Ventilation in the obese: physiological insights and management

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Obesity hypoventilation syndrome (OHS) is observed in 1–10% of obese subjects. OSA is an often-associated condition. When untreated, OHS has a substantial impact on morbidity and mortality. Ventilatory management includes CPAP or non-invasive ventilation. https://bit.ly/43kvTe0

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Abstract

Obesity can have profound adverse effects on the respiratory system, including an impact on pulmonary function, respiratory mechanics, respiratory muscle strength and endurance, gas exchange, control of breathing, and exercise capacity. Lung mechanics are modified by increased pleural pressure resulting from increased abdominal mass and subsequent peripheral airway occlusion and worsening of lung compliance due to reduced functional residual capacity without impairment of chest wall compliance. Arterial blood gases are frequently altered in these subjects and these abnormalities are directly proportional to body mass index. Mechanisms that may account for gas exchange abnormalities are multiple: ventilation/perfusion inequality (responsible for isolated hypoxaemia) and alveolar hypoventilation (responsible for so-called "obesity hypoventilation syndrome" (OHS)). Hypoventilation in obese patients results from a diversity of mechanisms, among which the two most frequently raised are mechanical limitation and blunted ventilatory drive. OHS is frequently underappreciated and diagnosis is frequently made during a first acute exacerbation. Obstructive sleep apnoea is a condition frequently associated with obesity and must be systematically screened for in this population because of its impact on morbidity and therapeutic management. Ventilatory management of these patients will depend on the patient's underlying situation, clinical presentation and physiology, including sleep study results; it may include continuous positive airway pressure or non-invasive ventilation. The goal of this narrative review is to provide a physiological-based overview of the impact of obesity on the respiratory system with a special focus on ventilatory management of patients with obesity-related respiratory disturbances.

Introduction

Obesity hypoventilation syndrome (OHS) is defined as the association of body mass index (BMI) $\geqslant 30\ kg \cdot m^{-2}$, daytime hypercapnia (arterial carbon dioxide tension (P_{aCO_2}) >45 mmHg) and sleep disordered breathing (SDB), after ruling out any other respiratory disorder which may cause alveolar hypoventilation [1]. It is frequently associated with obstructive sleep apnoea (OSA). Prevalence of daytime hypercapnia in subjects with OSA and obesity increases with BMI and approaches 24% when BMI is $>40\ kg \cdot m^{-2}$ [2, 3].

Obesity is a major contributor to morbidity and mortality from non-communicable diseases [4–7]. According to the World Health Organization, in 2022, 890 million people were living with obesity, *i.e.* 16% of the world adult population. Adult obesity has doubled since 1990 and affects most parts of the world [1]. In the USA, the prevalence of obesity in adults aged ⩾20 years increased from 22% in 1988 to 42.5% in 2018 [8]. According to the Centers for Disease Control and Prevention, 7.6% of the US adult population has severe obesity ($\geqslant 40\ kg \cdot m^{-2}$) [8]. Prevalence of OHS in the USA is estimated at ∼0.4% of the general population [1].

The goal of this narrative review is to provide a physiological-based overview of the impact of obesity on the respiratory system with a special focus on ventilatory management of patients with obesity-related respiratory disturbances.

Methods

A comprehensive background literature search was carried out in PubMed and Embase without temporal limits using English, French and Spanish language as a restriction. The MeSH (Medical Subject Headings) terms and keywords used were: "obesity", "respiratory failure", "continuous positive airway pressure", "non-invasive ventilation", "sleep apnoea" and "pulmonary function tests". Abstracts from conferences and commentaries were excluded. In the case of a guideline written by the same society or author group that underwent multiple publications, only the latest version was included. All articles underwent title and abstract screening for relevance to the aims of this review; potentially eligible articles were retrieved for full-text review. Publications for potential citation were identified by one author and agreed by consensus. With this approach, we tried to cover the literature related to OHS, its physiological aspects and ventilatory approach as comprehensively as possible.

Pathophysiological insights regarding pulmonary function tests in obesity

Static lung volumes

Total lung capacity (TLC) depends on the compliance of the respiratory system and the strength of the inspiratory muscles. Obesity affects static lung volumes mainly by modifying the compliance of the respiratory system [9]. Compliance of the lung is decreased but not that of the chest wall. As functional residual capacity (FRC) is the point of equilibrium between elastic recoil of the lung and that of the chest wall, FRC decreases as BMI increases (22% in mildly obese subjects and 33% in severely obese subjects) [10]. Suggested mechanisms for the decrease in lung compliance are increased pleural pressure due to the load of increased abdominal mass and thus a lower FRC, closure of dependent airways during tidal volume (V_T) (increased closing volume) leading to atelectasis and increase in surface tension, increased thoracic blood volume, and mediastinal fat compressing the lung [11–14].

TLC values in obese subjects are either normal or show minor decreases [5, 15–18]; the highest prevalence of pulmonary restriction (TLC <lower limit of normal) is reported in "super obese" (BMI 50–59.9 $kg \cdot m^{-2}$: 26.9%) and "super super obese" subjects (BMI >60 $kg \cdot m^{-2}$: 38.6%) [19]. Extrapolating the presence of pulmonary restriction by measuring forced vital capacity (FVC) yields unreliable results because of unpredictable variations in residual volume (RV) [11]. RV may be affected by premature closure of small airways and/or limitation of excursion of the diaphragm. A meta-analysis of static lung volumes after bariatric surgery showed no significant changes in isolated values of TLC, FRC or RV [20].

In summary, FRC decreases at higher BMI values, resulting in a decrease in lung compliance.

Non-invasive assessment of respiratory muscles

Obesity modifies the geometry of the diaphragm and its pressure-generating capacity: the diaphragm is elevated compared to non-obese individuals and its downward excursion is limited [10, 21]. However, the correlation between maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) or sniff inspiratory pressure and BMI yields inconsistent results. After bariatric surgery, de Campos *et al.* [22] found a significant increase in MIP (from 102% to 113% of predicted) in 24 women who underwent bariatric surgery and decreased their BMI after 6 months from an average of 48 to 35 $kg \cdot m^{-2}$. MEP improved similarly. In a study comparing lean subjects (n=20) with moderately obese subjects (n=31; average BMI 32 $kg \cdot m^{-2}$), both MIP and MEP were above predicted values although slightly lower in obese subjects [21]. de Sant'Anna *et al.* [23] compared MIP and MEP values between non-obese subjects and morbidly obese subjects (BMI 52 $kg \cdot m^{-2}$), and found that values were slightly but not significantly lower in morbidly obese subjects, but within the range of predicted values. A Brazilian study including 31 subjects with moderate to severe OSA and a BMI of 31.2 $kg \cdot m^{-2}$ found MIP and MEP values of 60±22 and 81±22 cmH_2O, respectively, *i.e.* lower than normal values [24]. Interestingly, in these studies, most values were within normal limits or clearly not low enough to cause alveolar hypoventilation. Finally, in subjects under long-term non-invasive ventilation (NIV) for OHS (n=22), Masa *et al.* [25] found markedly reduced values for MIP (55±14 cmH_2O) and MEP (56±13 cmH_2O), which did not improve under NIV. Conversely, Janssens *et al.* [26] found only slightly reduced values for MIP (70±24 cmH_2O) and normal values for MEP (108±42 cmH_2O) in 71 subjects under long-term NIV for OHS.

