Key points

❯ Obesity, well known as a cardiovascular risk factor, is also a 'respiratory' risk factor and can have profound adverse effects on the respiratory system, such as alterations in pulmonary function, respiratory mechanics, respiratory muscle strength and endurance, gas exchange, control of breathing, and exercise capacity.

❯ Arterial blood gases are frequently altered in obese subjects and abnormalities are directly proportional to body mass index. Two main pathophysiological mechanisms may account for gas exchange abnormalities: ventilation/perfusion inequality (responsible for isolated hypoxaemia) and alveolar hypoventilation (responsible for the 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. Two other clinical entities (chronic obstructive pulmonary disease and obstructive sleep apnoea (OSA)) frequently present in obese patients and may potentiate or aggravate this hypoventilation.

❯ OHS is frequently underappreciated and diagnosis is rarely made at the steady state. Diagnosis is frequently made in two situations: during an exacerbation, or when, presenting with symptoms of respiratory sleep disturbances, a patient is referred to a sleep laboratory for screening for OSA.

❯ Evidence suggests that OHS is associated with significant morbidity and mortality. Hypercapnia and hypoxaemia in the obese individual may be complicated by pulmonary hypertension, polyglobulia and cor pulmonale.

❯ Ventilatory management will depend on the patient's underlying situation and on sleep study results: it may include continuous positive airway pressure or noninvasive ventilation (NIV), with additional O_2 frequently necessary. OHS is one of the most frequent indications for NIV worldwide.

Respiratory complications of obesity

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Educational aims

❯ To make readers aware of the importance of obesity in respiratory medicine.
❯ To outline the mechanisms of breathing problems in obesity.
❯ To explain strategies for management of breathing problems in obesity.

Summary

Obesity has become a public health problem because of its epidemic proportions in the population. There are many associated respiratory problems with sleep apnoea, obesity hypoventilation and obesity-associated asthma. The mechanisms of diminished breathing in the obese are complex and involve central control, peripheral drive, airway calibre and probably metabolic pathways.
All pulmonologists need to know how to manage obesity-related problems and make informed choices about modalities of treatment.

❮ Obesity is a major public health problem and obesity-related respiratory problems play a major role in the morbidity and increased mortality associated with it. Obesity has important repercussions on the mechanics of ventilation and can lead to chronic respiratory failure. Recent studies suggest that obesity is an independent risk-factor for asthma. Effort-related dyspnoea is a frequent symptom in obese patients and contributes to their handicap. Thus, the respiratory specialist has an important role to play in the multidisciplinary management of these patients.

Only in the past 40 years have obesity-related respiratory disorders begun to be mentioned in medical publications. As often, fictional literature preceded science: as early as 1836, Charles Dickens presented, in *The Posthumous Papers of the Pickwick Club*, a marvellous description of an obese man with respiratory disturbance: 120 years later, BICKELMANN *et al*. [1] gave a pathophysiological explanation for the 'phenotype' of Joe, when they described apnoeas and alveolar hypoventilation in obese subjects, and suggested the name 'the Pickwickian syndrome' for this condition.

Epidemiology of obesity

Obesity is classified in terms of the body mass index (BMI; weight/height^2) into moderate (BMI 30–35 kg per m^2), severe (BMI 35–40 kg per m^2) and massive or morbid obesity (BMI >40 kg per m^2). A BMI of 25–30 kg per m^2 is considered as overweight. Obesity has become a major public health problem in Europe. In France, the ObEpi Study on 23,747 individuals aged >15 years, compared the situation in 2006 with previous samples studied using the same methodology. The prevalence of obesity was 12.4%, which represents 5.91 million obese people; a major increase from 8.2% in 1997, 9.6% in 2000 and 11.3% in 2003. In contrast, the proportion of people

who are overweight is more stable: 29.2% in 2006, compared with 30.3% in 2003. The prevalence of massive obesity rose from 0.3% in 1997 to 0.8% in 2006.

Obesity, especially central obesity, can have profound adverse effects on the respiratory system, causing alterations in pulmonary function, respiratory mechanics, respiratory muscle strength and endurance, gas exchange, control of breathing, and exercise capacity. Breathlessness on exertion is very common in obese subjects and manifests a variety of factors related to the abnormal physiological effects of obesity itself and to comorbidities such as diastolic dysfunction, coronary heart disease and pulmonary hypertension [2]. The respiratory consequences of obesity are aggravated if the patient also suffers from obstructive sleep apnoea (OSA) or chronic obstructive respiratory disease (COPD), which may explain the occurrence of life-threatening respiratory failure in these patients.

Consequences of obesity for ventilatory mechanics

The primary consequence of obesity is a diminution in thoracic wall compliance, related to difficulties in thoracic cage expansion and diaphragm movement. The fall in lung compliance is smaller, and results from increased pulmonary blood volume and airway closing plus alveolar collapse in the zones of low ventilation/perfusion ratio (V'/Q') in the lung bases.

Maximal inspiratory and expiratory pressures may be diminished in massive obesity and in obesity associated with diurnal alveolar hypoventilation. In massively obese patients achieving a marked reduction in BMI by gastroplasty, there is an improvement in the endurance of respiratory muscles [3]. Ventilatory work is increased in obese subjects. In massively obese people, the proportion of oxygen uptake (V'_{O_2}) dedicated to respiratory work at rest reaches 16% of the total V'_{O_2}, while it does not exceed 3% of total V'_{O_2} in normal-weight subjects in good health [4].

An absence of reduction in end-expiratory lung volume with effort has been demonstrated in obese subjects and may place the diaphragm at a mechanical disadvantage and thus favour the appearance of breathlessness [5].

