Published in final edited form as:

Curr Pulmonol Rep. 2015 March 1; 4(1): 42–55. doi:10.1007/s13665-015-0108-6.

Obesity Hypoventilation Syndrome

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Abstract

Obesity hypoventilation syndrome is a respiratory consequence of morbid obesity that is characterized by alveolar hypoventilation during sleep and wakefulness. The disorder involves a complex interaction between impaired respiratory mechanics, ventilatory drive and sleep-disordered breathing. Early diagnosis and treatment is important, because delay in treatment is associated with significant mortality and morbidity. Available treatment options include non-invasive positive airway pressure (PAP) therapies and weight loss. There is limited long-term data regarding the effectiveness of such therapies. This review outlines the current concepts of clinical presentation, diagnostic and management strategies to help identify and treat patients with obesity-hypoventilation syndromes.

Keywords

Obesity hypoventilation syndrome; Obstructive sleep apnea; Obesity; Noninvasive ventilation

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Compliance with Ethics Guidelines

Conflict of Interest Statement

Dr. Parthasarathy reports grants from NIH/NHLBI, Patient Centered Outcomes Research Institute, US Department of Defense, grants from NIH (National Cancer Institute) NCI, US Department of Army, Johrei Institute, personal fees from American Academy of Sleep Medicine, Younes Sleep Technologies, Ltd., Niveus Medical Inc., and Philips-Respironics, Inc., outside the submitted work. Dr. Parthasarathy also reports personal fees from American College of Chest Physicians, non-financial support from National Center for Sleep Disorders Research of the NIH (NHLBI), USMLEWorld Inc., UpToDate Inc., and Philips-Respironics, Inc., outside the submitted work. Dr. Parthasarathy also states has a patent UA 14-018 U.S.S.N. 61/884,654; PTAS 502570970 pending.

Dr. Shetty does not have any conflict of interest to declare.

Human and Animal Rights and Informed Consent

This article contains no studies with human or animal subjects performed by the author.

Introduction

Obesity is a global epidemic with increased prevalence over the last three decades. A recent study on the prevalence of obesity in adults in the United States showed a prevalence of 35.5% among adult men and 35.8% among adult women [1]. Obesity hypoventilation syndrome (OHS) is defined as a combination of Obesity ($\text{BMI} > 40 \text{ kg/m}^2$), daytime hypoventilation characterized by hypercapnia and hypoxemia ($\text{PaCO}_2 > 45 \text{ mm Hg}$ and $\text{PaO}_2 < 70 \text{ mm Hg}$ at sea level) and sleep-disordered breathing (SDB) in the absence of an alternative cause for hypoventilation like obstructive or restrictive lung disease, chest wall disorders like kyphoscoliosis, neuromuscular disorders and congenital central hypoventilation [2–4]. Approximately 90% of SDB in obesity hypoventilation syndrome is Obstructive sleep apnea (OSA), with the remaining 10% of patients manifesting sleep-related hypoventilation characterized by hypoxemia which is unrelated with obstructive events of OSA – namely obstructive apneas or hypopneas [5, 6].

Epidemiology

The precise prevalence of OHS in the general population is unclear, but is estimated to be between 0.15% and 0.3% [7]. The prevalence of OHS in obese individuals was found to be much higher at 19 to 31 % [8, 9]. A recent prospective and observational study with an objective to determine the prevalence of OHS in hospitalized patients was conducted in 9,480 patients at a tertiary care hospital. [7] Patients with wake hypercapnia as demonstrated by $\text{PaCO}_2 > \text{or equal to } 45 \text{ mmHg}$ after arterial blood gas analysis were included. Three hundred and thirty patients (3.4%) meeting the inclusion criteria were analyzed and 35.5% of patients had chronic hypoventilation of which 24.6% (27 patients) was related to OHS [7]. Other studies including a total of 1,326 patients, on evaluation of patients referred to sleep centers with clinical symptoms of OSA found the prevalence of OHS to range from 11–20%, with an overall prevalence rate of nearly 16% [5, 10–12]. Retrospective studies on evaluation of 1,927 patients with a known diagnosis of OSA found the prevalence of OHS to range from 9–14%, with an overall prevalence of 11% [13–15]. Therefore, the prevalence of OHS can be said to be variable and dependent on the population that was studied, with the prevalence rate to be least in population-based cohorts and the most in hospitalized patients. The hospitalized patients are more likely to meet the hypercapnia criterion, which has led some to suggest that the definition of OHS may need to be revisited. [16]

Pathophysiology

In healthy individuals, the arterial pH is maintained within a narrow range that is effected by changes in alveolar ventilation in relation to the metabolic rate and renal acid-base status. In patients with OHS, a complex interaction between abnormal respiratory mechanics, central respiratory drive, sleep-disordered breathing and Leptin resistance takes place and leads to centrally (“respiratory controller”) facilitated alveolar hypoventilation. During sleep, alveolar hypoventilation leads to nocturnal hypercapnia and hypoxia, which over time leads to resetting of the chemostat of the respiratory controller and consequent daytime hypercapnia and hypoxemia. The hypercapnia of OHS may be augmented by Leptin resistance. Essentially, Leptin is a respiratory stimulant that augments respiratory controller function and both leptin resistance associated with obesity and leptin deficiency can produce

defects in upper airway neuromechanical control.[17] However, the application of PAP over a short period of time can correct daytime hypercapnia [18].

Respiratory Mechanics

OHS patients have significant impairment of the respiratory system mechanics when compared to equally obese eucapnic patients with or without sleep disordered breathing [10]. In morbid obesity, central fat accumulation imposes a significant load on the respiratory system, with overall effect of marked decrease in lung volumes, in lung and chest wall compliance and increased airway resistance, in all contributing to a higher work of breathing.[19] OHS patients show reductions in vital capacity (VC), total lung capacity (TLC) and residual volume (RV) in comparison to eucapnic obese individuals at similar levels of BMI [20, 21]. Individuals with OHS have greater degree of central obesity reflected by larger neck circumferences and higher waist: hip ratios than those with eucapnic obesity or OSA, which explains the lower lung volumes seen in such individuals [10].

