Curr Sleep Medicine Rep (2016) 2:12–19
DOI 10.1007/s40675-016-0035-2

SLEEP AND CARDIOVASCULAR DISEASE (S JAVAHERI, SECTION EDITOR)

Obesity Hypoventilation Syndrome

Carlos Egea-Santaolalla[1,2,3] · **S. Javaheri**[4]

Published online: 23 February 2016

Abstract Obesity is a highly prevalent disorder associated with excess healthcare cost and multiple medical complications. Two major respiratory consequences of obesity are obstructive sleep apnoea and obesity hypoventilation syndrome, which are sometimes comorbid. This comorbidity of obstructive sleep apnoea and obesity hypoventilation most commonly manifest in morbidly obese individuals. However, a small number of patients with the syndrome do not suffer from comorbid obstructive sleep apnoea. Meanwhile, these two phenotypes of obesity hypoventilation syndrome are clinically indistinguishable from each other. Patients with obesity hypoventilation syndrome have poor quality of life and are at great risk for excess hospitalization and premature mortality because of cardiopulmonary complications including exacerbation of respiratory and congestive heart failure. Not surprisingly, long-term management of patients with obesity hypoventilation syndrome is associated with excess healthcare cost as well.

Keywords Hypercapnia · Obesity · OSA

This article is part of the Topical Collection on *Sleep and Cardiovascular Disease*

✉ S. Javaheri
shahrokhjavaheri@icloud.com

[1] Araba University Hospital, Vitoria, Spain

[2] Basque Country University, Vitoria, Spain

[3] Ciberes, Madrid, Spain

[4] Bethesda North Hospital, Cincinnati, OH, USA

Introduction

At present, obesity is the queen of the chronic non-communicable diseases, doubling its prevalence since the 1980s.

In 2014, globally, 10 % of men and 14 % of women aged 18 or over were obese. Moreover, 42 million children under the age of 5 were already overweight in 2013 [1]. In USA, about 35 % of the population suffers from obesity and a significant number are super obese. This rise in the obesity epidemic appears unlikely to revert. The 15-year projections by the WHO, in Spain, for instance, is a further increase to 30 % (men 36 %; women 21 %) with 70 % being overweight [2] (men 80 %; women 58 %). It is, therefore, obligatory for the entire health sector to be aware of all the metabolic, cardiovascular and respiratory complications it may present, allowing not only to exercise preventive measures but also to allow early diagnosis of associated comorbidities, particularly those associated with morbid obesity, to minimize morbidity and mortality.

The two main obesity-associated respiratory problems, each known to the medical world for barely 50 years, are sleep apnoea and the obesity hypoventilation syndrome. Although the link between obesity and secondary alterations [3] in terms of haematologic and cardiac alterations were described over 2000 years ago, it was not until the last century [4] when arterial blood gases were quantified and description of the obesity hypoventilation syndrome [5] also known as Pickwick syndrome became possible. However, this did not include the respiratory disorders during sleep (sleep apnoea) which were described 10 years later in this patient group [6, 7].

Within these obesity-related respiratory complications associated with obesity, obesity hypoventilation syndrome is the one with the worst consequences, giving rise to an increase in

healthcare costs, excess cardio-respiratory comorbidity and mortality [8].

Definition

In the clinical practice, obesity hypoventilation syndrome (OHS) is the frequently first diagnosed, in emergency room, as a results of acute respiratory failure or as result of a sleep study. Due to the different clinical scenarios described in the literature, a Task Force was created by the American Academy of Sleep Medicine, with the aim of unifying the diagnostic criteria of OHS, as described below [9]:

- Arterial blood PCO_2 at sea level of ≥45 mmHg.
- Body mass index equal to or higher than 30 m^2/kg
- Absence of pulmonary or chest wall pathologies that would justify the presence of hypercapnia
- In 90 % of cases, it may coexist with obstructive sleep apnoea, while a remaining 10 % presents with a predominance of nocturnal hypoventilation without significant number of apnoeas or hypopnoeas.

Mention should be made of the fact that the body mass criteria is currently under review, given that in the majority of non-Asian studies published BMI is close to 40 kg/m^2 (prevalence 18 to 31 %), than that established as the diagnostic criteria [10].

Pathogenesis

Obesity hypoventilation syndrome is the by-product of the complex interactions among a number of pathological processes including commonly obstructive sleep apnoea, diminished ventilatory drive, and obesity-related excess metabolic production of CO_2, and structural and functional respiratory impairment

In obese individuals, chronic steady state hypercapnia, hypoventilation, occurs when the normal compensatory ventilatory mechanisms fail to maintain arterial PCO_2 normal. The main physiological alterations of the OHS are obesity-related increased CO_2 production, respiratory disorders of sleep (obstructive sleep apnoea [OSA] and/or sleep hypoventilation), altered pulmonary mechanisms and weakened ventilatory control, with a complex interaction between each one of these factors (Fig. 1).

