

The Obesity Hypoventilation Syndrome

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We only need to look around us to see that we are in an epidemic of obesity and obesity-related medical problems. The obesity hypoventilation syndrome is a disorder in which an obese person with normal lungs chronically hypoventilates. Obesity impairs ventilatory mechanics, increases the work of breathing and carbon dioxide production, results in respiratory muscle dysfunction, and reduces ventilatory response to hypercapnia. Sleep-disordered breathing is present in most patients with the obesity hypoventilation syndrome. When noninvasive ventilation can be successfully introduced, hypoventilation can usually be corrected. Weight loss is the desirable long-term treatment for the obesity hypoventilation syndrome. This paper concisely overviews the physiologic factors that lead to the obesity hypoventilation syndrome and discusses therapies for it. Key words: obesity hypoventilation syndrome, OHS, Pickwickian syndrome, simple obesity, ventilatory drive, compliance, airways resistance, work of breathing, respiratory muscle endurance, sleep apnea syndrome, noninvasive positive-pressure ventilation. [Respir Care 2008;53(12):1723–1730. © 2008 Daedalus Enterprises]

Introduction

Those who requested “Super Size Me” in the 1990s were more likely than not granted their wish. That phrase sold billions of burgers, fries, and sweet drinks. Recent data from the Centers for Disease Control and Prevention reveal that one third of the United States population is now

obese, defined as having a body mass index (BMI) in excess of 30 kg/m², and two thirds are overweight (BMI 25–30 kg/m²) or obese.¹ Excess weight is associated with multiple health problems and with a shorter life expectancy. A 20-year-old white male with a BMI of 45 kg/m² can expect to live 12 years less than a lean white male with a BMI of 18–25 kg/m². A 20-year-old African-American male with a BMI of 45 kg/m² can expect to live 20 years less than if he were lean.²

Charles Dickens’s 1837 description of “a wonderfully fat boy” who seemed to fall asleep in the middle of knocking on a door,³ gave birth to the label “Pickwickian syndrome” for a patient described by Burwell et al in 1956. Their patient fell asleep with a full house of aces over kings in his weekly poker game and was then finally convinced to check into the hospital. His findings included obesity, hypersomnolence, periodic respirations, polycy-

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themia, hypoxemia, hypercapnia (P_{aCO_2} 73 mm Hg), features of cor pulmonale, ventilatory impairment, and reduced hypercapnic drive, which corrected with weight loss. His P_{aCO_2} was 37 mm Hg after an 18-kg weight loss.⁴

The obesity hypoventilation syndrome (OHS) is defined as obesity ($BMI > 30 \text{ kg/m}^2$) with hypoventilation ($P_{aCO_2} > 45 \text{ mm}$) without another coexisting pulmonary, chest-wall, or neuromuscular condition contributing to ventilatory impairment. Simple obesity is defined as obesity without hypoventilation. Though BMI has been used to define obesity, body-fat percentage may be a more accurate measure of obesity. BMI correlates more closely with body fat percentage (measured with bioelectric impedance) in men ($r = 0.89$) than in women ($r = 0.80$).⁵ Most of the medical literature uses BMI to define levels of obesity. Increasing BMI predicts an increased likelihood of OHS. Nowbar et al found that 33 (27%) of 121 hospitalized patients with BMI 35–49 kg/m^2 had OHS, and 14 (48%) of 29 with BMI $> 50 \text{ kg/m}^2$ had OHS.⁶

Compared to patients with simple obesity, patients with OHS visit their physicians more than twice as often, have more than twice the yearly medical fees, and have significantly more hospital days per year. Hospital days were reduced from 7.9 d/y before diagnosis to 2.5 d/y after diagnosis and treatment of OHS in Berg et al's review of health-care utilization in patients with this disorder.⁷ Hospitalized patients with OHS had a subsequent one-year mortality rate of approximately 20% in Nowbar et al's series, which is more than twice the mortality rate of hospitalized patients with simple obesity.⁶

Obesity and Pulmonary Function

Obesity affects respiratory mechanics. Pulmonary function tests are frequently performed with obese patients who have respiratory symptoms or are being considered for surgical procedures. The predicted values for interpreting pulmonary function tests use age and height and are based on a nonsmoking population studied in leaner times. We then must determine if the "abnormal" results in an obese patient's pulmonary function tests are from obesity or a lung disorder.