Tidal breathing at low resting lung volumes is partly responsible for significant reduction in both chest wall and lung compliance [22–24] and the observed increase in airway resistance[25]. When compared to subjects who are of normal weight, respiratory system compliance has been shown to be about 20% less in eucapnic obese individuals and almost 60% less in patients with OHS[23, 26]. Small airway closure during exhalation can occur while breathing at low lung volumes, thus creating expiratory flow limitation and intrinsic positive and expiratory pressure (PEEPi) [27–29]. Such PEEPi, in turn, imposes an additional threshold load on inspiratory muscles before any inspiratory flow is generated thereby further increasing the work of breathing [27, 28, 30].

Patients with OHS have a significantly greater work of breathing when compared to individuals with normal weight or eucapnic obese patients with OSA while breathing spontaneously on room air [27, 31]. Supine posture can further worsen the respiratory system compliance [23] and functional residual capacity (FRC)[29], while increasing upper airway inspiratory resistance to airflow [28]. Increased upper airway resistance is seen in both the sitting and in the recumbent position in patients with OHS when compared to eucapnic OSA patients who demonstrate resistance only in the supine position [32].

Hypoxemia is much more common in patients with OHS when compared to individuals with eucapnic obesity [10]. Low ERV in morbidly obese individuals contributes to ventilation perfusion mismatch, which is worsened in the supine posture. In order to optimize the oxygen cost of breathing obese individuals adapt by breathing small tidal volumes and at higher respiratory rates or “rapid shallow breathing” which is energy inefficient [19, 33–35]. This pattern of breathing contributes to dead space ventilation and to hypoxia. [33]Individuals with OHS are exposed to prolonged periods of daytime and nocturnal hypoxia and are consequently at higher risk for pulmonary hypertension [36], congestive heart failure and cor pulmonale [37, 38].

Respiratory muscle function is impaired and worse in the supine position in OHS when compared to eucapnic morbidly obese individuals [39–41]. Several theories have been postulated to explain this observation. Diaphragmatic impairment by mechanical

overstretching by abdominal fat [41], chronic hypoxia and hypercapnic state [42], low insulin growth factor (IGF-I) levels, reduced ventilatory drive are all potential mechanisms [43].

Central Respiratory drive

Eucapnic obese individuals have a higher rate of oxygen consumption and CO₂ production at baseline. This is generally compensated by increased respiratory drive to increase minute ventilation and maintain alveolar ventilation [28, 44]. However, individuals with OHS fail to compensate their respiratory drive in response to the added load created by excess weight, thus permitting a gradual increase in PCO₂ [32, 45, 46]. Central ventilatory responsiveness to both hypoxia and hypercapnia are attenuated in OHS compared to non-obese and eucapnic obese patients with or without OSA [47, 48]. The decreased ventilatory response is attributed secondary to the blunted neural response to hypercapnia [46, 47], which in turn has been shown to improve within days or weeks after initiating PAP therapy, in the absence of significant change in weight [49–52].

Sleep disordered breathing

OHS is strongly associated with sleep disordered breathing (90%), most commonly OSA [53] and about 10% of the time of the time being primarily sleep-related hypoventilation [54]. Wake hypercapnia is seen only in minority of patients with severe OSA. Meta-analysis of 15 studies, found that patients with hypercapnia had higher BMI and AHI and lower lung volumes consistent with restrictive lung physiology and more significant hypoxia on overnight pulse oximetry when compared to eucapnic obese patients with OSA[8].

Leptin resistance and OHS

Leptin is a protein synthesized by adipose tissue. Leptin acts on the central respiratory center to stimulate ventilation and Leptin levels are noted to be increased in obese individuals with higher serum leptin levels in patients with OSA and OHS when compared to those without such sleep-disordered breathing [55–58]. Increased levels of Leptin in human obesity may compensate for the increased load on the respiratory system by maintaining adequate ventilation [59]. But, this stimulatory effect of Leptin is reduced in some individuals hence predisposing them to hypoventilation and consequent hypercapnia [56].

Campo and colleagues found that in obese patients, higher concentrations of serum leptin are associated with a reduced respiratory drive and a reduced hypercapnic response [60]. Hypercapnic OSA patients have significantly lower hypercapnic ventilatory response when compared to eucapnic OSA patients with similar leptin levels [56]. Consequently, in humans with OHS, Leptin resistance is thought to contribute to the pathophysiology in a manner similar to that described in a leptin-deficient mouse model manifested by reduction in lung volumes, compliance, abnormal respiratory muscle function, and defects in upper airway neuromechanical control[17] [61, 62].

Clinical features and diagnosis

OHS is a diagnosis of exclusion that requires evaluation for other potential causes of hypoventilation and hypercapnia such as obstructive or restrictive lung diseases,

neuromuscular disease, severe restrictive chest wall disorders, metabolic causes like hypothyroidism and congenital hypoventilation syndromes [2–4]. Patients with OHS are diagnosed either with a presentation of acute on chronic respiratory failure to the hospital or on routine outpatient evaluation by a pulmonologist or sleep physician [6]. Diagnosis is usually in the fifth or sixth decade of life and is frequently delayed. The delay translating into higher use of health care resources when compared to that of obese eucapnic patients [37]. Patients with OHS are frequently misdiagnosed during hospitalization and treated as Chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF) or as a combination of both [7]. Nowbar et al have previously reported that a majority of hospitalized patients identified as having OHS were subsequently discharged without home-based PAP therapy [9].

