Obesity Hypoventilation Syndrome —A Concise Clinical Review

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Obesity hypoventilation syndrome (OHS) is defined by the presence of awake hypoventilation in the setting of obesity. As nearly 1 in 10 adults today have a body mass index ≥30 kg/m^2, increased prevalence of this severe consequence of obesity is expected. Sleep disordered breathing, in the form of obstructive sleep apnea or sleep-related hypoventilation, is present in almost all individuals with OHS. Diagnosis requires arterial blood gas measurement, which may not be readily available in the outpatient setting. Delays in diagnosis are common, with some patients only presenting when hospitalization is required for acute or chronic respiratory failure. Positive airway pressure therapy is the mainstay of treatment, as it has been shown to treat sleep disordered breathing and resolve daytime hypercapnia. Weight-loss interventions, especially bariatric surgery, can improve OHS as well. Untreated OHS leads to increased morbidity and mortality; thus recognition, diagnosis, and patient-centered shared decision-making are key.

Keywords

Obesity, hypoventilation, sleep disordered breathing, obstructive sleep apnea, positive airway pressure therapy

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Obesity hypoventilation syndrome (OHS) is defined as daytime hypercapnia (awake resting $PaCO_2$ of ≥45 mmHg) in the setting of obesity (body mass index [BMI] ≥30 kg/m^2). Most, if not all, patients have some sleep disordered breathing in the form of obstructive sleep apnea (OSA) or sleep-related hypoventilation. Alternative causes of hypoventilation, such as severe pulmonary disease, neuromuscular disease, other chest wall disorders, central causes, and potential contributing medications, should be ruled out before making a diagnosis of OHS. First described in 1955, OHS has become increasingly common, as the prevalence of obesity has increased worldwide, with nearly 1 in 10 adults having a BMI ≥30 kg/mg^2.[1] In those with severe obesity (BMI ≥40 kg/mg^2), about 50% of patients will have OSA, and 10–20% of these patients will have OHS. This has led to an estimated prevalence of OHS in the USA of 0.4–0.6%.[2] Patients with OHS are known to have higher rates of heart failure, pulmonary hypertension, hospitalization, and mortality than the general population, and by definition, all have chronic hypercapnic respiratory failure. Unfortunately, many patients are diagnosed late in their disease course, either once they are referred to pulmonary or sleep sub-specialty clinics, or if they require hospitalization for acute on chronic respiratory failure. Due to the severe health consequences of OHS, it is paramount that these patients are diagnosed and treated as early as possible in the course of their disease. In this article we will review the basics of the pathophysiology, workup and diagnosis, and guideline-based treatment options of OHS for the practicing clinician.

Pathophysiology

In patients diagnosed with OHS, about 90% will have OSA, with 70% of these patients having severe OSA (apnea-hypopnea index [AHI] ≥30 events/hour). The remaining 10% of patients will have sleep-dependent hypoventilation without OSA.[3] It is important to determine whether patients with obesity have OSA alone versus OSA with OHS, because the risk of mortality is much higher in those with OHS.[4] In fact, even when appropriately treated with positive airway pressure (PAP) therapy, patients with OHS have a twofold increased risk of mortality compared with patients who have OSA alone,[4] which is likely related to the underlying systemic effects that OHS has on the body. Additionally, defining a phenotype for these patients is important, as it may guide therapy. Patients with OHS and severe OSA are more likely to respond to continuous PAP (CPAP), while patients with OHS and mild to moderate OSA or hypoventilation alone may do better with non-invasive ventilation (NIV).[1] To understand the pathophysiology of OHS, it helps to break it into three groups: respiratory mechanics, respiratory drive, and sleep changes (*Figure 1*).

In physics, work is defined as force (mass × acceleration) × distance × cosine (theta). Essentially, to do work, a force must cause a displacement. This means that the amount of work it takes to breathe depends on the weight of what we have to displace—the chest wall and the abdominal contents—to expand the lungs. By definition, this amount of work will increase if the weight of our chest wall

