Obesity hypoventilation syndrome

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Extreme weight loss is the ideal treatment for obesity hypoventilation syndrome but is difficult to achieve without bariatric surgery. These patients can have higher risk for this surgery. Therefore, positive airway pressure is the first-line treatment. http://ow.ly/IFyf30nxrAv

ABSTRACT   Obesity hypoventilation syndrome (OHS) is defined as a combination of obesity (body mass index $\geqslant 30$ kg·m^{-2}), daytime hypercapnia (arterial carbon dioxide tension $\geqslant 45$ mmHg) and sleep disordered breathing, after ruling out other disorders that may cause alveolar hypoventilation. OHS prevalence has been estimated to be ~0.4% of the adult population. OHS is typically diagnosed during an episode of acute-on-chronic hypercapnic respiratory failure or when symptoms lead to pulmonary or sleep consultation in stable conditions. The diagnosis is firmly established after arterial blood gases and a sleep study. The presence of daytime hypercapnia is explained by several co-existing mechanisms such as obesity-related changes in the respiratory system, alterations in respiratory drive and breathing abnormalities during sleep. The most frequent comorbidities are metabolic and cardiovascular, mainly heart failure, coronary disease and pulmonary hypertension. Both continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) improve clinical symptoms, quality of life, gas exchange, and sleep disordered breathing. CPAP is considered the first-line treatment modality for OHS phenotype with concomitant severe obstructive sleep apnoea, whereas NIV is preferred in the minority of OHS patients with hypoventilation during sleep with no or milder forms of obstructive sleep apnoea (approximately <30% of OHS patients). Acute-on-chronic hypercapnic respiratory failure is habitually treated with NIV. Appropriate management of comorbidities including medications and rehabilitation programmes are key issues for improving prognosis.

Diagnosis and epidemiology of obesity hypoventilation syndrome
Definition

Obesity hypoventilation syndrome (OHS) is defined by the combination of obesity (body mass index (BMI) $\geqslant$30 kg·m^{-2}), sleep disordered breathing and daytime hypercapnia (arterial carbon dioxide tension (P_{aCO_2}) $\geqslant$45 mmHg at sea level) during wakefulness occurring in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation [1]. Approximately 90% of patients with OHS have obstructive sleep apnoea (OSA) defined by an apnoea/hypopnoea index (AHI) $\geqslant$5 events·h^{-1}. Nearly 70% of patients have concomitant severe OSA (AHI $\geqslant$30 events·h^{-1}) [2]. The remaining patients have non-obstructive sleep hypoventilation with no or mild OSA. The American Academy of Sleep Medicine has arbitrarily defined sleep hypoventilation in adults by the following criteria: P_{aCO_2} (or surrogate such as end-tidal carbon dioxide tension or transcutaneous carbon dioxide) >55 mmHg for >10 min or an increase in P_{aCO_2} (or surrogate) >10 mmHg compared to an awake supine value to a value >50 mmHg for >10 min [3]. This point is relevant because, while the definition suggests a diurnal pathology, overnight polysomnography or respiratory polygraphy is required to determine the pattern of nocturnal sleep-disordered breathing including hypoventilation (obstructive or non-obstructive) and to individualise therapy, particularly the optimal mode of positive airway pressure. A recent European Respiratory Society task force has proposed severity grading for OHS including early stages defined by elevated bicarbonate level and/or sleep hypoventilation [4]. The highest grade of severity was defined by daytime hypercapnia plus cardiovascular and metabolic comorbidities [4].

Epidemiology

Worldwide, nearly one out of three adults are overweight (BMI $\geqslant$25 kg·m^{-2}) and almost one in 10 adults are obese (BMI $\geqslant$30 kg·m^{-2}). Between 1986 and 2005 the prevalence of morbid obesity (BMI $\geqslant$40 kg·m^{-2}) increased five-fold in the USA, affecting one in every 33 adults. The prevalence of a BMI $\geqslant$50 kg·m^{-2} has increased by 10-fold in the USA, affecting one in every 230 adults [5]. According to the most recent estimates from the Centres for Disease Control and Prevention, 7.6% of the adult US population has severe obesity (BMI $\geqslant$40 kg·m^{-2}) [6]. With such epidemic obesity, the prevalence of OHS is likely to increase.

Multiple studies have reported a prevalence of OHS between 8% and 20% in obese patients referred to sleep centres for evaluation of sleep disordered breathing [7–10]. In East Asian populations, OHS may occur at a lower BMI range than in non-Asian populations [8, 11]. In contrast to OSA, in which male predominance has been well established, the prevalence of OHS is similar in men and women [12]. In fact, a recent study by BaHammam et al. [13] reported that among patients referred to the sleep disorders clinic in Saudi Arabia, OHS was more prevalent in women than men (15.6% and 4.5%, respectively) but women with OHS were significantly older than men (mean age 61.5 versus 49.1 years).

Prevalence estimates for OHS vary significantly across studies, owing partly to differences in sample characteristics, differences in disease definitions, and differences in assessment procedures [7]. In populations of OHS patients with concomitant OSA, as the degree of obesity increases, the prevalence of OHS increases (figure S1) [7]. The 1.1% prevalence of OHS found in unselected ambulatory obese was lower than previous estimations based on hospitalised patients or clinical cohorts with sleep breathing disorders [14]. The prevalence of OHS in the general population is unknown but can be estimated. According to the most recent report from the Centers for Disease Control and Prevention, an estimated 7.6% of the adult US population has severe obesity (BMI $\geqslant$40 kg·m^{-2}) [6]. With a conservative estimation that half of people with this degree of obesity have some degree of OSA (AHI >5 events·h^{-1}) and that approximately 10% of the individuals with severe obesity and OSA have OHS, the prevalence of OHS can be estimated as ~0.4% (approximately one out of 260 in the adult US population). Of note, this may be an overestimate of OHS prevalence in countries with a lower prevalence of obesity compared to the USA.