Obesity

In patients with SA, the higher BMI increases the likelihood of OHS [11, 12] being present. This in part has to do with increasing the severity of sleep apnoea-hypopnoea, as well as

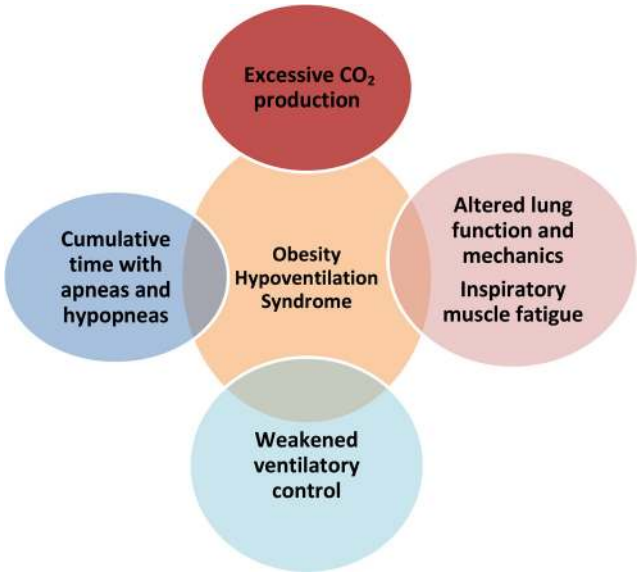

Fig. 1 Pathophysiological alterations in obstructive sleep apnea comorbid with obesity hypoventilation syndrome

increasing CO_2 production, an independent determinant of arterial PCO_2. The latter finding has not been much emphasized in the literature until very recently. As determined by alveolar equation, arterial PCO_2 is directly proportion to CO_2 production ($\dot{V}CO_2$) and inversely proportional to alveolar ventilation ($\dot{V}A$)

$$PaCO_2 = K\,\dot{V}CO_2 \Big/ \dot{V}A, \quad \text{where } K \text{ is a constant}$$

In a prospective study [13], respiratory variables were measured to determine the pathophysiological mechanisms of steady-state diurnal hypercapnia in patients with obstructive sleep apnoea and OHS matched for apnoea–hypopnoea index with patients without hypercapnia. Patients with any known causes of hypercapnia were excluded. Comparing the two groups, the mean values for $PaCO_2$ (52 vs. 40 mmHg) were significantly higher, and PaO_2 (59 vs. 75 mmHg) significantly lower in the hypercapnic patients. However, surprisingly, the mean values for minute ventilation (12.2 vs. 11.6 L/min), alveolar ventilation, breathing rate, VT and dead space did not differ significantly. The major difference between the two groups accounting for steady-state hypercapnia was a significantly greater CO_2 production (336 vs. 278 mL/min) in those with OHS. Importantly, when adjusted for body surface area, the mean values for CO_2 production were similar between the two groups. Interestingly, though the disorder is referred to as hypoventilation syndrome, the absolute level of ventilation is similar between OSA patients with and without chronic hypercapnia. Secondly, these data emphasize the importance of weight loss, which could potentially reverse hypercapnic OSA to eucapnic OSA, hypothetically even in the absence of improvement in apnoea–hypopnoea index. However, with weight loss, OSA also may improve. We emphasize, however,

that the effects of obesity are complex. In this context, the distribution of the excess weight is also important, as the abdominally obese patients present with more hypercapnia compared to those with eucapnic obesity, even when they have the same body mass index [12].

Sleep-Related Breathing Disorders

Patients with OHS may present with obstructive sleep apnoea, hypoventilation while sleeping or a combination of both [14].

a. *Obstructive sleep apnoea* is the largest contributory factor to the etiopathogenesis of OHS: First, OSA is present in about 90 % of the patients with OHS [15, 16], and second, elimination of OSA (whether through positive pressure therapy or tracheotomy) results in eucapnia in many patients even without any significant alteration in the body mass index [17–19].

   A meta-analysis analysing predictive factors of daytime hypercapnia in patients with sleep apnoea/hypopnoea (SAH) found that the apnoea–hypopnoea index (AHI) was higher in hypercapnic than eucapnic patients [11]. Nonetheless, the mean difference was of just 12 events per hour, with both groups presenting an AHI of over 50 events per hour, which would suggest that just the frequency of events *was not the key aspect in the development of daytime hypercapnia*. In this regards, another study [20], in which groups were matched for apnoea-hypopnoea index, showed hypercapnic patients were either heavier or had altered pulmonary function tests when compared to eucapnic group.