Inspiratory muscle training (IMT) has been explored as an option to improve respiratory muscle strength and performance in severe obesity. A recent meta-analysis showed that IMT can significantly improve inspiratory muscle strength (average change in MIP −28 (95% CI −42– −15) cmH_2O) in obese subjects

and results of a 6-min walk test (6MWT) [27]. There was no significant impact on lung function. Arterial blood gases (ABGs) were not reported. To the best of our knowledge, no study has explored IMT in OHS.

In summary, geometric modifications may affect inspiratory muscle function, but inspiratory or expiratory muscle strength is not sufficiently impaired to explain the occurrence of pulmonary restriction or alveolar hypoventilation leading to OHS.

Dynamic lung volumes

Forced expiratory volume in 1 s (FEV_1), FVC and slow vital capacity tend to decrease in severe obesity although there is wide variability in data reported. Usually, unless COPD is associated, FEV_1/FVC is preserved [12]. Wise *et al.* [28] showed, in patients who quit smoking and gained weight, that FVC decreased by 17.4 $mL \cdot kg^{-1}$ of weight gained in men and 10.6 $mL \cdot kg^{-1}$ in women. Decrease in dynamic lung volumes does not appear to result from a decrease in inspiratory muscle strength or TLC, except for the most severe cases [19]. Decreases in FEV_1 and FVC result mostly from variations in RV. Lowest values for FEV_1 and FVC are reported in OHS subjects under NIV [1, 5, 26, 29, 30]. Moderately reduced values have been documented in obesity with severe OSA [24]. Only slightly reduced or normal values are found in obese subjects not fulfilling criteria for OHS [17, 24], including patients undergoing bariatric surgery [22], with small but significant improvements after surgery.

Interestingly, when compared to non-obese, morbidly obese subjects have increased airway resistance and reactance measured by impulse oscillometry, and thus expiratory flow limitation. This is explained by anatomical changes in small airways occurring in the obese subjects (reduced airway diameter) and the impact of the reduction in FRC *per se*, increasing the risk of dynamic compression and collapse of peripheral airways even during resting V_T [23, 31, 32]. This may increase work of breathing (WOB). These changes are more prominent in the supine position.

It is noteworthy that central ("android") obesity has a stronger impact on pulmonary function tests than peripheral obesity.

In summary, airway resistance is increased and contributes to increased WOB and premature closing of peripheral airways; FEV_1 and FVC are slightly reduced, while the FEV_1/FVC ratio usually remains normal.

Respiratory drive

The impact of obesity on ventilatory drive is heterogeneous [18]. Adipokines and cytokines produced by interstitial macrophages in adipose tissue (*i.e.* interleukin (IL)-1, tumour necrosis factor-α, IL-6, IL-8, monocyte chemoattractant protein-1, leptin, adiponectin, RANTES) play a crucial role in modifications of the respiratory drive in obesity [10, 11, 16, 33]. Leptin, produced by adipocytes, has a role in the regulation of appetite, energy expenditure and ventilatory drive. Leptin-related reduction in the ventilatory drive in OHS may result from either peripheral resistance to leptin (with high circulating levels) or a decrease in circulating levels of leptin [34–37]. Mice genetically deficient in leptin (*ob*/*ob*) develop a blunted respiratory response when compared to wild-type mice, even prior to the development of significant obesity. This is particularly striking during sleep, with an almost absent response to an increase in inspiratory carbon dioxide fraction in *ob*/*ob* mice [35]. Interestingly, *ob*/*ob* mice also have an increased airway resistance when challenged by methacholine, suggesting a role of leptin in airway resistance [38]. In some obese subjects with OHS, there is an inverse relationship between ventilatory response to carbon dioxide during wakefulness and alveolar ventilation during rapid eye movement sleep [18].

In obese subjects with associated severe OSA, the time interval between apnoeic events may be too short to ensure carbon dioxide excretion, leading to blunted ventilatory responses *via* renal compensation of respiratory acidosis, and diurnal hypoventilation [39, 40].

Acute sleep deprivation may decrease hypoxic and hypercapnic ventilatory responses in normal subjects [41] but the impact of more chronic disruption which occurs in OSA is less clear. Genetic predisposition may also play a role in the development of hypoventilation.

The V'_E/V'_{CO_2} slope reflects the balance between minute ventilation (V'_E) and metabolic requirements (carbon dioxide production (V'_{CO_2})). Therefore, it reflects respiratory drive, respiratory efficiency and the ability of the respiratory system to cope with the exercise-related WOB. During exercise, V'_E increases proportionally to metabolic requirements (V'_{CO_2}). In obese subjects, metabolic and cardiovascular costs of exercise are increased [42]. Lung mechanics may limit the capacity to increase V'_E because of an increase

in WOB (see later). Thus, the V'_E/V'_{CO_2} slope and end-tidal carbon dioxide tension (P_{ETCO_2}) reflect the capacity to adapt (or not) to an increase in workload and WOB while maintaining a pre-set P_{aCO_2}. BALMAIN *et al.* [15] studied the V'_E/V'_{CO_2} slope as a marker of ventilatory drive during exercise in candidates for bariatric surgery. The V'_E/V'_{CO_2} slope decreased with increasing BMI, and more so in women. Also, P_{ETCO_2} was higher in subjects with BMI $\geqslant 50\ kg \cdot m^{-2}$ than in those with a lower BMI. Therefore, ventilatory response to exercise decreased at higher BMI values; this may result from a blunted respiratory drive, an overburdened respiratory system or both. HAN *et al.* [43] showed that subjects with OHS but a lower BMI than in the study by BALMAIN *et al.* [15] were capable of maintaining a normal V'_E/V'_{CO_2} slope [38]. When ventilatory drive is decreased in OHS, NIV improves markers such as V'_E/V'_{CO_2} slope or airway occlusion pressure at 0.1 s ($P_{0.1}$)/P_{ETCO_2} and V'_E/P_{ETCO_2} slopes [41].