Clinical presentation and diagnosis

OHS is typically diagnosed either when an afflicted patient reaches a high state of acuity, in the form of acute-on-chronic hypercapnic respiratory failure [15], or alternatively, when ambulatory care is escalated to include evaluation by pulmonary or sleep specialists (figure 1) [16]. Unfortunately, a delay in diagnosis is common; the diagnosis typically occurs during the 5th and 6th decades of life, and during this delay OHS patients utilise more healthcare resources than comparably obese eucapnic patients [7]. In one study, 8% of all admissions to a general intensive care unit met diagnostic criteria for obesity-associated hypoventilation (BMI >40 kg·m^{-2}, P_{aCO_2} >45 mmHg and no evidence of musculoskeletal disease, intrinsic lung disease or smoking history). All of these patients presented with acute-on-chronic hypercapnic respiratory failure [17]. Of these patients, nearly 75% were misdiagnosed and treated for obstructive lung disease (most commonly chronic obstructive pulmonary disease) in spite of having no evidence of obstructive physiology on pulmonary function testing.
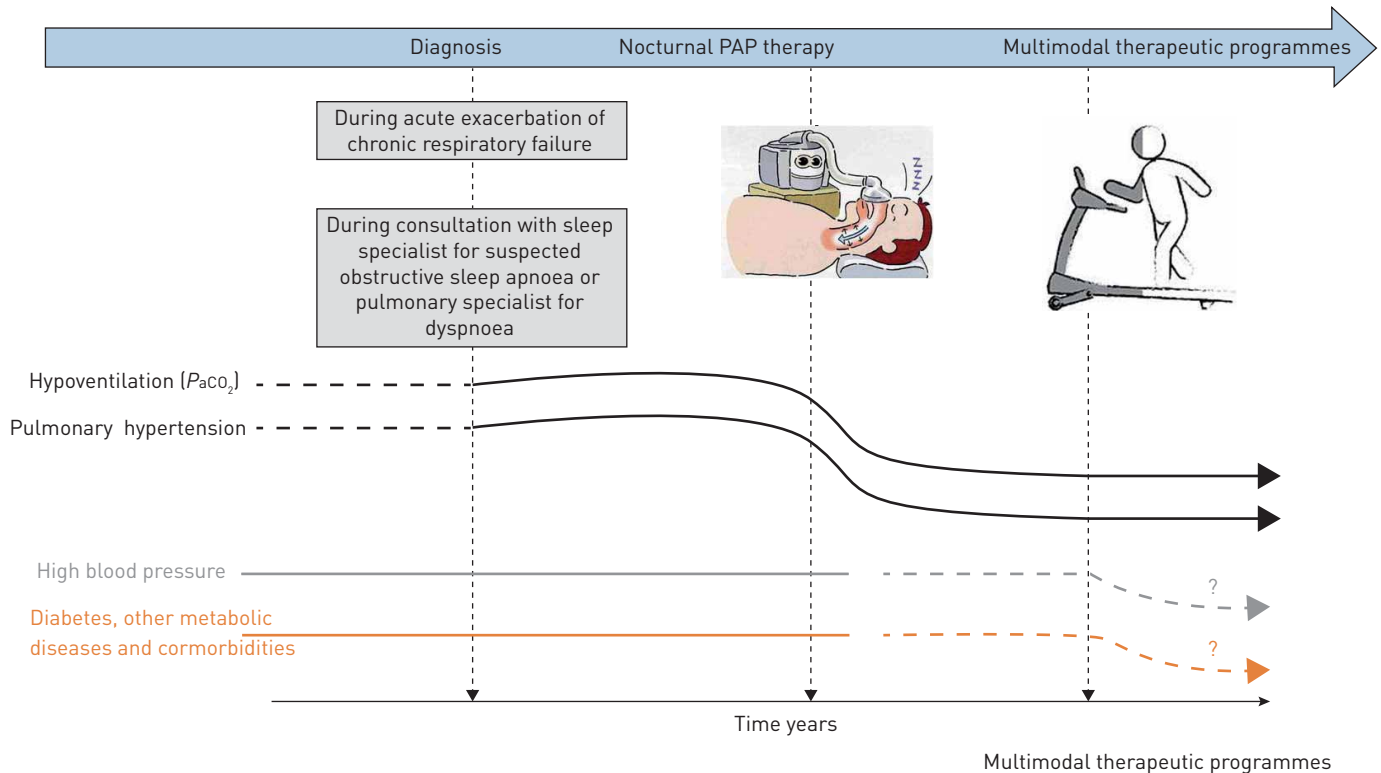
FIGURE 1 Management of patients with obesity hypoventilation syndrome (OHS) from diagnosis to integrated care to modify health trajectories. After being diagnosed with OHS, these patients are typically initiated on positive airway pressure (PAP) therapy (continuous positive airway pressure or noninvasive ventilation). Although respiratory insufficiency improves quite consistently in patients adherent to PAP therapy, pulmonary hypertension may also improve in some patients with OHS. There is no evidence that other cardiovascular and metabolic comorbidities improve with PAP treatment alone. Therefore, a multimodality therapeutic approach is necessary to combine PAP therapy with strategies aimed at weight reduction and increased physical activity. P_{aCO_2}: arterial carbon dioxide tension.

Patients with OHS tend to be severely obese (BMI $\geqslant$40 kg·m^{-2}), have severe OSA ($\geqslant$30 events·h^{-1}) and are typically hypersomnolent. Compared with patients with eucapnic OSA and similar BMI, patients with OHS are more likely to report dyspnoea and manifest cor pulmonale. Table 1 provides the typical portrait of an OHS patient, based on the clinical features of a large combined cohort of OHS patients reported in the literature [7].