   During obstructive apnoea or hypopnoea events, the arterial carbon dioxide pressure ($PaCO_2$) increases for few reasons: not only cessation (or reduction) of ventilation, but continued metabolic production of CO_2 and increased work of breathing with occluded breaths. Eucapnic patients with SAH are capable of normalizing their $PaCO_2$ levels between these breathing events, via compensatory augmentation of alveolar ventilation which increases CO_2 clearance [20]. To accomplish this task, an intact ventilatory control system and normal respiratory system function/mechanics are essential. On the contrary, in patients with OHS, the level of ventilation between events and the duration of the period between apnoea episodes compared to the apnoea length are shorter, meaning the CO_2 that has accumulated during the apnoea events is not cleared appropriately [21, 22], particularly if CO_2 unloading is impaired due to altered lung function (V/Q mismatch, impaired mechanics or diminished intrinsic chemosensitivity). This gives rise to transitory hypercapnia during sleep. Depending on the duration and severity of hypercapnia, renal system response is a decrease in bicarbonate (and increase in chloride) clearance in order to modulate the hypercapnic pH drop. Plasma bicarbonate increases (and chloride decreases), and if the renal system is not capable of correctly clearing the retained bicarbonate before the following sleep period, a gradual bicarbonate build-up will take place. The plasma bicarbonate levels accumulated decrease the ventilatory response to carbon dioxide [23], making it even more difficult to augment ventilation appropriately in response to increases in the carbon dioxide, thus fostering the development of nocturnal and eventually chronic daytime hypoventilation (Figs. 2 and 3) [20, 24, 25].

b. *Sleep hypoventilation*—About 5 to 10 % of individuals with OHS present with sleep hypoventilation, and a $PaCO_2$ elevation during sleep of 10 mmHg or higher, though AHI is less than 5 events per hour of sleep. These patients are clinically indistinguishable from those with concomitant OSA. The percentage of total sleeping time with $SpO_2 < 90$ % has been shown to be associated with the development of waking hypercapnia [11]. Sustained hypoxia delays the warning signals in the event of resistive loading in airway obstruction in healthy individuals and could be an additional factor that contributes to hypoventilation [26].

Altered Respiratory Structure and Functions

a. Abnormal spirometry—In morbid obesity, the accumulation of fat around the abdominal wall and chest contributes to a reduction in the pulmonary volumes and chest wall distensibility. Total lung capacity (TLC), the expiratory reserve volume (ERV) and the residual functional capacity (RFC) are reduced in patients with OHS as opposed to eucapnic obese patients [27, 28]. They have a pattern of breathing that results in an increase in the airway resistances, an increase in the small airway collapse and a decrease in the distensibility leading to increased respiratory effort. These changes are more pronounced in OHS patients than eucapnic obese patient [29, 30].

b. Alteration in the ventilation/perfusion (V/Q)—Obese people have reduced ventilation in the lower pulmonary lobes associated with pulmonary distensibility, difficulty moving the chest wall and diaphragm, and closing some of the alveoli before the end of the expiration [31]. Some patients with OHS also may have a breathing pattern characterized by a low tidal volume and an increased breathing rhythm, thus increasing the dead ventilation space [32]. The combination of the decreased ventilation and the increased perfusion of the lower lobes may cause alterations in the ventilation-perfusion (V/Q), triggering hypoxemia.

c. Respiratory muscle strength and endurance—The contribution of impaired muscle strength to hypoventilation is

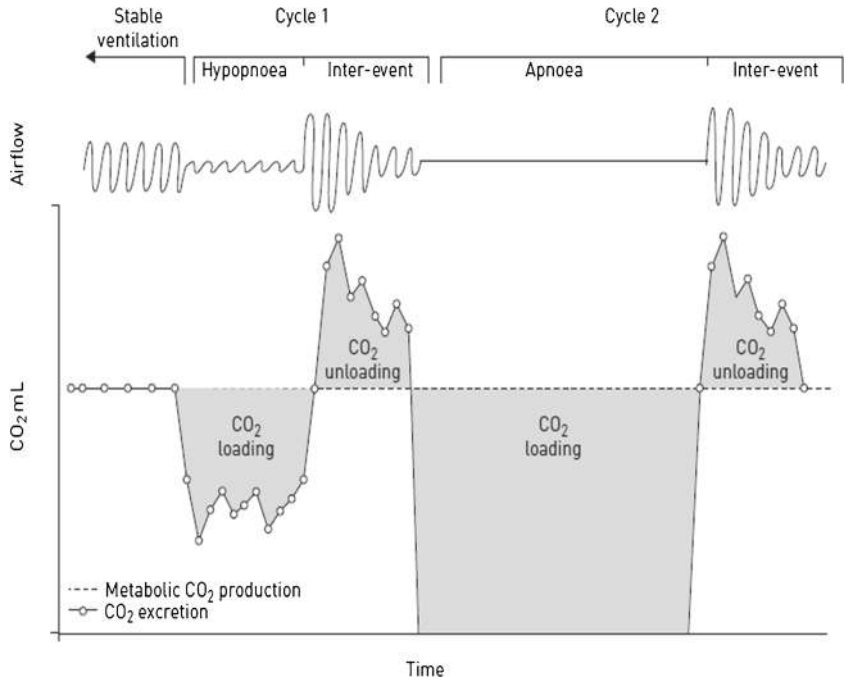

Fig. 2 CO_2 "loading" mechanism during the short breathing events and unloading of the same, as well as the CO_2 loading in more prolonged events

not quite clear, and normal and reduced values have been reported, though it may be reduced in some patients with OHS [33, 34]. OHS patients often experience a moderate reduction of their respiratory muscle strength, which worsens in supine position [35], and when respiratory effort increases [35, 36]. Respiratory muscle endurance [33] and maximum voluntary ventilation [20] are lower in patients with OHS compared to eucapnic obese patients. Maximum voluntary ventilation is closely related to carbon dioxide levels in OHS patients [20].