Figure 1: Pathophysiology of obesity hypoventilation syndrome

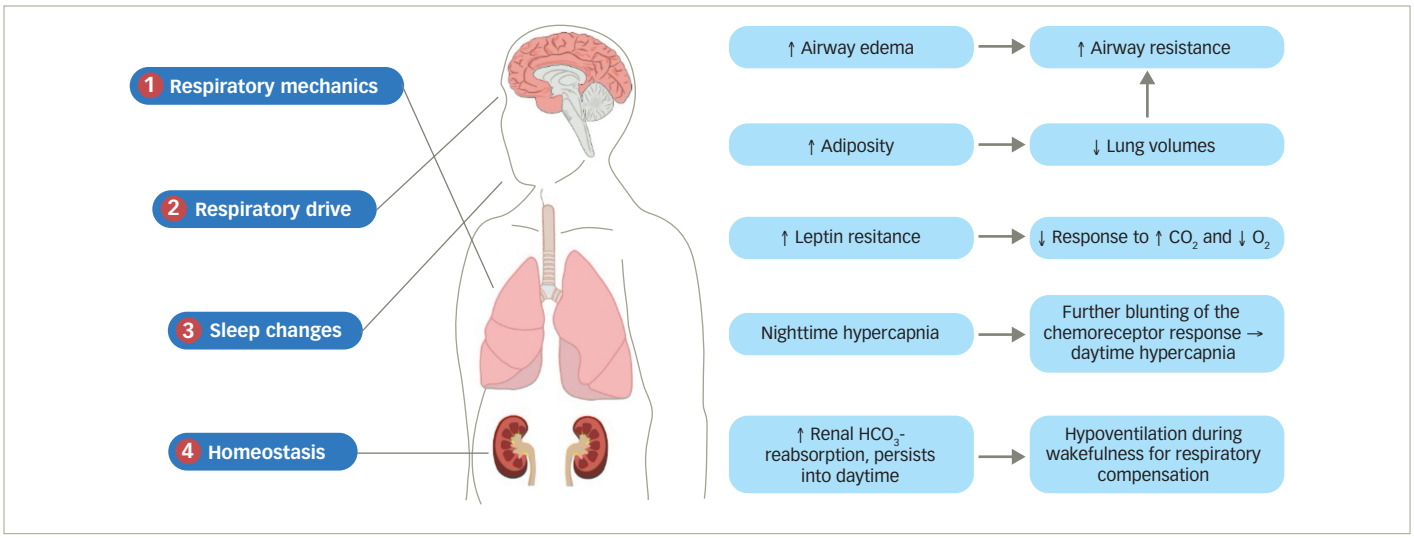

Image credit: Caroline Coleman, MD.

and abdominal contents increase and will increase even further when we lie down, as the angle between our displacement changes with respect to gravity. The increase in adipose tissue in the chest wall and abdomen increases pleural pressure and reduces respiratory system compliance as well as diaphragm motion. This leads to lower total lung volumes overall via decreased expiratory reserve volume and thus decreased functional residual capacity. Moreover, in the setting of lower lung volumes, airway resistance is increased due to decreased elastic recoil and traction on the small airways, which leads to air trapping, thereby increasing intrinsic positive end-expiratory pressure. Not only does this contribute to further increased work of breathing with fatigue of the respiratory muscles,[5] but it also leads to ventilation/perfusion mismatching—all of which is worse in the supine position, and thus during sleep.[6,7]

Most patients with obesity will increase their ventilatory drive to maintain eucapnia in the setting of an increased respiratory workload, but this is not the case in patients with OHS. This reduced response is thought to be due, in part, to leptin resistance.[1,8] Leptin is a protein released by adipose tissue that acts on the hypothalamus to inhibit hunger and regulate fat stores, and has been found to act as a respiratory stimulant. Although circulating levels of leptin are found to be higher in patients with OHS, resistance to leptin in these patients may lead to an attenuated response to hypoxia and hypercapnia.[8] Generally, this hypoventilation is first noticed during rapid eye movement (REM) sleep, as this is when skeletal muscle atonia ensues and ventilation is primarily dependent on the diaphragm and the central respiratory drive. Ultimately, recurrent nighttime hypercapnia leads to further blunting of the chemoreceptor response, manifesting with daytime hypercapnia, which is consistent with OHS.[1]

In addition to hypoventilation, up to 90% of these patients will have OSA, as mentioned above, the cause of which is multifactorial.[3] First, increased amounts of adipose tissue around the upper airway lead to increased collapsibility, thus increased pharyngeal critical pressure—the intraluminal pressure at which the airway will collapse. Second, reduced lung volumes lead to a fall in the caudal traction force of the airways, which can lead to a reduction in the pharyngeal airway cross section, further increasing the risk of airway closure. A third important cause of upper airway obstruction in these patients is airway edema. Fluid overload, due to heart failure, generally accumulates in the legs during the day due to gravity. At night when patients lay down, this fluid is shifted upward toward the chest and neck, not only decreasing the pharyngeal cross section passively, but also actively via reduction of pharyngeal dilator muscle activity.[9] It is important to note that, because of their decreased response to hypercapnia, patients with OHS do not have adequate hyperpneic responses to apneic or hypopneic events during sleep, thus there is a net gain of CO_2 overnight. As the kidneys attempt to compensate by reabsorbing more bicarbonate to maintain homeostasis and buffer pH,[10] if this elevated bicarbonate persists into daytime, hypoventilation will continue during wakefulness to compensate from a respiratory standpoint.[11] Thus, ventilatory drive will be further reduced the next night leading to a vicious cycle of CO_2 retention and hypoventilation ultimately persisting around the clock.