Patients with mild obesity ($BMI 30\text{--}35 \text{ kg/m}^2$) have significantly lower forced vital capacity (FVC), total lung capacity (TLC), and residual volume (RV) than lean subjects (Fig. 1). Functional residual capacity (FRC) is the volume at which tidal breathing occurs and is determined by a balance of the lungs' tendency to collapse (elasticity) and the chest wall's tendency to expand. FRC is significantly reduced, even in overweight subjects ($BMI 25\text{--}30 \text{ kg/m}^2$). The decline in FVC, TLC, and RV is linear, and the decline in FRC and expiratory reserve volume ($ERV = FRC - RV$) is exponential with increasing BMI (see Fig. 1).⁸ Though the reductions in FVC, TLC, and RV

may be modest, the marked decline in ERV results in tidal respirations near RV, where airway caliber is narrowest.

Central obesity (excess weight located mostly in the abdomen and a waist-to-hip ratio of > 0.95) has more impact on pulmonary function than when excess weight is distributed more around the hips (waist-to-hip ratio < 0.95).⁹

The diffusion capacity of the lung for carbon monoxide consists of contributions from the alveolar membrane and capillary volume of the pulmonary circulation. Some obese patients have an increase in diffusion capacity of the lung for carbon monoxide from an elevation of capillary volume associated with an increase in blood volume and cardiac output.¹⁰ Cardiac output and stroke volume increased with BMI by 0.08 L/min and 1.35 mL for each 1 kg/m^2 of BMI in a series of 700 consecutive patients without coronary disease reported by Stelfox et al.¹¹

Compliance and Resistance

Elastance of the respiratory system is the sum of lung and chest-wall (including diaphragm) elastance. Compliance is the inverse of elastance and measures the change in volume from an applied pressure. Naimark and Cherniack found the compliance of the respiratory system (C_{rs}) to be 119 mL/cm H_2O in seated lean subjects, and 52 mL/cm H_2O in seated obese subjects. C_{rs} declined further, to 43 mL/cm H_2O , in the supine position in the obese subjects, but did not change in the supine position in the lean subjects. Most of the C_{rs} reduction was from reduced chest-wall compliance with obesity. Lung compliance was also reduced.¹² Explanations for reduced lung compliance include an expanded capillary blood volume, or respiring with portions of the lungs below the lower inflection point (of the pressure-volume curve), where lung compliance is reduced. Abdominal surgery further lowers compliance. Pelosi et al found C_{rs} (measured postoperatively on mechanical ventilation) to be 34 mL/cm H_2O in postoperative obese patients, versus 62 mL/cm H_2O in lean patients.¹³

Airways are at their maximum caliber at TLC and are narrowest at RV. Tidal breathing at low FRC causes the obese to respire with greater airways resistance (R_{aw}). Zerah et al found the R_{aw} to be 56% higher in subjects with a mean BMI of 46 kg/m^2 than in those with a mean BMI of 27 kg/m^2 . The higher R_{aw} was related to the decrease in FRC ($r = 0.7$, $P < .001$). The total resistance of the respiratory system is the sum of chest-wall resistance and R_{aw} , and is measured with forced oscillation. Further increase in respiratory-system resistance (beyond the increase in R_{aw}) occurs with increasing obesity, which reflects increased chest-wall resistance.¹⁴