Basaglu et al performed a case-control study aimed at comparing the clinical characteristics of patients with OSA and OHS and factors that predict the occurrence of hypercapnia in patients with OSA. In 2,188 consecutive patients admitted to the sleep laboratory for evaluation for sleep-disordered breathing by polysomnography over a 6-year period clinical characteristics of 59 patients with OHS and 295 patients with OSAS were compared. The cases and controls were matched for BMI. Daytime hypersomnia was measured by a Turkish version of Epworth sleepiness scale (score > 10). Pulmonary function tests, Chest X-rays, arterial blood gas and overnight in-lab polysomnogram was performed in all individuals. Individuals with OHS were found to have a greater proportion of individuals with hypersomnia (90% versus 69%) and manifest lower FVC and FEV₁ measured by pulmonary function testing than controls. Arterial blood gas analysis showed lower PaO₂ (72 ± 13 versus 81 ± 13 mmHg) and higher PCO₂ (49 ± 5 versus 35 ± 4 mmHg) and serum bicarbonate (32 ± 4 versus 25 ± 3.5 meq/dL) in the OHS than in the control group. Overnight polysomnography revealed greater degree of nocturnal oxygen desaturation and amount of time spent with oxygen saturation < 90% in the OHS than in the control group [63]. Multivariate analysis showed hypercapnia to be associated independently with serum bicarbonate and oxygen saturation. A serum bicarbonate > or equal to 27 Meq/L and oxygen saturation < or equal to 95% had a high sensitivity and specificity to identify patients with OHS [63].

In a recent prospective observational study to determine the predictors of OHS in hospitalized patients at a tertiary care hospital, arterial blood gas on 9,480 patients with hypercapnia were evaluated over a one year period. Three hundred and thirty patients met the inclusion criteria for hypoventilation based on arterial blood gas PCO₂ > or equal to 45 mmHg, normal PH and elevated serum bicarbonate. Chronic hypoventilation was found in 36% (n=118) patients. Twenty-seven patients were identified as having OHS. Patients in the OHS group were found to have a higher BMI (43 ± 9 versus 26 ± 5 kg/m²), lower PaO₂ and oxygen saturation. Than those without OHS No significant difference was found between the PCO₂ and serum bicarbonate between the two groups. OHS was misdiagnosed as either COPD or CHF in twenty patients. Only five cases (17%) had been diagnosed correctly as OHS. The ratio of PCO₂/BMI had the highest diagnostic accuracy for identifying OHS as measured by area under ROC curve analysis (AUC: 0.90, 95% CI: 0.84–0.98, *P* < 0.001)

with the sensitivity and the specificity of PaCO₂/BMI ratio for diagnosing OHS at <1.5 being 97% and 69% [7].

In a retrospective study, Macavei et al determined the prevalence of OHS and predictors of OHS in patients with OSA. In 525 consecutive patients referred to the sleep medicine clinic Prevalence of OSA among obese patients was 79.9% (275/344 patients) and OHS prevalence among OSAHS patients was 22.1% (61/275 patients) in those undergoing polygraphy. Patients with OHS had lower lung volumes, lower mean oxygen saturations, and greater time spent below 90% oxygen saturation and higher oxygen desaturation index when compared to OSA patients. A calculated bicarbonate threshold of 27 mmol/L was most effective in detecting obesity hypoventilation syndrome with 85.7% sensitivity and 89.5% specificity [47]. Mokhlesi and colleagues in an observational study demonstrated similar findings and identified three independent variables to predict OHS; AHI, lowest oxygen saturation during sleep and serum bicarbonate. They found that the serum bicarbonate less than 27 had a negative predictive value of 97% to exclude hypercapnia during wakefulness [5]. Moreover, Manuel et al hypothesized that isolated elevation of serum bicarbonate or base excess in the absence of a wakefulness hypercapnia may be a marker for a subset of patients may develop OHS patients subsequently [64].

OHS if untreated at hospital discharge is associated with a mortality of 23% at 18 months and this reduces to 3% in adequately treated patients of OHS. Untreated OHS patients are also likely to require invasive mechanical ventilation and hence prolonged hospital stay [9]. Early diagnosis of patients with OHS is important with careful emphasis and recognition of factors predictive of OHS. Although the gold standard for diagnosis for OHS remains an arterial blood gas and exclusion of other causes of hypercapnia in the correct setting, less non-invasive testing like measurement of serum bicarbonate may help in the early recognition of patients with OHS. But, it is still unclear as to how the coexistence of metabolic alkalosis due to loop diuretics in patients with CHF may affect the predictive power of this test.

Treatment

The treatment for OHS is directed at the underlying pathophysiological factors contributing to hypoventilation. It may be broadly divided into PAP therapy, weight loss induced by medical or surgical means and pharmacotherapy.

Positive airway pressure (PAP) therapy

PAP therapy has a significant favorable impact on health-related quality of life, health care costs and mortality [65]. PAP therapy has been shown to improve daytime blood gases and quality of sleep [65–68]. PAP therapy is usually in the form of continuous positive airway pressure (CPAP) therapy or non-invasive positive pressure ventilation (NIPPV) using a bi-level PAP or other advanced PAP modalities.

Since majority of patients with OHS have OSA, CPAP therapy is recommended initially to improve nocturnal gas exchange by preventing obstructive apneas and hypopneas and reducing the work of breathing related to small airway closure and expiratory flow limitation [28, 31]. PAP therapy improves FRC and the abrogates the effects of PEEP_i [28] which in

turn decreases the cost of breathing by reducing swings in intrathoracic pressures needed to maintain breathing. Additionally, PAP therapy opens up the smaller airways and thereby decreases ventilation perfusion mismatch and consequently improves oxygenation. Following initiation of therapy over a period of few months, improvement in other physiological parameters such as gas exchange during wakefulness[69, 70] and ventilatory response to hypoxia and hypercapnia [49, 51, 52] and also improvement in symptoms[71] and health-related quality of life[70, 71] has been reported following use of CPAP in OHS. Most studies that demonstrated the efficacy of CPAP therapy in OHS patients have been small and retrospective in nature.