Workup and diagnosis

Workup for OHS is fairly straightforward; key measurements include height, weight, and daytime resting $PaCO_2$. However, one limiting factor is that arterial blood gasses are not routinely assessed in the outpatient setting, as they can be logistically cumbersome, costly, and painful for patients. For this reason, serum bicarbonate levels have been studied as a surrogate marker of CO_2 retention to screen for OHS. The consensus statement from the 2019 American Thoracic Society guidelines states that in patients with a low to moderate pre-test probability, a serum bicarbonate level <27 mmol/L has a high negative predictive value (99%) for OHS; thus these patients may forego arterial blood gas analysis, as they are unlikely to have OHS.[3] Low to moderate pre-test probability was defined as <20% and corresponded to the likelihood of having OHS given a certain BMI in the setting of sleep disordered breathing, with higher BMIs corresponding to higher likelihood.[2] If a patient's pre-test probability for OHS is high (>20%) given their BMI and associated symptoms, and/or if their serum bicarbonate is ≥27 mmol/L, an arterial blood gas analysis should be pursued. Additionally, it has been hypothesized that a rising bicarbonate level, and/or base excess (≥2 mmol/L), in the setting of awake eucapnia, could be suggestive of early OHS,[12] but more studies are needed to further evaluate this phenomenon.

Interestingly, based on the current definition of OHS, polysomnography is not required for diagnosis. However, polysomnography, or at least home sleep apnea testing, is indicated to determine the phenotype of OHS: either OHS with severe OSA, or OHS with mild to moderate OSA, or hypoventilation alone. If home sleep apnea testing is performed first, due to cost considerations or insurance requirements, an oxygen saturation on pulse oximetry of <88% for more than 5 minutes—without obstructive events or underlying identifiable respiratory disease—may be suggestive of hypoventilation. These patients should be brought to the sleep laboratory for further evaluation. End-tidal or transcutaneous CO_2 monitoring should be performed where possible, as a rise in ≥10 mmHg from the patient's awake supine baseline to a value exceeding 50 mmHg, or a measured CO_2 >55 mmHg lasting ≥10 minutes, is consistent with sleep hypoventilation as well.[13] In all patients, a titration study should be considered in order to optimize treatment with PAP therapy,[3] as discussed below.

As patients with OHS are at risk for developing left and/or right-sided heart disease,[14] obtaining a transthoracic echocardiogram (TTE) should be considered. While patients with obesity are at higher risk of diastolic dysfunction, this risk may be compounded in those with OSA and OHS, with a prevalence as high as 60–68%.[15] This is thought to be due to increased sympathetic activity and renin–aldosterone–angiotensin system activation ultimately leading to cardiac remodeling.[15] Compared with patients with obesity, but not OHS, those with OHS also have a higher risk of developing pulmonary hypertension and subsequent right-sided heart failure, with a prevalence of 52–88%.[15] This may be, in part, due to chronic hypoxia and hypercapnia leading to pulmonary artery vasoconstriction and subsequent remodeling, with other contributing factors being large fluctuations in intrathoracic pressure seen in OSA and restrictive lung disease secondary to obesity.[16]

Treatment options

Positive airway pressure therapy

PAP therapy has been well established as the mainstay of treatment in OHS; however, debate continues regarding the optimal mode for these patients. Current guidelines recommend starting CPAP in patients with an established diagnosis of OHS and severe OSA (AHI ≥30 events/hour), and titrating NIV for those with mild to moderate OSA or hypoventilation alone.[3] CPAP is thought to improve daytime hypercapnia in patients with OHS with severe OSA by treating apneas and hypopneas, thus reducing CO_2 accumulation that occurs overnight due to upper airway obstruction. However, CPAP will not augment ventilation, which is why NIV is currently recommended for those whose predominate problem is hypoventilation. NIV modes include bi-level PAP, volume-assured pressure support (VAPS), and control modes available on home mechanical ventilator devices. Although algorithms vary, the basic concept of NIV modes is to reduce the work of breathing and to improve ventilation using an expiratory PAP (EPAP) and an inspiratory PAP (IPAP) to create a pressure gradient that correlates to a tidal volume and thus, a minute ventilation. Additionally, some devices allow a back-up respiratory rate to be set if needed, particularly if central events are noted on therapy. However, due to the paucity of data comparing spontaneous bi-level PAP with spontaneous-timed modes (i.e., spontaneous-timed bi-level PAP or VAPS) in patients with OHS without severe OSA, one mode over another has not been demonstrated to be superior.[17] Thus, an individualized approach considering patient response to treatment, economic feasibility, and provider preference is recommended.

