Obesity and the lung: 2 · Obesity and sleep-disordered breathing

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ABSTRACT

As the prevalence of obesity increases in both the developed and the developing world, the respiratory consequences are often underappreciated. This review discusses the presentation, pathogenesis, diagnosis and management of the obstructive sleep apnoea, overlap and obesity hypoventilation syndromes. Patients with these conditions will commonly present to respiratory physicians, and recognition and effective treatment have important benefits in terms of patient quality of life and reduction in healthcare utilisation. Measures to curb the obesity epidemic are urgently required.

The prevalence of overweight (body mass index (BMI) >25 kg/m^2), obese (BMI 30–40 kg/m^2) and morbidly obese (BMI >40 kg/m^2) adults and children is increasing dramatically in all developed countries including the USA,[1] Europe[2] and Australia.[3] The incidence of morbid obesity is increasing at a rate faster than that of moderate obesity,[4] with BMI increasing 2 kg/m^2 per decade and weight 1 kg per annum.[3] While the prevalence of obesity in developing countries is much less than in the developed world (20% in China vs 60% in Australia), the incidence in China in the last 20 years has outstripped that in Australia (400% vs 20%). This is similar to the pattern seen in Latin American countries,[5] reflecting the economic posterity and resultant changes in diet and exercise. Thus, while the developed world is currently in the throes of an obesity epidemic, this pattern can be expected to be reflected in the developing world. Despite the high prevalence of obesity, there appears to be poor recognition and appreciation of the clinical consequences of obesity.[6 7]

In this review we outline the impact of obesity on three aspects of respiratory medicine: obstructive sleep apnoea (OSA), overlap syndrome (chronic obstructive pulmonary disease (COPD) and OSA) and obesity hypoventilation syndrome (OHS) (table 1).

OBSTRUCTIVE SLEEP APNOEA (OSA)

Definition

OSA is defined as the repetitive collapse of the upper airway (either partial or total collapse resulting in a hypopnoea or apnoea, respectively) during sleep, occurring more than 5 times per hour of sleep (the apnoea-hypopnoea index, AHI). Episodic hypoxaemia, hypercapnia, large negative intrathoracic pressure swings (to −120 mm Hg) and surges in systemic blood pressure (to 250/150 mm Hg) associated with arousals and sleep fragmentation occurring up to 100 times per hour of sleep characterise the condition. Symptoms include excessive daytime sleepiness, unrefreshing sleep, nocturia, loud snoring (above 80 dB), witnessed apnoeas and nocturnal choking. Signs include systemic (or difficult to control) hypertension, premature cardiovascular disease, atrial fibrillation and heart failure.[8] The obstructive sleep apnoea syndrome (OSAS) is arbitrarily defined by >5 apnoeas or hypopnoeas per hour plus symptoms of daytime sleepiness.

Almost 20 years ago the prevalence of OSA and OSAS in the USA was reported to be 24% and 4% in men and 9% and 2% in women, respectively.[9] Since then the average BMI has increased by about two units per decade and the prevalence of OSA and OSAS is very likely to have increased significantly.[10]

Pathogenesis of OSA

Factors contributing to the development of OSA include increasing age, gender (men>women), an anatomically narrow upper airway, a tendency to have a more collapsible upper airway (made worse by obesity), individual differences in neuromuscular control of upper airway muscles and variations in ventilatory control mechanisms (fig 1). Of these, obesity explains 30–50% of the variance in AHI and is the only variable that can be modified.[11]

Obesity and its link with OSA

Obesity may predispose to OSA by accumulation of fat around the neck, resulting in increased extraluminal pressure and a propensity to upper airway collapse which can sometimes be seen on flow-volume loops (fig 2). Fat distribution may affect the geometry of the airway, again making collapse more likely. Neck circumference is the anthropometric measurement most closely associated with OSA, even in those with a normal BMI.[12] Increasing levels of abdominal obesity cause decreases in lung volumes[13] which may cause a reduction in longitudinal traction predisposing to upper airway collapse. Obesity also reduces chest wall compliance and increases whole body oxygen demand, again predisposing to OSA. The degree to which common conditions associated with obesity, such as diabetes, may cause vascular or neuropathic damage to the dilator pharyngeal muscles and reduced upper airway sensation remains to be fully elucidated.[14] Asian populations appear to have a higher percentage of body fat and associated increased cardiovascular risk at lower BMIs than European populations,[15] leading the World Health Organization to change the BMI value considered overweight to 23 kg/m^2 for Asians. Asian populations have an increased prevalence of OSA at a lower BMI than in a comparable European

Table 1 Comparison of adult patterns of BMI, lung function and $Paco_2$ in normal patients and those with OSA, overlap and OHS

	BMI	Lung function	↑ $Paco_2$ nocturnal (mm Hg)	↑ $Paco_2$ diurnal
Normal	18–25	Normal	2–3	No
OSA	>18	Normal	>5	No
Overlap	>27	Obstructive	>10	Yes
OHS	>30	Restrictive	>15	Yes

BMI, body mass index; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; $Paco_2$, arterial carbon dioxide tension.

population, although some increase in prevalence is also related to the difference in cephalometric features of the upper airway.[16] There is an increased prevalence of OSA in obese women with polycystic ovary syndrome compared with age- and weight-matched controls.[17] This may reflect differential parapharyngeal fat deposition related to androgen excess, although direct effects of androgens on ventilatory control may also contribute.