Consequences of obesity on respiratory function at rest

Gas exchange in obese individuals

Arterial blood gases (ABG) are frequently altered in obese subjects. The abnormalities are directly proportional to BMI. Two main pathophysiological mechanisms may account for gas-exchange abnormalities in these patients. First, V'/Q' inequality is responsible for isolated hypoxemia; secondly, alveolar hypoventilation causes so-called 'obesity hypoventilation syndrome'. Isolated hypoxaemia is the most frequent abnormality found in severe obesity, and is present in up to 30% of patients. This hypoxaemia is generally mild, though more pronounced in patients with small lung volumes. It is often only present in the supine position and is aggravated during sleep [6, 7]. The main mechanism for this abnormality is increase in the alveolar oxygen tension (P_{A,O_2}) gradient secondary to V'/Q' mismatching, mainly in the pulmonary bases. This abnormality has a double mechanism: first, the lung bases are over-perfused as a consequence of the hypervolaemic and hyperdynamic states that increase pulmonary blood volume; and secondly, the lung bases are under-ventilated owing to airway closure and alveolar collapse or even microatelectasis. Nevertheless, in hypoventilating obese subjects, at least a part of the reduction in arterial oxygen tension (P_{a,O_2}) is proportional to arterial carbon dioxide tension (P_{a,CO_2}) increase and is thus related to hypoventilation.

Hypoxaemia is more frequent and more severe in massive obesity (BMI >40 kg per m^2) and in android obesity [8]. It seems to correlate with expiratory reserve volume (ERV) reduction. A decrease in ERV while inspiratory capacity remains unchanged, may lead to a decrease in functional reserve capacity (FRC), which may fall below closure volume and lead to a collapse of distal airways. Hypoxaemia in these patients is typically aggravated in the supine position, because the condition impairs V'/Q' inequality.

Mechanisms of alveolar hypoventilation in obesity: 'Can't breathe or won't breathe?'

Alveolar hypoventilation is observed in ~10% of obese subjects, particularly in massive obesity. Compared with uncomplicated simple obesity, hypercapnic obese patients have reduced chest wall compliance, lower respiratory system

compliance and resistance, more severely altered pulmonary function (in particular lower ERV, total lung capacity (TLC) and vital capacity (VC)), more abnormal pattern of breathing (increased respiratory rate and decreased tidal volume while inspiratory time as a fraction of total breath time remains unchanged), diminished respiratory muscle strength and endurance, and depressed ventilatory responses. Thus, the work and energy cost of breathing are higher in these patients. Indeed, the work of breathing may be 280% higher than normal and the oxygen cost of breathing almost 10 times normal in this population.

The development of hypoventilation in obese patients is probably multifactorial (table 1). Mechanisms of hypoventilation are poorly understood and it is not clear why some morbidly obese patients hypoventilate while the majority do not. Nevertheless, two main hypotheses are proposed. The first ('mechanical hypothesis') suggests that hypoventilation accounts for mechanical limitation and decreased chest compliance that impose an insurmountable load on these patients and obliges them to devote an exaggerated energy cost to maintain normal ventilation. This places an overwhelming burden on inspiratory muscles that leads to hypoventilation. Although seductive, this theory that hypercapnic obese patients 'can't breathe' has some limitations: first, there is a poor correlation between BMI and the degree of hypoventilation. Moreover, even if obesity increases the elastic load, no correlation has been demonstrated between BMI and thoracic compliance.

The second hypothesis (the 'blunted ventilatory drive hypothesis') implicates diminished ventilatory responses in the genesis of hypoventilation. That means that the respiratory centres are unable to increase their ventilatory output at the rate achieved by the nonhypercapnic obese [9]. Defenders of this hypothesis argue that, even if hypercapnic, obese individuals have an increased basal ventilatory drive, and mouth occlusion pressure ($P_{0.1}$), response to CO_2 challenge is impaired or at least inappropriate. In other words, in order to produce the same amount of ventilation, obese subjects need more ventilatory output than normal and a subgroup of these patients, unable to generate sufficient output, develop hypercapnia. GILBERT et al. [10], by measuring CO_2 responsiveness using the rebreathing technique, found that the hypercapnic obese differed from those with simple obesity on the basis of their depressed ventilatory responsiveness not in terms of weight or other

clinical parameters. Others have confirmed this hypothesis by measuring diaphragmatic electromyographic responses to hypercapnia [11]. In fact, even if these patients fail to increase minute ventilation when stressed, which may lead to hypercapnia, they can voluntarily hyperventilate to normalise P_{a,CO_2}. This provides strong evidence that ventilatory control, or at least CO_2-related ventilatory regulation, is abnormal in these patients [12].

Recently, CHOURI-PONTAROLO et al. [13] failed to demonstrate a stereotypical ventilatory response in hypercapnic obese subjects. They identified, in fact, two subgroups, showing blunted and normal responses, respectively. The authors failed to demonstrate any difference between the two groups in terms of age, BMI, sleep quality as measured by polysomnography or diurnal ABG, but those with blunted responses were sleepier and hypoventilated more than those with normal responses. LAABAN et al. [8] have stressed that hypercapnia may be more an adaptative response than a consequence of abnormal ventilatory responsiveness. Therefore, rather than fight against an increased load to normalise P_{a,CO_2}, subjects tolerate hypercapnia and consequently save the oxygen

Table 1	Pathophysiological mechanisms potentially implicated in respiratory failure in the obese
Hypoxaemic respiratory failure	
Increase of $P_{(A-a),O_2}$ gradient secondary to V'/Q' mismatching (specially in the bases)	
Hypervolaemic and hyperdynamic state (over-perfusion)	
Airway closure and alveolar collapse	
Hypercapnic respiratory failure	
Impaired or inappropriate ventilatory drive	
Decreased chest wall and lung compliance	
Inappropriate ventilatory load compensation	
Increased upper airway resistance and inspiratory threshold load	
Impaired response to elastic and resistive loads	
Increased work of breathing and oxygen cost of breathing	
Decreased ventilatory muscle strength and endurance	
Neuromuscular uncoupling	
Respiratory muscle fatigue (peripheral and/or 'central'?)	
Diaphragmatic dysfunction secondary to:	
Increased adipose tissue deposition	
Mechanical disadvantage (inadequate length–tension relationship)	
Changes in respiratory patterns (more rapid and shallow breathing)	
Increased total respiratory resistance	
Increased V'_{CO_2}	
Coexisting conditions	
OSA or upper airway resistance syndrome	
COPD	
Aggravating conditions	
Supine position	
REM sleep	

$P_{(A-a),O_2}$: alveolar-arterial oxygen tension difference; V'_{CO_2}: carbon dioxide production.

cost of superimposed work of breathing. These authors propose the hypothesis that such obese subjects 'won't breathe'.

