at least 35 as 30%, only 23% of these patients actually received the diagnosis of OHS and only 13% were discharged with recommendations for long-term treatment such as noninvasive or invasive ventilation. Marik and Desai⁷ reported that of OHS patients admitted to the ICU, 75% had had multiple hospitalizations and had been diagnosed with asthma or COPD in the absence of supportive smoking history or pulmonary function testing. These findings indicate a lack of recognition and, hence, underdiagnosis of this disease. Marik and Desai⁷ coined the term “malignant obesity hypoventilation syndrome” to describe patients admitted to the ICU with hypercapnic respiratory failure and multisystem organ dysfunction related to obesity. A BMI greater than 40 and a PaCO₂ greater than 45 mm Hg with comorbid diseases of type 2 diabetes and metabolic syndrome were identified in all ICU patients, and 13% had a history of deep venous thrombosis.⁷ In addition, 86% of patients were treated with diuretics for congestive heart failure. Echocardiographic findings of left ventricular hypertrophy, left ventricular dysfunction, and pulmonary hypertension were reported in most patients.⁷ Eighteen percent of patients died during the index hospitalization, confirming the high mortality associated with the disease.⁷

**TREATMENT**

It is important to recognize that treatment of OHS in the critically ill patient should include acute management of respiratory failure but also consideration of long-term care strategies to deal with chronic respiratory failure, comorbid disease, and obesity. Management of acute respiratory failure includes invasive and noninvasive ventilatory
strategies. Ventilation via PAP, oxygen, or both will more than likely be needed at home to manage chronic respiratory failure. Because pathophysiology centers on the detrimental effects of obesity, weight loss is prudent. Bariatric surgery and pharmacologic management of hypoventilation have varied success regarding certain measures and outcomes. Each approach is examined separately.

**Positive Airway Pressure Therapy**

CPAP, BPAP, and AVAPS have each been examined in OHS patients. The initial choice of PAP therapy in the critically ill OHS patient should be chosen after careful review of the clinical history and physical examination. Critically ill OHS patients may have contraindications to the use of PAP via a nasal or oronasal interface, and should instead be intubated and receive mechanical ventilation. Reasons for invasive mechanical ventilation would include mental obtundation, hemodynamic instability, multiorgan failure, and severe acidosis. Additional important considerations in invasive airway management of critically ill obese patients include difficulty in intubation because of limited neck mobility and mouth opening in obese subjects, and rapid oxygen desaturation when obese patients assume the supine position owing to an additional decrease in the FRC and ERV. Successful intubation of the difficult airway in obese critically ill patients requires technical skill and familiarity with advanced techniques if needed.

At present there are no guidelines for pulmonary management of the critically ill OHS patient. Providers should keep in mind that much of the current knowledge of the effects of PAP on OHS were conducted in sleep laboratories in ambulatory patients and not in a critically ill population, nor exclusively in patients with OHS in the ICU. Gur- sel and colleagues reported that higher positive end-expiratory pressure (PEEP) levels and longer times are needed to reduce PCO2 in ICU obese patients in comparison with nonobese counterparts. There was no difference in the mode of NIV between obese and nonobese patients admitted to the ICU for acute hypercapnic respiratory failure; however, both pressure control and pressure support modes were used more frequently than AVAPS.71