The association between obesity and OSA has been noted in cross-sectional and longitudinal studies.[18] Data from the Wisconsin sleep cohort suggest that weight gain has a greater effect on OSA than an equivalent weight loss.[10] In that study a 20% increase in weight was associated with a 70% increase in AHI, whereas a 20% reduction in weight was associated with a 48% decrease in AHI.

Leptin and ventilatory control

While obesity has important effects on airway collapsibility and geometry, there is also evidence that the metabolic consequences of obesity may have direct effects on ventilatory control. Leptin is an adipose derived hormone which signals satiety and reduces appetite.[18] Leptin levels have been found to be elevated in obesity, indicating a degree of leptin resistance. High levels of leptin may impair the response to hypercapnia,[19] leading to greater apnoea-related hypercapnia and acidosis and subsequent impairment of the arousal response. Leptin may also be important in the development of OHS which is discussed later in this review.

Sleep deprivation, appetite and weight gain

There is also increasing interest in the link between sleep deprivation and changes in appetite. Recurrent airway obstruction and subsequent arousal lead to poor sleep quality and excessive daytime somnolence in OSAS. Spiegel *et al*[20] investigated the effects of sleep deprivation on leptin and ghrelin (a hormone signalling hunger) levels in 12 healthy volunteers.

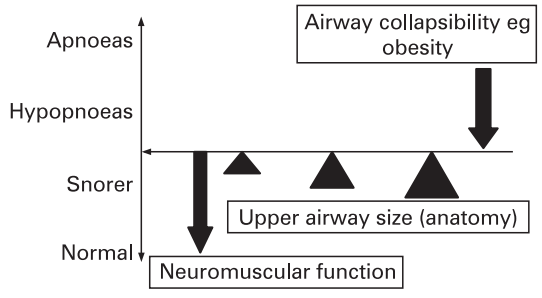

Figure 1 Balance of forces as applied to the upper airway and the impact exerted by weight gain. Note the rightward shift of the fulcrum with enlarging upper airway size and the reduced impact of obesity on upper airway collapse.

They found that restricting sleep to 4 h per night for two nights resulted in an increase of 28% in ghrelin levels and an 18% reduction in leptin levels compared with 10 h of sleep per night for two nights. In addition, sleep restricted subjects reported an increase in appetite for calorie-dense foods with high carbohydrate content.

Whether these perturbations are seen in other populations and whether the sleep disruption occurring in OSA causes similar changes remains to be seen. However, there remains the possibility that sleep disruption as a consequence of OSA may cause obesity, potentially leading to a self-perpetuating cycle.

The inflammatory state associated with OSA

Both obesity and OSA seem to be inflammatory conditions. OSA is considered an independent cause of endothelial dysfunction due to high sympathetic activation, oxidative stress due to intermittent hypoxia and reperfusion, high levels of cytokines such as interleukin 6, C-reactive protein and increased platelet aggregation.[21] Obesity alone is an inflammatory state, and it has been shown that adipose cells may themselves secrete a number of biologically active molecules including tumour necrosis factor α, transforming growth factor β and interferon δ.[22] Separating the effects of OSA and obesity on inflammatory activity and potential cardiovascular morbidity and mortality may therefore prove to be difficult.

Impact of treatment for obesity on OSA

Despite the close epidemiological links between obesity and OSA, there is a paucity of data on the effects of weight loss as part of the treatment of sleep apnoea. A 2001 Cochrane review of the effects of lifestyle modification on treatment was unable to find any suitable randomised controlled trials.[23]

However, epidemiological and small uncontrolled studies suggest that weight loss reduces AHI. Norman *et al*[24] studied the effects of a supervised exercise programme in nine subjects with OSA. After completion of 6 months of exercise there was a mean reduction in BMI from 31.2 to 29.6 kg/m^2 associated with a reduction in AHI from 21.7 to 11.8 events/h ($p<0.01$). Improvements in subjective sleepiness and quality of life were also noted. Lam *et al*[25] studied the effects of conservative measures (sleep hygiene advice and attendance at a dietetics programme) alone and the use of either an oral device or continuous positive airway pressure (CPAP) in 105 subjects with mild to moderate OSA. Only the CPAP group showed any significant weight loss (from 27.6 to 27.2 kg/m^2). However, the authors noted that 8 out of 34 subjects achieved normalisation of AHI to <5 events/h (from a baseline of 14.6) using conservative measures alone with an average weight loss of 3 kg. Barnes *et al*[26] reported interim data from a supervised weight loss programme similar to that with pulmonary and cardiac rehabilitation programmes, suggesting a mean weight loss of 7 kg resulted in a fall in AHI from 42 to 27 events/h. In view of these data, it would appear prudent that all overweight subjects should be advised to lose weight, although it is likely that this will be achieved in <10% of patients.