Obesity and restrictive lung dysfunction

The lung function abnormality most commonly found in obesity is diminution of ERV that is most marked in the dorsal-decubitus position and is associated generally with a fall in FRC. In a recent study of 373 patients without any cardiopulmonary disorder and with a normal forced expiratory volume in one second (FEV_1)/VC ratio and no reduction in gas transfer, diminution in ERV and in FRC was exponentially correlated with an increase in BMI [14]. In patients with moderate obesity, ERV was 42% of normal and in massive obesity, mean ERV was 25% of normal. Residual volume was normal. TLC and VC were normal in moderate and severe obesity and were reduced in massive obesity to 88% of normal. Thus in an obese subject, a marked reduction in TLC indicates an associated respiratory disorder, even in massive obesity. Marked weight loss generally leads to an improvement in respiratory function with improvement in ERV and FRC [15, 16].

The pattern of obesity plays an important role in the ventilatory consequences. Android or abdominal obesity is characterised by a disproportionate distribution of fat in the upper body and especially in the abdomen, while gynaecoid obesity is characterised by a predominance of fat in the lower body. In a study of 40 patients with massive obesity who had an evaluation of fat distribution by abdominal computed tomography, ERV was more decreased in the group with android obesity than in those with gynaecoid obesity, while BMI was similar in the two groups [17]. In men with moderate obesity or normal weight, an android distribution of fat was associated with lower values of TLC and VC [18]. Thus android obesity at the same level of BMI seems to lead to a greater loss of respiratory function than gynaecoid obesity. However, larger studies with subjects with different degrees of obesity are needed.

Obesity and obstructive ventilatory disturbance

FEV_1 is sometimes moderately reduced in patients with severe or massive obesity, but the FEV_1/VC ratio is normal in the absence of associated bronchial disease. In a case-control study of nonsmokers, there was a significant reduction in maximal flow between 25 and 75% of VC ($MMEF_{25-75}$) in patients with massive obesity compared with subjects of normal weight, matched for age, sex and height, but in men only [19]. Thus, obesity can be associated with ventilatory obstruction in peripheral airways in the absence of tobacco smoking. In contrast, a transverse epidemiological study [20] showed the $MMEF_{25-75}$ to be normal in patients with moderate or severe obesity. In obese patients, carbon monoxide transfer is normal or slightly increased because of the increase in pulmonary blood volume [14, 21].

Consequences of obesity on respiratory function during exercise

Cardio-respiratory exercise tests show that for a comparable level of sub-maximal exercise, obese patients without any other cardiac or respiratory disease have a greater V'_{O_2}, a higher minute ventilation, a greater respiratory rate and a lower tidal volume than normal-weight subjects [22, 23]. Additionally, the anaerobic threshold is reduced in obese subjects [22, 24]. Maximal V'_{O_2} is reduced in obese patients [22, 24] and, in patients with massive obesity, it is reduced markedly to the levels found in patients with severe left ventricular dysfunction [25].

Fat mass distribution has an influence on respiratory performance during exercise

In 164 women with massive obesity, who were separated into two groups on the basis of height/waist ratio, a cycle-ergometer exercise test showed that for each level of exercise, V'_{O_2} was greater in the group with android obesity than in the group with gynaecoid obesity, for a similar BMI in both groups [26]. Minute ventilation was also greater in subjects with android obesity, who had a greater respiratory rate and a lower tidal volume. Thus, for a similar level of obesity, an android distribution of fat leads to a greater change in exercise performance with a greater loss of capacity.

Obesity and asthma

Since the prevalences of both obesity and asthma have increased in recent years, a number of studies have examined the possibility of an

epidemiological link between the two. Transverse cohort studies have revealed an independent relationship between obesity and the prevalence of asthma in adults, with a relative risk of asthma in obese subjects of 1.4–2.2 [20, 27, 28]. This relationship between obesity and asthma is stronger in women than in men. Several studies have shown a dose-effect relationship, as the prevalence of asthma increases in proportion to BMI [29, 30]. These transverse studies do not identify obesity as the cause of the asthma as they have not shown that the obesity precedes the asthma.

Several longitudinal cohort studies have shown that levels of obesity independently increase the risk of asthma in adults [30–35]. The length of follow-up in these studies ranged 2–10 years. The relative risk of developing asthma in an obese subject in these studies was 1.6–2.7, and was again greater in women than in men. Furthermore, these studies have shown that the risk of developing asthma during the follow-up period increased in relation to the level of weight gain since inclusion, with the relative risk being 1.2–2.5 [31, 32, 35]. Reduction in weight in obese asthmatic subjects has a favourable effect on airflow, with augmentation of MMEF25-75 and reduction in peak-flow variability, as well as reduction in dyspnoea and number of asthma attacks, and improvement in quality of life [36–38].