**Continuous positive airway pressure**

As most patients with OHS have concomitant OSA, it seems reasonable to use CPAP in these patients. CPAP improves daytime hypercapnia, can prevent obstructive events, and can reduce the work of breathing and expiratory flow limitation. Reiterating that the effects of CPAP on OHS were conducted in sleep laboratories on ambulatory patients with OHS, providers should caution its use in critically ill OHS patients, as usually such patients present with acute hypercapnic respiratory failure, so a mode that promotes ventilation may be more suitable. Nevertheless it is important to address the effects of CPAP on OHS, particularly as management of this condition in the chronic setting is important. In a prospective study in severely obese patients with BMI of 50 or higher with OSA and with OSA and OHS matched for spirometry, BMI, and AHI, a single night of CPAP was able to effectively improve AHI and sleep measures in both groups. Higher CPAP pressures of 13.9 ± 3.1 cm H2O were needed in the OHS group; however, 43% of OHS patients still had evidence of hypoxemia, with greater than 20% of total sleep time with SpO2 less than 90% compared with 9% of those with OSA alone. Higher levels of BMI and more total sleep time with SpO2 less than 90% during the diagnostic polysomnogram was associated with this finding. In a randomized trial of CPAP or BPAP in OHS patients without severe nocturnal desaturation (defined as SpO2 <80% for >10 minutes or CO2 retention >10 mm Hg despite optimal CPAP), change in daytime PCO2, awake SpO2,
bicarbonate levels, and sleepiness were not different at 3 months in those who received CPAP or BPAP.\textsuperscript{72} Probably just as important as the mode of PAP therapy is adherence to treatment. Mokhlesi and colleagues\textsuperscript{74} reported that the use of CPAP or BPAP therapy for longer than 4.5 hours per day led to greater improvement in P\textsubscript{CO\textsubscript{2}} (7.7 vs 2.4 mm Hg) and P\textsubscript{O\textsubscript{2}} (9.2 vs 1.8 mm Hg) compared with less adherent use, with no between-group differences in CPAP or BPAP. In summary, then, CPAP can be used to treat OHS in most patients in the chronic setting. However, it must be emphasized that polysomnography with titration and follow-up is needed to determine which patients may require BPAP.

\textit{Bilevel positive airway pressure}

BPAP delivered through an oronasal mask or nasal mask (also known as NIV) allows providers to set an expiratory positive airway pressure (EPAP) to alleviate the upper airway obstruction, which is important in addressing the OSA component of OHS, but also to set inspiratory positive airway pressure (IPAP) above the EPAP level to improve alveolar ventilation in patients with OHS. BPAP effectively improves P\textsubscript{O\textsubscript{2}} and reduces P\textsubscript{CO\textsubscript{2}} and pH in patients with OHS whether treatment is initiated in the acute or the ambulatory setting,\textsuperscript{75} and improves the quality of life and ventilatory responsiveness to CO\textsubscript{2}.\textsuperscript{59,72,76} Although there is no universally accepted approach to titration of PAP in the sleep laboratory, a good rule of thumb is that the EPAP should be increased until there is resolution of obstructive events. Thus if the O\textsubscript{2} saturation remains persistently less than 90\%, the IPAP should be added above the EPAP level. The difference between the IPAP and EPAP values generally needs to be 8 to 10 cm H\textsubscript{2}O, and should be titrated to achieve oxygen saturation greater than 90\%. Oxygen may need to be added and titrated despite improvement in ventilation in some patients. Unfortunately, for most ICUs this type of strategy is not used owing to the absence of polysomnography.

Taken together, the use of a strategy and protocol for noninvasive management in other forms of acute hypercapnic respiratory failure, such as COPD, may be useful in acute hypercapnic respiratory failure caused by OHS. It is well known that NIV improves outcomes in COPD\textsuperscript{77}; however, the efficacy of this approach in acute hypercapnic respiratory failure caused by OHS remains unclear. In a prospective study of 716 consecutive patients with COPD and OHS admitted to an ICU,\textsuperscript{78} the investigators used a protocol of initiating BPAP with IPAP 12 cm H\textsubscript{2}O and increased pressure by 2 to 3 cm H\textsubscript{2}O as tolerated. Initial EPAP of 5 cm H\textsubscript{2}O was used, increasing by 1 to 2 cm H\textsubscript{2}O if needed to improve hypoxemia or comfort, with supplemental oxygen to achieve an oxygen saturation of 92\% or more or Pa\textsubscript{O\textsubscript{2}} greater than 65 mm Hg. Similar outcomes of avoidance of intubation in comparison with COPD patients were reported.\textsuperscript{78}