These recommendations are notably conditional, as there are not many trials with control groups. However, prospective observational trials have shown similarities in improvements between CPAP and NIV. Most recently, the Pickwick group published data looking at the effects of long-term (3 years) PAP therapy in patients with OHS and concomitant severe OSA.[15] They evaluated multiple outcomes including blood gas results, pulmonary function testing, 6-minute walk distance (6MWD), need for daytime supplemental oxygen therapy, estimated systolic pulmonary artery pressures (based on TTE), and weight loss. All of these parameters, except for 6MWD, showed a significant improvement with the use of PAP therapy with no difference between CPAP or NIV. However, 6MWD was improved in those patients with baseline pulmonary hypertension defined by estimated systolic pulmonary artery pressure >40 mmHg on TTE.[15] Prior studies have shown trends toward superiority of NIV over CPAP with regard to $PaCO_2$ reduction;[18] however, it is thought that this could be due to short study time, as the effects of CPAP may take longer to manifest, but ultimately be equal to that of NIV.

It is important to note that although CPAP is effective in many patients, close follow-up after initiation to ensure efficacy is key. As stated above, in patients who do not have concomitant severe OSA the current recommendation is to start with NIV titration, and in patients in whom CPAP fails, NIV titration should be the next step.[3] There are no established guidelines regarding NIV titration in OHS. Generally, titration starts with a minimum EPAP of 4–6 cmH_2O with a pressure support of 4 cmH_2O, meaning that IPAP will be 4 cmH_2O above EPAP. These pressures should be raised together initially. The EPAP at which apneas are eliminated will be the set EPAP. Some centers continue to increase the EPAP until hypopneas are also eliminated. If hypopneas are eliminated by EPAP, then the IPAP should be raised until hypoventilation is improved. This is assessed by evaluating tidal volume (target 8–10 mL/kg), transcutaneous or end-tidal CO_2, and desaturations not secondary to obstructive events.[19] Historically, these patients have been brought into the sleep lab for overnight titration as described above, but with the advent of "smart modes," which are volume-assured and can augment both IPAP and EPAP, we may see less need for formal titration going forward, although more studies are needed to examine this approach.[1] It should be noted that while many patients may require supplemental O_2 prior to and during titration, once therapy is optimized and apneas, hypopneas, and hypoventilation are treated, patients may no longer require O_2. This is important as lower baseline PaO_2 and the ongoing need for supplemental O_2 corresponds to higher mortality in patients with OHS.[19]

Long-term effects of positive airway pressure therapy

As mentioned above, the general consensus for patients with OHS with severe OSA is that there is no difference between outcomes with CPAP versus NIV. There are also data to suggest that, regardless of OSA status, treatment with some form of PAP therapy in OHS has long-term benefits (including improvements in PaO_2, $PaCO_2$, forced expiratory volume in 1 second, and forced vital capacity), which persisted up to 10 years.[20] Additionally, there does not appear to be a difference in long-term outcomes in patients started on PAP therapy in the setting of acute exacerbation versus those with stable, chronic disease.[21] Overall, when comparing across studies, survival seems to be improved with the use of PAP compared with no treatment,[20–23] thus this is our current standard of care.

Weight loss

Weight loss of ~25–30% of starting body weight is recommended to improve, if not resolve, OHS.[3] However, it should be emphasized that achieving this degree of weight loss is difficult and is not common—especially without surgery. Even with weight loss, OSA and the need for PAP therapy may persist.[17] The use of commercially available weight-loss programs, intensive lifestyle intervention, and bariatric surgery have all been evaluated in these patients. Among these approaches to weight loss, bariatric surgery appears to be consistently associated with significant weight loss that is sustained in the long term.[24] Bariatric surgery also has been observed to be associated with improvements in AHI, PaO_2, $PaCO_2$, pulmonary artery pressures, subjective daytime somnolence,[21] and improvement in pulmonary function.[25]

Despite the benefits of bariatric surgery, is important to note that it can be a high-risk operation, with mortality ranging from 2 to 8% with an open surgical approach in those with higher BMI, older age, hypertension, and a history of venous thromboembolism.[25] However, lower complication rates have been noted in lower-risk patients and in those undergoing laparoscopic banding procedures,[24,26] and better outcomes may be seen as surgical techniques continue to improve. Given that the decision to get bariatric surgery can be high-risk/high-reward, shared decision-making with the patient, their family, and the bariatric surgeon is the best approach.