Contradictory results have been published regarding the relationship between obesity and bronchial hyperreactivity (BHR). In a transverse, multicentre cohort study in Europe, a metacholine challenge test in 11,277 participants [39] showed a significant correlation between BHR and BMI, but only in men, when results were adjusted for baseline ventilatory function, for biological markers for atopy (total and specific immunoglobulin E), for age and for smoking history. In a transverse cohort study of 1,971 adults, SCHACHTER et al. [20] did not show any relation between severe obesity and BHR (using the histamine test) in Australian adults, despite a raised prevalence of asthma (wheeze in the previous 12 months and a diagnosis of asthma by a doctor). This suggests that there may be an over-diagnosis of asthma in the obese. AARON et al. [40] did not show a diminution in BHR (methacholine test) in 24 obese women with asthma after a large loss of weight (mean 20 kg). Thus, there is a probable epidemiological link between asthma and obesity: but many questions remain unanswered, such as the role of obesity in different phenotypes of asthma, in particular severe asthma. Other questions are the role of android or gynaecoid obesity and what mechanisms can be implicated in the relationship between obesity and asthma. Bronchial inflammation could be induced by the increased synthesis of leptin by adipocytes or by the systemic inflammation associated with obesity, such as an increase in tumour necrosis factor. However, these are speculative hypotheses so far.

Obesity and effort dyspnoea

Effort related dyspnoea is a frequent symptom in the obese but is not simply the direct consequence of obesity on the mechanics of ventilation and respiratory function alone. Indeed, effort dyspnoea may also be related to the consequences of obesity on cardiac function, such as hypertension, left ventricular systolic or diastolic dysfunction, or the consequences of obesity on peripheral muscle function related to dysfunction in energy use by the muscles during effort. In addition, obesity is often associated with other cardiovascular comorbidities, such as pulmonary hypertension (post-embolic appetite suppressants), and coronary disease, either of which may lead to effort dyspnoea. Several mechanisms of dyspnoea may coexist in the same patient but there are no prospective studies of the respective roles of respiratory, cardiac or muscular components.

The effects of a large loss of weight have been evaluated in the Swedish Obese Subjects Study, a prospective, controlled, nonrandomised study comparing gastric surgery for obesity with conventional treatment (dietary advice) [41]. After 2 years, the operated patients had lost a mean of 28 kg while the control patients had not lost any weight. In the surgical group, the percentage of patients admitting to effort dyspnoea on occasions such as climbing stairs, walking or dressing had diminished considerably. Thus, weight loss can lead to a reduction in dyspnoea, OSA, hypertension and diabetes.

Role of OSA

Two-thirds of OSA patients are obese, particularly with android type obesity. Looked at another way, >50% of severely obese patients (BMI >40 kg per m^2) are affected by severe OSA [42]. The pathophysiological basis of this relationship was underlined by REMMERS et al. [43], for whom

five main conditions determine upper airway calibre; baseline pharyngeal area, collapsibility of the airway, intraluminal pressure, pressure outside the pharyngeal wall and opposing pressure exerted by pharyngeal dilating muscles. Moreover, lung volume independently influences upper airway calibre. Obese patients, in particular those with upper body obesity, have excess fat deposition in the soft palate and tongue and in the posterior and lateral oropharyngeal areas, increasing pressure outside the pharyngeal wall and modifying airway collapsibility. Moreover, lung volumes are reduced in these patients. All these factors could interact to modify airway patency and predispose to OSA.

What's in a name? The conflicting relationship between OHS and OSA

Obesity hypoventilation syndrome (OHS) is commonly defined as a combination of obesity (BMI >30 kg per m^2) and waking arterial hypercapnia (Pa,CO_2 >45 mmHg) [44]. There are many similarities and some overlap between OHS and OSA. First, patients present with similar symptoms, such as excessive daytime sleepiness, fatigue or morning headaches. Moreover, 11–15% of obese OSA patients present with hypercapnia [45], and a majority of the hypercapnic obese manifest OSA. Hypercapnia is more frequent in obese than in non-obese OSA subjects [42]. Nevertheless, although most hypoventilating obese patients have OSA, the relationship between the two conditions and in particular the exact contribution of OSA to hypercapnia is unclear. The lack of a standardised definition of OHS in general, and of OHS–OSA relationships in particular, leads to confusion [46, 47]. Some authors suggest including OSA as part of the definition of OHS, since only a small minority of patients with OHS have no significant OSA.

The mechanisms by which OSA may favour hypercania are not well understood. It may be that hypercapnia in OSA develops as a consequence of a reduced inspiratory effort against an obstructed airway. Therefore, ventilatory load compensation (the normal response to maintain alveolar ventilation in the face of mechanical impediments) is impaired in OSA. This impairment may be the result either of an inability of

fatigued muscles to recover between apnoeic episodes or of diaphragmatic dysfunction as a consequence of periodic hyperventilation episodes following apnoeas [48]. Also, there may be depressed ventilatory response to chemical stimuli leading to a reduction in inter-apnoea compensatory ventilation. Thus, AYAPA *et al.* [49] demonstrated in a group of hypercapnic OSA patients that Pa,CO_2 was directly related to the apnoea/inter-apnoea duration ratio. In fact, the maintenance of eucapnia during sleep requires a balance between CO_2 loading during apnoea and CO_2 clearance in the intervening period. Thus, hypercapnia occurs when, after an apnoea, the amount of ventilation is insufficient to eliminate the CO_2 loading that occured during apnoea. Whether this type of blunted response is a consequence of increased load or represents a protective adaptation to chronic hypoxia, hypercapnia and sleep fragmentation is unknown. Therefore, because arousals from sleep following apnoeas are related to the degree of inspiratory effort (more than to oxygen desaturation), this results in fewer arousals as a consequence of a decreased inspiratory effort. Thus apnoeas, hypopnoeas and arousals are replaced by hypoventilation. Then, for some authors, so-called OHS may represent an 'end stage' of OSA [50, 51]. In this context, a study published recently showed that a group of patients initially diagnosed as having OHS (and whose initial polysomnography eliminated OSA) demonstrate the development of obstructive apnoeas after correction of alveolar hypoventilation [50]. The authors' hypothesis is that noninvasive ventilation (NIV)-induced restitution of respiratory centre sensitivity may unmask OSA. Patients with these concurrent syndromes may be trapped in a vicious cycle of apnoea-induced hypoxaemia and sleep fragmentation that may blunt ventilatory response. This, combined with abnormal pulmonary mechanics, may prevent restoration of post-apnoeic eucapnia and may lead to more severe gas-exchange abnormalities