The definitive test for diagnosing alveolar hypoventilation is room air arterial blood gas. However, simple tests to screen for OHS may aid clinicians and patients who may be reluctant to undergo an arterial puncture or in clinical scenarios when arterial blood gas analysis is not readily available. The tests evaluated by many investigators to identify patients likely to have OHS are natural consequences of hypoventilation, namely an elevated serum bicarbonate levels and hypoxaemia. Although serum bicarbonate <27 mEq·L^{-1} has a 97% negative predictive value for excluding a diagnosis of OHS, a serum bicarbonate level $\geqslant$27 mEq·L^{-1} should lead the clinicians to perform a confirmatory arterial blood gas analysis [18, 19]. Apart from hypercapnia, increased bicarbonate level may also reflect multimorbidity and polypharmacy, which should be taken into account when used to screen for OHS [14]. Hypoxaemia assessed by pulse oximetry is simple and makes it an attractive tool for identifying obese patients that are likely to be hypercapnic. However, clinicians must recognise that there are a variety of reasons for which severely obese patients may be hypoxaemic but not hypercapnic (e.g. microatelectasis and increased right to left shunt).

Ultimately, a rise in carbon dioxide levels ($\geqslant$45 mmHg) during wakefulness is necessary to define hypoventilation. There are a variety of techniques to measure carbon dioxide such as daytime arterial blood gases, arterialised capillary blood gases, venous blood gases, end-tidal carbon dioxide and transcutaneous carbon dioxide monitoring. Each of these techniques has advantages and disadvantages [20, 21]. The reliable and practical method for identifying sleep hypoventilation is to measure carbon dioxide levels continuously during sleep by end-tidal or transcutaneous monitoring [22]. Improving technologies should greatly expand our ability to identify and quantify nocturnal hypoventilation in sleep laboratories, or even at home.

TABLE 1 Clinical features of patients with obesity hypoventilation syndrome based on an aggregated sample of 757 patients from 15 studies

Clinical features	Mean (range)
Age years	52 (42–61)
Male %	60 (49–90)
Body mass index $kg \cdot m^{-2}$	44 (35–56)
Neck circumference cm	46.5 (45–47)
pH	7.38 (7.34–7.40)
Arterial P_{CO_2} mmHg	53 (47–61)
Arterial P_{O_2} mmHg	56 (46–74)
Serum bicarbonate $mEq \cdot L^{-1}$	32 (31–33)
Haemoglobin $g \cdot dL^{-1}$	15
Apnoea–hypopnoea index	66 (20–100)
S_{pO_2} nadir during sleep %	65 (59–76)
Per cent sleep time S_{pO_2} <90%	50 (46–56)
FVC % predicted	68 (57–102)
FEV_1 % predicted	64 (53–92)
FEV_1/FVC	0.77 (0.74–0.88)
Medical Research Council Dyspnoea class 3 or 4 %	69
Epworth sleepiness scale score	14 (12–16)

P_{CO_2}: carbon dioxide tension; P_{O_2}: oxygen tension; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s. Reproduced from [1] with permission from the publisher.

Pathophysiology of OHS

The pathophysiology of OHS is related to three major mechanisms: 1) obesity-related changes in the respiratory system; 2) alterations in respiratory drive; and 3) breathing abnormalities during sleep (figure 2). The identification of one predominant or a combination of these key mechanisms in a patient is crucial to characterise the OHS phenotype and to anticipate responses to the different modalities of positive airway pressure (PAP) therapies [23]. However, the precise contribution of each of the above-mentioned mechanisms to the genesis of daytime hypercapnia has not been fully elucidated.

Obesity-related changes in the respiratory system in OHS

The excess of adipose tissue in the abdomen and surrounding chest wall reduces lung volume, namely functional residual capacity with a significant decrease in the expiratory reserve volume [24]. Fat deposits have direct mechanical effects on respiratory function by impeding diaphragm motion, reducing lung compliance and augmenting lower airway resistance. Gas trapped due to premature airway closure generates intrinsic positive end-expiratory pressure and favours ventilation/perfusion mismatches [25], with the development of atelectasis of the lower lobes of the lungs. OHS patients exhibit a greater impairment in respiratory mechanics than the morbidly obese without OHS, with associated weakness in respiratory muscles. Overall, there is an increase in the work required for breathing that needs to be compensated by elevated drive from the respiratory centres to the respiratory muscles.

Central hypoventilation in OHS and its correlate: rapid eye movement sleep hypoventilation