Banerjee et al conducted a prospective study whereby they compared 23 patients with (moderate to severe) OSA with an equal number of subjects with OHS and OSA of similar severity and then measured the effect of one night of CPAP therapy on sleep architecture [72]. CPAP therapy failed to correct the oxygen desaturation in 43% of subjects with OHS and OSA who continued to spend > 20% of total sleep time with oxygen saturation less than 90% [72]. In a recent prospective study, Salord and colleagues followed newly diagnosed patients with OHS and OSA (n=29) for a period of three months to evaluate the effect the long-term effect of CPAP therapy on oxygen saturation and daytime PaCO₂ and to explore factors that might predict the failure of CPAP. The effect of CPAP therapy on the pro-inflammatory markers adipokine and C-reactive protein (CRP); which are thought be raised in response to chronic inflammation due to hypoxia was also assessed. Treatment failure after 3 months was defined by a daytime PaCO₂ > 45 mm Hg and/or SpO₂ < 90% for > 30% of the night. All patient underwent overnight polysomnography or respiratory polygraphy. Patients with an AHI > 15/hour had a CPAP titration. Patient with a mean nighttime oxygen saturation <85% were switched over to bi-level PAP therapy. An early morning arterial blood gas and another repeated after 4 hours of awakening were obtained. After three months of CPAP treatment there was a significant decrease in nighttime oxygen desaturation, daytime PaCO₂, early morning PaCO₂, and improvement in early morning PaO₂. At the end of the study, seven patients met the criteria for treatment failure: six with persistent daytime PaCO₂ > 45 mmHg and one with persistent nocturnal hypoxemia. Significant improvement in sleep architecture was also seen with more slow wave and REM sleep and subjective improvement in daytime sleepiness. No significant changes were seen with respect to the levels of the inflammatory markers at the end of the study. Seven patients met the criteria for treatment failure. Patients with CPAP failure had lower mean nocturnal oxygen saturations following CPAP titration, lower daytime PaO₂ and higher PaCO₂ at one month following initiation of CPAP therapy when compared to patients with a favorable response. The study showed a favorable effect of CPAP therapy on nighttime oxygenation and daytime PaCO₂. The study also emphasized the importance of early monitoring of daytime PaCO₂ in the first month after initiating CPAP therapy and low overnight oxygen saturation on the night of CPAP titration as a tool to detect patients are more likely to fail long term treatment [73].

Bi-level PAP

CPAP is recommended as first line treatment in stable OHS patients with mild-to-moderate hypercapnia OSA. Close attention to early identification of patients with OHS who will

benefit from long-term treatment with CPAP therapy and early treatment failure is important [73]. NIPPV (with bilevel PAP or advanced modalities) when used long-term in patients with OHS who have failed CPAP therapy has been shown to effectively improve hypoventilation and daytime symptoms.[50, 74–76]

Bi-level PAP therapy is beneficial in preventing obstructive events, improving expiratory flow limitation and also improves tidal volume by providing inspiratory pressure support. Bilevel therapy when used long term has been shown to improve blood gases, quality of life and ventilator responsiveness to CO₂ [50, 70, 77–81]. Bi-level PAP therapy unloads inspiratory muscles and has been shown to reduce diaphragmatic effort by nearly 40% [34]. Piper et al performed a randomized controlled trial in patients with OHS whereby they compared the efficacy of CPAP versus bi-level PAP therapy to compare their efficacy in treating daytime hypercapnia, health-related quality of life, cognitive function while also comparing adherence to such treatment. Thirty-six patients were enrolled and underwent baseline sleep study, spirometry and arterial blood gas analysis and PAP titration study. Patients with significant desaturation (oxygen saturation remaining below 80% continuously for > 10 min) in the absence of obstructive events, acute rise in transcutaneous carbon dioxide retention of 10 mmHg or greater during REM sleep or increase in afternoon to morning PaCO₂ of 10 mmHg or greater in those patients with an awake PaCO₂ greater than 55 mmHg during an initial CPAP trial were excluded from participation. Patients were randomized to receive Bilevel PAP or CPAP therapy over three months. Repeat measurements performed at baseline, including a repeat sleep study while the patient was receiving the PAP therapy. No significant difference was seen in daytime PaCO₂, weight loss, adherence to therapy or daytime sleepiness. The bi-level PAP therapy group reported better subjective sleep quality and performed better on a psychomotor vigilance task than the CPAP group [70].

In observational studies, NIPPV has been shown to have a favorable effect on metabolic and cardiovascular parameters. A recent randomized control trial aimed to compare the effects of NIPPV to lifestyle counseling in patients with mild OHS [82]. In this study, Borel et al noted that NIPPV improved daytime arterial blood gas measurements and ventilation during sleep when compared with the lifestyle counseling group. All patients underwent an overnight polysomnogram, measurement of biomarkers for inflammation, spirometry and measurement of arterial wall stiffness. Thirty-five newly diagnosed OHS patients were randomized to either the treatment arm to receive NIPPV (Bi-level) for a duration of one month or be part of the control group with lifestyle modification. Participants undergoing lifestyle modification were educated on health risks associated with obesity, and advised to reduce fat intake and change eating behavior and increase physical activity. At one month follow up, baseline measurements were repeated. Significant improvements in nocturnal hypoxemia and daytime PaCO₂ which consequentially improved sleep architecture in the NIPPV group were noted when compared to that in the control group. There was no difference between the cardiovascular, metabolic and inflammatory parameters or in daytime sleepiness between the two study arms [82].

Bi-Level ventilators provide 3 different modes: (1) Spontaneous mode, in which each pressurization by the ventilator is triggered and cycled by the patient; (2) Spontaneous/timed

(S/T) mode, in which, if the patient fails to initiate a pressurization within a time frame based on a back-up respiratory rate, the device will deliver a machine-triggered cycle for a defined inspiratory time; (3) Timed mode, in which the device delivers pressurizations at a preset respiratory rate, during a preset inspiratory time, without taking into account the patient's inspiratory efforts [83]. Although OHS remains one of the most common indications for NIPPV [74], there remains a paucity of evidenced-based guidelines on the choice of equipment, modes of ventilation and ventilator settings. American Academy of Sleep Medicine (AASM) guidelines for the adjustment of NIPPV in chronic alveolar hypoventilation syndromes that were derived mostly from expert consensus recommended the spontaneous mode as the default setting, unless patients manifests a significant number of central apneas or a low spontaneous respiratory rate and are unable to trigger the ventilator [84]. In the latter case a back-up respiratory rate was recommended.