Respiratory pattern

Because of the obesity-related changes in respiratory mechanics, for a given V'_E, V_T tends to be lower and respiratory rate higher in obese subjects. Several factors may contribute to this observation, including decreased compliance of the respiratory system, mechanical constraints related to abdominal adipose tissue and increased abdominal stiffness, limitation of diaphragmatic excursion, and cranial displacement and overstretching of the diaphragm related to dynamic hyperinflation putting it at a mechanical disadvantage [44]. This is well reported during cardiopulmonary exercise testing, with a lesser increase in V_T during exertion and therefore a relative increase in the dead space (V_D)/V_T ratio [42].

Work of breathing

WOB is increased in severe obesity as a result of the mechanical constraints mentioned previously: increase in pleural pressure due to the load of the abdominal mass, and in airway resistance, and decrease in FRC and thus in pulmonary compliance [12, 13]. In subjects with severe obesity (BMI $53\pm14\ kg \cdot m^{-2}$), sedated before bariatric surgery, metabolic cost of breathing represents 16% of total oxygen uptake (V'_{O_2}) [45]. WOB increases compared to normal subjects because of: 1) increased metabolic requirements (increase in V'_{O_2} and V'_{CO_2}) leading to an increase in V'_E for any give effort; 2) increase in upper and lower airway resistance; and 3) decreased compliance of the respiratory system. Increased metabolic cost of breathing has also been measured in obese women during exercise, and decreases after bariatric surgery [46].

Gas exchange

ABGs are frequently altered in obese subjects. The abnormalities are directly proportional to BMI. Two main pathophysiological mechanisms account for these abnormalities. Ventilation/perfusion (V'/Q') inequality causes isolated hypoxaemia; alveolar hypoventilation causes OHS. Isolated hypoxaemia is present in up to 30% of patients with severe obesity [47]. It is generally mild. Obesity leads to premature closure of peripheral airways, breathing within closing volume, zones of micro-atelectasis and inequality of V'/Q' distribution, which all contribute to hypoxaemia and increase the alveolar–arterial oxygen gradient (P_{A-aO_2}). These phenomena are aggravated when supine [48]. Diffusing capacity of the lung in obese subjects is seldom reported but most often within normal limits. Slight decreases in diffusion capacity related to decrease in alveolar volume tend to be compensated by an increase in cardiac output. Transfer coefficient of the lung for carbon monoxide (*i.e.* transfer factor of the lung for carbon monoxide/alveolar volume) values are therefore usually normal or increased due to the increase in pulmonary capillary blood volume [49].

Alveolar hypoventilation is observed in 1–10% of obese subjects [46]. Probability of nocturnal and diurnal hypoventilation increases with BMI [3, 6, 27]. When present, sleep alveolar hypoventilation with or without OSA will lead to daytime hypercapnia. As previously mentioned, OSA may by itself lead to daytime hypercapnia because of insufficient inter-apnoea intervals to allow carbon dioxide excretion, renal compensation of respiratory acidosis and secondary blunted ventilatory response [39, 40].

Exercise training and rehabilitation in OHS

Data regarding exercise training and specific rehabilitation programmes in OHS are very limited. To the best of our knowledge, the only randomised controlled study of exercise rehabilitation in OHS was performed by MANDAL *et al.* [50]. These authors randomised 37 OHS patients, all under NIV, with mean BMI $51\pm7.7\ kg \cdot m^{-2}$, to NIV plus a 3-month rehabilitation programme *versus* NIV and usual care. Recruitment was a major difficulty, leading to a premature interruption of the trial. Retention of patients within the programme was also problematic. The initial benefit on weight loss (primary end-point) at 3 months was lost at 12 months. Both groups had similar benefits of NIV on ABGs and bicarbonate (HCO_3^-). Both groups improved their 6MWT, with a significant difference in favour of the rehabilitation group. Therefore, although multidisciplinary management of OHS patients is strongly recommended, the benefit of specific rehabilitation programmes in OHS is yet to be established [1].

A systematic review of peri-bariatric exercise programmes has shown a benefit on BMI, weight loss, functional capacity, muscle strength, fat-free mass, cardiorespiratory endurance and quality of life in patients undergoing bariatric surgery [51], suggesting that further research is necessary for rehabilitation in OHS.

Screening for respiratory abnormalities in the obese patient

OHS is underdiagnosed and, when untreated, is associated with an important increase in morbidity and mortality [6, 7]. In fact, a high proportion of subjects with OHS are first diagnosed only when presenting with acute respiratory failure (ARF). In a large study of patients under long-term NIV, Patout *et al.* [52] noted that 49% of patients with OHS had their NIV set-up during an acute admission.

The use of serum HCO_3^- as a screening tool for OHS has been reviewed in the American Thoracic Society (ATS) 2019 guidelines [53]. The authors state that HCO_3^- <27 mmol·L^{-1} effectively rules out hypercapnia and has a high negative predictive value (99% (95% CI 97.9–99.6%)) in patients where the expected prevalence can be up to 20% (estimated according to BMI). Estimated positive predictive value is low and not clinically useful.

Because the prevalence of OHS increases sharply in subjects with OSA and BMI ⩾35 kg·m^{-2} [2, 3], daytime ABGs and nocturnal sleep studies with transcutaneous carbon dioxide tension (P_{tcCO_2}) monitoring should be performed in subjects suspected of having SDB and/or with mild daytime hypoxaemia. ATS recommendations suggest measuring ABGs in subjects with HCO_3^- ⩾27 mmol·L^{-1} when pre-test probability is 10–20% (*i.e.* BMI ⩾35 kg·m^{-2}) [51]. Oxygen saturation by pulse oximetry is not recommended to decide when to perform ABGs because of insufficient data to propose a threshold value.

Screening scores such as the NoSAS or the Berlin questionnaire score can be used to estimate pre-test probability of associated OSA.

Ventilatory management in the obese patient

Management of ARF in obesity

Management of ARF in an obese patient will depend on clinical status. Patients presenting with the severity criteria (severe encephalopathy, severe pneumonia, multiorgan failure) must be admitted to a critical care unit where intubation can be performed rapidly if required. In less severe cases, NIV must be privileged as the gold standard first-line treatment. Many patients initially also require oxygen supplementation.

Invasive ventilation

The current indications for invasive ventilation during ARF in the obese are limited to contraindications and failures of NIV. These situations are becoming increasingly rare, but it is important to be well aware of these criteria and to re-evaluate them regularly in order not to prolong an ineffective NIV and thus delay invasive ventilation.

Obesity is associated with both difficult intubation and extubation. Intubation of a morbidly obese patient should be considered as high risk due to the frequent presence of a short neck, macroglossia and thickening of the oropharyngeal soft tissues. These changes lead to a reduction in the size of the oral cavity and difficulties in visualising the larynx. An abnormal ratio between the volume of the tongue and the oral cavity leads to difficulty in exposing the glottis during direct laryngoscopy. Difficulties in intubation can be anticipated using the Mallampati score [54]. Another predictive test for difficult intubation in the obese is the presence of a chin–anterior neck angle (chin angle) >90°. In the intensive care unit (ICU), performing intubation under video-laryngoscopic guidance is a recommended option [55].