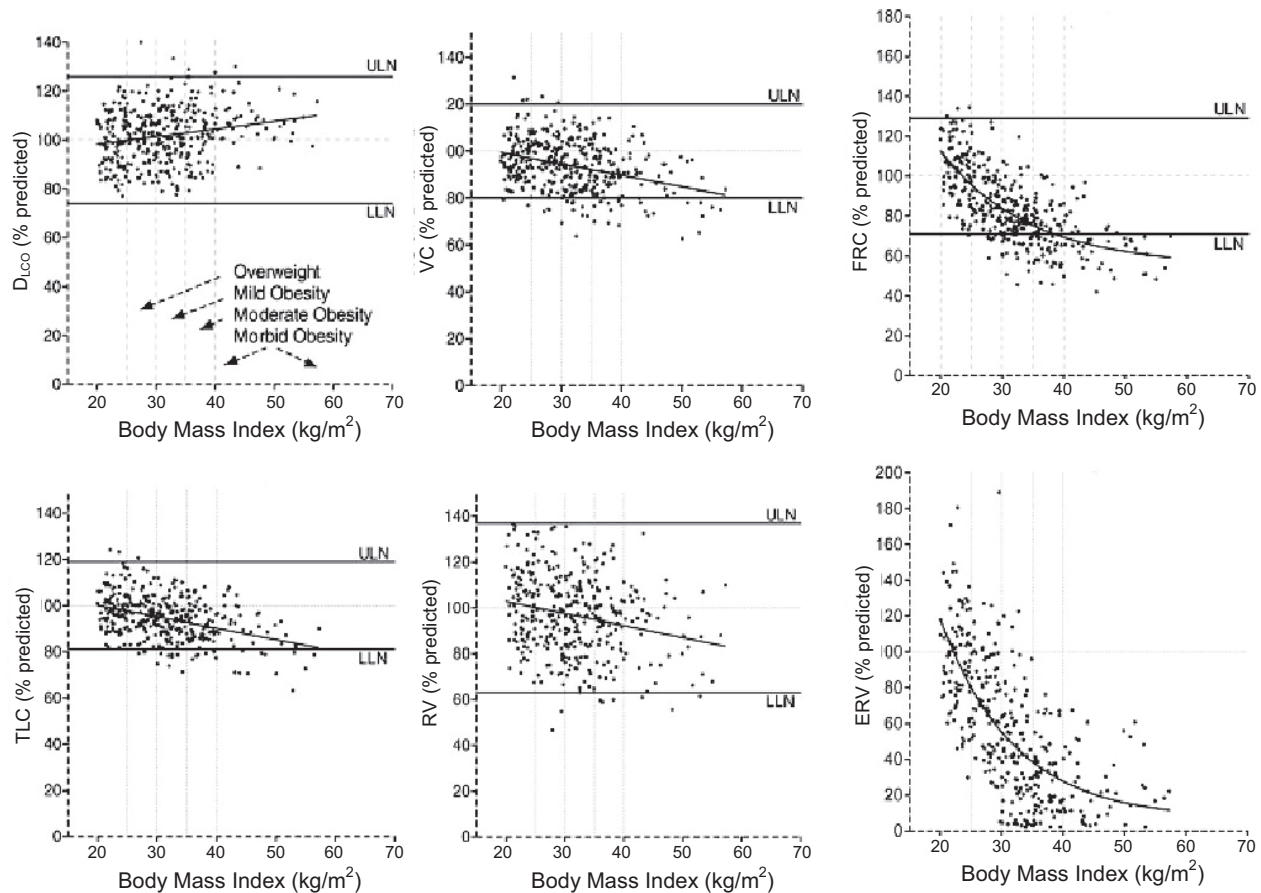


Fig. 1. Changes in pulmonary function measurements with increasing body mass index (BMI). Forced vital capacity (FVC), total lung capacity (TLC), and residual volume (RV) decline linearly. Functional residual capacity (FRC) and expiratory reserve volume (ERV) decline exponentially. The diffusion capacity of the lung for carbon monoxide (D_{LCO}) tends to increase with increased pulmonary capillary blood volume. (From Reference 8, with permission.)

Work of Breathing and CO_2 Production

Reduced compliance and increased resistance increase the work of breathing (WOB). In 1960, Naimark and Cherniack reported WOB to be 540 kg·m/L in obese subjects and 227 kg·m/L in lean subjects.¹² Based on pressure-volume curves from ventilated patients, Pelosi et al estimated WOB to be 1.30 J/L in obese patients, versus 0.52 J/L in lean patients. Most of the WOB increase was attributable to elastic work on the lung and chest wall in the obese patients.¹³

Oxygen consumption (\dot{V}_{O_2}) is increased in obesity. Kress et al found \dot{V}_{O_2} to be 355 mL/min in obese patients and 221 mL/min in lean patients who were sedated and tranquil in the preoperative area. These patients were then anesthetized and paralyzed for surgery, and \dot{V}_{O_2} was then measured with respiration supported. \dot{V}_{O_2} declined to 297 in the obese patients: a reduction of 16%. The lean patients' \dot{V}_{O_2} declined less than 1%. These results indicate

that the portion of \dot{V}_{O_2} required for spontaneous respiration is negligible in most lean subjects but substantial in obesity, which reflects the increased WOB.¹⁵

Carbon dioxide production (\dot{V}_{CO_2}) is directly proportional to \dot{V}_{O_2} by the relationship

$$\dot{V}_{CO_2} = \dot{V}_{O_2} \times \text{respiratory quotient}$$

Respiratory quotient is determined by the fuel being metabolized, and is 1 for carbohydrates and 0.7 for fats. P_{aCO_2} is directly proportional to \dot{V}_{CO_2} and inversely proportional to alveolar ventilation. The obese patient produces significantly more CO_2 and has an impaired ventilatory apparatus with which to clear it.