Contal et al performed a randomized controlled trial that aimed to determine the impact of changes in back-up respiratory rate with respect to efficacy of ventilation and quality of sleep in stable patients with chronic hypercapnic respiratory failure under long-term treatment with a bi-level NIPPV device [85]. In this study, ten patients with OHS were identified and underwent three consecutive polysomnograms which were performed in a random order with different backup respiratory rate settings. The different settings were no back-up respiratory rate (spontaneous mode), low back-up respiratory rate (S/T mode with 2 breaths below the average nocturnal respiratory rate) and high back-up respiratory rate (S/T mode with respiratory rate set at the 95th percentile of nocturnal respiratory rate). During the spontaneous mode, participants had significantly increased apnea-hypopnea index (consisting mainly of central and mixed apneas), and higher oxygen desaturation index when compared to patients on S/T mode. No significant difference in sleep architecture or quality of sleep was observed between the spontaneous and S/T modes. The quality of sleep was slightly better with lower perceived arousals in the low back-up respiratory rate when compared to the high back-up respiratory rate mode. The findings of this study were limited by the small sample size [85].

In summary, a recommendation can be made that bi-level PAP should be strongly considered in patients who fail a CPAP trial, in OHS patients without OSA and in severe hypercapnic OHS where CPAP has not proven to be effective. However, larger and adequately powered randomized controlled trials are needed to document the long effect of NIPPV on patient-outcomes in this population. Additionally, the effects of such therapy on metabolic, cardiovascular and inflammatory parameters needs closer study. In a recent study, Chironos and colleagues demonstrated that in adults with obesity and OSA, CPAP combined with a weight-loss intervention did not reduce CRP levels more than either intervention alone[86]. However, they did not target patients with OHS and OSA, nevertheless, and therefore the effect of combinatorial therapies that include PAP and weight-loss intervention needs to be performed in patients with OHS.

Volume assured pressure assistance

Newer PAP modalities like averaged volume-assured pressure support (AVAPS) combine the benefits of targeting minute ventilation and tidal volumes while delivering the comfort

and advantages of pressure support ventilation making them ideal for patients with hypoventilation[79, 87]. This modality was initially used in critically ill patients receiving mechanical ventilation. Subsequently, the application of AVAPS has been extended to use in sleep disordered breathing and hypoventilation syndromes [65, 88].

AVAPS modality is designed to detect tidal volume (or minute ventilation) over a variable (1–5 minute) period of time. The device detects decrease in tidal volume below a certain threshold with an increase in IPAP (or pressure support) in order to restore the tidal volume approximately to the preset tidal volume [65]. The inspiratory pressure is aimed at ensuring a tidal volume, calculated based on the ideal body weight (usually 8 mL/Kg ideal body weight or at 110% of the patients tidal volume)[87]. These devices combine the technology of auto-PAP therapy to help determine optimal EPAP pressures.

Storre et al in a randomized crossover trial aimed to investigate the physiologic and clinical benefits of AVAPS versus bilevel-PAP with a backup respiratory rate mode of ventilation alone in patients with OHS. Ten patients with stable OHS who had failed CPAP therapy were randomized to receive one of the two modes of ventilation and then followed up over six weeks of home ventilation. No significant difference was seen in terms of the quality of sleep, health-related quality of life parameters, or daytime gas exchange between the two groups. The beneficial physiological effect of addition of AVAPS to bilevel PAP with backup rate was seen as a significant decrease in nighttime end tidal CO₂ [79].

In a different study, Ambrogio et al performed a randomized controlled trial aimed at comparing sleep efficiency between AVAPS and bilevel PAP therapy with the majority of the patients carrying a diagnosis of OHS and found no significant differences between sleep architecture, sleep quality or quantity between the two groups [87]. AVAPS was comparable to bilevel PAP therapy with regard to sleep, but statistically greater minute ventilation was observed during AVAPS than bilevel PAP therapy, but this difference is of unclear clinical significance. Potentially, AVAPS modality may prevent alveolar hypoventilation and improve oxygenation by assuring the fixed tidal volume [87].

Murphy et al in a recent large single blind, randomized control trial on patients with OHS aimed to evaluate the effect of AVAPS on daytime hypercapnia, physical activity and health-related quality of life when compared to individuals on fixed-level pressure support ventilation [89]. In 50 morbidly obese participants (BMI 50±7 kg/m²) who were randomized to receive AVAPS and bilevel PAP therapy for 3 months, there was no difference in sleep architecture or efficiency, PaCO₂, gas exchange, lung volumes, daytime somnolence or health-related quality of life measures. Also, there was no change in overnight oximetry, transcutaneous CO₂, or the need for supplemental oxygen.

Kelly et al performed a crossover randomized controlled trial to evaluate physiological outcomes and adherence on individuals with hypoventilation randomized to receive Intelligent Volume assured pressure support (iVAPS, with automated selection of ventilator settings) and standard bilevel PAP therapy [67]. Eighteen participants (eight patients with OHS) underwent polysomnography and transcutaneous CO₂ monitoring at baseline and one month after each treatment period. No significant difference was noted between the

treatment arms with respect to lung volumes, respiratory muscle strength, sleep efficiency and architecture, overnight pulse-oximetry and transcutaneous CO₂. The adherence was slightly better in the iVAPS mode with greater average daily use of by one hour and better subjective measure of ventilator comfort than the fixed pressure support mode, probably because of the lower median pressure support with the iVAPS mode needed to achieve the comparable respiratory outcomes [67].

In summary, (a) AVAPS possibly may demonstrate better treatment adherence secondary to better patient-ventilator synchrony and lower median pressure support; (b) No significant improvements were noticed for AVAPS modality when compared to bilevel PAP therapy with regards to patient-outcomes (such as daytime hypercapnia, nocturnal gas exchange, sleep architecture and efficiency and health-related quality of life measures); and (c) We need to undertake larger, adequately powered randomized controlled trials in to better understand the role of such treatment modalities.