Altered Ventilatory Control

Severe obesity is associated with a compensatory increase in the conduction of the respiratory impulse compared to normal weight subjects, in order to maintain eucapnia, in spite of the high ventilation loading in the respiratory system [20, 35, 37]. Individuals with OHS do not present this increase in the respiratory impulse [27, 38] and maintain a decreased ventilatory response to hypoxia and hypercapnia [20, 39–42]. However, the impairment in the ventilatory response may improve with continuous positive airway pressure (CPAP) or nasal intermittent mandatory ventilation (NIMV) treatment, showing reversibility. Yet, it is still plausible that an intrinsically diminished chemosensitivity of each individual contributes to CO_2 retention in OHS, a condition similar to that in chronic obstructive pulmonary disease [43]. However, in contrast to that in chronic obstructive pulmonary disease [43], this predisposition of decreased chemosensitivity has not been found to have familial basis when immediate family members of OSA patients with or without hypercapnia were tested [44].

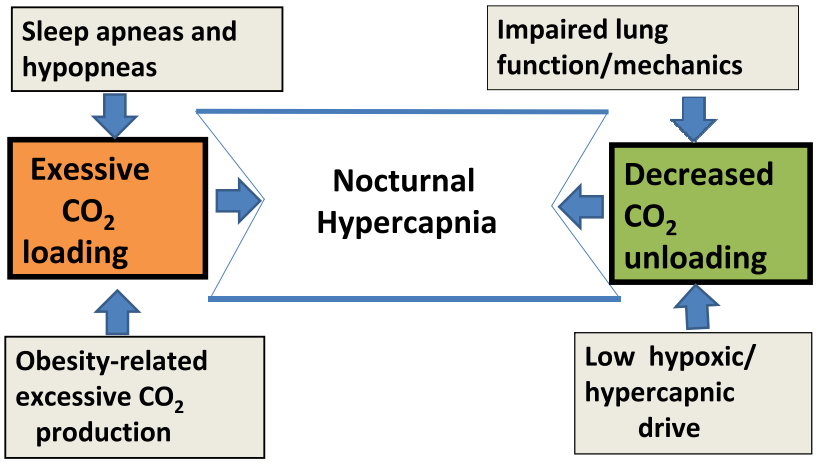

Fig. 3 Determinants of nocturnal hypercapnia is a balance between total CO_2 delivery to the lung and the clearance of CO_2 via the alveolar ventilation. If the balance is impaired, pulmonary veins leave with high partial pressure of CO_2 [20]

However, it is conceivable that familial diminished hypoxic and hypercapnic chemosensitivity could be the underlying reason for hypoventilation in patients with "idiopathic" obesity hypoventilation syndrome, i.e. those without comorbid OSA.

Leptin—Leptin an adipokine produced in the adipose tissue regulates appetite and energy expenditure, and stimulates ventilation. It exerts it effect after crossing the blood–brain barrier [45] and binding with receptors. Compared to wild-type mice, genetically altered obese mice with a leptin deficit are phenotypically similar to patients with OHS. These mice develop obesity, suffer from chronic hypercapnia while awake [45, 46], in spite of increased ventilation which is in response to increased metabolic production of CO_2 [47], and have depressed ventilatory response capacity. Importantly, replacement of leptin reverses chronic hypercapnia [48].

Treatment

Untreated OHS is associated with a high rate of mortality, diminished quality of life and numerous comorbidities, including pulmonary hypertension, right cardiac insufficiency, angina and insulin resistance [49–51]. Therefore, early diagnosis and treatment are mandatory.

The therapeutic goals for OHS patients are to minimize morbidity and mortality. The goals are normalization of the arterial carbon dioxide pressure during wakefulness (that is, $PaCO_2$ <45 mmHg) and sleep; prevention of oxyhemoglobin desaturation during wakefulness and sleep, reversal of erythrocytosis, cor pulmonale and relief of the hypersomnia.

To achieve these goals, a multidisciplinary approach is recommended with the most important treatment options being immediate positive airway pressure therapy and long-term lifestyle changes oriented towards weight loss. Bariatric surgery may be considered for those patients who do not lose enough weight through lifestyle changes or who do not tolerate positive pressure therapy.

Positive Airway Pressure Therapy

Non-invasive positive pressure is the first-line treatment for OHS, regardless of whether the patient presents with a coexistent sleep-related breathing disorder (SAH). It is indicated in all patients with OHS and should not be delayed while the patient is attempting to lose weight.