Faced with an abnormal respiratory workload, the majority of obese patients develop increased respiratory drive to compensate and thus remain eucapnic. If this increased respiratory drive cannot be maintained, hypoventilation, initially confined to rapid eye movement (REM) sleep, will develop. During REM sleep there is generalised postural muscle atonia and the persistence of ventilation is primarily dependent on diaphragm activity and central drive. REM sleep hypoventilation occurs in OHS owing to a combination of obesity-related mechanical constraints affecting the function of the diaphragm and reduced central respiratory drive. The repetitive occurrence of hypoventilation, initially limited to REM sleep, induces a secondary depression of respiratory centres leading to daytime hypercapnia and obesity hypoventilation syndrome [4]. The high prevalence of central hypoventilation during REM sleep in OHS is hypothesised to be due to dysfunction of the leptin axis. Leptin acts as a powerful stimulant of ventilation and in OHS the central resistance to leptin may lead to a deterioration of respiratory control and also favours cardiometabolic consequences. One major OHS phenotype is morbid obesity with significant impairment
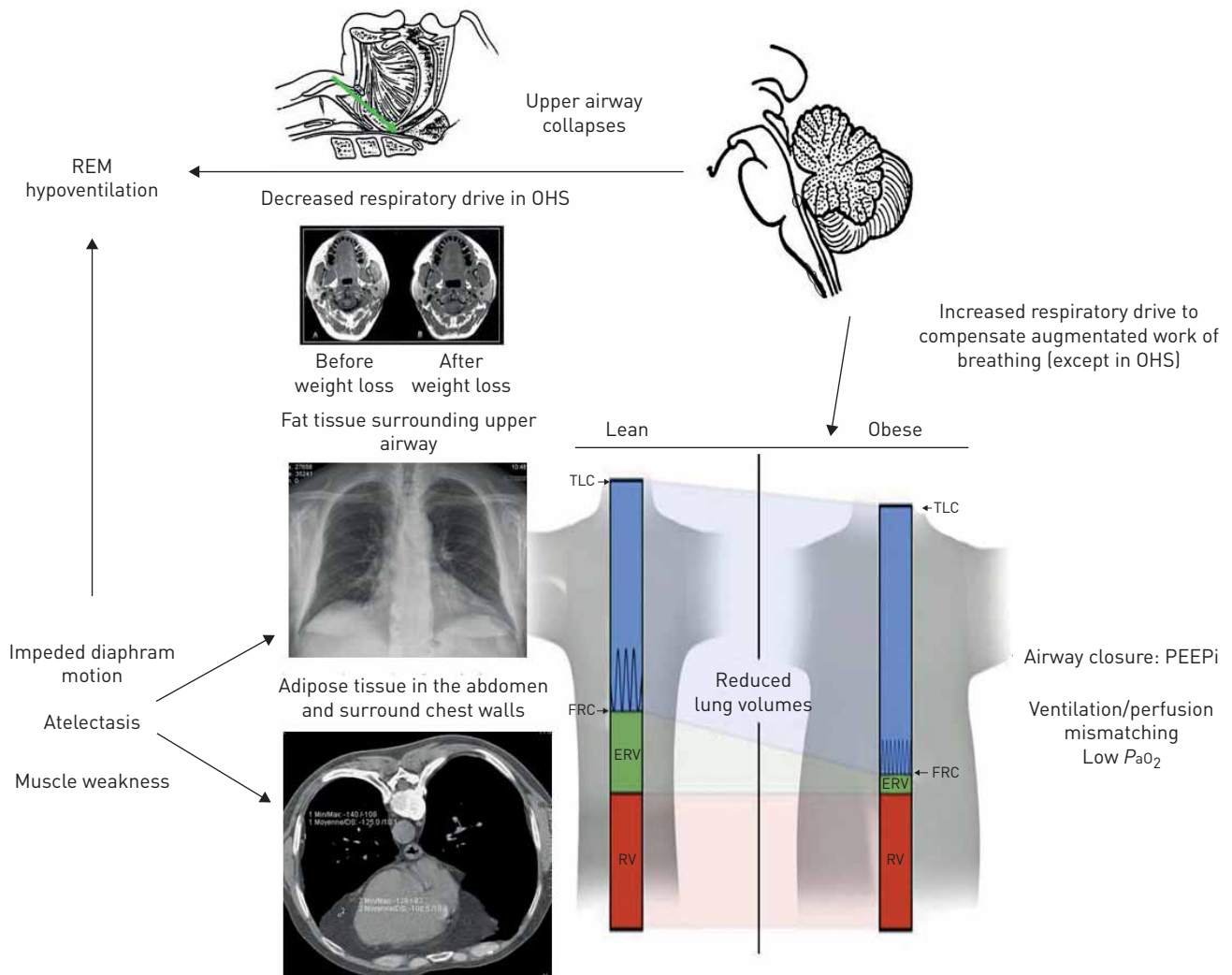
FIGURE 2 Pathophysiology of obesity hypoventilation syndrome (OHS). The implicated mechanisms leading to daytime hypercapnia are, potentially, the obesity-related changes in the respiratory system, central hypoventilation, obstructive sleep apnoeas and hypoventilation during sleep, mainly during rapid eye movement (REM). PEEPi: intrinsic positive end-expiratory pressure; P_{aO_2}: arterial oxygen tension; FRC: functional residual capacity; ERV: expiratory reserve volume; RV: residual volume; TLC: total lung capacity.

in respiratory mechanics, severe hypercapnia and typical REM sleep hypoventilation. This OHS phenotype is usually responsive to noninvasive ventilation (NIV) [26].

Sleep apnoea syndrome in OHS

Obesity-related physiological changes are heightened during supine sleep. The frequent occurrence of OSA, with prevalence close to 90% in the morbidly obese, is explained by a combination of co-existing factors. Excessive fat depositions surrounding the upper airway and reduced lung volume are key features by which obesity synergistically decreases pharyngeal size and increases collapsibility, predisposing the upper airway to closure or significant narrowing during sleep [27]. Fluid overload and lower extremity oedema are likely to be prevalent in the obese (especially in decompensated acute conditions of cardiac or respiratory failure) and may lead to a nocturnal rostral fluid shift [28] from the legs to the neck (owing to the recumbent position) and potentially contributes to narrowing of the upper airway and obstructive events during sleep. Patient with OHS predominantly experience OSA with relatively long-lasting apnoeas and hypopnoeas with insufficient post-event ventilatory compensation owing to reduced activity of the respiratory centres [29, 30]. In this situation, the carbon dioxide overload associated with obstructive respiratory events during sleep contributes to diurnal hypoventilation at the end of the night [30]. This OHS phenotype, which occurs in less severely obese patients without respiratory muscle impairment, exhibiting long-lasting apnoeas and hypopnoeas, but free of REM sleep hypoventilation, is more likely to exhibit a positive response to continuous positive airway pressure (CPAP) [2, 31].

Comorbidities in patients with OHS

Although the current definition of OHS is based on the co-existence of hypercapnia during wake after ruling out other causes of alveolar hypoventilation, a recent European Respiratory Society task force has suggested to include the presence of cardiometabolic comorbidities at the most severe stage [4]. Such a statement suggests that comorbidities are of major importance since they impact healthcare resource utilisation [32] and compromise the outcome of these patients [33, 34].

The prevalence of hypertension in patients with OHS is very high, ranging between 55% and 88% [2, 9, 19, 26, 31, 33, 35–42]. Metabolic and cardiovascular diseases are the most prevalent comorbidities and are usually diagnosed prior to the recognition of OHS [43, 44]. These comorbidities reinforce the frailty of patients with OHS; indeed, among the two clinical presentations commonly encountered in OHS, patients who are diagnosed during an acute exacerbation of chronic respiratory failure present more often with heart failure, coronary heart disease and pulmonary hypertension than patients referred to sleep specialist for suspected OSA [33].