The impact of the supine body position during sleep is well known to increase snoring, AHI and worsen hypoxaemia compared with the lateral position.[27] Risk factors for positional OSA are BMI (<30 kg/m^2), AHI (<40 events/h) and age (<60 years).[28] Weight loss in morbidly obese patients has been shown to convert non-positional OSA to positional OSA (ie, supine only), thereby obviating the need for CPAP in some patients.[27]

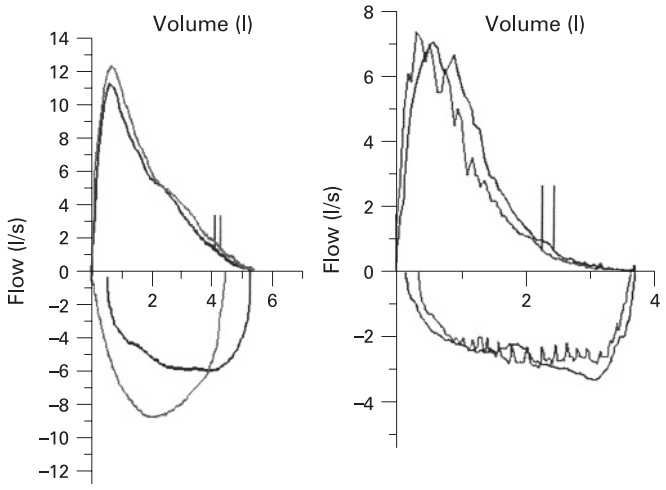

Figure 2 Flow-volume characteristics of (left) a normal subject and (right) a patient with severe obstructive sleep apnoea (OSA). Note the "saw tooth pattern" on the inspiratory and expiratory loops, suggesting a floppy oropharynx.

The use of surgical interventions on those with morbid obesity has been well studied. In a meta-analysis of the use of gastric surgery for weight loss in morbidly obese subjects, Buchenwald *et al*[29] showed that 86% of patients had resolution of OSA following the significant weight loss associated with this intervention.

The detailed methods for achieving weight reduction are beyond the scope of this review. However, interventions include behavioural modification, use of appetite suppressing and fat binding medications and high protein/low calorie replacement diets and, in the most severe cases, bariatric surgery. While it seems that many patients with OSA will be unable to achieve significant weight loss, if it is achieved it may result in significant improvement in the condition and a resultant decrease in other obesity-related co-morbidities and thus should be advised in all overweight patients with OSA. A history of weight change should be obtained including estimates of maximal weight and dates. Accurate measurement of weight—rather than self-reported weight—with large platform scales (reading up to 300 kg) in a private area should be mandatory and repeated periodically to assess changes in weight over time. Moreover, patients being assessed for snoring should have other obesity and cardiovascular-related conditions assessed (eg, glucose, cholesterol, blood pressure control) as this could influence the decision and choice of OSA management options.

COPD AND OSA: THE OVERLAP SYNDROME

Sleep in a normal individual results in hypoventilation and mild hypercapnia (2–3 mm Hg) owing to a decrease in response to ventilatory stimuli, supine-related reduction in functional residual volume (FRC), altered ventilation-perfusion matching and reduced accessory, intercostal and upper airway muscle tone.

Patients with COPD often have resting hypoxia and/or hypercapnia, predisposing them to more exaggerated changes in ventilation and greater hypercapnia (>10 mm Hg) during sleep. In addition, if they develop apnoeas they may fail to return to normoxia after cessation of the apnoea in contrast to those with pure OSA. This combination of COPD and OSA is known as the overlap syndrome.

The Sleep Heart Health Study (SHHS) concluded that, in patients with mild COPD, any association with OSA was by chance rather than by a common pathophysiological linkage.[30] The lower frequency of OSA in this study may have been a reflection of lower BMI in the subjects with mild COPD. In this study, patients with the overlap syndrome had greater sleep disruption and nocturnal desaturation which was mainly attributable to the presence of the OSA rather than the presence of COPD per se.

The prevalence of the overlap syndrome in patients with OSA has been estimated at approximately 10%.[31] Patients with overlap syndrome tended to be older, male and have greater airways dysfunction, higher pulmonary artery pressures and to be more hypercapnic than those with pure OSA.[31]

Compared with patients with pure COPD, patients with overlap syndrome are more obese, have a greater neck circumference, higher alcohol consumption[32] and have disproportionately greater degrees of hypoxia and hypercapnia for their lung disease. The diagnosis should therefore be considered in patients with COPD who are obese, whose ventilatory failure is out of proportion to their airflow obstruction or have greater than expected degrees of pulmonary hypertension.

This group of patients should be specifically asked about symptoms of OSA and should have assessment of their breathing at night. Although overnight oximetry may be helpful diagnostically, polysomnography with transcutaneous CO_2 pressure ($PtcCO_2$) may be required if supplemental oxygen is being used. The mainstay of treatment includes routine management of the COPD and the institution of CPAP, bilevel positive airway pressure (BPAP) with supplemental oxygen if necessary. Implementation of CPAP or BPAP may require a titration polysomnography to assess synchrony between patient and machine. Moreover, oxygen toxicity during sleep—which might lead to type 2 respiratory failure—should be excluded.

Clinicians should also be aware that many of the drugs that are used in the treatment of COPD exacerbations may worsen any co-existent OSA. Oral steroids may have detrimental effects by causing oedema, weight gain, a metabolic alkalosis with compensatory respiratory acidosis and myopathy. Benzodiazepines, which can be prescribed as anxiolytics in this group of patients, may cause respiratory depression, decrease arousal threshold and may worsen hypoxia and hypercapnia during sleep. The use of these medications should therefore be minimised where possible.