In patients with OHS, non-invasive nocturnal positive pressure therapy reduces the nocturnal arterial carbon dioxide tension ($PaCO_2$) [52], daytime $PaCO_2$ [16, 53] and sleepiness during daytime [49]. It also improves quality of life [54, 55]. Adherence to nocturnal non-invasive positive pressure therapy is essential for improved $PaCO_2$ [56, 57].

There are no randomized trials that assess the effect of non-invasive positive airway pressure on long-term mortality. However, a prospective study of 130 patients who received nocturnal bilevel positive airway pressure for OHS (along with supplementary oxygen for persistent nocturnal hypoxemia) found 1-, 2-, 3- and 5-year survival rates of 98, 93, 88 and 77 %, respectively [53]. These survival rates were better than the 18-month survival rate of 77 % found in a prospective cohort study of OHS patients, the majority of which were not receiving treatment [50].

Currently, the available treatment options for positive airway pressure therapy are CPAP (continuous positive airway pressure), bilevel PAP and other forms of non-invasive ventilation (NIV). The criteria used for the use of each treatment mode lack uniformity. The current recommendations of some groups, with scientific evidence based on panels of experts' recommendations, is to initiate the use of CPAP if concomitant SAH present (which would include approximately 90 % of the patients with SAHS), and NIMV for those patients in whom the main problem is hypercapnia in the absence of *significant apnoea or hypopnoeas* or in those patients in whom CPAP has failed.

In its NIMV for chronic respiratory failure guidelines, the German Society of Pneumology recommends the use of NIMV in the absence of OSA, if there are significant comorbidities with OSA and in the presence of CO_2 levels of over 55 mmHg for over 5 min, or saturation of under 80 % for over 10 min [58].

The Canadian Thoracic Society recommends first-line NIV treatment in OSA. In this recommendations, CPAP will be possible in patients with a minor degree of nocturnal desaturation and no nocturnal rise in PaCO2, although in patients with OHS who experience significant nocturnal desaturation or a nocturnal increase in PaCO2, bilevel PAP remains the therapy of choice [59].

Although SAH is the norm in patients with OHS, it is essential to determine whether the patient is a CPAP "responder": in some series of clinical cases patients with higher obesity levels (BMI >40), higher carbon dioxide levels and lower nocturnal saturation and pO2 levels have been identified as non-responders to CPAP [60–62].

The *Spanish Sleep Network* group recently published data on patients with OHS [63]. This study is the only reported study to date comparing three alternative treatments for OHS (NIV, CPAP and historic treatments). Conceptually, CPAP is not a hypoventilation treatment. Since the main function of CPAP is prevention of obstructive events, it is likely that patients with high AHI levels can achieve reductions in daytime $PaCO_2$ with CPAP treatment and that patients with low AHI may not. For this reason, we arbitrarily chose to include patients with severe OSA with an AHI greater than or equal to 30 based on the Spanish sleep apnoea guideline [64]. In this

study, the control group exhibited significant improvements in $PaCO_2$ (3.2 mm Hg). Both NIMV and CPAP improved polysomnography parameters, symptoms, and quality of life, with a greater improvement in daytime hypercapnia in the NIMV group. In total, 351 patients were selected, and 221 were randomized. Compared to baseline, at 2 months, the three treatment arms showed improvement in awake arterial PCO_2. The reductions in PCO_2 were 5.5, 3.7 and 3.2 mmHg, with volume-assured ventilation device, CPAP and lifestyle changes, respectively. NIV yielded the greatest improvement in PCO_2 and bicarbonate, with significant differences relative to the control group *but not relative to the CPAP group. In this study*, NIV and CPAP *were equally effective* in improving clinical symptoms and polysomnographic parameters, although NIV was superior in improving respiratory parameters. For this reason, we argue that the CPAP may be the first-line treatment.

Weight Loss

Should be considered as the mainstay in the therapeutic armamentarium for OHS patients and a number of studies are available showing that weight loss improves $PaCO_2$ [65, 66].

Apart from improving the general health, weight loss is associated with decreased CO_2 production, improvement in sleep apnoea severity and compromised respiratory mechanics all of which collectively could improve alveolar ventilation. Weight loss reduces the risk of cardio-respiratory compromise and improves pulmonary arterial hypertension, left ventricular dysfunction and lung function [59–69]. These benefits may occur regardless of whether the weight loss was due to lifestyle modification (that is, diet and exercise) or surgery.

All OHS patients need to change their lifestyles in order to lose weight. For patients in whom, for a variety of reasons, lifestyle modifications are insufficient, surgical approach should be considered.

Pharmacological Treatment

Here, we mention respiratory stimulants and nocturnal supplemental oxygen therapy.

Stimulants (for example, progetins [70, 71] and acetazolamide [72, 73]) have been used in patients with OHS to reverse hypercapnia. However, due to a variety of reasons [74–78] and long-term side effects [79–81], we do not recommend their use.

Nocturnal supplemental oxygen to minimize nocturnal desaturation is an appealing approach which is not recommended since it causes further CO_2 retention [82]. However, nocturnal supplemental oxygen could be used along with a positive airway pressure device if indicated.