Pulmonary hypertension is the condition likely to be directly linked to chronic hypoventilation; it is highly prevalent with about half of patients with OHS exhibiting pulmonary hypertension [45–47]. NIV may be more effective in improving pulmonary hypertension than CPAP [45, 46]. CORRAL *et al.* [46] hypothesised that NIV may allow for a better control of nocturnal hypoventilation than CPAP, consequently leading to a more significant reduction in pulmonary hypertension. They observed significant improvement in pulmonary hypertension with NIV only and these improvements were accompanied by a concomitant reduction in left ventricular hypertrophy and improvement in exercise performance. However, daytime blood pressure did not improve [46]. Although few short-term studies have specifically assessed the impact of NIV on blood pressure and other cardiometabolic or inflammatory markers, none have reported any significant improvement with NIV alone [2, 26, 31]. Therefore, to further reduce the high cardiovascular and metabolic burden in OHS, there is a need for a multimodal therapeutic approach combining home NIV/CPAP with lifestyle interventions and rehabilitation programmes [48–50].

In addition to significant comorbidities, patients with OHS also have elevated mortality. Several observational studies have reported an all-cause mortality of 24% at 1.5–2 years in untreated OHS patients [32, 37]. Two observational studies including patients with acute-on-chronic hypercapnic respiratory failure described 1-year mortality of 18% (PAP was prescribed to 55% of the patients) [51] and 3-year mortality of 31.3% (proportion of patients treated with PAP was unknown) [52].

PAP treatment: medium- and long-term results

PAP therapy (CPAP or various modes of NIV) is the principal treatment modality in patients with OHS [53, 54]. NIV consists of the application of positive-pressure ventilation, usually with bi-level pressure settings. CPAP consists of a continuous pre-set pressure during the respiratory cycle to prevent obstructive apnoeas and hypopnoeas but unlike NIV, it does not provide additional ventilatory support. Nevertheless, CPAP can permit the unloading of carbon dioxide accumulated during long-lasting complete or partial obstructive events during sleep [55]. There is no clear demonstration of superiority of either mode of PAP therapy and, therefore in practice, it usually depends on several factors including, but not limited to, the predominance of respiratory disturbances during sleep (obstructive events or hypoventilation), adjustment complexity and cost. Both PAP modalities seek to correct sleep hypoxaemia, obstructive events and hypercapnia. Regardless of the chosen modality, PAP titration during sleep is strongly recommended [56].

NIV results

Many observational studies have shown the medium- and long-term benefits of NIV on different outcomes. Ventilatory support produces an improvement in gas exchange, which translates into a significant reduction in daytime wake P_{aCO_2} and an increase in arterial oxygen tension [38, 42, 50, 57–59]. There appears to be a dose–dependent relationship between hours of NIV use and improvements in gas exchange [59]. Symptoms, such a sleepiness and dyspnoea, improve significantly with NIV therapy [38, 42], as do measures of health-related quality of life (HRQoL) [60]. Patients treated with NIV therapy seem to have an improvement in survival compared to other untreated patients [42, 57]. Observational studies have detailed 5-year mortality with NIV treatment from 5% to 32% [33, 34, 42, 60, 61]. Moreover, a reduction in hospitalisation days is observed after NIV treatment in comparison with the pre-treatment period [36, 60].

In a randomised controlled trial (RCT) of 35 patients with mild OHS, 1 month of NIV therapy led to a significant decrease of daytime P_{aCO_2} and an improvement of sleep disordered breathing in contrast to the lifestyle modification as a control group [31]. The largest study (n=307), with two parallel RCTs and performed in Spain (Pickwick project), compared the effectiveness of NIV with a lifestyle intervention as a control group [2, 26]. After 2 months, in the group of 221 patients with concomitant severe OSA, NIV

significantly improved daytime P_{aCO_2} as well as sleep parameters measured by polysomnography, HRQoL and daytime sleepiness. NIV also achieved a significant improvement in respiratory functional parameters such as forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and 6-min walk distance [2]. In addition, in the group of 86 patients without severe OSA, daytime P_{aCO_2}, sleepiness, some HRQoL assessments and polysomnographic parameters improved significantly with NIV in comparison with lifestyle modification [26].

High prevalence of pulmonary hypertension and right ventricular dysfunction have been reported in patients with OHS [45–47, 62–64]. Some studies found potential benefits of NIV on cardiac outcomes. In an observational study of 30 patients, NIV therapy led to a reduction in pulmonary systolic artery pressure in patients who had echocardiographic evidence of right ventricular overload at baseline and a concomitant improvement in the 6-min walk distance test [45]. In a secondary analysis of the Pickwick project, in patients with OHS and concomitant severe OSA, 2 months of NIV therapy decreased systolic pulmonary artery pressure (especially in the group of patients with pulmonary hypertension at baseline) and left ventricular hypertrophy in contrast to the same period of therapy with lifestyle modification [46].

CPAP results

CPAP therapy is a highly effective treatment for OSA. Most patients with OHS have concomitant severe OSA [2, 47]. As such, it is reasonable to expect that CPAP can help improve the gas exchange in a substantial group of patients by stabilising the upper airway. In an observational study, daytime P_{aCO_2} improved in a group of 29 patients with OHS and severe OSA, treated with CPAP for 3 months, although these patients presented with mild-to-moderate baseline nocturnal hypoventilation [41]. In the Pickwick study, MASA et al. [2] compared 2 months of CPAP treatment to lifestyle modification. CPAP therapy significantly improved sleepiness polysomnographic measures of sleep disordered breathing compared to control. Daytime P_{aCO_2} also improved but only after adjusting for CPAP compliance. CPAP therapy led to improvement in some HRQoL assessments and functional respiratory parameters (FEV_1, FVC and 6-min walk distance) but without reaching statistical significance compared to the control group. In a retrospective study of 20 patients with OHS, BERG et al. [36] noted a significant reduction in hospital resource utilisation during the 2 years after initiating NIV or CPAP therapy compared to the 5 years prior to treatment.