Evidence in favour of long term CPAP, BPAP or other forms of non-invasive ventilatory support (NIV) in the overlap syndrome is scant. Although randomised controlled trials of CPAP are lacking, an uncontrolled trial suggested that stabilisation of OSA with CPAP may impart a benefit on lung function and hospital readmission rates in patients with overlap syndrome.[33] The largest (n = 122) and longest (2-year) published randomised controlled trial of NIV in hypercapnic COPD (specifically exclusive of moderate to severe OSA defined by an overnight oximetry 2% dip rate of >10/h) did not show a benefit on mortality or lung function. However, trends in improved quality of life and hospitalisation rates were observed.[34] Limitations of this study were the absence of NIV titration with polysomnography, low levels of expiratory positive airway pressure (likely to be insufficient to overcome intrinsic positive end expiratory pressure (iPEEP)) and verbal rather than objective assessment of adherence to treatment. Future mechanistic and therapeutic studies into the overlap syndrome and COPD patients with chronic hypercapnia are urgently

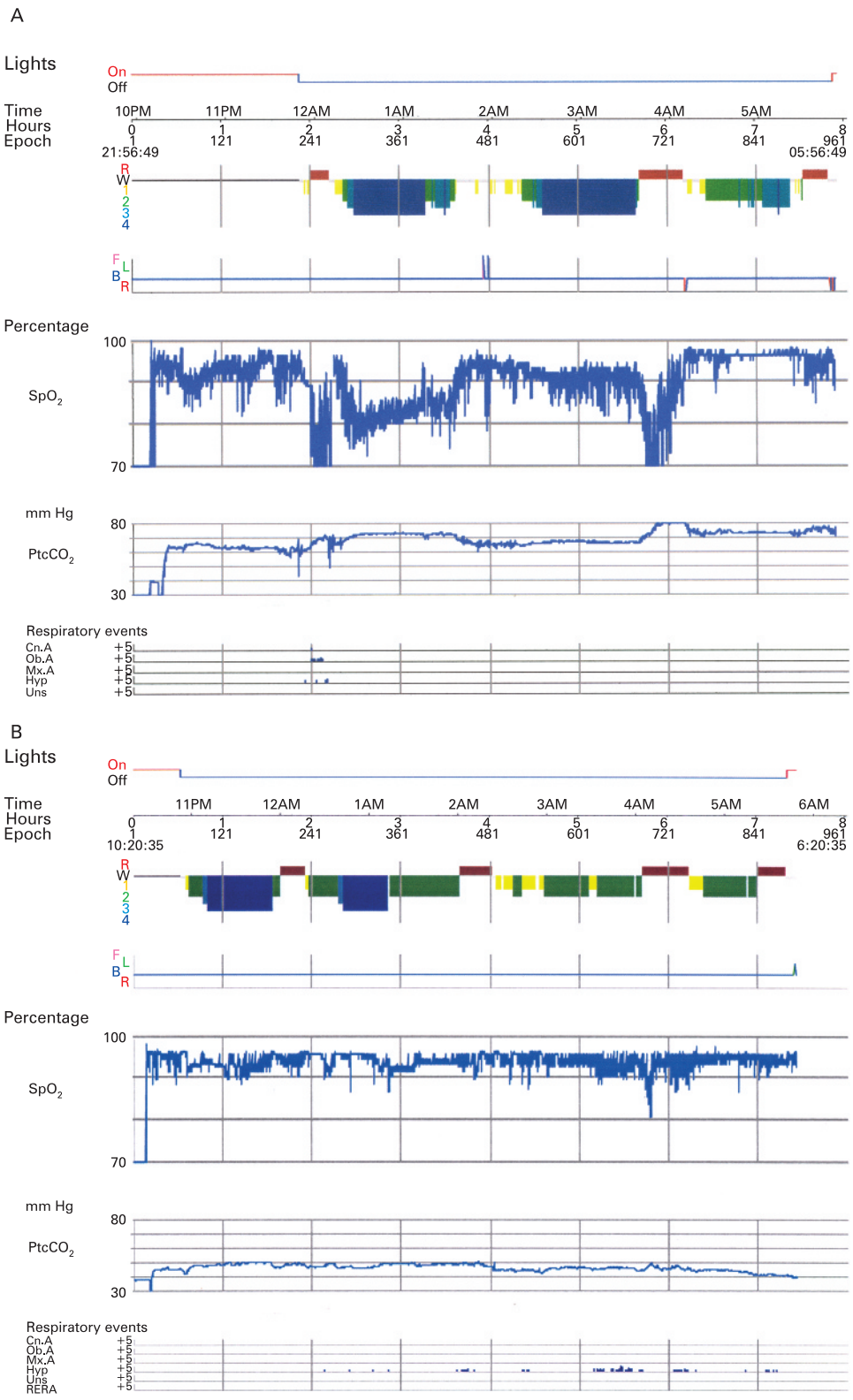

Figure 3 (A) Eight-hour polysomnogram of obesity hypoventilation syndrome (OHS) in 22-year-old man (weight 228 kg, height 158 cm, $Paco_2$ 67 mm Hg). Note spiralling oxygen saturation (Spo_2) with inadequate correction above 90%, marked and progressive hypercapnia across the night and fragmented sleep. (B) Same patient 18 months later weighing 110 kg less following dietary restriction.