NIV in AHRF in OHS

Patients with OHS often present with symptoms of acute hypercapnic respiratory failure (AHRF) with a need for hospitalization and noninvasive ventilation. The role of non-invasive ventilation during an episode of AHRF in COPD patients is well documented. Previous studies on similar effects in patients with OHS have been retrospective and limited by small sample size. Carrillo et al conducted a study aimed at assessing the efficacy of NIPPV in OHS patients during an episode of AHRF with the hypothesis that they would respond similarly to patients with COPD with a similar presentation [66]. Consecutive patients (n=716) who were admitted to the ICU with AHRF were identified as either OHS or COPD. Patients with arterial pH less than 7.35 and PaCO₂ > 45 mmHg were identified as being in AHRF. NIPPV (bi-level PAP ventilation) was initiated in any patient with symptoms of respiratory distress with moderate to severe dyspnea and with accompanying use of accessory muscles of respiration, respiratory acidosis and respiratory rate > or equal to 25. Patients who received NIV were followed over a period of 1 year after discharge to as assess hospital readmissions and survival. Patients with OHS had lower rates of late NIPPV failure (defined as a new episode of AHRF with respiratory acidosis at least 48 hours after initial stabilization), better outcomes seen as lower rates of readmission to the ICU and lower ICU and hospital mortality, and lower PaCO₂ on hospital discharge when compared to patients with COPD. The results of the study suggest that patients with OHS in AHRF respond more favorably to NIPPV with improved outcomes, gas exchange and mortality than patients with COPD [66].

Oxygen therapy in OHS

In a recent double-blind randomized crossover study, Hollier et al investigated the effect of moderate concentrations of supplemental oxygen and on changes in PaCO₂, pH and respiratory variables over a period of time in patients with stable untreated OHS and compared this to healthy controls [90]. Arterialized-venous PCO₂ (PavCO₂), pH, minute ventilation and dead space fraction were measured at baseline, then every 5 min over a 20 min of exposure to They both 28% and 50% FiO₂. At FiO₂ of 28%, PavCO₂ increased by 0.3 ± 0.2 kPa and was accompanied by an increase in dead space fraction of 1 ± 5% (p =

0.012) without any significant change in minute ventilation. At FiO_2 of 0.50 PavCO_2 increased by 0.5 ± 0.4 kPa, induced acidemia and increased dead space fraction by $3 \pm 3\%$ with a reduction of minute ventilation of 1.2 ± 2.1 L/min [90]. In summary, hyperoxia induced by increments in FiO_2 initially caused minimal changes in pH or minute ventilation, but further increments in FiO_2 caused hypoventilation and acidemia. The effect on ventilation was more pronounced in obese patients with hypercapnia receiving 100% FiO_2 , with marked decrease in minute ventilation and increase in PavCO_2 [91, 92]. These findings suggest that a greater degree of respiratory depression occurs with higher oxygen concentrations. The mechanisms by which hyperoxia induces hypoventilation in OHS remain unclear. Inter-individual variability of response, in the study suggests OHS patients with higher baseline PCO_2 and serum bicarbonate are more likely to develop worsening hypercapnia to hyperoxia [90]. But, the precise factors that underlie such inter-individual differences and the role of concomitant NIPPV remain less clear [92]. Clinicians should be aware and monitor for PaCO_2 retention in states of acute-on-chronic hypercapnic respiratory failure related to OHS.

Long term effects, mortality and prognosis of PAP therapy

Limited data is available on the long-term effects of NIPPV for OHS. In a prospective observational study, Heinemann et al studied the long term effect of home nocturnal ventilation with NIPPV on lung function and gas exchange on patients with OHS [93]. In 35 patients they performed physiological measurements prior to initiation of NIPPV and repeated them at 12 and 24 months after NIPPV therapy. Significant improvements in pulmonary function tests (total lung capacity, vital capacity, residual capacity and expiratory reserve volume) were seen at 12 months. There was no further change in such measurements at 24 months. Blood gas analysis showed significant decrease in wake daytime PaCO_2 and base excess with improved hypoxemia at 12 and 24 months. No significant difference in alveolar-arterial gradient was seen. Significant improvement in polycythemia was seen at 12 months and mortality at 24 months was 9% [93].

Priou et al performed a retrospective study to compare long term outcomes and treatment adherence in consecutive patients discharged home with NIPPV for OHS. Patients were initiated with NIPPV under stable conditions following an episode of acute hypercapnic respiratory failure. In 92 of the 130 patients with OHS, NIPPV was initiated in a stable condition and in 38 following ICU management of an acute episode of acute hypercapnic respiratory failure with a follow-up period of 10 years. At 6 months, there was significant improvement in PaO_2 , PaCO_2 , bicarbonate, and pH. No significant difference in the arterial blood gas results were noticed between the acute and stable groups. On Kaplan-Meier analysis, 1-, 2-, 3-, and 5-year survival probabilities were 97.5%, 93%, 88.3%, and 77.3%, respectively with no significant difference noted between the two groups. Analysis of possible prognostic factors like heart disease, baseline $\text{PCO}_2 > 50$ mmHg, baseline serum bicarbonate > 30 meq/dL and hypoxia showed that supplemental oxygen was the only independent predictor of mortality [77].

Budweiser et al performed a retrospective analysis on patients with OHS on NIPPV to assess the long-term survival and predictors of mortality [94]. A total of 126 patients with a

diagnosis of OHS were assessed at 3–6 months following hospital discharge. In these patients who were receiving NIPPV at home, they found significant improvement in arterial blood gases and lung volumes. Additionally, they found significant decrease in hematocrit and CRP levels. During the mean observation time of 41.3 months, the all-cause mortality was 12.7%. After 1, 2 and 3 years, the survival was 97%, 92% and 70%. Analysis of factors predictive of mortality showed that baseline $\text{PaO}_2 < 50$, $\text{pH} > 7.44$, white blood cell count of $> 7,800/\text{mm}^3$ were independent predictors of mortality. After initiation of NIPPV, a reduction in both nocturnal PaCO_2 by $> 23\%$ and hemoglobin level compared to baseline were associated with better prognosis [94].