However, other authors reject the hypothesis that OSA is a part of OHS. They argue that, by definition, OHS is characterised as a development of obesity-related alveolar hypoventilation after exclusion of other conditions causing respiratory failure. Therefore, since OSA is a recognised independent cause of respiratory failure, it is logical to include it among those conditions that must be excluded. Moreover, there is clinical evidence that some non-obese OSA patients may develop hypercapnia. In a study including >30,000 OSA patients recruited from the French

ANTADIR Observatory, 7.2% of those patients with BMI >30 kg per m² (excluding COPD patients) had P_{a,CO_2} >45 mmHg [45]. On the other hand it has been demonstrated that obesity itself, in the absence of OSA, may lead to daytime hypercapnia [51]. These patients could be divided into two subsets: those with coexisting severe OSA and those without. For this reason, it seems more logical not to include sleep apnoea patients in the definition of OHS and to restrict the term OHS to patients in whom the only mechanism responsible for alveolar hypoventilation is obesity itself (independent of apnoeas) or in whom hypercapnia persists after eliminating apnoeas and hypopnoeas (*i.e.* after a trial of continuous positive airway pressure (CPAP) ventilation [45] at an effective pressure). To clarify this issue, some authors propose calling the condition obesity-linked hypoventilation (OLH) [47], sleep hypoventilation syndrome (SHS) [44] or even 'OHS without OSA' [52]. For them, this entity may be diagnosed in two situations: hypercapnia in obese patients without OSA or COPD ('pure OLH', 'pure SHS' or OHS without OSA); and persistence of hypercapnia in OSA patients who are receiving CPAP (OLH combined with OSA, SHS combined with OSA or OHS with OSA).

Leptin and hypercapnia: the missing link?

Leptin is an endogenous protein described as an adipocyte-derived hormone. Leptin receptors are founded in the hypothalamus and its main action seems to be participation in the metabolic regulation of body weight. This hormone may act in a negative feedback system by activating specific receptors associated with appetite suppression and increased energy expenditure. Recent investigations suggest a role for leptin in the control of breathing, particularly in obese people. The initial evidence for this relationship was suggested by studies in animal models that lack the gene responsible for leptin production. These animals show marked abnormalities in breathing control that lead to chronic respiratory failure. This breathing control dysfunction is aggravated during sleep and is reversed after leptin replacement therapy [53]. It is fascinating to extend this hypothesis to humans and to postulate that leptin may act by stimulating ventilatory drive in response to an increase in the

ventilatory load typical of obesity, and that, in this context, leptin deficiency may lead to OHS. However, leptin deficiency in human obesity is extremely rare and circulating leptin levels are high. Thus, some authors hypothesise that human obesity represents a leptin-resistant state [54].

Some published evidence underlines the importance of leptin-pathway abnormalities in the pathophysiology of the two most relevant obesity-associated respiratory diseases, and the probable role of these abnormalities as a link between these two conditions (i.e. by promoting hypercapnia in OSA patients). It has been hypothesised that leptin levels may act to maintain alveolar ventilation to compensate for the increased ventilatory load in obesity. For those who support this hypothesis, abnormalities in the leptin metabolic pathway may explain why, at a given ventilatory load, some obese patients hypoventilate but others do not. According to this hypothesis, hypercapnia is a consequence of complex interactions leading these patients into a vicious circle in which leptin may play a crucial role (figure 1).

Sleep and breathing in obesity

From sleep-study data, five ventilatory disorders may be identified in obese patients [13, 55] (table 2). First, the obstructive apnoeas and hypopnoeas that define OSA are very frequent in this population. Secondly, central apnoeas are also frequent in obese patients. They may be isolated or generated as a consequence of the hyperventilation response that follows obstructive apnoea. This hyperventilation response may induce P_{a,CO_2} below the apnoeic threshold and then trigger a central event. Both abnormalities are seen as periodic dips in saturation and simple nocturnal oximetry will not allow differentiation between them. The three other
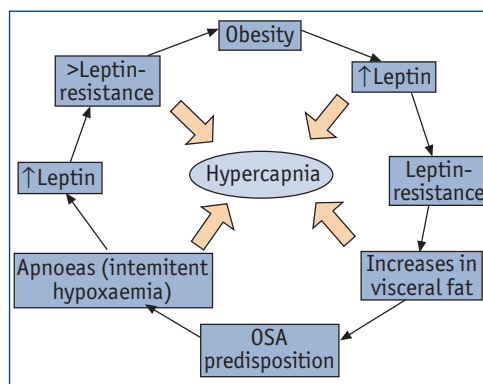

Figure 1
Leptin and obesity hypoventilation: potential pathophysiological interactions.