required, given the high mortality and morbidity rates observed.[35]

OBESITY HYPOVENTILATION SYNDROME (OHS)

OHS is defined by the development of diurnal hypercapnia ($PaCO_2$ >45 mm Hg) in obese individuals (BMI >30 kg/m^2) in the absence of other reasons for hypoventilation such as coexistent lung or neuromuscular disease (fig 3). While these individuals share many of the same clinical characteristics as those with OSA, OHS is associated with a significantly greater degree of morbidity and mortality,[7 36 37] primarily related to respiratory and cardiac compromise.[38]

The prevalence of OHS in the general population is unknown since arterial blood gas measurements are not routinely performed

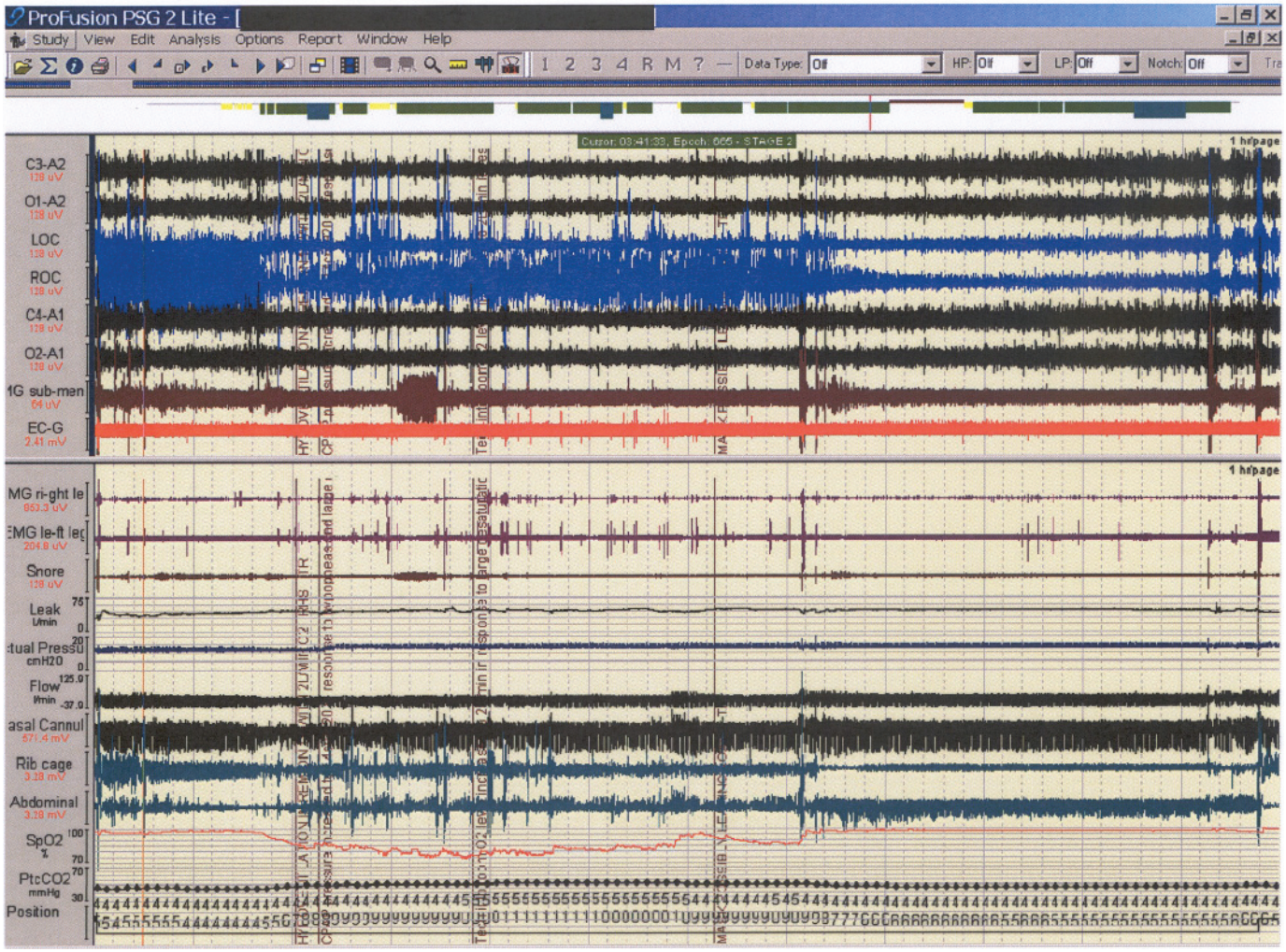

Figure 4 One-hour polysomnogram showing an adequate response of obesity hypoventilation syndrome to continuous positive airways pressure in non-rapid eye movement (REM) sleep; however, hypoventilation (hypoxaemia and hypercapnia) occurs without changes in mask leak during REM sleep.

in the community. In a small cross-sectional study of healthy non-smoking obese women (BMI ⩾30 kg/m^2) presenting to an obesity clinic, 11% had a raised daytime P_{CO_2}.[39] The prevalence of chronic daytime hypercapnia in patients attending sleep laboratories ranges from 11%[40] to 38%,[41] with the incidence increasing with increasing BMI levels.[40] In hospitalised patients with a BMI >35 kg/m^2, 31% had daytime hypercapnia.[7]