Leptin therapy. As noted earlier, leptin plays an important role in control of breathing and OHS in mice model. Pho et al. [83] using high-fidelity polysomnographic recordings measured sleep and breathing patterns in conscious, unrestrained ob/ob mice in a crossover study, comparing subcutaneous leptin vs. vehicle. Authors showed that leptin replacement stabilized pharyngeal patency and increased drive to both the upper airway and diaphragm during sleep. These respiratory responses to leptin replacement therapy indicate that leptin can relieve nocturnal hypoventilation and upper airway obstruction during sleep. How these findings translate to human OHS remains to be established as obesity comorbid with obstructive sleep apnoea is associated leptin-resistance rather than leptin-deficient as it is in ob/ob mice.

Tracheostomy

Tracheostomy is quite effective in patients with obstructive sleep apnoea and OHS as it relieves the upper airways obstruction during sleep, with the resultant improvement in alveolar ventilation and waking $PaCO_2$ [22]. Not all patients regain eucapnia following the tracheostomy given that the upper airway obstruction is just one of the numerous factors contributing to chronic hypoventilation in patients with concomitant OHS and OSA; another factor involved is continued CO_2 production (in the absence of weight loss) and potentially impaired respiratory muscle strength.

Compliance with Ethical Standards

Conflict of Interest Carlos Egea-Santaolalla and Shahrokh Javaheri declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. WHO. Global status report of noncommunicable diseases 2014. Geneva: WHO
2. 22nd European Congress on Obesity (ECO2015), Prague, Czech Republic, May 6–9, 2015. WHO Forecasts Obesity Epidemic in Prague.
3. Kryger MH. Sleep apnea. From the needles of Dionysius to continuous positive airway pressure. Arch Intern Med. 1983;143(12): 2301–3.
4. Colice G. A historical perspective on intensive care monitoring. In: Tobin M, editor. Principles and practice of intensive care monitoring. St Louis (MO): McGraw-Hill Health Professions Division; 1998. p. 1–31.