Obesity-related decreases in FRC, particularly when recumbent, result in lower oxygen stores, explaining that time spent in apnoea before arterial desaturation occurs is reduced [56]. Pre-oxygenation should be optimised using positive pressure ventilation (continuous positive airway pressure (CPAP) or NIV) or nasal high-flow cannula (HFNC) therapy [57]. Furthermore, both obesity and OSA predispose to gastro-oesophageal reflux, increasing the risk of pulmonary aspiration while the airways remain unprotected [58, 59].

Mechanical ventilation is often difficult in obese patients, due to the decrease in lung compliance and increase in airway resistance as a consequence of a reduction in FRC secondary to increased pleural pressure. Those abnormalities contribute to atelectasis, impairing shunt fraction and oxygenation [60, 61]. Some authors suggest that lung protective ventilation (low V_T, moderate to high positive end-expiratory pressure (PEEP; ∼10 cmH_2O) and recruitment manoeuvres) should be applied to protect against volo- and barotrauma while keeping the lung "open" [62]. Nevertheless, the common safety limit of inspiratory airway plateau pressure may not reflect the true lung distending pressure in morbidly obese patients,

because of the increased pleural pressure and the altered lung volumes that lead to a higher part of the pressure generated by the ventilator being used to distend the chest wall rather than the lung [59].

Moreover, the optimal level of PEEP may vary substantially between patients [61]. By studying a cohort of obese patients with ARF, De Santis Santiago *et al.* [62] demonstrated that high airway pressure and lung recruitment manoeuvres are required to reduce atelectasis and improve respiratory mechanics while causing minimal overdistension and maintaining haemodynamic stability. Fumagalli and coworkers suggested the same effect by using recruitment manoeuvres followed by applying a PEEP decremental trial [63, 64]. V_T should be set according to ideal body weight (IBW) and not actual body weight, between 6 and 8 mL·kg^{-1} IBW, and adjusted according to airway pressures and ABGs [65].

The ventilatory mode used to deliver invasive mechanical ventilation (IMV) in obese patients does not differ from general recommendations and should favour a volume-assisted controlled mode in case of sedation and a pressure support (PS) mode during weaning.

Several clinical studies have documented a prolonged duration of artificial ventilation in critically ill obese patients [66]. The increased dependency on mechanical ventilation in this population has been attributed to the increased WOB resulting from altered respiratory mechanics, neuromuscular strength and ventilatory drive [32]. In addition, morbidly obese patients have a high prevalence of OSA, increasing the risk of re-intubation. During recovery from sedation, drive to upper airway muscles is reduced. Moreover, the endotracheal tube may blunt upper airway reflexes. In addition, the adipose tissue overload in these patients may induce a prolonged residual effect of sedatives. This combination may favour post-extubation upper airway obstruction [57]. Hence, duration and dose of sedation should be minimised, and adoption of rapid weaning protocols should be encouraged [67].

In addition, obese patients are particularly at risk of post-extubation stridor [68]. A cuff-leak test should be systematically performed, and in case of suspicion of laryngeal oedema, intravenous steroids should be administered at least 4 h before extubation [68].

Although obesity is associated with an increased incidence of difficult weaning, a meta-analysis suggests that, compared to subjects with a normal BMI, obese patients receiving mechanical ventilation had a lower mortality rate both in the ICU and long term [61].

Several factors may explain this “obesity paradox”. First, adipose tissue produces leptin, adiponectin and other biological mediators [69]. Leptin may increase host defences in the lungs [70]. Also, adiponectin has anti-inflammatory properties and could improve glucose tolerance and reduce the requirement for vasopressors [71]. Additionally, obese patients have higher energy reserves that may compensate for the increased catabolic stress [72].

Some authors suggested that early tracheotomy is associated with a reduced duration of mechanical ventilation, shorter ICU stay and a lower incidence of nosocomial pneumonia in morbidly obese patients [73], while others underline that tracheostomy is problematic in those patients for anatomical reasons [58].

The use of prophylactic NIV alone [74, 75] or in alternance with HFNC [76] appears to be a useful strategy to facilitate successful weaning and extubation and to reduce the risk of re-intubation in obese patients. NIV must be instituted in most cases immediately after extubation. Furthermore, these patients may frequently require long-term NIV support.

Non-invasive ventilation

The use of NIV in the management of ARF has been largely driven by the excellent outcomes seen in patients with COPD. NIV is now the gold standard of care for ARF secondary to an exacerbation of COPD [77]. The reduced harm achieved by avoiding IMV has extended the use of NIV to other indications, including obesity [78]. The first trials demonstrating the efficacy of NIV as first-line treatment in obese patients with severe hypercapnic acidosis were published in the late 1990s. In a pioneer study, Rabec *et al.* [79] showed that NIV was effective in avoiding intubation in 39 out of 40 obese patients with severe hypercapnic acidosis. Expiratory positive airway pressure (EPAP) was progressively increased to correct desaturation dips, and inspiratory positive airway pressure (IPAP) to obtain an acceptable level of mean saturation.

While there are no randomised controlled trials of NIV *versus* IMV in patients with ARF secondary to obesity, there have been comparative studies indicating similar outcomes in ARF associated with obesity

compared to acute exacerbations of COPD [80]. There are also observational data showing acceptable outcomes in patients presenting with obesity-related ARF treated with NIV [81]. Of note, the outcome for patients declining or failing NIV in this context are extremely poor [82, 83]. Care must be taken when comparing data from ARF due to COPD and extrapolating to patients with obesity-related ARF. Exacerbations of COPD are a well-characterised presentation and it is accepted that the precipitant factor may be viral, bacterial or unknown [82]. Patients with obesity may similarly present with ARF secondary to a range of pathologies, the commonest being respiratory infections, but also heart failure, non-respiratory infections or idiopathic [82, 84]. The clinician managing a patient with ARF and obesity must actively seek and treat the cause of decompensation and be aware that NIV represents a supportive therapy, providing clinical stability while the underlying pathology is treated. Management could be performed either in the respiratory critical care unit, in the ICU or even in the general ward, depending on severity and experience and skill with NIV of the medical team.