Morbid obesity has a significant impact on the respiratory system, producing changes in pulmonary mechanics, upper airway resistance and respiratory muscle function. Although the likelihood of developing diurnal hypercapnia increases as BMI rises, weight alone does not explain the presence of hypercapnia[42] and there continues to be significant interest in the mechanisms underlying the development of this syndrome. A restrictive defect in pulmonary function occurs in OHS, most likely due to decreased chest wall compliance.[43] Typically, total lung capacity, expiratory residual volume and FRC are reduced,[43] contributing to an abnormal distribution of ventilation and worsening gas exchange. Expiratory flow limitation and iPEEP have been found in morbidly obese subjects.[44] This would result in an additional elastic load being placed on the inspiratory muscles and could contribute to a substantial increase in respiratory muscle work even during quiet breathing.[45] Subjects with OHS have significantly higher diaphragmatic work of breathing than those with obesity or OSA alone.[46] These alterations in lung mechanics along with the high work of breathing could contribute to respiratory muscle dysfunction and eventually a reduction in ventilation. However, despite significant impairments in respiratory mechanics, this cannot be the sole mechanism underlying the development of daytime hypoventilation in OHS since normalisation of awake CO_2 with voluntary hyperventilation is possible.[47]

Abnormalities in ventilatory control of patients with OHS have been demonstrated by a number of investigators.[48–50] It appears that obese eucapnic patients increase respiratory drive to compensate for the respiratory system changes associated with obesity.[49 51] In contrast, those individuals who develop awake hypoventilation lack this augmented drive.[48] This lack of responsiveness is more likely an acquired phenomenon,[52] with improvements in the ventilatory responsiveness to CO_2 achieved by appropriately treating sleep-disordered breathing.[50 53 54]

Interest has arisen in the pattern of sleep-disordered breathing and the possible contributory effects of upper airway obstruction to the syndrome.[42 55 56] Only a few patients have non-obstructive sleep hypoventilation, with most demonstrating varying degrees of frank obstruction or obstructive hypoventilation.[38 42 56] However, the clinical presentation of OHS with and without OSAS is identical. Interestingly, results from a small

Table 2 Acute effects (<3 months) of positive airway pressure in OHS

Author	N	Study type	Intervention	Duration	Outcomes	Comments
Sullivan[74]	2	Case reports	CPAP	1–3 months	↑ Pao_2; ↓ $Paco_2$; ↓ oedema; ↓ EDS; ↑ mentation	↓ Reduced SDB off therapy
Piper[78]	13	Retrospective	NIV	3 months	Improved ABGs	Long-term CPAP effective in 9/13 subjects
Berg[37]	20	Retrospective	BPAP or CPAP	2 years	68% ↓ hospitalisations following therapy	
Hida[38]	26	Before/after	CPAP	3 months	↓ EDS; improved QoL	
de Miguel Diez[57]	12	Before/after	BPAP withdrawal	3 months	No change in weight, daytime or nocturnal ABGs with treatment withdrawal; slight ↓ $\Delta P_{0.1}/\Delta Paco_2$, $\Delta VE/\Delta Paco_2$	12/22 patients managed off BPAP; 7/12 demonstrated OSA and required CPAP therapy
Storre[80]	10	RCT, crossover	BPAP-S/T ±AVAPS	6 weeks	Improved sleep quality on BPAP; improved QoL; ↓ $Ptcco_2$ during sleep on BPAP	BPAP with AVAPS more effective in ↓ CO_2 but no additional effects on sleep or QoL. CPAP non-responders studied
Banerjee[77]	23	Prospective	CPAP	1 night	Improved sleep quality, ↓ AHI and improved oxygenation compared with baseline	43% of OHS patients studied continued to desaturate <90% for >20% of TST
Piper[79]	36	RCT	CPAP vs BPAP	3 months	Comparable improvements in awake CO_2 and Spo_2; subjective sleep quality better with BPAP; no difference in compliance	Subset of OHS patients without severe persistent REM hypoventilation on CPAP. Majority of patients managed longer term with CPAP
Chouri-Pontarollo[50]	15	Before/after	BPAP	5 nights	↓ EDS; ↓ AHI; improved objective vigilance in those with low CO_2 responses	Daytime ventilatory responses to CO_2 associated with amount of REM hypoventilation and daytime sleepiness

ABG, arterial blood gas; AHI, apnoea-hypopnoea index; AVAPS, average volume assured pressure support; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EDS, excessive daytime somnolence; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; $P_{0.1}$, occlusion pressure; $Paco_2$, Pao_2, arterial carbon dioxide and oxygen tensions; QoL, quality of life; RCT, randomised controlled trial; REM, rapid eye movement; SDB, sleep-disordered breathing; Spo_2, oxygen saturation; TST, total sleep time; VE, minute ventilation.