5. Auchincloss Jr JH, Cook E, Renzetti AD. Clinical and physiological aspects of a case of obesity, polycythemia and alveolar hypoventilation. J Clin Invest. 1955;34(10):1537.
6. Gastaut H, Tassinari CA, Duron B. Polygraphic study of the episodic diurnal and nocturnal (hypnic and respiratory) manifestations of the Pickwick syndrome. Brain Res. 1966;1(2):167–86.
7. Jung R, Kuhlo W. Neurophysiological studies of abnormal night sleep and the Pickwickian syndrome. Prog Brain Res. 1965;18: 140–59.
8. Berg G, Delaive K, Manfreda J, et al. The use of health-care resources in obesity-hypoventilation syndrome. Chest. 2001;120(2): 377–83.
9. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22 (5):667–89.
10. Balachandran JS, Masa JF, Babak M. The obesity-hypoventilation syndrome. Epidemiology and diagnosis. Sleep Med Clin. 2014;9: 341–7.
11. Kaw R, Hernandez AV, Walker E, et al. Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review and meta-analysis of cohort studies. Chest. 2009;136:787–96.
12. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55:1.347–62.
13. Javaheri S, Simbartal L. Respiratory determinants of diurnal hypercapnia in obesity hypoventilation syndrome: what does weight have to do with it? Ann Am Thorac Soc. 2014;11:945–50.
14. Resta O, Foschino-Barbaro MP, Bonfitto P, et al. Prevalence and mechanisms of diurnal hypercapnia in a sample of morbidly obese subjects with obstructive sleep apnoea. Respir Med. 2000;94:240–6.
15. Kawata N, Tatsumi K, Terada J, et al. Daytime hypercapnia in obstructive sleep apnea syndrome. Chest. 2007;132:1832.
16. Piper AJ, Wang D, Yee BJ, et al. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax. 2008;63:395.
17. Kessler R, Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001;120:369.
18. de Llano LA P, Golpe R, Ortiz Piquer M, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128: 587.
19. Berger KI, Ayappa I, Sorkin IB, et al. Postevent ventilation as a function of CO_2 load during respiratory events in obstructive sleep apnea. J Appl Physiol (1985). 2002;93:917.
20. Javaheri S, Colangelo G, Lacey W, Gartside PS. Chronic hypercapnia in obstructive sleep apnea-hypopnea syndrome. Sleep. 1994;17: 416.
21. Berger KI, Ayappa I, Chatr-Amontri B, et al. Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. Chest. 2001;120:1,231–8.
22. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the "Pickwickian syndrome". Chest. 1986;89:627.
23. Javaheri S, Shore NS, Rose B, Kazemi H. Compensatory hypoventilation in metabolic alkalosis. Chest. 1982;81:296–301.
24. Norman RG, Goldring RM, Clain JM, et al. Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model. J Appl Physiol(1985). 2006;100: 1733.
25. Berger KI, Goldring RM, Rapoport DM. Obesity hypoventilation syndrome. Semin Respir Crit Care Med. 2009;30:253–61.
26. Hlavac MC, Catcheside PG, McDonald R, et al. Hypoxia impairs the arousal response to external resistive loading and airway occlusion during sleep. Sleep. 2006;29:624.
27. Lopata M, Onal E. Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. Am Rev Respir Dis. 1982;126:640.
28. Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. J Appl Physiol(1985). 2010;108:199.
29. Zerah F, Harf A, Perlemuter L, et al. Effects of obesity on respiratory resistance. Chest. 1993;103:1470.
30. Behazin N, Jones SB, Cohen RI, Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. J Appl Physiol (1985). 2010;108:212.
31. Rochester DF, Arora NS. Respiratory failure from obesity. In: Mancini M, Lewis B, Contaldo F, editors. Medical complications of obesity. London: Academic Press; 1980. p. 183.
32. Pankow W, Hijjeh N, Schüttler F, et al. Influence of noninvasive positive pressure ventilation on inspiratory muscle activity in obese subjects. Eur Respir J. 1997;10:2847.
33. Collet F, Mallart A, Bervar JF, Bautin N, Matran R, Pattou F, et al. Physiologic correlates of dyspnea in patients with morbid obesity. Int J Obes. 2006;31:700–6.
34. Amanda J, Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. J Appl Physiol. 2010;108:199–205.
35. Sharp JT, Druz WS, Kondragunta VR. Diaphragmatic responses to body position changes in obese patients with obstructive sleep apnea. Am Rev Respir Dis. 1986;133:32.
36. Lee MY, Lin CC, Shen SY, et al. Work of breathing in eucapnic and hypercapnic sleep apnea syndrome. Respiration. 2009;77:146.
37. Steier J, Jolley CJ, Seymour J, Roughton M, Polkey MI, Moxham J. Neural respiratory drive in obesity. Thorax. 2009;64:719–25.
38. Budweiser S, Jörres RA, Criée CP, et al. Prognostic value of mouth occlusion pressure in patients with chronic ventilatory failure. Respir Med. 2007;101:2343.
39. Chouri-Pontarollo N, Borel JC, Tamisier R, et al. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. Chest. 2007;131:148.
40. Monneret D, Borel JC, Pepin JL, et al. Pleiotropic role of IGF-I in obesity hypoventilation syndrome. Growth Horm IGF Res. 2010;20:127.
41. Zwillich CW, Sutton FD, Pierson DJ, et al. Decreased hypoxic ventilatory drive in the obesity-hypoventilation syndrome. Am J Med. 1975;59:343.
42. Jokic R, Zintel T, Sridhar G, et al. Ventilatory responses to hypercapnia and hypoxia in relatives of patients with the obesity hypoventilation syndrome. Thorax. 2000;55(11):940–5.
43. Mountain R, Zwillich CW, Weil JV. Hypoventilation in obstructive lung disease: the role of familial factors. N Engl J Med. 1978;298: 521–5.
44. Javaheri S, Colangelo G, Coarser B, Zahedpour MR. Familial respiratory chemosensitivity does not predict hypercapnia of patients with sleep apnea-hypopnea syndrome. Am Rev Respir Dis. 1992;145:837–40.
45. Kalra SP. Central leptin insufficiency syndrome: an interactive etiology for obesity, metabolic and neural diseases and for designing new therapeutic interventions. Peptides. 2008;29:127.
46. O'Donnell CP, Schaub CD, Haines AS, et al. Leptin prevents respiratory depression in obesity. Am J Respir Crit Care Med. 1999;159: 1477–84.
47. Javaheri S, Schwartz A. Leptin and ventilation in heart failure. Chest. 2015;147:e197–8.
48. Tankersley C, Kleeberger S, Russ B, Schwartz A, Smith P. Modified control of breathing in genetically obese (ob/ob) mice. J Appl Physiol. 1996;81:716–2350.