When initiating acute NIV in patients with obesity, the clinician should be aware of the factors which may indicate a higher failure rate, including super obesity, pneumonia at presentation and severe physiological abnormalities [85, 86]. Additionally, if patients have home positive airway pressure (PAP), a poor compliance with this intervention in the home setting predicts failure during the acute admission [86]. This does not imply that patients with risk factors for treatment failure cannot be considered for NIV as initial therapy, but that NIV should be implemented in a setting which can escalate the patient to IMV if required. The clinician should be aware of the poor outcomes for patients failing NIV in the acute setting who are not intubated, which can be as high as 50–100% [83, 85]. If escalating patients from NIV to IMV, several factors must be considered. Initially, the need to intubate an obese patient may pose a technical challenge, with risk of a life-threatening complication during intubation in the ICU being up to 20-fold higher in obese patients, and thus requiring an experienced operator and/or additional techniques to reduce the risk of failure [87]. Furthermore, obesity is associated with a range of non-respiratory comorbidities which can impact on management and outcomes within critical care [88]. There is a paradox within critical care when assessing the impact of obesity on survival. The presence of multiple comorbidities and poor outcomes has led to the term “malignant obesity” describing patients with extreme obesity and multi-organ failure with a poor outcome [85]. However, when accounting for comorbidities, obesity *per se* does not appear to lead to worse outcomes in invasively ventilated patients and may even be associated with a survival benefit [87]. This benefit may be mediated by the lung mechanics and reduction in ventilator-associated lung damage during critical care, but this remains debated.

Patients presenting *de novo* with acute-on-chronic respiratory failure (ACRF) should be assessed for long-term home PAP after the acute decompensation has resolved but prior to discharge [53]. There are strong observational data to suggest a significantly lower mortality in patients discharged with PAP compared to those without PAP (relative risk 0.12 (95% CI 0.05–0.30)) [53]. It is not clear if NIV or CPAP offer similar outcomes in this context, but the recommendation from expert consensus opinion, given the high morbidity and mortality following an acute episode, is to discharge patients with NIV set with empiric settings, with a detailed assessment within 3 months to consider long-term home NIV and/or a step down to CPAP if appropriate [79]. The same authors underline the primary role of polysomnography (PSG) recordings in the follow-up of these patients after achieving a stable condition [79].

Management of chronic respiratory failure: CPAP or NIV?

Providing PAP is presently the treatment of choice to treat SDB in stable OHS patients. The primary therapeutic strategy for managing OHS includes CPAP and NIV. Both methods aim to treat SDB by improving ventilation and gas exchange, but they differ in their mechanisms, applications and outcomes.

CPAP applies a pneumatic splint to the airways which maintains upper airway patency. It decreases apnoeas and hypopnoeas. Even if it is not strictly a ventilatory mode, CPAP can improve respiratory failure by facilitating the clearance of carbon dioxide accumulated during apnoeic or hypopnoeic events and may restore, in a number of those patients, daytime eucapnia [86]. Because >70% of people with OHS have severe OSA, CPAP may be effective in treating at least a subset of these individuals [88, 89].

NIV encompasses a range of techniques. Compared to CPAP, NIV provides a ventilatory support assist by applying an additional PS or volume during inspiration. NIV is usually provided by using a pressure-targeted bilevel ventilator [47, 90]. These devices deliver separately adjustable IPAP and EPAP. Differences between both pressures (*i.e.* PS) assist lung inflation during each cycle, thereby increasing V_T and reducing WOB. Hence, this ventilatory mode is able to correct both upper airway obstruction (by increasing EPAP) and residual hypoventilation (by increasing PS level). Bilevel devices can be used in a spontaneous (S) mode (the patient cycles the device from EPAP to IPAP), spontaneous timed (ST) mode

(a backup rate is available to deliver IPAP for the set inspiratory time if the patient does not trigger an IPAP/EPAP cycle within a set time window) and timed (T) mode (inspiratory time and respiratory rate are fixed). The most common mode used is the ST mode, which allows the patient to maintain spontaneous ventilatory activity while providing a substitute device-controlled respiratory cycle if the patient does not trigger the ventilator within a specified time. In a randomised controlled trial conducted in stable OHS patients, CONTAL *et al.* [91] demonstrated that switching from S to ST mode allowed to significantly reduce the residual apnoea–hypopnoea index (AHI), improving efficacy of NIV.

While NIV is considered the first-line treatment in patients with OHS without OSA, the optimal initial treatment for OHS combined with severe OSA remains the subject of debate.

Three published randomised controlled trials compared NIV to CPAP in stable hypercapnic obese patients with concomitant OSA (mean AHI >60 events·h^{-1}) [89, 92–94]. One of the studies excluded patients with severe persisting nocturnal desaturation or increase in P_{tcCO_2} during the first night of CPAP titration [94]. In two studies, the follow-up was 3 months [92, 94] and in the third, 2 years [89, 93].

The pooled results of these three studies showed no significant differences between CPAP and NIV in terms of compliance (5–6 h per day), awake P_{aCO_2} and arterial oxygen tension (P_{aO_2}) improvement, requirement for oxygen supplementation, emergency department visits, quality of life or Epworth Sleepiness Scale score. In the study by PIPER *et al.* [94], subjective quality of sleep and vigilance testing were significantly better in the NIV group.

In the long-term study by MASA *et al.* [93], there was no difference between NIV and CPAP groups at 2 years in the occurrence of cardiovascular events (risk ratio 1.17 (95% CI 0.56–2.44)) or in the rate of hospitalisations or all-cause mortality. Also, CPAP and NIV similarly improved exercise capacity. A comparative analysis of the results of these trials is provided in table 1.

Even if these relevant randomised controlled trials comparing CPAP and NIV showed a similar efficacy overall, controversy exists about the optimal mode to correct ABGs and improve long-term outcomes in patients with OHS-OSA.

First, we must consider to what extent these randomised controlled trials can be extrapolated to "real-life" clinical practice. In the three studies, the patients were screened and included in a steady state. However, several reports show that prescription of home NIV frequently follows an episode of ARF [95–97]. In the ANTADIR GAVO$_2$ cohort, a French multicentre cohort with 3600 patients on home NIV, NIV was initiated after an acute admission for ARF in 66% of OHS patients [98]. The fact that in the MASA *et al.* [93] study it took >5 years to recruit 221 patients in 16 expert centres suggests that this is a selected population (2.7 patients per year per centre).