study monitoring the outcome of ventilation support withdrawal in OHS found that a high proportion of patients with OHS with pure sleep hypoventilation at presentation went on to develop OSA once daytime hypercapnia—and presumably respiratory drive—had improved with nocturnal ventilation.[57] Most studies have not demonstrated a significant difference in the AHI between markedly obese patients with OSA and those with OHS,[42 58] nor has a correlation between AHI and CO_2 been established.[58] How obstructive events isolated to sleep can produce awake hypercapnia and why only a small proportion of patients even with severe obesity and OSA develop hypoventilation therefore remain interesting clinical questions.[55] One explanation is that patients with OHS fail to eliminate P_{CO_2} during the post-apnoea period.[59] Norman *et al*[60] identified bicarbonate retention compensating for the acute rise in CO_2, plus the inability to unload the increased P_{CO_2} and bicarbonate during wakefulness, as important mechanisms which would further blunt respiratory drive and promote awake hypercapnia. Clinically, raised serum bicarbonate levels seen in OHS support this proposal.[61]

Emerging evidence also suggests a role for leptin in the development of OHS, with altered levels having the potential to diminish respiratory output to both the respiratory pump and upper airway muscles.[62] Unlike the ob-ob mouse model of leptin deficiency,[63] human obesity is characterised by up to a fourfold increase in circulating levels of leptin compared with lean humans, with further increases in the presence of OSA or OHS.[64 65] It has been speculated that increased leptin levels in obesity may assist in maintaining ventilation in the face of an increased ventilatory load.[62] However, if resistance to leptin developed, this compensatory mechanism would be lost[62] and awake hypercapnia could emerge.[64] An association between higher serum leptin levels and reductions in baseline respiratory drive and chemoresponsiveness to CO_2 has been found in obese subjects,[19] although whether this is also linked to daytime hypercapnia has yet to be established.

Pulmonary hypertension is more frequently seen in patients with OHS than in those with eucapnic OSA[42] or simple obesity,[66] and is likely the result of both left ventricular dysfunction and pulmonary vasoconstriction.[66] Heart failure is also common in this population[67] and appears to be related to a number of factors including the obesity itself, the degree of nocturnal hypoxaemia and systemic hypertension.[68] Even on effective treatment, most deaths in this group are from cardiopulmonary causes including respiratory failure, pulmonary embolism or heart attack.[38] Raised levels of C-reactive protein have been shown in OHS and are associated with a poorer prognosis.[38] Further studies into the cardiovascular consequences of OHS and response to treatment are required.

Failure to recognise this disorder and initiate effective treatment is associated with increased hospitalisation[37] and reduced survival[7] compared with individuals with eucapnic obesity. Patients with OHS who do not receive NIV treatment have an 18-month mortality of 23%[7] and a 7-year mortality of 46%.[69] In contrast, patients with OHS treated long-term with NIV experience a 3% all-cause mortality after 18 months of treatment[35] with 3- and 5-year survival rates of 88%.[70] Quality of life has also been shown to be significantly impaired in patients with OHS compared with normal controls, with increased levels of subjective daytime sleepiness compared with patients with OSA.[36] In a more recent study, 40% of patients with OHS had objective sleepiness and this was related to lower responses to CO_2 and more marked REM hypoventilation.[50]

Treatment options: oxygen, CPAP or ventilatory support (bilevel or volume)

Significant weight loss can improve blood gases,[71] respiratory muscle function[72] and haemodynamic function.[66] However, this process takes time, even with surgery, and more immediate improvements in respiratory failure can be achieved through the correction of sleep-disordered breathing by NIV therapy.[56 73]

Table 3 Long-term studies (>3 months) of positive airway pressure in OHS

Author	N	Study type	Intervention	Duration	Outcomes	Comments
Masa[76]	22	Before/after	NIV and BPAP	>4 months	Improved symptoms; ↓ hospitalisations; improved ABGs	
Berger[56]	23	Before/after	BPAP or CPAP	7 years	↓ $Paco_2$	Therapy aimed at correcting specific sleep abnormality
de Lucas-Ramos[53]	13	Before/after	BPAP	12 months	Improved, Pao_2, $Paco_2$, FVC, $\Delta P_{0.1}/\Delta Paco_2$, $\Delta VE/\Delta Paco_2$	Likely recovery of chemoreceptor sensitivity to hypercapnia following BPAP
Perez de Llano[69]	54	Retrospective	CPAP, BPAP and NIV	7 years	↑ Pao_2; ↓ $Paco_2$; ↓ dyspnoea, no weight change	On review, substantial number on BPAP able to be switched to CPAP
Mokhlesi[73]	75	Retrospective	BPAP and CPAP	Variable	Changes in Pao_2 and $Paco_2$ dependent on adherence rather than mode of therapy	
Redolfi[54]	6	Before/after	BPAP	6–20 months	↓ $Paco_2$; ↑ leptin levels correlating positively with $P_{0.1}/Petco_2$ slope; ΔBMI by 2 kg/m^2	
Budweiser[38]	126	Retrospective	BPAP	10 years	↓ Nocturnal $Paco_2$ by >23% and Hb compared with baseline associated with improved prognosis	
Heinemann[75]	35	Before/after	BPAP	12 and 24 months	Normalisation of $Paco_2$ and reduced base excess; ↓ polycythemia; ↑ in VC and TLC; ↓ RV/TLC	

ABG, arterial blood gas; BMI, body mass index; BPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; FVC, forced vital capacity; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; $P_{0.1}$, occlusion pressure; $Paco_2$, Pao_2, arterial carbon dioxide and oxygen tensions; RV, residual volume; TLC, total lung capacity; VC, vital capacity; VE, minute ventilation.

