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/m²), obese (BMI 30–40 kg/m²) and morbidly obese (BMI >40 kg/m²) adults and children is increasing dramatically in all developed countries including the USA,1 Europe6 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/m² per decade and weight 1 kg per annum.5 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,2 reflecting the economic poverty 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.5 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. Snoring include systemic (or difficult to control) hypertension, premature cardiovascular disease, atrial fibrillation and heart failure. Since 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.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 volumes13 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 neurovascular 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 25 kg/m² for Asians. Asian populations have an increased prevalence of OSA at a lower BMI than in a comparable European
population, although some increase in prevalence is also related to the difference in cephalometric features of the upper airway.\textsuperscript{13}

There is an increased prevalence of OSA in obese women with polycystic ovary syndrome compared with age- and weight-matched controls.\textsuperscript{25} 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.\textsuperscript{18} Data from the Wisconsin sleep cohort suggest that weight gain has a greater effect on OSA than an equivalent weight loss.\textsuperscript{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.\textsuperscript{19} 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,\textsuperscript{20} 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 OSA. Spiegel et al\textsuperscript{21} investigated the effects of sleep deprivation on leptin and ghrelin (a hormone signalling hunger) levels in 12 healthy volunteers. They found that restricting sleep to 4 h per night for two nights resulted in an increase of 28% in ghrelin levels and a 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.\textsuperscript{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 $\alpha$, transforming growth factor $\beta$ and interferon $\delta$.\textsuperscript{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.\textsuperscript{23}

However, epidemiological and small uncontrolled studies suggest that weight loss reduces AHI. Norman et al\textsuperscript{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 42 to 27 events/h. In 105 subjects treated with mild to moderate OSA, only the CPAP group showed any reduction in AHI (from 30 to 23 events/h) and it has been shown that there are significant improvements in subjective sleepiness and quality of life were also noted. Lam et al\textsuperscript{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\textsuperscript{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.\textsuperscript{27} Risk factors for positional OSA are BMI (<30 kg/m$^2$), AHI (<40 events/h) and age (<60 years).\textsuperscript{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.\textsuperscript{29}

Table 1  Comparison of adult patterns of BMI, lung function and $P_{aco_2}$ in normal patients and those with OSA, overlap and OHS

<table>
<thead>
<tr>
<th>BMI</th>
<th>Lung function</th>
<th>$\uparrow P_{aco_2}$ nocturnal (mm Hg)</th>
<th>$\uparrow P_{aco_2}$ diurnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18–25</td>
<td>Normal</td>
<td>2–3</td>
</tr>
<tr>
<td>OSA</td>
<td>&gt;18</td>
<td>Normal</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Overlap</td>
<td>&gt;27</td>
<td>Obstructive</td>
<td>&gt;10</td>
</tr>
<tr>
<td>OHS</td>
<td>&gt;30</td>
<td>Restrictive</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

BMI, body mass index; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; $P_{aco_2}$, arterial carbon dioxide tension.

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.
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. 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 (2–5 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.

Compared with patients with pure COPD, patients with overlap syndrome are more obese, have a greater neck circumference, higher alcohol consumption 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 CO₂ pressure (PtccO₂) 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.32

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.33 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 (PEEP)) 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 needed.
required, given the high mortality and morbidity rates observed.

**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, primarily related to respiratory and cardiac compromise.

The prevalence of OHS in the general population is unknown since arterial blood gas measurements are not routinely performed.
in the community. In a small cross-sectional study of healthy non-smoking obese women (BMI $\geq 30$ kg/m$^2$) presenting to an obesity clinic, 11% had a raised daytime $PCO_2$. The prevalence of chronic daytime hypercapnia in patients attending sleep laboratories ranges from 11% to 38%, with the incidence increasing with increasing BMI levels. In hospitalised patients with a BMI $>35$ kg/m$^2$, 31% had daytime hypercapnia.

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 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. Typically, total lung capacity, expiratory residual volume and FRC are reduced, contributing to an abnormal distribution of ventilation and worsening gas exchange. Expiratory flow limitation and iPEEP have been found in morbidly obese subjects. 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. Subjects with OHS have significantly higher diaphragmatic work of breathing than those with obesity or OSA alone. 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.

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

Interest has arisen in the pattern of sleep-disordered breathing and the possible contributory effects of upper airway obstruction to the syndrome. Only a few patients have non-obstructive sleep hypventilation, with most demonstrating varying degrees of frank obstruction or obstructive hypventilation. However, the clinical presentation of OHS with and without OSAS is identical. Interestingly, results from a small
have not demonstrated a significant difference in the AHI between subjects, although whether this is also linked to daytime drive and chemoresponsiveness to CO2 has been found in obese higher serum leptin levels and reductions in baseline respiratory deficiency, human obesity is characterised by up to a fourfold increased ventilatory load. However, if resistance to leptin hypercapnia has yet to be established.