Respiratory muscle function is impaired with increasing obesity. This may be from a myopathy or the disadvantage imposed on the diaphragm by a large pannus. Maximum voluntary ventilation reflects ventilatory mechanics as well as respiratory muscle function, and declines with increasing BMI at a rate greater than the decline in forced expi-

ratory volume in the first second (FEV_1) and FVC, which suggests an impairment or inefficiency of respiratory muscle function.¹⁶ After bariatric surgery, weight loss (BMI declined from 41.5 kg/m² to 31.7 kg/m²) increased maximum inspiratory and expiratory pressure by 21% and 22%, respectively, and increased respiratory muscle endurance 13%. These improvements were greater than the improvements in FVC (9%), FEV_1 (3%), or lung volumes (7–10%), which suggests a direct effect of weight loss on respiratory muscle function.¹⁷

Central Respiratory Drive

Although obesity impairs respiratory mechanics and creates excess CO₂ production, a feature of OHS is that the patient retains enough pulmonary function to voluntarily normalize P_{aCO_2} . Leech et al documented that his patients were able to voluntarily lower mean P_{aCO_2} from 53 mm Hg to 35 mm Hg, and only 2 of 14 patients could not lower P_{aCO_2} below 45 mm Hg.¹⁸ The ventilatory impairment and increased CO₂ production in obesity are therefore usually not the only explanations for the chronic hypercapnia in OHS.

The ventilatory response (as measured by increased minute ventilation) to induced hypercapnia is reduced even in patients with simple obesity, compared to lean controls, which suggests that obesity impacts the drive to correct hypercapnia.¹⁹ The ventilatory response to hypercapnia is further reduced in subjects with OHS, versus simple obesity, and measurements of central ventilatory drive (including airway occlusion pressure 0.1 s after the onset of inspiratory effort [$P_{0.1}$], diaphragmatic electromyogram, and change in diaphragmatic pressure) are all significantly lower in subjects with OHS than in subjects with simple obesity, despite similar BMIs (Fig. 2).²⁰ Subjects with OHS also have a reduced ventilatory response to hypoxemia.²¹

Sleep Apnea and Obesity Hypoventilation Syndrome

Sleep events contribute to the reduced central drive. When healthy nonobese physicians and respiratory therapists were subjected to a single night of sleep deprivation, the ventilatory response to induced hypercapnia was attenuated, and then was fully restored to baseline after a night's sleep.²² Most, but not all, patients with OHS have sleep apnea syndrome and are therefore chronically sleep deprived. Perez de Llano found that 87% of 54 hospitalized patients with OHS had sleep apnea syndrome, and that 6% had hypothyroidism.²³ As a potentially treatable aspect of OHS, hypothyroidism should always be tested for.

Laaban et al found an 11% prevalence of hypercapnia in 1,141 patients with sleep apnea syndrome. Risk factors for OHS in that study included higher BMI and reduced FVC.²⁴