Table 2	Classification of ventilatory sleep disorders in obese subjects

Obstructive apnoeas and/or hypopnoeas
Central apnoeas
Continuous oxygen desaturation
    With nocturnal hypercapnia
        Central hypoventilation (also named 'sleep hypoventilation')
        'Obstructive' hypoventilation
    Without nocturnal hypercapnia
        Impairment of V'/Q' inequality

abnormalities, central hypoventilation (also called sleep hypoventilation), 'obstructive' hypoventilation and V'/Q' inequality are diagnosed on nocturnal oximetry by a pattern of continuous oxygen desaturation. The first two differ from the third by the fact that they occur together with nocturnal hypercapnia. Central hypoventilation is a manifestation of a sleep-induced reduction in ventilatory drive. These episodes occur much more frequently in REM sleep [13], which is characterised by general muscle hypotonia. Chronic diaphragmatic fatigue due to increased mechanical load has also been demonstrated in this population. Obstructive hypoventilation corresponds to sustained periods of hypoventilation due to partial airway obstruction as described by BERGER *et al.* [55]. The two types of hypoventilation may be differentiated in sleep studies by the analysis of the flow-time contour. While central hypoventilation is characterised by a reduction in flow amplitude with a rounded inspiratory (non-limited) flow contour, accompanied by a proportional reduction in thoraco-abdominal strain gauges but without paradox, obstructive hypoventilation is characterised by a flow-limited inspiratory flow contour, generally accompanied by a thoraco-abdominal paradox on strain gauges. The therapeutic approach differs in the two cases. Thus, obstructive hypoventilation, as in the face of a partially collapsed airway, requires an increase in CPAP pressure levels to stabilise the airway, while central hypoventilation as a result of reduced ventilation requires ventilatory assistance.

Obesity hypoventilation in the clinical setting

A patient presenting with gross obesity, sleepiness, dyspnoea and signs of cor pulmonale provides an unforgettable picture. Nevertheless, hypoventilation in these patients is frequently misdiagnosed as depression, congestive heart failure or even atypical COPD. Furthermore, hypoventilation is sometimes underappreciated even in severely obese patients, particularly in mild variants of the syndrome. Therefore, the diagnosis is rarely made in the stable state. In a cohort study conducted at a general hospital, undiagnosed obesity hypoventilation was present in 31% of patients with a BMI >35 kg per m^2. Although weight alone did not predict hypoventilation, almost half of the patients with BMI >50 kg per m^2 had diurnal hypercapnia [56] as already described. Alveolar hypoventilation in obesity results from complex interactions between obesity, ventilatory mechanics, ventilatory control, sleep apnoea and degree of FEV_1 abnormality. Therefore, three entities (OSA, COPD and OLH) may be incriminated in the pathogenesis of hypoventilation in an obese subject. These three conditions are frequently involved in the same patient. Thus, in the clinical setting, five pathophysiological-based clinical patterns resulting from occurrence of one or more of these conditions may be defined (table 3).

Diagnosis of alveolar hypoventilation in an obese individual is frequently made in two situations

The first situation is during a decompensation episode that is typically slowly progressive over several days, and less frequently acute. Patients typically present following a respiratory infection, but it is not uncommon for no recognised trigger factor to be identified. Therefore, clinical repercussions are disproportionate and more severe than those expected for the underlying cause that unmasks the underlying ventilatory abnormality.

The second circumstance of discovery is when, following symptoms of respiratory sleep disturbances, patients are referred to a sleep laboratory for screening for OSA. Even in this situation, hypoventilation may be underdiagnosed if patients are screened only for OSA, and ABG measurements are not performed. This is because data recorded during conventional polysomnography (in particular pulse oximetry) reflects only oxygen saturation without analysis of P_{a,CO_2} patterns.

Finally, since chronic hypercapnia in obesity is most frequently diagnosed following a decompensation, the underlying diagnosis is often made after the patient's condition improves. Therefore, tests to be performed should include

Table 3   Hypoventilation in obese subjects: clinical patterns

Clinical pattern	Diagnostic criteria	Treatment
'Hypercapnic' OSA	1) OSA confirmed by polysomnography 2) Normocapnia corrected and/or maintained by a single CPAP	CPAP
Obesity-linked hypoventilation	Persisting hypercapnia in patient in whom: 1) Polysomnogram excludes OSA 2) FEV_1/FVC >70%, FEV_1 >70% predicted	Bilevel ± O_2 (generally low positive end-expiratory pressure)
COPD	1) Chronic airflow limitation (FEV_1/FVC <70% and FEV_1 <70% predicted) 2) Polysmnography excludes OSA	Long-term oxygen therapy Bilevel ± O_2 if - Symptomatic and - P_{a,CO_2} >55 mmHG and - multiple exacerbations
OSA associated with OLH	1) OSA confirmed by polysomnography 2) Remained hypercapnic under a single CPAP	Bilevel ± O_2 (generally high positive end-expiratory pressure)
Overlap syndrome (OSA associated with COPD)	1) OSA confirmed by polysomnography 2) Chronic airflow limitation (FEV_1/FVC <70% and FEV_1 <70% predicted)	Bilevel or CPAP±O_2

Reproduced from [59], with permission from the publisher. Bi level: Bi level positive airway pressure

at least ABG, pulmonary function tests and polysomnography (table 3).

This syndrome is associated with significant morbidity and mortality. Hypercapnia and hypoxaemia in the obese individual may be complicated by pulmonary hypertension, polycythaemia and cor pulmonale. Pulmonary hypertension may be present in up to 60% of patients [56]. These patients are more likely to require invasive ventilation and tend to need more intensive care unit management and longer lengths of stay. Most notably, mortality at 18 months after discharge is nearly twice the rate of that for simple obesity [57]. Another study demonstrated that the use of healthcare resources is increased when compared with a group of obese controls. That proportion significantly decreased after institution of ventilatory support and these patients were no more likely to be hospitalised than controls after 2 years of treatment [58]. Therefore, systematic screening and early detection of this condition and its appropriate management may reduce morbidity and mortality in this population.

Ventilatory approach in obesity hypoventilation: CPAP or NIV?

Since a variety of associated respiratory disturbances may be found in hypoventilating obese subjects, management of these patients implies treating respiratory sleep disturbances, diurnal hypercapnia and additional hypoxaemia that may persist after correcting alveolar hypoventilation. In general, treatment that corrects sleep-related breathing disorders results in the reversal of chronic daytime hypercapnia. The therapeutic approach depends on the patient's underlying situation and on sleep study results.