The acute rise in CO2, plus the inability to unload the increased awake hypercapnia. Clinically, raised serum bicarbonate levels would further blunt respiratory drive and promote upper airway muscles. Unlike the ob-ob mouse model of leptin deficiency, 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. It has been speculated that increased leptin levels in obesity may assist in maintaining ventilation in the face of an increased ventilatory load. However, if resistance to leptin developed, this compensatory mechanism would be lost and awake hypercapnia could emerge. An association between higher serum leptin levels and reductions in baseline respiratory drive and chemoresponsiveness to CO2 has been found in obese subjects, 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 or simple obesity, and is likely the result of both left ventricular dysfunction and pulmonary vasoconstriction. Heart failure is also common in this population and appears to be related to a number of factors including the obesity itself, the degree of nocturnal hypoxaemia and systemic hypertension. Even on effective treatment, most deaths in this group are from cardiopulmonary causes including respiratory failure, pulmonary embolism or heart attack. Raised levels of C-reactive protein have been shown in OHS and are associated with a poorer prognosis. 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 and reduced survival compared with individuals with eucapnic obesity. Patients with OHS who do not receive NIV treatment have an 18-month mortality of 25% and a 7-year mortality of 46%. In contrast, patients with OHS treated long-term with NIV experience a 5% all-cause mortality after 18 months of treatment with 3- and 5-year survival rates of 88%. 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. In a more recent study, 40% of patients with OHS had objective sleepiness and this was related to lower responses to CO2 and more marked REM hyperventilation.

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

Significant weight loss can improve blood gases, respiratory muscle function and haemodynamic function. 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.
Although the optimal management of OHS has yet to be determined, both CPAP\(^{56, 74}\) and BPAP\(^{59, 69, 73}\) have been used effectively in this disorder. Supplemental oxygen may also be required.\(^{74, 75}\) 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 splits open the upper airway,\(^{56, 74}\) 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,\(^{56, 58, 74, 76, 77}\) 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.\(^{78, 79}\) Support for this concept is provided by observational studies.\(^{59, 69, 75}\)

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 adherence rather than mode of therapy.\(^{65}\) Table 3 shows the improvements and changes in Pa\(_2\) and Pa\(_{	ext{CO}_2}\) dependent on adherence rather than mode of therapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massa(^{44})</td>
<td>22</td>
<td>Before/after</td>
<td>NIV and BPAP</td>
<td>&gt;4 months</td>
<td>Improved symptoms; ↓ hospitalisations; improved ABGs</td>
<td>Therapy aimed at correcting specific sleep abnormality</td>
</tr>
<tr>
<td>Berger(^{44})</td>
<td>23</td>
<td>Before/after</td>
<td>BPAP or CPAP</td>
<td>7 years</td>
<td>Improved, Pa(<em>2), Pa(</em>{	ext{CO}<em>2}), FVC, ΔP(</em>{	ext{aCO}_2})/ΔPaco(_2), ΔVE/Paco(_2)</td>
<td>Likely recovery of chemoreceptor sensitivity to hypcapnea following BPAP</td>
</tr>
<tr>
<td>de Lucas-Ramos(^{44})</td>
<td>13</td>
<td>Before/after</td>
<td>BPAP</td>
<td>12 months</td>
<td>↑ Pa(<em>2); ↓ Pa(</em>{	ext{CO}_2}); ↓ dyspnoea, no weight change</td>
<td>On review, substantial number on BPAP able to be switched to CPAP</td>
</tr>
<tr>
<td>Perez de Llanos(^{44})</td>
<td>54</td>
<td>Retrospective</td>
<td>CPAP, BPAP and NIV</td>
<td>7 years</td>
<td>Changes in Pa(<em>2) and Pa(</em>{	ext{CO}_2}) dependent on adherence than mode of therapy</td>
<td></td>
</tr>
<tr>
<td>Mokhtaries(^{73})</td>
<td>75</td>
<td>Retrospective</td>
<td>BPAP and CPAP</td>
<td>Variable</td>
<td>Changes in Pa(<em>2), Pa(</em>{	ext{CO}<em>2}), FVC, ΔP(</em>{	ext{aCO}_2})/ΔPaco(_2), ΔVE/Paco(_2)</td>
<td></td>
</tr>
<tr>
<td>Redolfi(^{44})</td>
<td>6</td>
<td>Before/after</td>
<td>BPAP</td>
<td>6–20 months</td>
<td>↓ Pa(_2), ↑ leptin levels correlating positively with Pa(_2V/Paco(_2) slope; ΔBMI by 2 kg/m(^2)</td>
<td></td>
</tr>
<tr>
<td>Budweiser(^{44})</td>
<td>126</td>
<td>Retrospective</td>
<td>BPAP</td>
<td>10 years</td>
<td>↑ Nocturnal Pa(_2) by &gt;23% and Hb</td>
<td></td>
</tr>
<tr>
<td>Heinemann(^{44})</td>
<td>35</td>
<td>Before/after</td>
<td>BPAP</td>
<td>12 and 24 months</td>
<td>Normalisation of Pa(_2) and reduced base excess; ↑ in VC</td>
<td></td>
</tr>
</tbody>
</table>

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; Pa\(_2\), occlusion pressure; Pa\(_{	ext{CO}_2}\), arterial carbon dioxide and oxygen tensions; RV, residual volume; TLC, total lung capacity; VE, vital capacity; VE, minute ventilation.

REFERENCEs

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/mm³ 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.

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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Competing interests: None.

Patient consent: Obtained.

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

Figure 2 Bronchoalveolar lavage fluid showing filariform larva.