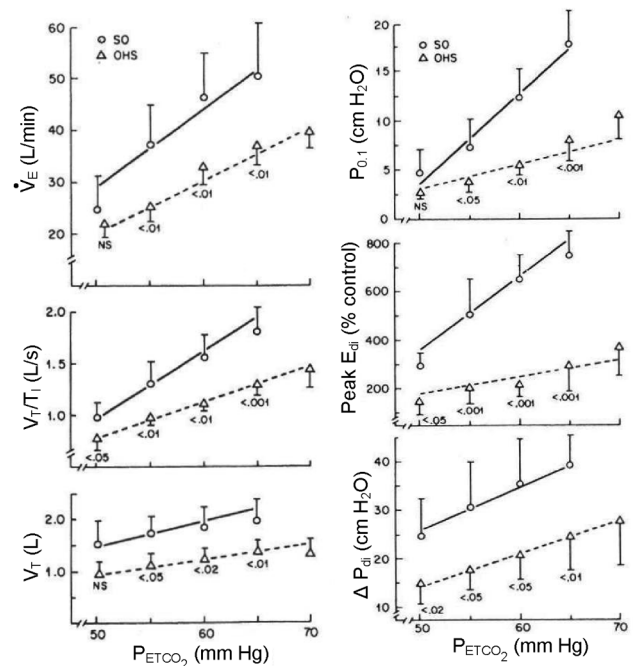


Fig. 2. Ventilatory response to hypercapnia in subjects with simple obesity (SO) versus subjects with obesity hypoventilation syndrome (OHS). Minute volume (V_E), the ratio of tidal volume (V_T) to inspiratory time (T_I), and V_T response to increasing P_{aCO_2} are lower in OHS than in simple obesity. Measurements of ventilatory effort (airway occlusion pressure 0.1 s after the onset of inspiratory effort [$P_{0.1}$], diaphragmatic electromyogram (E_{di}), and change in diaphragmatic pressure [ΔP_{di}], in response to increasing P_{aCO_2} , are lower in OHS than in simple obesity. (From Reference 20, with permission.)

The prevalence of OHS in sleep apnea syndrome is 8–10% if BMI is 30–34 kg/m² and 18–25% if BMI is > 40 kg/m².²⁵ Akashiba et al found the risk factor most strongly associated with hypoventilation was a low mean nocturnal arterial oxygen saturation, which suggests that recurrent nocturnal hypoxemia reduces central respiratory drive. Higher BMI and lower FVC were also significant risk factors.²⁶ Mokhlesi et al found that 25% of 522 obese patients with sleep apnea syndrome had OHS. When patients with obstruction (identified via spirometry) were excluded, 20% had OHS. Elevated bicarbonate (> 27 mEq/L) increased the likelihood of OHS in sleep apnea syndrome to 50%, which suggests that P_{aCO_2} should be measured in these patients. Among patients whose serum bicarbonate was < 27 mEq/L, only 3% with sleep apnea syndrome had OHS.²⁷

The development of OHS has been likened to a vicious cycle in which the recurrent episodes of hypoxemia and hypercapnia in sleep apnea are the inciting events. Sleep deprivation then leads to a reduced sensitivity to hypercapnia. Altered ventilatory mechanics impair recovery and allow more severe hypoventilation.²⁸ However, not all pa-

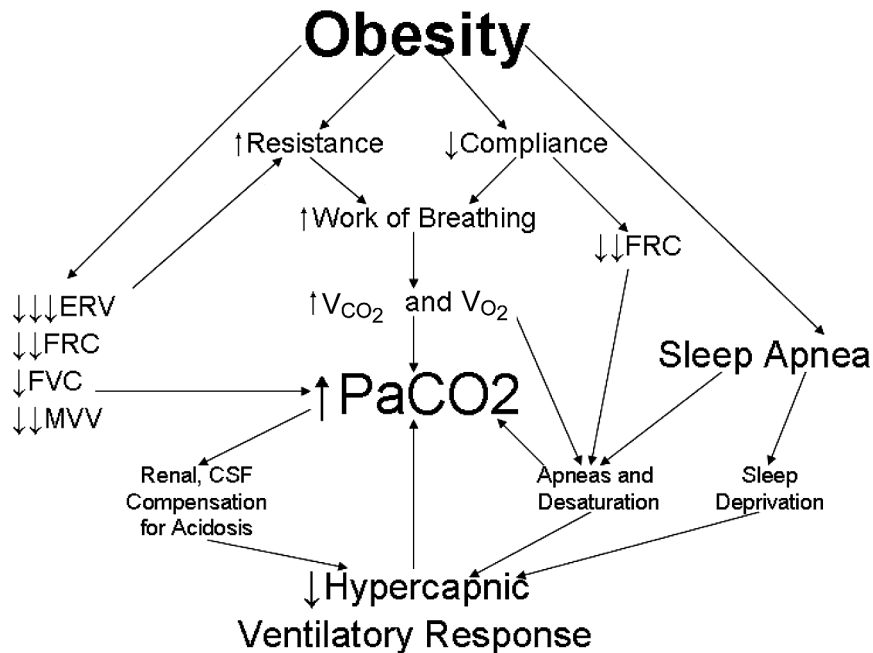


Fig. 3. Mechanism of hypercapnia in obesity hypoventilation syndrome. ERV = expiratory reserve volume. FRC = functional residual capacity. FVC = forced vital capacity. MVV = maximum voluntary ventilation. \dot{V}_{CO_2} = carbon dioxide production. \dot{V}_{O_2} = oxygen consumption. CSF = cerebrospinal fluid.