Hypoxia has been shown to be an independent predictor of mortality in OHS [77, 94]. Pulmonary arterial vasoconstriction secondary to hypoxia may cause pulmonary arterial hypertension but there appears to be significant inter-individual differences in such a response [95–97]. In a study by Held et al, a cohort of 18 patients were identified to have with pulmonary hypertension and hypoventilation [68]. The goal of the study was to characterize the association of pulmonary arterial hypertension due to hypoventilation and exercise capacity (with preserved cardiac index), and the effect of noninvasive ventilation on hemodynamics and functional capacity. Functional capacity was characterized by a 6 min walk test and pulmonary hypertension was confirmed by either right heart catheterization or echocardiography. All 18 patients were treated with NIPPV and were followed up 3 months after initiation of the ventilation therapy to assess for changes from baseline hemodynamics and functional capacity. Significant improvement in both mean and systolic pulmonary arterial pressure, pulmonary vascular resistance, six minute walk distance (in meters), increase in maximum work rate, right ventricular systolic function, lung volumes and gas exchange. These findings demonstrate the favorable effect of NIPPV on hemodynamics and functional capacity in these patients [68]. Similar findings were documented in another study by Castro et al who demonstrated the hemodynamic effects of NIPPV in patients with OHS that was measured by echocardiography and six-minute walk test [98]. After 6 months of NIPPV therapy, significant decrease in pulmonary arterial pressure and improvement in six-minute walk distance was seen [98].

Withdrawal from positive airway pressure therapy has been shown to be associated with worsening nocturnal gas exchange in patients with chronic respiratory insufficiency related to restrictive thoracic disorders [99]. The recovery of chemoreceptor secondary to improved gas exchange following NIPPV constitutes a very important factor in producing both clinical and functional improvements in patients with OHS [75]. De Miguel Díez et al performed an open-label prospective design study of the effect of withdrawal of NIPPV on 12 patients with OHS who had been on NIPPV for at least one year [100]. The hypothesis was that improved gas exchange at the end of one year of NIPPV with normalization of central controller response to the chemical stimuli. After a 3-month follow-up of these patients, there was no change in body weight, lung function, daytime or nighttime arterial blood gases or nighttime oxygen saturation. The study was limited by the small sample size and short follow up. A follow up within 3 months might be too short to predict the appearance of respiratory insufficiency later [100]. In summary, based on the above findings of long-term effects of NIPPV in OHS patients, NIPPV can be noted to improve lung function as evidenced by significant improvement in lung volumes, better gas exchange and is

associated with reduced mortality. Moreover, NIPPV improves pulmonary hemodynamics and functional capacity in patients with comorbid pulmonary hypertension.

Adherence to therapy

Long-term adherence was better in patients with OHS when compared to patients with OSA alone. In mild OSA the discontinuation rate is expected to be between 12% to 25% [101, 102]. Priou et al in their study found the discontinuation rate of 20% at 3 years and with average nightly use of > 7 hours with female sex being the only significant predictive factor for NIPPV discontinuation [77]. Budweiser et al, observed similar adherence to NIPPV in OHS patients of 82% and an average nightly use of 6.5 hours after a mean follow-up of 41 months [94]. Mokhlesi et al performed a retrospective study that studied the effect of PAP therapy on hypercapnia and hypoxia in patients with OSA and daytime hypercapnia. In patients with OSA (AHI > 10/hr) and hypercapnia (stable daytime PaCO₂ > 45 mmHg) on PAP therapy, 45% of patients had PAP adherence more than 4.5 hrs/day and the average drop in PaCO₂ was 7.7 ± 5 mmHg, compared to 2.4 ± 4 mmHg (in patients with less than 4.5 hours per day) and average increase in PaO₂ was 9.2 ± 11 mmHg compared to 1.8 ± 9 mmHg in patients whose adherence was < 4.5 hrs/day. A nonlinear relationship between hours of PAP therapy use and improvement in PCO₂ was demonstrated with a plateau in improvement after 7 hours of PAP therapy [103]. The adherence of NPPV is high in patients with OHS, likely because these patients may be perceiving the most health benefits when being adherent to PAP therapy.

Non-PAP treatment modalities in OHS

NIPPV has been shown to be beneficial in patients with OHS by improving diurnal hypoventilation, quality of sleep, improve gas exchange and symptoms associated with hypercapnia and mortality. The benefits are somewhat limited by poor adherence and intolerance in some patients. It has been shown to have a limited impact on weight loss and may not reduce the co-morbidities associated with obesity [104]. Non-PAP treatment options include exercise and rehabilitation, weight reduction, tracheostomy respiratory stimulants and oxygen therapy.

Weight loss has been shown to improve lung function, respiratory muscle strength, and respiratory drive and sleep disordered breathing. Several studies have documented the impact of weight loss by showing significant improvements in pulmonary function testing [105–108] and improvement in gas exchange [40, 105, 109]. Substantial weight loss is needed for such benefits to be realized, which are seldom achieved with medical and conservative approaches alone. Dixon et al performed a randomized controlled trial aimed at determining the effectiveness of conventional (medical) weight loss therapy in comparison to surgically induced weight loss in the management of OSA [110]. The BMI ranged from 35 to 55 Kg/m² with moderate to severe OSA (AHI > 20/hr) prior to bariatric surgery and OHS on PPV were excluded from the study. Patients on the conventional weight loss therapy arm had access to diet, physical activity and behavioral programs. The patients on the surgical therapy arm underwent lap-band procedure. Both groups underwent a polysomnogram at baseline and at the end of 2 years of follow up. The surgical group achieved a significantly greater mean weight loss of 27.8 kg compared to 5.1 kg in the

medical group. Both groups had a significant reduction in total AHI between baseline and two years, with the reduction being more pronounced in the surgical (post lap-band) group with a reduction in AHI of 25 events/hour when compared to a reduction of 14 events/hour in the medical group. The health-related quality of life outcomes were not statistically different between the groups although the surgical group had greater improvement in scores at two years when compared to baseline [110].

In a meta-analysis of RCTs aimed at comparing the effectiveness of bariatric surgery versus non-surgical treatment for obesity, 11 RCTs with 796 participants and mean BMI of 30–52 kg/m² were analyzed. Patients allocated to bariatric surgery lost more weight mean difference –26 kg (95% confidence interval –31 to –21 kg) and were found to have greater improvement in health-related quality of life when compared to individuals who received non-surgical weight loss therapy [111].