It is imperative that providers carefully monitor OHS patients who present with acute hypercapnic respiratory failure to determine response to NIV. Lemyze and colleagues\textsuperscript{79} aimed to identify the determinant of NIV success or failure in morbidly obese patients with severe acute respiratory decompensation of OHS, irrespective of the cause of acute respiratory failure, in a single ICU. In 76 consecutive patients with BMI greater than 40, factors associated with NIV failure were pneumonia, high Sequential Organ Failure Assessment Score, and high Simplified Acute Physiologic Score 2 at admission. Such patients were admitted with hypoxic respiratory failure, had early NIV failure, and a significant mortality of 92\% versus 17.5\%. Factors associated with successful response to NIV included high P\textsubscript{CO\textsubscript{2}} at admission. Although a delayed response to NIV (defined as inability to decrease P\textsubscript{CO\textsubscript{2}} by 15\% or raise pH to >7.3 in the first 2 hours) was observed in most patients, NIV was still successful.\textsuperscript{79}
BPAP with spontaneous and spontaneous timed modes are available. In the spontaneous mode, the patient triggers the BPAP whereas in the spontaneous timed mode, a backup rate is ordered whereby if the patient fails to trigger the BPAP, the device delivers a machine-triggered cycle. Both modes are effective in the management of OHS, although the spontaneous mode is associated with an increase in respiratory events owing to the development of central and mixed events without a difference in transcutaneous PCO2 between modes.80

Average volume-assured pressure support
AVAPS is a form of NIV that is adjunctive to BPAP, whereby tidal volume is set by the provider. In traditional bilevel pressure ventilation the tidal volume is pressure limited, in contrast to volume assurance by AVAPS. Although pressure-limited NIV has been shown to be better tolerated owing to its less varying peak inspiratory pressure, volume-assured NIV provides greater stability of the tidal volume.81 Three studies have examined the outcomes of AVAPS in OHS, all of which, notably, excluded critically ill patients. Storre and colleagues82 performed a randomized crossover trial in 10 patients with OHS (BMI >30 and Paco2 ≥45 mm Hg) for which CPAP failed to reduce the transcutaneous PCO2 level (PtccO2) to less than 45 mm Hg and reach a respiratory disturbance index of less than 10 events per hour. Sleep measures, health-related quality of life, the Severe Respiratory Insufficiency Questionnaire, and PtccO2 were measured and compared after 6 weeks of each modality. Although AVAPS led to significant improvements in PtccO2 compared with BPAP (−12.6 ± 12.2 vs −5.6 ± 11.8 mm Hg), this did not translate to improved clinical outcomes of sleep time, health-related quality of life, or severe respiratory insufficiency compared with BPAP. Perhaps this was due to variance in the peak inspiratory pressures leading to a higher respiratory disturbance index associated with AVAPS. In the second study, Murphy and colleagues83 compared AVAPS with fixed pressure support in a randomized controlled trial including 50 patients with OHS. Both modalities improved the primary outcome of daytime PaCO2 at 3 months compared with baseline, but there was no between-group difference between fixed pressure support and AVAPS in daytime Paco2 or health-related quality of life. Lastly, Janssens and colleagues84 reported decreased objective total sleep time and subjective reports of lighter sleep with more awakenings with AVAPS in comparison with BPAP in a study of 12 patients with stable OHS. AVAPS, however, did significantly improve PtccO2 when compared with BPAP. At present there is no defined role for the use of AVAPS in stable OHS, although it can be considered in certain cases. Further research that includes studies with larger numbers of subjects and the inclusion of hospitalized patients is needed.

Bariatric Surgery
Many patients with obesity turn to bariatric surgery to bring about weight loss. Large population studies support that weight loss is associated with an improvement in the severity and likelihood of sleep-disordered breathing. A weight loss of 10% reduces the AHI by 26%.85 In addition, weight loss can substantially improve outcomes in obese patients not only by reducing the severity of sleep-disordered breathing but also through improvement in respiratory mechanics, hypoxia, hypercapnia, and pulmonary function tests. Common types of bariatric surgical therapies include Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), laparoscopic sleeve gastrectomy, laparoscopic biliopancreatic diversion, and biliopancreatic diversion/duodenal switch, and achieve weight loss via malabsorption, restriction of food intake, and hormonal mechanisms. Bariatric surgery is considered for patients with a BMI of 40 or higher or 35 or higher for those with significant
comorbidities, including obesity hypoventilation. Whereas outcomes of bariatric weight-loss surgery are well known, its effects in strictly OHS patients are not. Nevertheless, in the largest prospective trial comparing bariatric surgery with controls, surgery led to a 23% reduction in the BMI compared with 0.1% in controls, with reductions in overall mortality and rates of obesity-related comorbidities. Although bariatric surgery resulted in resolution of OSA in 63% of patients, it is equally important to recognize that despite significant amounts of weight loss, patients may still have OSA of moderate severity owing to the fact that patients are still moderately obese 10 years after surgery. Furthermore, the greatest weight loss occurs within the first 2 years postoperatively, and some patients regain some of that weight. Hence, discontinuing the use of PAP devices without objective evidence of the resolution of sleep-disordered breathing is discouraged.