tients with OHS have sleep apnea syndrome. Obesity hypoventilation syndrome is actually more like a “perfect storm.” Simultaneous overpowering waves from ventilatory impairment, excess CO_2 production, and reduced central response to hypoxemia and hypercapnia combine to submerge the obese patient into the OHS (Fig. 3). The contribution of each of these factors varies with the individual.

Leptin

A 10-year-old Pakistani girl with congenital leptin deficiency was found to have hyperphagia from an early age, which led to morbid obesity (BMI 48.2 kg/m²). Leptin injections substantially decreased her fat mass, without change in lean mass.²⁹ Congenital leptin deficiency is extremely rare in humans. Leptin-deficient mice developed obesity and hypoventilation. When these mice received a leptin infusion, minute ventilation and hypercapnic ventilatory response increased significantly within 3 d, independent of weight, awake and asleep. Obese wild type mice had leptin levels 10 times normal and were eucapnic. Leptin infusions did not increase their hypercapnic ventilatory response.³⁰

In humans the role of leptin is not well defined. Phipps et al found that leptin increased with increasing body fat and was almost twice as high (39.1 ng/mL vs 21.4 ng/mL, $P < .005$) in hypercapnic ($n = 12$) as in eucapnic ($n = 44$) patients with sleep apnea syndrome with the same percent-

age body fat.³¹ Central leptin resistance was suggested as the cause of hypercapnia. A larger study ($n = 185$) by Shimura et al also found that leptin levels increased with increasing BMI and were higher in hypercapnic subjects.³² The theory that there is central-nervous-system leptin resistance in OHS may be supported by the finding that the ratio of leptin in the cerebrospinal fluid to serum was 4.3-fold lower in obese than in lean subjects, which suggests a saturation of transport at the blood-brain barrier. Yet the *absolute* cerebrospinal fluid leptin level was still 30% higher in the obese group, which argues against the idea that low leptin levels in the cerebrospinal fluid leads to hypoventilation.³³

Conversely, in a small study of 6 patients with OHS but without sleep apnea syndrome (apnea-hypopnea index < 5 events/h), the mean leptin level was *lower* in the patients with OHS than in the matched obese eucapnic subjects (35 ng/mL vs 88 ng/mL) before NIV, and leptin increased to 50 ng/mL after NIV and correction of hypercapnia. Hypercapnic ventilatory drive (as measured by the ratio of $P_{0.1}$ to end-tidal CO_2) increased after NIV.³⁴ Those researchers postulated hypoxic suppression of leptin production and leptin as a respiratory stimulant.

Another small study by Lee et al, with 14 patients with OHS, found a significant decline in leptin (from 47.1 ng/mL to 29.8 ng/mL) in the 9 patients who used NIV, and no change (19.6 ng/mL to 20.4 ng/mL) in the 5 patients who did not use NIV.³⁵ Though there were no differences in

baseline clinical measurements, baseline leptin levels differed markedly.

Though leptin appears to have a role in satiety in the congenitally deficient state in humans and increases hypercapnic ventilatory response in deficient mice, it may be an epiphenomenon of obesity more than an active respiratory modulator in nondeficient humans. Future studies might investigate the respiratory effects of cerebrospinal fluid leptin administration in obese wild type mice, and cerebrospinal fluid and serum leptin levels in patients with OHS versus matched eucapnic controls before and after leptin injections, and the effect of these injections on ventilation and the hypercapnic response.

Treatment

Since most patients with OHS can voluntarily normalize their P_{aCO_2} , it is intuitive that an effective respiratory stimulant might benefit some. Acetazolamide would seem a reasonable pharmacologic intervention, because it benefits patients with central sleep apnea and subjects with periodic respiration at altitude. It would need to be coupled with continuous positive airway pressure (CPAP) or NIV in those with obstructive apnea, because it is not clinically effective for OHS.³⁶ This might be a fruitful area for future studies in the treatment of OHS.