TABLE 1 Summary of published randomised controlled trials comparing continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV)

Study	Clinical characteristics	Settings/PS level	Outcomes	Main results
PIPER, 2008 [94]	3 months 36 patients BMI 53±8 kg·m^{-2} P_{aCO_2} 50 (47–57) mmHg	EPAP 10 cmH$_2$O IPAP 16 cmH$_2$O S mode Mean PS 6 cmH$_2$O	Primary: P_{aCO_2} improvement Secondary: QoL, compliance, vigilance, sleepiness	ABGs: NIV>CPAP in more severe hypercapnic patients QoL: NIV=CPAP Sleep quality, vigilance: NIV>CPAP
MASA, 2015, 2019 [89, 93]	2 months, then 2 years 221 patients BMI 45±7.6 kg·m^{-2} P_{aCO_2} 50±4.5 mmHg	EPAP 8.2 cmH$_2$O IPAP 19.7 cmH$_2$O ST mode Mean PS 11.5 cmH$_2$O	Primary: short-term study: P_{aCO_2} improvement; long-term study: admissions per year Secondary: QoL, compliance, 6MWT, symptoms	ABGs, QoL, admissions: NIV=CPAP
HOWARD, 2017 [92]	3 months 60 patients BMI 54.9±11.9 kg·m^{-2} P_{aCO_2} 60.7±13.5 mmHg	EPAP 11.9 cmH$_2$O IPAP 18.3 cmH$_2$O ST mode Mean PS 6.4 cmH$_2$O	Primary: treatment failure (admissions, persistent hypercapnia or non-adherence) Secondary: QoL, sleepiness	Admissions, compliance, QoL: NIV=CPAP ABGs: NIV>CPAP in more severe hypercapnic patients

PS: pressure support; BMI: body mass index; P_{aCO_2}: arterial carbon dioxide tension; EPAP: expiratory positive airway pressure; IPAP: inspiratory positive airway pressure; S mode: spontaneous mode; QoL: quality of life, ABGs: arterial blood gases; ST mode: spontaneous timed mode; 6MWT: 6-min walk test.

Second, in the studies by PIPER *et al*. [94] and MASA *et al.* [93], patients included were moderately hypercapnic with average P_{aCO_2} ~50 mmHg. In the study by MASA *et al*. [93], only 12% of the entire cohort had baseline P_{aCO_2} >56 mmHg. A few published series identified having less severe hypoventilation as a predictor of CPAP response, and in these patients, most authors agree to begin by a CPAP trial [97]. If alveolar hypoventilation is reversed, one can assume that hypercapnia was predominantly OSA-related, and the patient will remain on long-term CPAP. Interestingly, in the HOWARD *et al*. [92] study, patients with P_{aCO_2} >60 mmHg had a >8-fold increase in risk of persistent hypercapnia on CPAP when compared to patients with P_{aCO_2} <50 mmHg, confirming the major role of hypercapnia level in the expected efficacy of both PAP treatments to correct hypoventilation.

Also, the levels of PS used in the NIV groups were lower than those usually applied in OHS patients in clinical practice and also lower than those suggested by expert consensus [26, 99]. For example, in both short-term trials, the mean level of PS applied was 6 and 6.4 cmH_2O [92, 94]. In the MASA *et al.* [93] Pickwick study, the mean level of PS applied was higher (11.5 cmH_2O), but lower than those used in other trials evaluating the efficacy of NIV in OHS patients (15 and 13 cmH_2O, respectively, in the studies by MURPHY *et al*. [29] and JANSSENS *et al.* [26, 99]). Severe obesity is characterised by a decrease in thoraco-pulmonary compliance [11]. The consequence of these changes in pulmonary mechanics is that these patients require high inspiratory pressures to overcome this increased elastic burden and improve alveolar ventilation.

This could explain why, in the long-term study by MASA *et al*. [93], 48% of patients treated by NIV had P_{aCO_2} >45 mmHg (*versus* 60% of patients randomised to CPAP) at 2 years, suggesting that the level of PS applied was too low to correct hypoventilation. Hence, one could infer that the lack of benefit of NIV *versus* CPAP is a consequence of an insufficient level of PS applied.

Finally, two studies found that many patients initiated on NIV for OHS who normalised their P_{aCO_2} could be stepped down from NIV to CPAP after a few months without worsening ABGs, sleep quality or quality of life [100, 101]. These data support the strategy of a sequential approach, by "hitting hard" to initially correct hypoventilation in severely hypercapnic patients and then simplifying the treatment if the patient becomes normocapnic [78].

In fact, in patients with OSA complicating OHS, hypercapnia may be related to OSA, to obesity itself or to both. Differential diagnosis between these two conditions is in general made retrospectively, according to P_{aCO_2} kinetics after either a CPAP trial or if the patient was at first treated by NIV, when, after correction of P_{aCO_2} levels and switching to CPAP, the patient remains normocapnic [79].

Indeed, some experts propose a "personalised approach" by proposing either NIV or CPAP taking into account two factors: the level of P_{aCO_2} and the presence or not of underlying OSA and its severity (figure 1) [47, 102–104]. This approach is based in published series that identified less severe hypoventilation and higher AHI as predictors of CPAP response [47, 105, 106]. If P_{aCO_2} <50 mmHg, and OSA was confirmed by PSG, most authors agree to begin by performing a CPAP trial [47, 102–104]. CPAP can be administered in auto-titrated mode or in fixed mode after calculating therapeutic pressure manually or by using an auto-titration algorithm. Treatment trials usually last for 3 months with an assessment of adequacy of therapy: control of P_{aCO_2}, improvement in cor pulmonale, improved sleep quality and reduced healthcare contacts. If there has been a clinical response, and alveolar hypoventilation is reversed, the patient will remain on long-term CPAP. In this case, one can assume that hypercapnia was only OSA related. However, if the patient remains hypercapnic despite adequate CPAP treatment and compliance, this suggests that another mechanism (*i.e.* obesity itself) is perpetuating alveolar hypoventilation [79]. Such patients require, additionally, increasing ventilation during sleep rather than simply stabilisation of the upper airway, and in that case it is logical to switch to NIV. In patients with P_{aCO_2} >50 mmHg and underlying OSA, the initial therapeutic choice should be NIV, knowing that it is always possible to step down to CPAP if the patient becomes normocapnic subsequently [100, 102].

In a subset of patients, hypoventilation cannot be reversed despite high PS levels. These patients may need higher peak inspiratory pressures which only volume ventilators can provide. However, high pressure levels must be managed carefully because in an open non-hermetic system (as is the case in NIV) they may override leak compensations and reduce therapeutic efficacy [47].

Finally, in some patients, respiratory failure cannot be managed by NIV. In this small subgroup of patients, and also in those who do not tolerate NIV, a tracheostomy may be required.

A proposed algorithm for ventilatory management of these patients is provided in figure 2.

