Editorial

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Obesity Hypoventilation Syndrome. Where do we stand 50 years later?

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Initial reports of Obesity Hypoventilation Syndrome (OHS) date back as early as 1889[1], but it was not until 1955 that Auchincloss[2] and colleagues described a case of obesity and hypersomnolence paired with alveolar hypoventilation. Burwell[3] coined the term *Pickwickian syndrome* describing the constellation of morbid obesity, plethora, oedema and hypersomnolence. Hypercapnia, hypoxaemia and polycythemia were described on laboratory testing. Obstructive Sleep Apnea (OSA) had not been described at that time and came to be recognized for the first time in the mid 1970s. With attention shifting to upper airway obstruction, hypercapnia began to get lesser emphasis and confusion began to emerge in describing OSA and OHS. The term 'Pickwickian' began to be used for OSA-related hypersomnolence in the obese patient regardless of the presence of hypercapnia. This confusion was finally settled by the American Academy of Sleep Medicine (AASM) in its published guidelines in 1999.[4] The AASM statement identified that awake hypercapnia may be due to a predominant upper airway obstruction (OSA) or predominant hypoventilation (Sleep Hypoventilation Syndrome) easily distinguished by nocturnal polysomnography (PSG) and response to treatment. Both disorders are invariably associated with obesity and share a common clinical presentation profile.

Salient features of OHS consist of obesity as defined by a BMI > 30kg/m^2, sleep disordered breathing, and chronic daytime alveolar hypoventilation ($PaCO2 \geq 45$ mmHg and $PaO2 < 70$ mmHg).[4] Sleep disordered breathing, as characterized by polysomnography in OHS, reveals OSA (Apnea-hypopnea index [AHI]>5) in up to 90% of patients and sleep hypoventilation (AHI<5) in up to 10%.[5] Daytime hypercapnia and hypoxaemia are the hallmark signs of OHS and distinguish obesity hypoventilation from OSA. Severe obstructive or restrictive lung disease, chest wall deformities and hypoventilation from severe hypothyroidism, and neuromuscular disease need to be excluded before a diagnosis of OHS is established. As obesity is becoming more prevalent in western society, this disorder has gained more recognition in recent years. However, patients with this syndrome may still go undetected and untreated. No population-based prevalence studies of OHS exist till date but, at present, can be estimated from the relatively well known prevalence of OHS among patients with OSA. Recent meta-analysis with the largest cohort of patients (n=4250) reported a 19% prevalence of OHS among the OSA population, confirming an overall prevalence of about 3 per 1000.[6]

Whilst transient rectifiable nocturnal hypercapnia is common in patients with OSA, awake hypercapnia in OHS appears to be a final expression of multiple factors. There has been a debate about BMI and AHI not being the most important independent predictors of hypercapnia in obese patients with OSA. More definitive evidence for the role of OSA, however, is suggested by resolution of hypercapnia in the majority of patients with hypercapnic OSA or OHS with treatment, with either PAP or tracheostomy, without any significant changes in body weight or respiratory system mechanics. Yet some recent studies have shown that nocturnal hypoxaemia and diurnal hypercapnia, persist in about 50% of such individuals even after complete resolution of OSA with CPAP or tracheostomy. This raises questions such as how good is AHI as a measure of severity of OSA?

It is intuitive to argue that obesity may exert its effect through mass loading of CO_2 due to (increased production via) higher basal metabolic rate or reduced functional residual capacity on lung function. But why do only some severely obese patients with OSA go onto develop OHS? Is the pathophysiology driven by the severity of BMI? Whilst weight loss, particularly surgically-induced, clearly shows resolution of both OSA and hypercapnia[7], the role of BMI as an independent factor for hypercapnia has been challenged by the fact that only a small fraction of severely obese patients do in fact develop chronic diurnal hypercapnia. More importantly, not only can $PaCO_2$ be normalized in a majority of patients without weight loss and with positive airway pressure therapy (PAP), but awake hypercapnia can develop even at lower BMIs among the Asian population. Some investigators have tried to explain the incremental role of BMI as follows. In situations where AHI is not a presumed independent predictor of nocturnal hypercapnia, potential pathophysiologic contributors can include pre-event (apnea or hypopnea) amplitude in relation to the post-event amplitude.[8] Such inciting events for nocturnal hypercapnia may then be perpetuated in the daytime by factors such as AHI, functional vital capacity (FVC), FVC/FEV_1, or BMI as shown in the largest pooled data to date.[6] It has been shown that, for a given apnea/interapnea duration ratio, a greater degree of obesity is associated with higher values of $PaCO_2$.[9] However the same group of investigators, in another

study, did not find any of these factors to be related to the post-event ventilatory response.[8]

Looking further at the breath by breath cycle, the post-event ventilatory response in chronic hypercapnia may relate to eventual adaptation of chemoreceptors perhaps in consequence to elevated serum bicarbonate known to blunt the ventilatory drive.[10] Or it may relate to whole body CO_2 storage capacity which is known to exceed the capacity for storing O_2.[11] With definite evolution in our understanding of hypercapnia among obese patients, these questions continue to dominate. Some of the more pressing ones include: are the predictors of daytime hypercapnia different from those of nocturnal hypercapnia in obese patients with OSA? An understanding of these facts can help us with the more important understanding of the associated morbidity and mortality from OHS and its correct management. In addition, what is the true effect of untreated OHS on mortality independent of the co-morbidities related to obesity and OSA? Can morbidities like cor pulmonale and pulmonary hypertension be reversed with treatment of OHS? How do we treat patients with OHS who fail CPAP/ BiPAP short of tracheostomy?

Competing Interests
None Declared
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