Patients with BMI > 40 kg/m² who have failed conservative management for weight loss or with BMI > 35 kg/m² who have obesity-related co-morbidities are candidates for bariatric surgery. Various surgical approaches exist but the Roux-en-Y gastric bypass procedure is considered the gold-standard for weight loss with the best long-term weight loss results [112]. Weight loss secondary to bariatric surgery has been shown to have a favorable outcome in terms of observed improvement of severity of sleep-disordered breathing, daytime and nighttime gas exchange, improved lung volumes and improved respiratory muscle strength [108, 113, 114]. In a recent study Lumachi et al evaluated the impact of weight loss and daytime oxygenation following bariatric surgery on 11 patients with an average BMI 52 Kg/m² and with baseline hypoxia. At three, six and twelve months after surgery, the estimated weight loss was 19%, 26%, and 39%, respectively. At one-year the daytime SpO₂, lung function tests, demonstrated significant improvement compared to baseline [115]. Sustained weight loss post-bariatric surgery has been shown to improve sleep apnea and OHS and can obviate the need for PAP therapy.

De Cesare et al evaluated the long and short term results of malabsorptive surgery in 102 morbidly obese patients. They showed that at before surgery 16 patients were identified as having OHS and 22 with OSA. Maximum weight loss occurred between 12–24 months post operatively at which time none of the patients fulfilled criteria for OHS and only 2 of the patients continued to need CPAP therapy for symptoms of OSA [116]. Similar findings were documented by Marti-valeri et al, wherein 30 morbidly obese patients on non-invasive ventilation by either CPAP or Bi-level PAP therapy (OHS (n=9) and OSA (n=14 patients)) were followed for one year after bariatric surgery. Most patient were able to be withdrawn from NIPPV [117]. In summary, the weight loss from medical management of obesity may not be sufficient when compared to surgical treatment. Benefits of bariatric surgery extend to improvements in BMI, AHI, alveolar ventilation and lack of need for NIPPV in most patients. More importantly, surgical weight loss provides additional metabolic effects such as better control of diabetes and hypertension and an overall reduction in mortality and morbidity [118]. Randomized controlled trials that examine the longer-term effects of surgery in comparison with conventional treatment on weight loss, comorbidities and health-related quality of life are not available so far, so it is unclear if the benefits are maintained over time.

Tracheostomy

Tracheostomy can reduce obstructive events associated with sleep-disordered breathing by bypassing the upper airway [18, 119]. Tracheostomy used to be the only effective treatment for obstructive sleep apnea until Sullivan et al successfully managed five patients with PAP therapy [120]. Since then tracheostomy is seldom performed and is reported in a small subset of patients receiving home mechanical ventilation. El Solh et al have previously reported on postoperative complications of tracheostomy in critically ill morbidly obese patients with BMI greater than or equal to 40. They found that morbid obesity was independently associated with tracheostomy related complications secondary to tube obstruction and malpositioning secondary to excess adipose tissue around the neck [121]. Tracheostomy is currently limited to management of OHS when other options for treatment have failed. No recent publications evaluating long term home ventilation on tracheostomy has been reported.

Pharmacotherapy

Pharmacological agents that alter the ventilatory response to hypercapnia could be considered as adjuncts or alternatives to NIPPV. Acetazolamide, a carbonic anhydrase inhibitor, may stimulate ventilation by decreasing the serum bicarbonate and creating metabolic acidosis.[122] Raurich et al, investigated the relationship between CO₂ response, BMI and plasma bicarbonate concentration, and the effect of acetazolamide on plasma bicarbonate and CO₂ response in 25 patients with OHS in the ICU recovering from acute hypercapnic respiratory failure. Patients with the highest bicarbonate had the lowest CO₂ response. Addition of acetazolamide decreased the serum bicarbonate and improved ventilatory response to hypercapnia. This ventilatory response has been shown to be variable [123–127] and also not high enough to treat OHS [128]. In a recent Cochrane review of 30 randomized controlled trials to determine the efficacy of 25 drugs involving 560 individuals with OSA, medications such as fluticasone, Donepezil, paroxetine and combination of high dose ondansetron and fluoxetine showed improved from baseline AHI and subjective sleepiness during the day. The studies were limited by the small sample size and short duration. Insufficient evidence was found to recommend pharmacological treatment in patients with OSA [129].

Exercise and Rehabilitation

Patients with OHS treated with NIPPV have been shown to improve their functional capacity (as measured by 6 minute walk test) [68, 98]. It is thought that the improved nocturnal ventilation and daytime symptoms might be contributing to increased physical activity during the day [89]. Patients with OHS are likely to benefit from exercise and rehabilitation program, though the benefits and timing of initiation of rehabilitation need to be confirmed with long term randomized control trials.

Conclusion

The prevalence of OHS is bound to increase with the obesity epidemic. OHS is frequently under diagnosed and sometimes misdiagnosed. Left untreated and undiagnosed these patients have a poor health-related quality of life, prolonged hospitalization and worsening

co-morbidities associated with the condition and high mortality. Emphasis to close attention to early diagnosis and institution of therapy is critical to reduce the significant mortality and morbidity of untreated OHS. Recognition of clinical characteristics and predictive factors during overnight polysomnogram and clinic visits may provide early diagnostic clue. A multimodal and multi-disciplinary approach to management with weight loss, rehabilitation programs in conjunction with NIPPV is likely to have a greater impact on cardiovascular, metabolic and HRQoL outcomes [130].

Acknowledgments

Funding support from NIH/NHLBI (5R01HL095748), and PCORI contract (IHS-1306-2505) to SP. The funding institutions did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Figure 1. Kaplan–Meier survival curves (log rank) from respiratory and cardiovascular causes of death in the total group of patients. Panels are referring to daytime PaO_2 (panel a; $P = 0.004$), and daytime pH (panel b; $P = 0.0034$) with supplemental oxygen as described above and leukocytes (panel c; $P = 0.0184$). The cut-off values used are indicated within the plots. Reproduced with permission from reference [94].