CPAP versus NIV results

Some studies compared the medium-term effectiveness between CPAP and NIV. One RCT conducted in 36 patients with OHS, excluding those with persistent nocturnal desaturation despite optimal CPAP titration during polysomnography, obtained similar improvement in daytime P_{aCO_2} and sleepiness after 3 months of NIV or CPAP treatment [65]. In another RCT of 60 OHS patients in a stable condition or after an episode of acute-on-chronic hypercapnic respiratory failure, 3 months of CPAP and NIV treatment obtained similar results in improving daytime hypercapnia, sleepiness, HRQoL measures, PAP treatment compliance and failure [66]. In the largest Pickwick study [2], 2 months of CPAP or NIV treatment in patients with OHS and concomitant severe OSA achieved similar improvements in daytime P_{aCO_2}, arterial bicarbonate, sleepiness and polysomnography measures. Likewise, compliance, dropouts and secondary side-effects were similar with both treatment modalities. The degree of improvement in the three previously mentioned RCTs was similar despite the fact that patients in the studies by PIPER et al. [65] and HOWARD et al. [66] had higher BMI and lower FVC ([66]), but similar baseline P_{aCO_2}.

In the Pickwick study, compared to CPAP, treatment with NIV led to a larger degree of improvement in some respiratory functional outcomes that were not assessed in the RCTs by PIPER et al. [65] and HOWARD et al. [66] (i.e. FEV_1 and 6-min walk distance). Moreover, only NIV had a positive effect on cardiac structure and function by echocardiography [46]. HOWARD et al.[66] observed a certain delay of CPAP treatment efficacy in improving daytime hypercapnia when compared to NIV treatment. This effect may explain the slightly lower medium-term efficacy of CPAP, emphasising the importance of long-term outcomes.

In order to better assess the long-term effectiveness of both PAP modalities, patients with OHS and concomitant severe OSA enrolled in the Pickwick study were followed for a minimum of 3 years and some results for this second phase of the RCT have already been presented in abstract format [67]. There was no significant difference between CPAP and NIV in the primary long-term outcome of hospitalisation days. Other hospital resource utilisation (hospital and intensive care unit admissions and emergency department visits), incident cardiovascular events and survival were similar for both treatments without significant differences in PAP compliance, dropouts and secondary side-effects.

Management strategy

From the data presented to date, it is evident that patients' characteristics or "phenotype of OHS" should be taken into consideration by clinicians when trying to the select the most appropriate mode of PAP therapy. Accordingly, for patients with more pure forms of hypoventilation and with fewer obstructive events during sleep (*i.e.* mild to no OSA), the treatment of choice would be NIV. In contrast, for patients with a greater number of obstructive events during sleep, the first-choice would be CPAP. However, we encourage clinicians to monitor these patients closely for the first 2–3 months after initiating PAP therapy. In case of CPAP therapeutic failure, arbitrarily defined as inadequate clinical response or insufficient improvement in gas exchange during wakefulness or sleep, or continued hospital admissions for acute-on-chronic hypercapnic respiratory failure, it would be clinically prudent to consider switching the patient to NIV therapy (figure 3). However, it is imperative not to label patients as therapeutic CPAP failure if adherence to home CPAP therapy is inadequate [39, 66]. Finally, although an AHI cut-off $\geqslant 30$ events·h^{-1} is partially arbitrary, it is in accordance with the current state of knowledge based on the largest RCT to date [68].

PAP treatment: volume targeted pressure support

Currently, initiation of PAP therapy for OHS consists of CPAP or NIV delivered at fixed pressures usually set during a titration study performed in the sleep laboratory or in a hospital setting. The notion that dynamic respiratory support with varying levels of PAP for different stages of sleep or body position leads to better control of sleep disordered breathing in OHS is empirically appealing. As home ventilator technology has evolved, it has been possible for devices to estimate tidal volume leading to the development of algorithms to adjust delivered inspiratory pressure support to reach a pre-set target tidal volume. Although studies have demonstrated the feasibility of volume-targeted pressure support modalities in effectively controlling sleep disordered breathing in patients with OHS [69], the setup strategy used to deliver therapy is important to consider when assessing the advantages compared to fixed bi-level PAP therapy. If very high (supra-physiological) target volumes are set, the delivered pressure support will be high leading to superior control of nocturnal hypoventilation but with a subsequent detrimental impact on
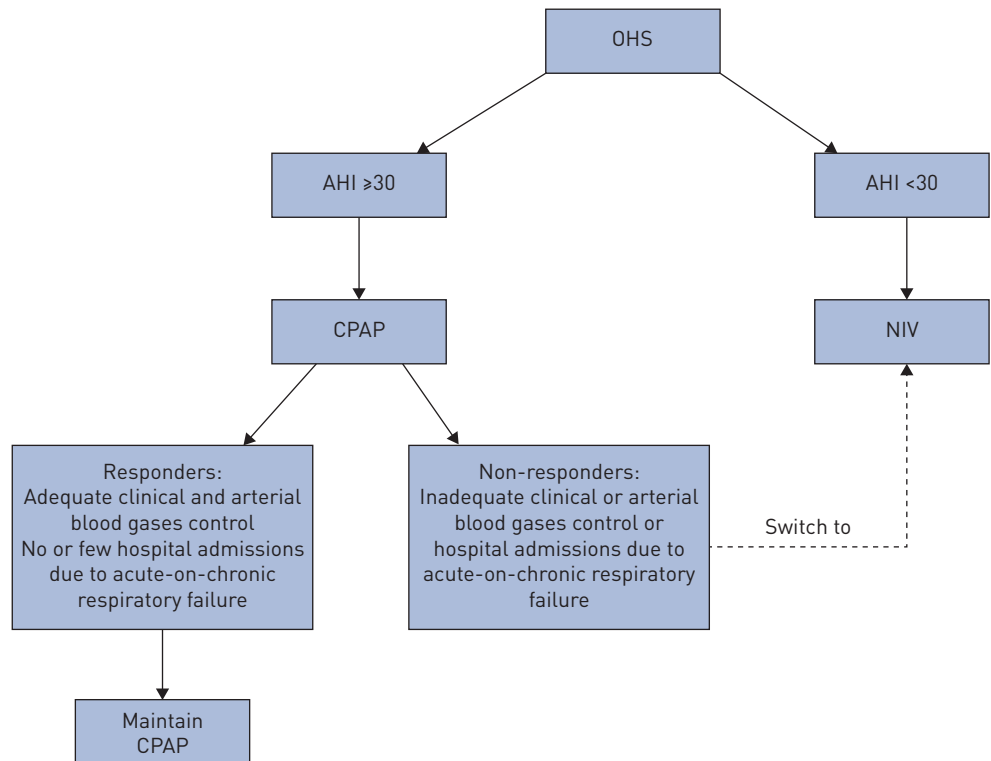