Ventilatory management in the acute or subacute setting

Management of respiratory failure in an obese patient will depend on the underlying clinical situation. A patient presenting with shock, severe encephalopathy, severe pneumonia or multi-organ failure must be transferred quickly to the critical care unit and intubation must be planned. In other cases, NIV may be planned as first-line treatment to manage acute or subacute respiratory failure in these patients. Many patients initially require oxygen supplementation to maintain adequate arterial oxygen saturation. Even though in theoretically pure obesity hypoventilation, P_{a,O_2} reduction must be proportional to P_{a,CO_2} increase, hypoxaemia in these subjects is frequently more severe than what would be expected on the basis of the degree of hypoventilation, reflecting an additional contribution of a V'/Q' inequality as described previously. Treatment may be carried out either in the respiratory critical care unit, the intermediate care unit or even the general ward, depending on severity and on the

experience and skills of the medical and paramedical team in NIV. In a retrospective study, NIV appeared to be effective as first-line treatment in a population including 41 obese patients with severe hypercapnic acidosis [59]. Using a continuous printed oximetry tracing in real time, the authors adjusted ventilatory parameters step by step to optimise ventilation. Expiratory positive airway pressure was increased progressively until desaturation dips were corrected, and inspiratory pressure was increased until an acceptable level of mean saturation was obtained (which the authors felt corresponded to alveolar ventilation). Once the clinical situation is improved, patients may be discharged on more physiological ventilatory support, depending on pulmonary function and the results of polysomnography. Some authors underline the primary role of polysomnography in the follow-up of these patients after a stable condition has been achieved [59, 60].

Figure 2
Proposed algorithm to manage hypercapnia in an obese patient.
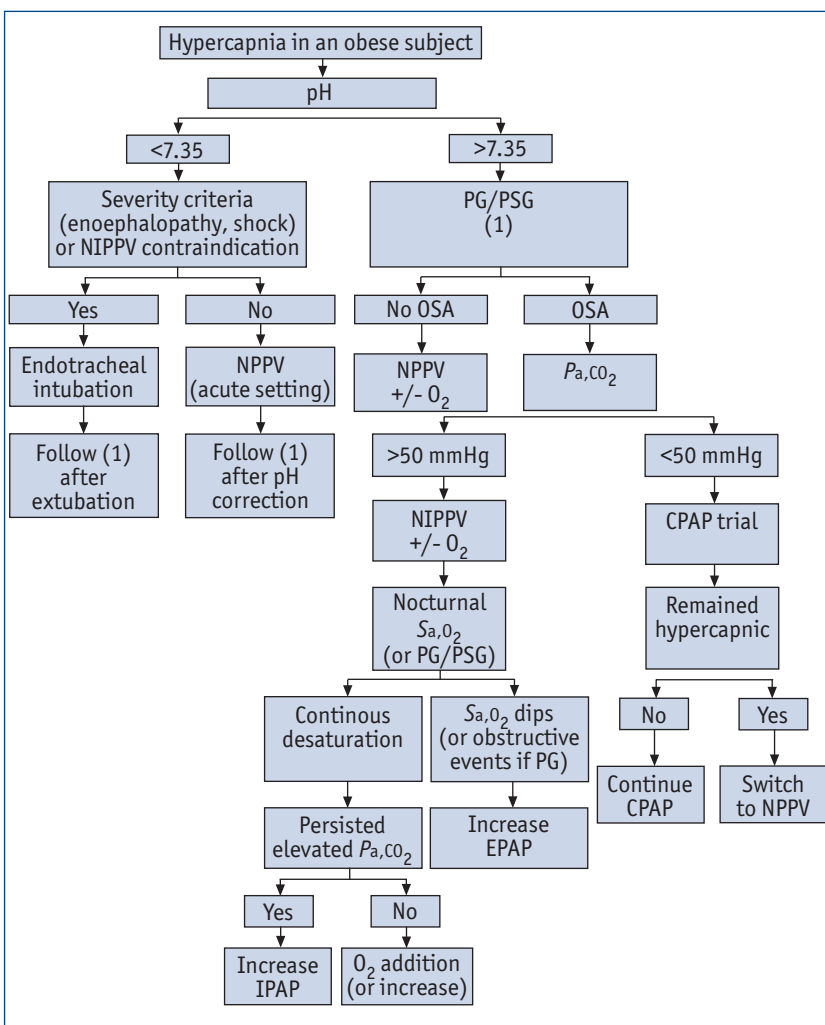
Ventilatory management in the steady state

In stable hypercapnic patients without acidosis, therapeutic choice will depend on two factors: underlying diagnosis (presence or absence of OSA) and severity of hypercapnia. If P_{a,CO_2} is <50 mmHg and OSA is confirmed by polysomnography, most authors begin by performing a CPAP trial. This therapy provides pressure that maintains upper airway patency, eliminates apnoeas and hypopnoeas and may restore daytime eucapnia. If alveolar hypoventilation is reversed, the patient will remain on long-term CPAP. In this case, it can be assumed that hypercapnia is only related to OSA. On the other hand, in a significant number of patients, hypercapnia may persist despite adequate CPAP treatment. This suggests that a secondary mechanism (*i.e.* obesity itself) is perpetuating alveolar hypoventilation. Such patients require augmentation of ventilation during sleep rather than simple stabilisation of the upper airway, so it is logical to use NIV. Differences between expiratory and inspiratory pressures assist lung inflation through each cycle, thereby supporting ventilation. Predicting which patients will respond to simple CPAP and which will not is frequently difficult. Some published series identified greater BMI and more severe hypoventilation as predictors of lack of response to CPAP [61, 62]. Nevertheless, the differential diagnosis between these two conditions is generally retrospective according to the P_{a,CO_2} kinetics under treatment.