In addition to positive outcomes for sleep-disordered breathing, weight loss improves respiratory mechanics, blood gases, and pulmonary function tests. Pulmonary function improves in morbidly obese patients following laparoscopic RYGB and LAGB. FEV1 increased to 112% and FVC to 109% of baseline value after just 3 months postoperatively, although the number of subjects who met the criteria for OHS in this study is unknown. In addition, at 1 year SpO2 improved from 88.3% to 96.2% following laparoscopic bariatric surgery in 11 patients with morbid obesity and OHS.

Tracheostomy

Failure of an OHS patient to wean from mechanical ventilation or inability of NIV to achieve targeted clinical measures may necessitate the placement of tracheostomy. Following tracheostomy, OSA and daytime hypercarbia improve but may not completely resolve. Furthermore, tracheostomy in morbidly obese patients is more challenging because of anatomic factors. Of note, a trend toward higher 30-day mortality after tracheotomy in morbidly obese patients has been observed.

Pharmacologic Therapy

As OHS patients have high serum bicarbonate levels, in theory acetazolamide, a carbonic anhydrase inhibitor, should reduce serum bicarbonate levels, thus promoting increased ventilation and lowering of PCO2. In a study of 25 OHS patients receiving invasive mechanical ventilation in 2 ICUs, acetazolamide reduced serum bicarbonate levels by 8.4 ± 3.0 mmol/L alongside an increase in hypercapnic drive and ventilator response. In 9 patients with OSA, acetazolamide reduced the AHI from 25 to 18 events per hour, but was unable to completely normalize the AHI. The effect of medroxyprogesterone is mixed. Medroxyprogesterone did not reduce AHI in comparison with placebo in 10 patients with OSA. However, in 10 patients with OHS, its use was associated with reduction of PCO2 by 13 mm Hg. In a Cochrane Database review of drug therapy for OSA, the investigators concluded that there is currently insufficient evidence to recommend any systemic pharmacologic treatment for OSA, which is present in most patients with OHS.

OUTCOMES

Nowbar and colleagues described the outcomes of OHS patients in a comparison with obese patients hospitalized with acute illness. Patients with OHS were more likely to require hospital admission and mechanical ventilation, and showed a trend toward higher ICU admission. At 18 months they had higher mortality (18% vs 9%) than obese patients without hypercapnia. The adjusted relative risk of death in OHS was 4-fold higher than that for obese controls. Although there were no in-hospital deaths, most
of the deaths occurred in the first 3 months following discharge. A smaller retrospec-
tive study of patients using NIV for OHS, with 22 of the 54 patients initiated for acute
hypercapnic respiratory failure, reported a low mortality, with only 1 death among the
patients on NIV. About 22% of patients refused NIV, and there was 46% mortality in
this population. This study from 2005 highlighted the adverse consequences of
noncompliance with NIV in OHS patients, since when most studies have reported
an increased use of NIV. Priou and colleagues assessed the long-term outcomes
of 130 consecutive patients with OHS patients on NIV, including 38 patients who
were started on NIV in the ICU for acute respiratory failure. Over a 10-year period
the mortality of these patients was 18.5% with an NIV discontinuation rate of
18.5%. Of note, treatment with oxygen was associated with higher mortality. Overall
5-year survival was 77.3%. This finding was similar to the results of Budweiser and
colleagues on 5-year survival in patients with OHS. A decrease in nocturnal PCO2
and hemoglobin was associated with improved survival whereas hypoxemia, low
pH, and elevated inflammation markers predicted worse survival. Carrillo and
colleagues prospectively studied the outcomes of acute hypercapnic respiratory
failure caused by OHS (173 patients) versus COPD exacerbation (543 patients)
when managed using NIV. The type of ventilator, duration of NIV, and complication
rate were similar in both groups. Patients with OHS were older, but the severity scores
were similar in both groups. Patients with OHS had lower rates of NIV failure, readmis-
tion to the ICU, and reduced in-hospital mortality (6% vs 18%). The 1-year survival
was higher for OHS patients (odds ratio 1.83; 95% confidence interval 1.24–2.69;