FIGURE 3 Obesity hypoventilation syndrome (OHS) management strategy. Continuous positive airway pressure (CPAP) could be first-line treatment for OHS patients with concomitant severe obstructive sleep apnoea (OSA). Noninvasive ventilation (NIV) should be considered as first-line therapy for OHS patients with no OSA or milder forms of OSA. If patients initially treated with CPAP have no favourable response to therapy despite objectively documented high levels of adherence to CPAP, they should be changed to NIV therapy. AHI: apnoea–hypopnoea index.

sleep quality [70]. Small cross-over trials have indicated enhanced patient comfort and less variability in sleep disordered breathing between body position and sleep stage with volume-targeted as opposed to fixed bi-level PAP in patients with chronic respiratory failure, including patients with OHS [71]. However, when fixed or volume-targeted PAP are established with a clear pre-defined titration policy, the control of sleep disordered breathing and subsequent changes in respiratory failure, HRQoL and physical activity do not significantly differ between modes [72]. In addition to titration of inspiratory pressure support, some auto-titrating ventilators also adjust backup rate automatically. The intelligent volume-assured pressure support algorithm is used to maximise patient triggering in an attempt to promote ventilator adherence. Whilst no studies have utilised this mode in an exclusive population of patients with OHS, it has been used in a mixed population of chronic respiratory failure patients, including patients with OHS. Similar to earlier work with volume-targeted modes, intelligent volume-assured pressure support has been shown to provide similar control of respiratory failure with no objective deterioration in sleep quality and a suggestion of enhanced ventilator adherence in single night and short-term studies. [73, 74] More recently, volume targeted modes have been combined with methods of assessment of upper airway patency facilitating an auto-titrating expiratory PAP level [74, 75]. This offers potential advantages of maintaining upper airway patency and maintaining the patient on the compliant part of the pressure–volume curve. These newer modes have recently been shown to be safe and effective in treating OHS over the medium term (3 months) compared to fixed bi-level PAP [76]. A potential benefit of these modes is that it may facilitate outpatient PAP setup with a device achieving titration in the home environment with subsequent reduction in healthcare utilisation of an in-patient or in-laboratory PAP titration study [77]. Further research is needed to examine long-term outcomes and cost-effectiveness of this strategy. Figure 3 illustrates the standard PAP titration strategy.

In summary novel modes of NIV require careful evaluation to ensure they are safe in controlling sleep disordered breathing and data from different algorithms should be carefully considered. The current data does not suggest a clear clinical advantage of these modes but the clinician should carefully consider their role when individualising patient care.

Non-PAP treatment

The fundamental process underpinning the pathophysiology of OHS is obesity, with its myriad of effects on the respiratory system [78–82]. Therefore, it is pertinent to incorporate weight management strategies into the care of patients with OHS. Whilst PAP therapy appears to be associated with weight gain in both RCTs and prospective cohort studies in patients with eucapnic OSA, it is associated with weight loss in OHS [72, 83, 84]. Interestingly, short-term data comparing lifestyle, CPAP and NIV in OHS demonstrated weight reduction in both lifestyle and NIV groups, but not in those patients randomised to CPAP [2]. An underlying biological rationale for weight gain with CPAP therapy in OSA is unclear. The weight loss demonstrated in patients with OHS starting PAP appears to be related to changes in physical activity [72], again in contrast to eucapnic OSA in which PAP therapy is not associated with changes in activity despite reduced daytime somnolence [85]. Despite the perceived nihilism surrounding rehabilitation in this patient group [86], it appears that these changes in physical activity and lifestyle can be enhanced by a comprehensive nutritional, exercise and rehabilitation programme [48]. Although, the short-term gains achieved by such lifestyle and rehabilitation strategies have not been demonstrated to translate to long-term weight loss or improved clinical outcomes. Bariatric surgery is a cost-effective strategy for managing severe obesity with comorbidity such as OSA with long-term efficacy data [87–89]. The risk of surgery in patients with untreated OHS is high but once successfully established on PAP therapy, these risks appear to be mitigated [90, 91]. No randomised controlled data exist supporting bariatric surgery specifically to treat OHS but extrapolation of data from general obesity would suggest a significant improvement in sleep disordered breathing and thus respiratory failure secondary to the likely weight loss achieved [92].

There are case report data and a small RCT assessing the role of respiratory stimulants, such as medroxyprogesterone and acetazolamide, which augment ventilation in patients with OHS and can be considered in patients intolerant of PAP [93, 94]. One concern with ventilatory stimulants is exposing the upper airway to increasingly negative intrathoracic pressure thereby promoting upper airway collapse. This is clinically relevant since nearly 70% of patients with OHS have concomitant severe OSA. Given the lack of robust data on clinically important outcomes, the failure of respiratory stimulants to alleviate OSA, and the fact that some respiratory stimulants may be associated with ongoing long-term risks, we recommend that patients started on these adjuvant therapeutic approaches be very closely monitored by specialised centres.