49. Fletcher EC, Shah A, Qian W, Miller 3rd CC. "Near miss" death in obstructive sleep apnea: a critical care syndrome. Crit Care Med. 1991;19:1158.
50. Nowbar S, Burkart KM, Gonzales R, et al. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004;116:1.
51. Miller A, Granada M. In-hospital mortality in the Pickwickian syndrome. Am J Med. 1974;56:144.
52. Waldhorn RE. Nocturnal nasal intermittent positive pressure ventilation with bi-level positive airway pressure (BiPAP) in respiratory failure. Chest. 1992;101:516.
53. Priou P, Hamel JF, Person C, et al. Long-term outcome of noninvasive positive pressure ventilation for obesity hypoventilation syndrome. Chest. 2010;138:84.
54. Hida W, Okabe S, Tatsumi K, et al. Nasal continuous positive airway pressure improves quality of life in obesity hypoventilation syndrome. Sleep Breath. 2003;7:3.
55. Tsolaki V, Pastaka C, Kostikas K, et al. Noninvasive ventilation in chronic respiratory failure: effects on quality of life. Respiration. 2011;81:402.
56. Heinemann F, Budweiser S, Dobroschke J, Pfeifer M. Noninvasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. Respir Med. 2007; 101:1229.
57. Mokhlesi B, Tulaimat A, Evans AT, et al. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med. 2006;2:57.
58. Windisch S, Walterspacher K, Siemon J, Geiseler H, Sitter H, et al. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Pneumologie. 2010;64: 640–52.
59. McKim D, Road J, Avendano M, Abdool S, Côté F, Duguid N. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011;18:197–215.
60. Resta O, Guido P, Pica V, et al. Prescription of nCPAP and nBIPAP in obstructive sleep apnea syndrome. Respir Med. 1998;92:820–7.
61. Rabec C, Merati M, Baudouin N, Foucher P, Ulukavac T, Reybet-Degat O. Management of obesity and respiratory insufficiency. The value of dual-level pressure nasal ventilation. Rev Mal Respir. 1998;15:269–78.
62. Schafer H, Ewig S, Hasper E, Luderitz B. Failure of CPAP therapy in obstructive sleep apnoea syndrome: predictive factors and treatment with NBL-positive airway pressure. Respir Med. 1998;92: 208–15.
63. Masa JF, Corral J, Alonso ML, Ordax E, Troncoso MF, Gonzalez M, et al. Efficacy of different treatment alternatives for obesity hypoventilation syndrome. Pickwick Study. Am J Respir Crit Care Med. 2015;192:86–95.
64. Lloberes P, Durán-Cantolla J, Martínez-García MÁ, Marín JM, Ferrer A, Corral J, et al. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Spanish Society of Pulmonology and Thoracic Surgery. Arch Bronconeumol. 2011;47:143–56.
65. Martı-Valeri C, Sabate A, Masdevall C, Dalmau A. Improvement of associated respiratory problems in morbidly obese patients after open Roux-en-Y gastric bypass. Obes Surg. 2007;17:1102–10.
66. Boone KA, Cullen JJ, Mason EE, Scott DH, Doherty C, Maher JW. Impact of vertical banded gastroplasty on respiratory insufficiency of severe obesity. Obes Surg. 1996;6:454–8.
67. Sugerman HJ, Fairman RP, Sood RK, et al. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr. 1992;55:597S.
68. Harman EM, Wynne JW, Block AJ. The effect of weight loss on sleep-disordered breathing and oxygen desaturation in morbidly obese men. Chest. 1982;82:291.
69. Nguyen NT, Hinojosa MW, Smith BR, et al. Improvement of restrictive and obstructive pulmonary mechanics following laparoscopic bariatric surgery. Surg Endosc. 2009;23:808.
70. Sutton Jr FD, Zwillich CW, Creagh CE, et al. Progesterone for outpatient treatment of Pickwickian syndrome. Ann Intern Med. 1975;83:476.
71. Lyons HA, Huang CT. Therapeutic use of progesterone in alveolar hypoventilation associated with obesity. Am J Med. 1968;44: 88158.
72. Raurich JM, Rialp G, Ibáñez J, et al. Hypercapnic respiratory failure in obesity-hypoventilation syndrome: CO_2 response and acetazolamide treatment effects. Respir Care. 2010;55:1442.
73. Powers MA. Obesity hypoventilation syndrome: bicarbonate concentration and acetazolamide. Respir Care. 2010;55:1504.
74. Jones JB, Wilhoit SC, Findley LJ, Suratt PM. Oxyhemoglobin saturation during sleep in subjects with and without the obesity-hypoventilation syndrome. Chest. 1985;88:9.
75. Orr WC, Imes NK, Martin RJ. Progesterone therapy in obese patients with sleep apnea. Arch Intern Med. 1979;139:109.
76. Strohl KP, Hensley MJ, Saunders NA, et al. Progesterone administration and progressive sleep apneas. JAMA. 1981;245:1230.
77. Cook WR, Benich JJ, Wooten SA. Indices of severity of obstructive sleep apnea syndrome do not change during medroxyprogesterone acetate therapy. Chest. 1989;96:262.
78. Sharp JT, Henry JP, Sweany SK, et al. The total work of breathing in normal and obese men. J Clin Invest. 1964;43:728.
79. Vasilakis C, Jick H, Del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. Lancet. 1999;354:1610.
80. Douketis JD, Julian JA, Kearon C, et al. Does the type of hormone replacement therapy influence the risk of deep vein thrombosis? A prospective case–control study. J Thromb Haemost. 2005;3:943.
81. Conway WA, Victor LD, Magilligan Jr DJ, et al. Adverse effects of tracheostomy for sleep apnea. JAMA. 1981;246:347.
82. Hollier CA, Harmer AR, Maxwell LJ, Menadue C, Willson GN, Unger G, et al. Moderate concentrations of supplemental oxygen worsen hypercapnia in obesity hypoventilation syndrome: a randomised crossover study. Thorax. 2014;69:346–53.
83. Pho H, Hernandez AB, Arias RS, et al. The effect of leptin replacement on sleep-disordered breathing in the leptin-deficient ob/ob mouse. J Appl Physiol. 2016;120:78–86.