P = .002), but this did not retain significance after adjusting for confounding variables.
In the report by Marik and Desai describing a “malignant obesity hypoventilation syn-
drome,” 61 patients with OHS (BMI >40) were admitted to the ICU with acute hyper-
capnic respiratory failure and had multiorgan dysfunction, with a high inpatient
mortality of 18%. There was a high rate of NIV failure (39.7%), and 7 patients needed
a tracheostomy. In 18 of the patients the end-expiratory esophageal pressure was 17
± 2.9 cm H2O, indicating the high work of breathing required to overcome the high
pleural pressures. All of these patients were ventilated using airway pressure release
ventilation, which has not been previously described. The investigators chose this to
optimize lung recruitment and minimize sedation requirements. Another study
compared the outcomes of 110 patients with OHS while on NIV with those of 220
patients with OSA using CPAP. Of interest, NIV was started following an episode of
exacerbation in 70.3% of the patients from the OHS arm. Patients were matched
for gender, age, and date of positive pressure therapy initiation. Patients with OHS
had higher BMI (42.4 vs 34.9) but frequencies of diabetes mellitus, ischemic heart dis-
ease, and stroke were the same. After titration, the patients with OHS were more often
on supplemental oxygen and the rate of lack of acceptance in the OHS cohort was
11.3%, contrasting with noncompliance and treatment withdrawal in 15.7% of
patients with OSA on CPAP. This case-control study reported a 2-fold increased
risk of 5-year mortality for those with OHS in comparison with those with OSA
(15.5% vs 4.5%), and suggests that despite similar rates of noncompliance, the
mortality remains higher for those with OHS than for those with OSA alone.

SUMMARY

OHS is a common cause of acute on chronic hypercapnic respiratory failure in patients
treated in the ICU. Understanding the mechanisms leading to this condition in obese
individuals can positively affect the ability of clinicians to treat OHS. Both obesity and
OSA are highly prevalent conditions in the adult population. It is estimated that 10% to
20% of patients with OSA also have OHS. OHS may be present in as many as 31% of obese patients admitted to the ICU, and obesity hypoventilation may be actually more prevalent than has been reported. Mechanisms for OHS include a restrictive respiratory physiology with a decreased FRC and ERV, lower respiratory system compliance, and the development of intrinsic PEEP. All of these factors are aggravated by a supine position, which increases hypercapnia and work of breathing. OSA per se may be implicated in the development of OHS when sustained hypoxia occurs. Patients with OHS have an impaired ventilatory drive, which can be improved with PAP therapy. Leptin, an adipokine, may lead to hypoventilation, and exists at higher levels in obese patients with OHS. Important diagnostic features of OHS include signs of cor pulmonale and hypoxemia in obese patients. An awake blood gas showing a PaCO_{2} greater than 45 mm Hg confirms the diagnosis. Other laboratory features include higher serum bicarbonate levels (>27 mEq/L). Both continuous and bilevel airway pressure therapy have been successfully used in the acute setting for OHS therapy, and certain presentations preclude their use (eg, multiorgan failure, obtundation). In general, patients with OHS need higher CPAP pressures than those with OSA. When used in the acute setting, bilevel pressures with an inspiratory to expiratory pressure difference of 8 to 10 cm H_{2}O are used and are titrated to achieve oxygen saturation greater than 90%. Engineered, more sophisticated modes of NIV can be applied to these patients in the acute setting. Different modalities can be set to use a backup rate while others can offer AVAPS. Pharmacotherapy has been attempted, but both acetazolamide and medroxyprogesterone lack substantial evidence of their effectiveness. Medical and surgical weight loss have been shown to improve hypoventilation in these patients and should be encouraged after the acute episode of respiratory failure has resolved, with patients being treated chronically with PAP therapy. Long-term mortality rates for OHS are higher than for patients with OSA, even when compliance to PAP therapy is similar. Mortality is higher for obese patients with OHS than for counterparts who do not have daytime hypercapnia. On the other hand, patients with OHS generally have a better survival than those with other causes of hypoventilation leading to respiratory failure, such as COPD.

REFERENCES