In patients with P_{a,CO_2} >50 mmHg, the initial therapeutic choice may be NIV. If, after some time under NIV, the patient becomes normocapnic, and sleep studies confirm OSA, it is advisable to switch to CPAP (after performing a polygraphic full-night titration to identify optimal pressure level). If the patient remains normocapnic, long-term CPAP may be proposed. Otherwise the patient may be switched back to NIV.

In all cases in which sleep studies do not show significant OSA, NIV will be the therapeutic choice. In this case, hypercapnia may be considered as obesity-related only, but additional causes such as COPD need to be sought.

Finally, in some patients, respiratory failure cannot be managed by NIV. In this small subgroup of patients and in patients who do not tolerate NIV, a tracheostomy may be required. A proposed algorithm for ventilatory management of these patients is shown in figure 2.

NIV in OHS: the great challenge

OHS represents one of the most frequent indications for NIV worldwide. In a prospective study of a 7-year follow up of NIV prescriptions in Switzerland, COPD and OHS were the most frequent indications for the use of this technique. The authors underlined that the increasing treatment of OHS patients by NIV is probably related to several factors: the demonstration that NIV is effective in relieving respiratory muscles in obese patients, a better knowledge of the consequences of morbid obesity on respiratory function, the wide use of CPAP for patients with OSA and therefore an earlier identification of patients who may benefit from NIV therapy [63].

Management of this type of patient implies mastery of hypoventilation and of apnoeas at the same time. In this context, the inspiratory and expiratory positive airway pressures must be adjusted separately in a 'step by step' approach, attempting to correct both abnormalities that typically coexist in the same patient. To achieve these aims, close monitoring is recommended to ensure optimal ventilatory quality and must include at least repeated ABG and overnight oximetry traces, ideally reinforced by recording continuous transcutaneous carbon dioxide tension measurements (Ptc,CO_2) coupled to oximetry. Ideally, polysomnography under NIV should be performed (if available) to better understand machine–patient interactions. If hypoventilation persists (as reflected by diurnal hypercapnia generally accompanied by nocturnal desaturation, or at least by a decrease in overnight arterial compared to diurnal values, and/or overnight increase of Ptc,CO_2 when available), inspiratory positive airway pressure must be increased. If, on
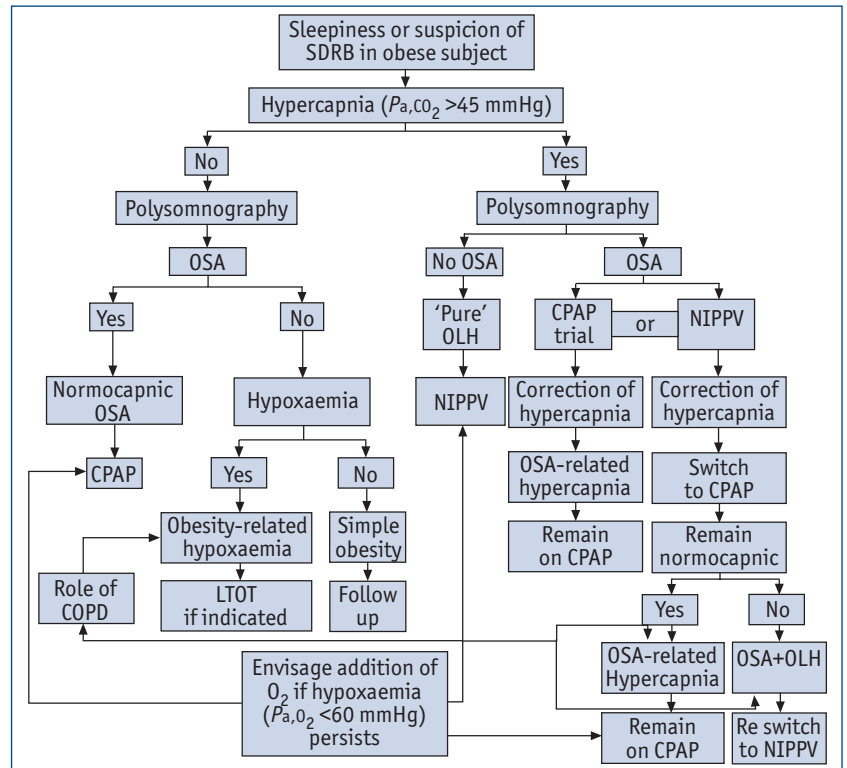
the other hand, intermittent desaturation dips persist, denoting residual apnoeas and/or hypopnoeas under NIV, expiratory positive airway pressure must be increased to stabilise the upper airway at end-expiration and prevent airway collapse at the beginning of inspiration, which may lead to patient–ventilator asynchrony [59]. In general, the target is to obtain progressive improvement of ABG and experience shows that is not necessary to achieve a total correction of diurnal blood gases in the first days of treatment.

A proposed algorithm for management of obese patients with sleep-related breathing disorders can be seen in figure 3.

Figure 3

Proposed algorithm to manage sleepiness and/or suspected sleep-related breathing disorders in an obese patient.

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Educational questions

Are the following statements true or false?

1. Isolated hypoxaemia in obesity is likely to be due to V'/Q' mismatch.

2. In massive obesity, gynaecoid fat distribution leads to a greater reduction in ERV than android distribution.

3. Hypoxaemia correlates poorly with ERV reduction in obesity.

4. Weight loss in obese subjects generally leads to an increase in ERV and FRC.

5. 10% of males with a BMI >35 kg per m^2 have obesity hypoventilation syndrome.

6. Pulmonary hypertension may be present in up to 60% of patients with OHS.

7. Expiratory positive airway pressure during NIV should be titrated to stabilise the upper airway, thereby controlling obstructive apnoeas and hypopnoeas.

8. The overlap syndrome is diagnosed by the coexistence of obstructive sleep apnoea and obstructive spirometry (FEV1/FVC <70%).

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Suggested answers

1. True.
2. False.
3. False.
4. True.
5. False.
6. True.
7. True (may also increase FRC).
8. True.