Theophylline also appears to stimulate ventilation in central apnea, but has no effect on obstructive apnea and may disrupt sleep.³⁶

Treatment of hypothyroidism may decrease apneas and increase hypercapnic drive, but thyroxine will not correct sleep apnea syndrome in all patients, and they may still need CPAP or NIV.³⁷

Progestational agents appear to stimulate hypercapnic drive in some patients, but are not adequate treatment for sleep apnea syndrome and increase the risk of thromboembolism.^{36,38}

In summary, there currently are no drugs that effectively treat OHS.

NIV has been documented to be an effective intervention for COPD exacerbations with hypercapnia,³⁹ and is usually also effective in correcting the hypoventilation of OHS. Perez de Llano reported on 69 patients who presented to the hospital with OHS and were treated with NIV (Fig. 4). Fifty-four patients tolerated the NIV and in those patients hypercapnia was corrected and remained corrected for > 2 years. Only 3 of those 54 died during follow-up. Of the 15 who did not use NIV, 7 died during follow-up. Sleep studies documented obstructive sleep apnea syndrome in 87% of the 54 patients who used NIV. Thirty-one eventually were treated successfully with CPAP without NIV.²³ The success of NIV and CPAP in treating OHS was confirmed by other investigators.⁴⁰ A prolonged prospective controlled trial with patients with OHS cared for

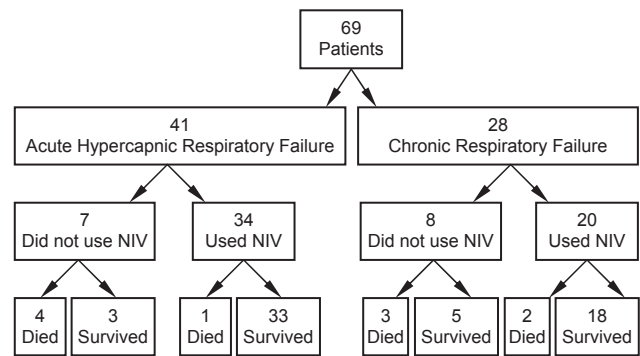


Fig. 4. Outcomes with and without noninvasive ventilation (NIV) in patients with obesity hypoventilation syndrome. Three of 54 patients who used NIV died during follow-up, whereas 7 of 15 patients who rejected NIV died. (Adapted from Reference 23, with permission.)

with and without maintenance CPAP or NIV could be considered unethical. Temporary interruption of CPAP or NIV, while closely monitoring the patients, would be more acceptable during future investigations.

A reasonable approach to the hospitalized patient with OHS is to introduce NIV with an expiratory pressure of 5 cm H_2O and an inspiratory pressure of 10–15 cm H_2O , then expeditiously titrate the pressure up, in 1–2-cm H_2O increments, until hypercapnia and hypoxemia improve. Respiratory rate, minute ventilation, and patient comfort should be closely followed. A higher inspiratory pressure will typically be needed to correct hypercapnia in patients with OHS than in lean hypercapnic patients (with chronic obstructive pulmonary disease or neuromuscular disease) because of the lower respiratory-system compliance and higher chest-wall resistance.

In relatively stable out-patients and after hospitalized patients have improved on NIV (and after acute processes such as infections and edema are treated), patients with OHS should be taken to the sleep laboratory. If obstructive sleep apnea is documented, CPAP should be quickly titrated up until upper-airway obstruction is corrected. An average pressure of 13.9 cm H_2O was needed to alleviate obstructive apneas in a recent study by Bannerjee et al, but 43% of the subjects continued to have > 20% of total sleep time with oximetry-measured oxygen saturation < 90%.⁴¹ If the apnea-hypopnea index remains > 5 events/h or if hypoxemia (> 10% total sleep time with oxygen saturation < 90%) persists despite a high CPAP pressure (> 20 cm H_2O), NIV (bi-level positive airway pressure) would be an appropriate next intervention (Fig. 5). Most of that group will require expiratory pressure of 6–10 cm H_2O and inspiratory pressure 10 cm H_2O higher.²⁵ The small fraction of patients with OHS without sleep apnea syndrome should all be treated with NIV.⁴² Despite these interventions, up to 25% may not become eucapnic, usually due to failure to use the prescribed NIV, but also from