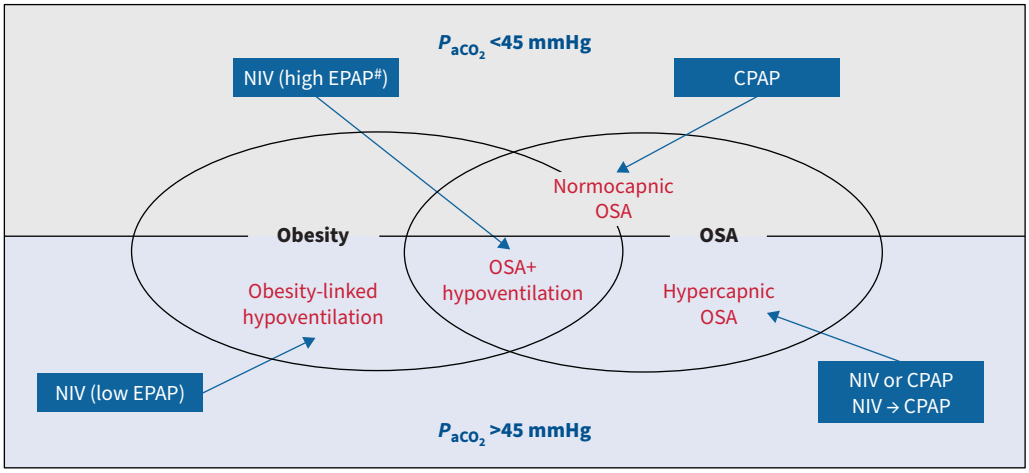

FIGURE 1 Obesity hypoventilation syndrome–obstructive sleep apnoea (OSA) relationships and pathophysiological-based therapeutic approach. #: higher expiratory positive airway pressure (EPAP) levels are needed in patients with underlying OSA to stabilise the upper airway. P_{aCO_2}: arterial carbon dioxide tension; NIV: non-invasive ventilation; CPAP: continuous positive airway pressure.

Role of hybrid modes of NIV

The majority of home non-invasive ventilatory support is delivered in a pressure-limited mode [90, 100]. This provides leak compensation, improves efficacy of ventilation and comfort *via* a reduction in the magnitude of pressure swings [107]. However, pressure-limited NIV does not account for the changes in the compliance of the respiratory system which occur according to body position, sleep stages, progression of underlying lung disease or intercurrent respiratory infections [108, 109]. The changes imposed on the respiratory system during positional changes in obesity can be significant, impacting on ventilatory efficiency [110, 111]. The development of ventilator technology has allowed for improved accuracy in estimating V_T, enabling the development of volume-targeted ventilation. These so-called advanced modes of ventilation are designed to provide the "comfort" of pressure-limited NIV with the "safety" of guaranteed volume ventilation. It must be appreciated that all these modes rely on calculated indices and specific algorithms and, without an understanding of the limitations of these processes, the use of these modes can be as problematic as they are helpful. Similarly, while the concepts and principals are generic, there must be caution when extrapolating evidence from one device, or algorithm, to another without understanding the systems used and accuracy of the calculated values [112, 113]. There are studies demonstrating that volume-targeted modes are safe and effective when established with traditional methods of titrating NIV, such as overnight P_{tcCO_2} monitoring [114]. These studies have been conducted in patients with chronic respiratory failure (CRF) secondary to neuromuscular disease, obesity or COPD [29, 114–116]. Many of the initial studies of hybrid modes demonstrated enhanced control of nocturnal ventilation in OHS but usually with a higher delivered mean PS overnight, without any change in daytime P_{aCO_2}, quality of life or other clinical outcomes [29, 114–116]. A study by Storre *et al.* [114] showed a reduction in mean nocturnal P_{tcCO_2} of 6.9±5.5 mmHg in patients with OHS receiving volume-targeted compared to fixed-level NIV. However, this was associated with a higher mean inspiratory pressure of 16.4±3.9 mbar in the volume-targeted mode compared to 14.7±2.4 mbar in the fixed bilevel NIV. The results of some of these studies raise the concern that the higher delivered pressures and the pressure variability may be associated with leak-associated arousals and sleep fragmentation [100].

Studies which used a home NIV titration algorithm with predefined targets to define successful set-up of both volume-targeted and fixed bilevel NIV, such as Murphy *et al.* [29], led to similar delivered levels of PS (volume-targeted NIV PS 13±5 cmH_2O, fixed bilevel NIV 13±4 cmH_2O) and thus similar control of nocturnal ventilation (volume-targeted NIV mean P_{tcCO_2} 7.1±0.7 kPa, fixed bilevel NIV mean P_{tcCO_2} 7.2±1.0 kPa) between the NIV modes. In patients with COPD, it seems that there is a consistent effect on compliance, with volume-targeted modes improving device compliance when compared to ST modes in intermediate duration crossover trials [116–118]. These trials were not powered or designed to examine clinical outcomes and any estimate of impact is an extrapolation of the data from these works. Additionally, the similarity in long-term outcomes between CPAP and volume-targeted NIV in OHS would suggest that any difference between fixed bilevel and volume-targeted NIV would be smaller [29, 89, 119].