The use of isolated oxygen therapy in OHS should be avoided due to the established detrimental effect on ventilation of even moderate oxygen concentrations in stable OHS with the risk of precipitating decompensated respiratory failure [95].

Management of acute-on-chronic exacerbations of OHS

Untreated OHS is associated with significant morbidity including hospital admission and need for respiratory or critical care support [36]. There are no prospective RCTs demonstrating the efficacy of NIV in the management of acute decompensated obesity-related respiratory failure. However, the use of NIV in this clinical context has been incorporated into standard practice [96]. Observational data suggests similar short- and long-term outcomes of patients with acute decompensated obesity-related respiratory failure treated with NIV as those with respiratory failure secondary to an exacerbation of COPD requiring NIV [51]. When assessing a patient presenting *de novo* with respiratory failure thought to be secondary to OHS it is important to fully evaluate for a precipitating cause, such as pneumonia or heart failure [97]. The underlying cause of the decompensation should be aggressively managed concurrently with supportive therapy for respiratory failure. When the decompensation is the result of untreated sleep disordered breathing without an underlying precipitant, *i.e.* idiopathic, the outcomes are good with infrequent failure of NIV [97]. The outcome of obese patients admitted to critical care is favourable and therefore a patient's location of care should be carefully considered [98]. Patients with poor domiciliary PAP compliance, super obesity (BMI >50 kg·m^{-2}) or multi-organ failure should be trialled on NIV in an environment with rapid access to endotracheal intubation due to higher rates of NIV failure, unless NIV is being utilised as the ceiling of care [99]. Patients with obesity presenting to acute general medicine wards for any reason have high rates of undiagnosed chronic respiratory failure and as such, systems should be available to systematically assess this patient group for evidence of respiratory failure facilitating early treatment [37]. Access to NIV should be available within 1 h of presentation to the emergency department for patients with acutely decompensated obesity-related hypercapnic respiratory failure with NIV delivered by specifically trained operators skilled in its application, including interface selection and fitting, along with a strategy to titrate ventilator settings in order to achieve adequate tidal volumes using supplementary oxygen as required (figure 4). NIV should be applied as much as tolerated during the first 24 h of admission and once the respiratory acidosis has resolved, weaned during the daytime can commence with continued nocturnal NIV. Whilst oxygen therapy is frequently required in the initial period, once correction of acidosis and hypercapnia has been achieved (*i.e.* with adequate adherence to nocturnal PAP therapy), oxygen therapy can be frequently weaned to cessation [39, 100]. Once patients have achieved clinical stability and the underlying cause for decompensation has resolved, consideration can be given to inpatient or outpatient assessment for OHS. The decision on location and timing of assessment for home PAP therapy for OHS following an acute decompensated admission depends on the presence of ongoing respiratory failure, in-hospital stability of NIV and local care pathways, but there should be access to rapid out-patient assessment in those patients discharged without therapy. If patients are already established on
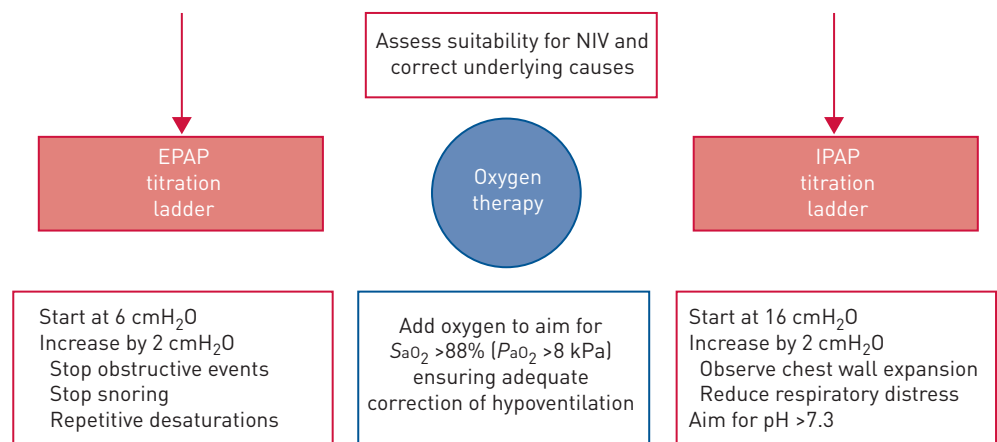

FIGURE 4 Positive airway pressure adjustment in acute decompensated obesity-related respiratory failure. The adjustment of continuous positive airway pressure/expiratory positive airway pressure (EPAP) has the objective of eliminating obstructive events, snoring and intermittent oxygen desaturations. Adjustments in inspiratory positive airway pressure (IPAP) are aimed at eliminating hypoventilation and sustained hypoxaemia. For both EPAP and IPAP, the pressure should increase progressively until attaining the objectives (resolution of upper airway obstructive events and sleep hypoventilation) or until the maximal tolerated pressure is reached. Alternatively, EPAP/continuous positive airway pressure can be adjusted to eliminate obstructive apnoeas and IPAP can be further increased to eliminate obstructive hyponoeas, snoring and hypoventilation. With this strategy, the patient may require lower EPAP and therefore achieve higher levels of pressure support in order to improve hypoventilation [96]. Supplemental oxygen is habitually added to positive airway pressure therapy when an adequate oxygenation level is not achieved despite adequate titration of positive airway pressure therapy. NIV: noninvasive ventilation; P_{aO_2}: arterial oxygen tension; S_{aO_2}: arterial oxygen saturation.

PAP, then consideration should be given to re-evaluation and re-titration of settings or transition from CPAP to NIV if there is evidence of residual sleep disordered breathing on pre-morbid therapy at the time of hospital discharge.

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