Pharmacologic therapy

In addition to treatment with PAP therapy and weight loss, there has been interest in respiratory stimulants, namely medroxyprogesterone and acetazolamide, as potential treatments for nocturnal hypoventilation.[27,28] However, there is a paucity of data in this area; these medications are not able to eliminate sleep apnea, and there is potential risk for adverse events long term.[1] Thus, these medications are not currently recommended as treatments for OHS.

Management of acute exacerbations

Patients with OHS are at high risk for emergency room visits and hospital admissions due to acute on chronic hypercapnic respiratory failure, especially when their disease goes untreated and/or when they are faced with an acute insult. Initial work-up should include arterial blood gas analysis, and if the pH is <7.35 and/or if the patient is somnolent thought to be secondary to hypercapnia, NIV should be initiated.[29] Current recommendations suggest starting EPAP at 6 cmH_2O and increasing by 2 cmH_2O increments with the goal of eliminating snoring, obstructive events, and desaturation. For IPAP, recommendations vary, but generally suggest starting pressure support at 6–10 cmH_2O above EPAP, increasing by 2 cmH_2O until the chest wall expands and reduced respiratory distress is observed, with the goal of reaching a pH >7.3.[1,19] It should be noted that up to 30 cmH_2O of IPAP and 10–15 cmH_2O of EPAP may be required to achieve these goals, and if desired volumes are still not being achieved at high pressures, the use of a volume-assured mode may be considered.[29]

Monitoring arterial blood gases in these patients is key, as worse initial pH and no improvement or worsened pH and $PaCO_2$ on subsequent arterial blood gases at 1–4 hours of NIV initiation are predictive of NIV failure.[30] In the case of failure of NIV, the managing team should be prepared to intubate or call for assistance with intubation. For this reason, it is appropriate for these patients to be admitted in the step-down unit or intensive care unit for the first 24–48 hours of their care.

Once these patients begin to improve, as indicated by mental status, pH, $PaCO_2$, work of breathing, and volume status, NIV settings may be adjusted as tolerated and they may be switched from 24-hour NIV to just with naps and at nighttime only. It is recommended that once their underlying condition is optimally treated, these patients be discharged with NIV and close follow-up with outpatient sleep medicine evaluation for optimal titration.[3] While there are no randomized controlled trials that have addressed this issue, multiple observational studies have noted improved 3-month mortality in those discharged on PAP therapy, but this is clearly an area where further research is needed.

Conclusion

OHS is associated with multiple medical co-morbidities and is known to lead to increased mortality. It is often diagnosed late in the course of disease when these patients are hospitalized for acute exacerbations of hypercapnic respiratory failure, or are referred to pulmonary or sleep medicine sub-specialty clinics. It is paramount that we recognize and diagnose OHS and initiate treatment as soon as possible to improve our patients' outcomes long term. Treatment with PAP therapy can control disease and improve outcomes, but only significant weight loss of ≥25% may provide a cure. A patient-centered approach with shared decision-making between provider and patient is key in this complex disease, where PAP therapy is the mainstay of treatment and weight loss via bariatric surgery may be considered. ❑

Highlights

- Obesity hypoventilation syndrome (OHS) is a disease with severe consequences and high mortality, which often is diagnosed late in the course of disease
- Diagnosis is made using body mass index ≥30 kg/m^2 and awake resting $PaCO_2$ ≥45 mmHg from an arterial blood gas analysis; however, a serum bicarbonate level <27 mmol/L can rule out OHS in patients with low to moderate pre-test probability of OHS
- Positive airway pressure therapy is the mainstay of treatment with continuous positive airway pressure recommended for those with concomitant severe obstructive sleep apnea, and non-invasive ventilation (NIV) recommended for those with mild to moderate sleep apnea or OHS alone
- NIV should be considered in the initial management of acute exacerbations of hypercapnic respiratory failure, and treatment-naive patients may be sent home on NIV with close outpatient follow-up in a pulmonary or sleep sub-specialty clinic
- Bariatric surgery leading to ≥25% weight loss generally improves all metrics associated with OHS and, in some cases, can resolve it

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