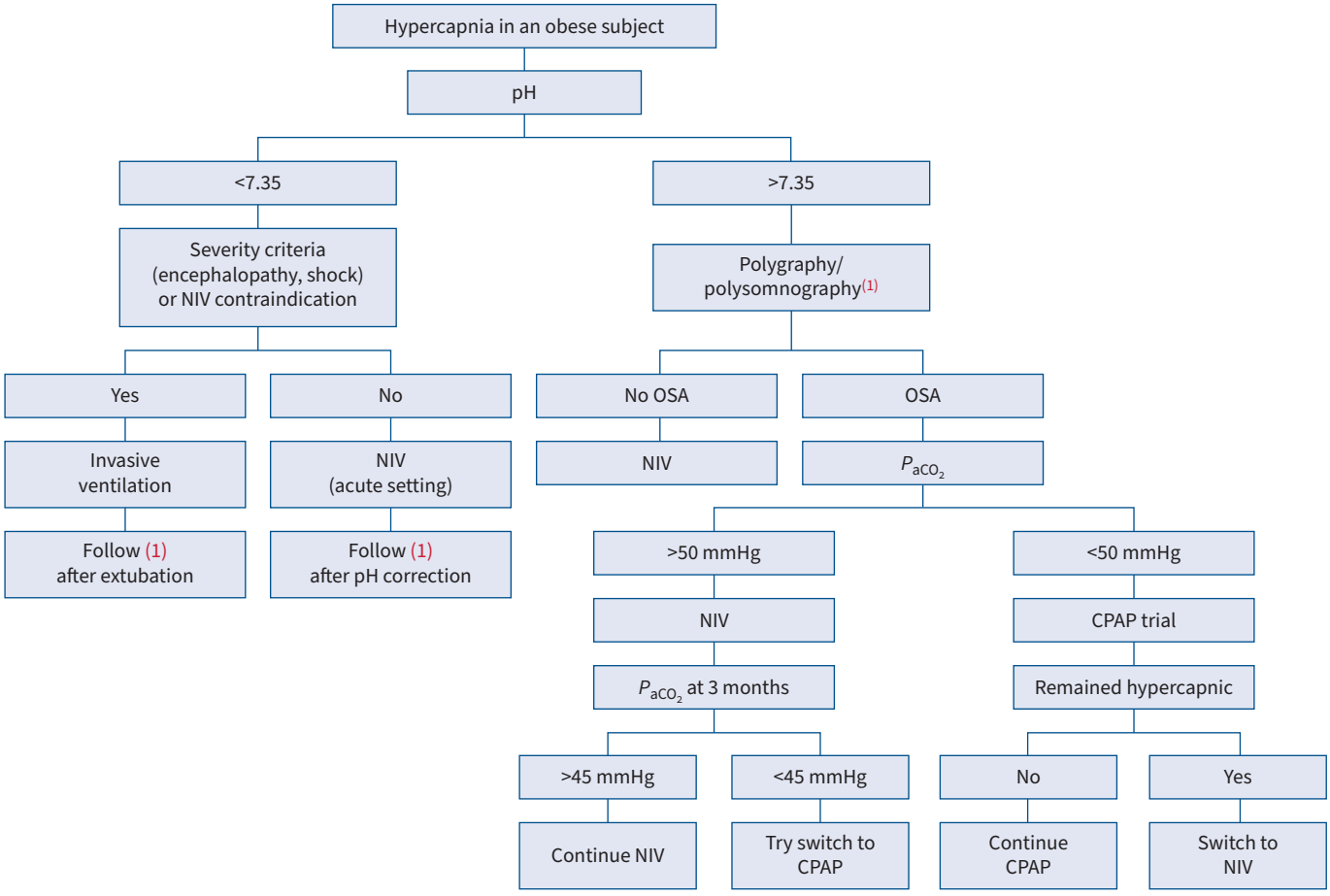

FIGURE 2 Proposed flowchart for ventilatory management of patients with obesity hypoventilation. OSA: obstructive sleep apnoea; NIV: non-invasive ventilation; P_{aCO_2}: arterial carbon dioxide tension; CPAP: continuous positive airway pressure.

After volume-targeted modes, NIV devices have been developed with algorithms that can automatically titrate EPAP by estimating upper airway patency [95]. Again, as with volume-targeted modes, there are different technological approaches to achieve this, and when utilising these modes, clinicians should be well informed as to the characteristics and data relevant to the device used. Auto-EPAP modes can use flow or forced oscillatory technology (FOT) to assess airway patency, and these techniques have different pros and cons [120]. Flow-based techniques can be used breath by breath and have been studied extensively in CPAP devices in the management of simple sleep apnoea. However, they become less reliable with high levels of leak and at higher flow rates seen with NIV [121]. FOT overcomes some of the flow-related issues and therefore may be more reliable in patients with high-pressure NIV. However, FOT is implemented in pre-set periods of breathing, *e.g.* at end-expiration every 10 breaths, and thus may miss apnoeas or capture an infrequent event and therefore over- or under-titrate EPAP [120]. There are short- and medium-term studies in patients with mixed causes of respiratory failure [117, 122] or specifically obesity [95] which show that these modes are clinically safe and effective in managing the OSA component of SDB. These evaluations have included detailed PSG to ensure that the modes are appropriately titrating pressures and not impacting on sleep disruption with similar sleep efficiency (auto-NIV 81±10%, fixed bilevel NIV 75±22%), arousal index (auto-NIV 19±10 events·h^{-1}, fixed bilevel NIV 20±12 events·h^{-1}) and wake after sleep onset (auto-NIV 65±39 min, fixed bilevel NIV 80±53 min) demonstrated in the auto-EPAP volume-targeted group when compared to bilevel [89]. These data also show similar improvements in daytime ABGs (change in P_{aCO_2} at 2-month follow-up 0.87 kPa in both groups) and compliance (6.3 h per night in both groups) but the time to set-up NIV effectively was reduced in the auto-NIV modes (auto-NIV 3 days, fixed bilevel NIV 4 days; p=0.001) [95].

The advent of combined auto-EPAP volume-targeted modes offers the potential to simplify the titration of NIV. Murphy *et al.* [123] compared in-patient titration of fixed bilevel NIV to outpatient set-up using an

auto-EPAP volume-targeted approach in patients with obesity-related respiratory failure. The study recruited 82 patients in the UK and France, and in both health systems demonstrated clinical safety, measured by control of daytime carbon dioxide (change in P_{aCO_2}: auto-NIV −0.85±1.04 kPa, fixed-pressure NIV −0.44±1.06 kPa), health-related quality of life (Severe Respiratory Insufficiency questionnaire: fixed bilevel 56.4±20.1, auto-NIV 62.9±21.2; difference −1.96 (95% CI −8.8–4.9)) and cost (non-significant increase in cost of auto-NIV compared to fixed bilevel NIV: GBP 188.20 (95% CI −61.61–438.01)) [123]. An important pitfall to avoid with auto-EPAP volume-targeted modes is the misconception that they simplify or obviate the need for a titration protocol. It is important to acknowledge the basic principle that to improve outcomes in patients with CRF, there needs to be an improvement in daytime carbon dioxide levels and that this is achieved by control of SDB. It is therefore essential, if using these modes, that control of SDB is demonstrated and that settings are adjusted in order to achieve this. Similar to the use of extended ramps rendering patients vulnerable to residual SDB during the pressurisation period, wide parameters set for these devices allow for periods of inadequate settings and residual pathology [124]. Similarly, if the target volume is increased but the PS limits are unchanged, the device may be unable to reach the desired goal, leaving the patient under-treated. The accuracy of these estimated parameters must also be considered, in particular during period of high leaks [112]. It must be clear that hybrid devices are no replacement for an experienced multidisciplinary team providing careful NIV titration, appropriate mask fit and patient education.

Summary

In summary, obesity has a major impact on respiratory mechanics and function. Obesity-related respiratory disturbances, including OSA, are associated with an increased incidence of ARF and CRF. Management of respiratory failure in these patients depends on the patient's underlying situation and on sleep study results.

In the acute setting, NIV must be prioritised and is the gold standard treatment in all but the most severe cases. In steady-state situations, for patients with stable CRF, administering non-invasive PAP is presently the treatment of choice to treat associated SDB in stable OHS patients. Both CPAP and NIV seem to be similarly effective, but they differ in their mechanisms, applications and outcomes. A personalised approach to the management of OHS should be considered by proposing either NIV or CPAP according to the severity of hypercapnia and the presence or absence of OSA and its severity. Further studies need to be conducted to better define the optimal role for each technique in managing OHS patients.

Points for clinical practice

- Obesity-related respiratory disturbances, including OSA, are associated with an increased incidence of ARF and CRF.
- Management of respiratory failure in these patients depends on the patient's underlying situation and on sleep study results.
- In the acute setting, NIV must be prioritised in all but the most severe cases.
- In steady-state situations, administering non-invasive PAP by using CPAP or NIV is presently the treatment of choice. Both CPAP and NIV seem to be similarly effective, but they differ in their mechanisms, applications and outcomes.

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