Although the optimal management of OHS has yet to be determined, both CPAP[36 56 74] and BPAP[50 53 69 75] have been used effectively in this disorder. Supplemental oxygen may also be required.[69 73] However, oxygen therapy alone has been shown to reduce ventilation, increase the AHI especially in REM sleep, and worsen nocturnal CO_2 levels.[76] In contrast, appropriately set NIV therapy is able to target the underlying respiratory abnormality. CPAP therapy splints open the upper airway,[56 73] increases lung volume (improving gas exchange) and overcomes iPEEP (reducing work of breathing).[44] BPAP may offer advantages above CPAP by providing additional inspiratory support to increase tidal volume and by providing a "back-up" rate, especially during REM sleep when inspiratory efforts may diminish. Although many patients with OHS will respond to CPAP as first-line therapy,[36 56 73 74 77] continued non-apnoeic desaturation may occur in some (fig 4). In this group, initial treatment with BPAP therapy may be more effective, with a switch back to CPAP for the longer term.[56 73] Support for this concept is provided by observational studies.[57 69 78]

The main studies that have looked at the impact of NIV (CPAP and BPAP) in OHS are shown in tables 2 and 3. Most have focused on the use of BPAP, and there are few data regarding the longer-term outcomes in patients either treated initially with CPAP[36 40 77] or after transferring to CPAP following a period on NIV.[57 69 78] There is also a lack of evidence from randomised trials regarding the most clinically effective form of treatment for this group.[61 70 79 80] Although BPAP may be seen as being more effective than CPAP in the presence of persisting nocturnal hypoxaemia or high AHI,[81] ineffective efforts[82] and poor patient-machine synchrony[83] have been shown to occur frequently in patients with stable OHS using this treatment. These abnormalities may result in poorer nocturnal gas exchange[82] and impaired sleep quality,[83] but the longer-term impact on compliance and clinical outcomes has not been evaluated.

Despite uncertainty about optimal treatment, OHS is becoming the major indication for home ventilatory support in many centres.[70 84] With increasing numbers of people joining the ranks of the morbidly obese,[4] the importance of identifying the best treatment to maximise clinical and psychosocial outcomes in this group is rising. The lack of good quality data regarding treatment options in this population highlights the need for well conducted large-scale randomised trials for this disorder.[81]

CONCLUSION

With the expected increase in obesity, respiratory disorders such as OSA, overlap syndrome and OHS are likely to increase. Patients with these conditions are high consumers of health care and, accordingly, early recognition and prompt treatment is required. The most effective approach is a public health intervention to reduce obesity.

Competing interests: None.

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Pulmonary puzzle

Bilateral nodular pulmonary infiltrates in an immunocompromised host

CLINICAL PRESENTATION

A 74-year-old man of Jamaican origin residing in the USA for 20 years presented to the hospital with progressively increasing shortness of breath and low-grade fever for 3 weeks. He had been diagnosed with non-Hodgkin's lymphoma 6 months prior to admission and started on chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone, with the last dose 12 days before presentation. In the hospital he was found to be hypoxic (82% saturation on room air) and required intubation and mechanical ventilation in the next 24 h. The clinical examination was unremarkable. His white blood cell count was 1100/mm^3 with a normal differential. A chest radiograph and CT scan of the chest revealed diffuse bilateral nodular infiltrates (fig 1). He was started on antibiotics without improvement.

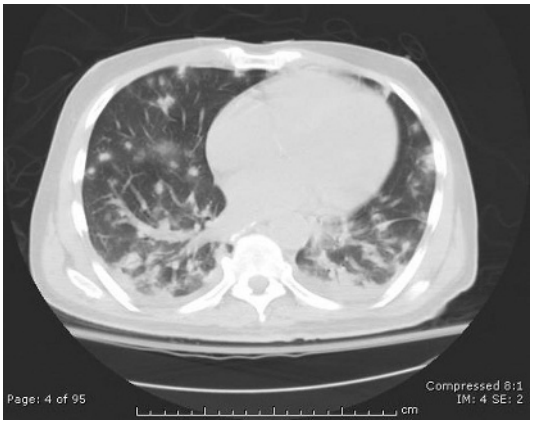

Figure 1 CT scan of the chest showing bilateral nodular infiltrates.

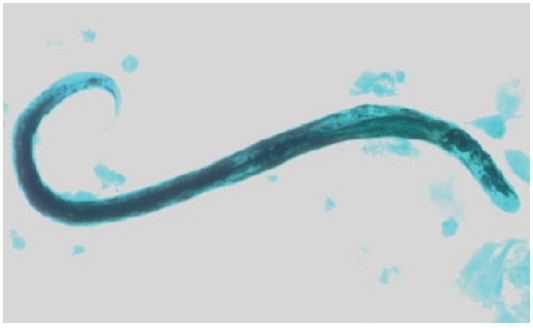

Figure 2 Bronchoalveolar lavage fluid showing filariform larva.

Bronchoscopy with bronchoalveolar lavage was performed on the second day. The airways were found to be inflamed and the lavage revealed abundant filariform larvae about 550 μm long with a notched tail (fig 2). His stool also showed similar larvae.

QUESTION

What is the diagnosis?

See page 753.

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