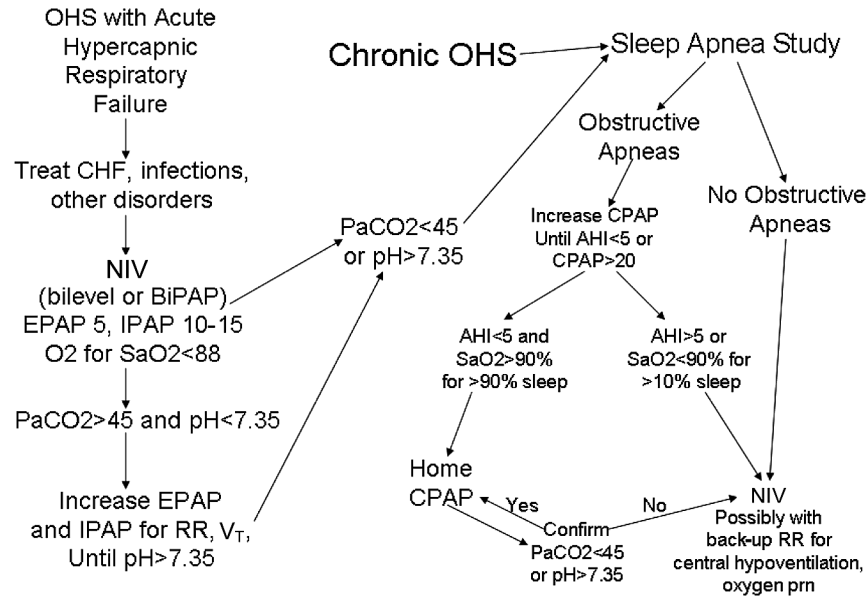


Fig. 5. Algorithm for approach to acute and chronic hypercapnic respiratory failure in obesity hypoventilation syndrome (OHS). CHF = congestive heart failure. NIV = noninvasive ventilation. BiPAP = bi-level positive airway pressure. EPAP = expiratory positive airway pressure. IPAP = inspiratory positive airway pressure. S_{aO_2} = arterial oxygen saturation. RR = respiratory rate. CPAP = continuous positive airway pressure. AHI = apnea-hypopnea index.

other medical factors (central hypoventilation, metabolic alkalosis, and undiagnosed pulmonary or metabolic disorders).⁴³ A minimum ventilator rate may be needed with patients with OHS with central hypoventilation. Tracheostomy with ventilation should be considered in patients with upper-airway obstruction that interferes with NIV, or in severe or refractory OHS. Excessive adipose tissue in the neck can make maintenance of a tracheostomy challenging in these patients.

Though NIV and CPAP are the immediate effective strategies for treating OHS, weight loss is the desirable long-term solution. Medical weight loss, when it can be accomplished, has been associated with correction of hypoventilation in individuals.^{4,23} Unfortunately, diet therapy and medications are usually ineffective in sustaining weight loss. Bariatric surgery has been followed by 16–23% loss of body weight, versus no significant weight loss in medical controls in weight-loss programs.⁴⁴ One study noted a decline in BMI, from 50 kg/m² to 32.6 kg/m², after weight loss surgery, a loss of 34.8%.⁴⁵ In 1981, Sugerman et al reported 3 patients with OHS who corrected their hypercapnia with a mean weight loss from 136 kg to 93 kg after gastroplasty.⁴⁶ In a larger series, in 1992, P_{aCO_2} declined from 53 mm Hg to 44 mm Hg with a BMI decrease from 56 kg/m² to 38 kg/m² after surgical weight loss from gastroplasty or gastric bypass. Spirometry, lung volumes, and maximum voluntary ventilation also improved significantly in those patients.⁴⁷

Summary

Obesity impairs respiratory mechanics and is associated with higher \dot{V}_{CO_2} . Sleep apnea is usually present and leads to repeated episodes of hypoxemia and hypoventilation. Sleep deprivation and nocturnal hypoxemia appear to reduce the central ventilatory response to hypercapnia. The combination of these factors leads to the OHS. NIV and CPAP can correct the hypercapnia. Weight loss, often after bariatric surgery, offers a long-term treatment. As the obese population expands, patients with OHS are likely to be encountered more frequently in our practices.

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