Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function

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Piper AJ, Grunstein RR. Big breathing: the complex interaction of obesity, hypoventilation, weight loss, and respiratory function. J Appl Physiol 108: 199–205, 2010. First published October 29, 2009; doi:10.1152/japplphysiol.00713.2009.—Obesity places a significant load on the respiratory system, affecting lung volumes, respiratory muscle function, work of breathing, and ventilatory control. Despite this, most morbidly obese individuals maintain eucapnia. However, a subgroup of morbidly obese individuals will develop chronic daytime hypercapnia, described as the obesity hypoventilation syndrome (OHS). While obesity is obviously a crucial component of this syndrome, the relationship between excess fat accumulation and the development of awake hypercapnia is complex and extends beyond simply impairments of pulmonary mechanics and lung volumes as a consequence of obesity. Various compensatory mechanisms operate to maintain eucapnia even in the presence of extreme obesity. However, if compensation is impaired, hypoventilation will ensue. While obesity alone does not account for the development of hypoventilation, weight loss will produce significant improvements in lung function and awake gas exchange. Such improvements have the potential to substantially reduce morbidity and mortality in these individuals. Nevertheless, many individuals remain overweight despite substantial weight loss, with persistence of upper airway obstruction. Attention to this residual abnormality is important given the high incidence of cardiovascular abnormalities, including pulmonary hypertension, in individuals with OHS.

obesity hypoventilation syndrome; pulmonary function

INCREASING RATES of obesity are being reported globally, with current data suggesting that the number of individuals in the heaviest body mass index (BMI) groups (>40 kg/m² and >50 kg/m²) are increasing at rates two and three times faster than those with a BMI of 30 kg/m² (87). While the clinical complications of severe obesity (SO) such as diabetes, vascular disease, and osteoarthritis are well established, less emphasis is traditionally placed on the effects of SO on the respiratory system (27). Nevertheless respiratory complications of obesity impact on general health, quality of life, and longevity (11). As a result, there is increasing interest in understanding the prevalence and management of pulmonary impairment and sleep-breathing disorders in severe obesity.

While the majority of individuals with SO are able to maintain awake eucapnia, a significant minority will develop obesity hypoventilation syndrome (OHS), characterized by alveolar hypoventilation [arterial partial pressure of carbon dioxide (Paco₂) > 45 mmHg] unexplained by other disorders such as neuromuscular or pulmonary disease. Compared with individuals with eucapnic SO, those with OHS consume more health care resources, are more likely to be hospitalized in the 5 years before diagnosis (3), and once hospitalized have a significantly lower postdischarge survival rate (60). Cardiovascular morbidity is increased in OHS patients compared with patients with similar degrees of obesity but who remain eucapnic (3, 53). Consequently, identifying individuals with this syndrome and intervening in a timely fashion has important clinical implications.

Although community-based data regarding the prevalence of OHS are not available, an association between increased body mass index (BMI) and the development of hypoventilation is well recognized (38, 54, 60). Obesity hypoventilation is present in 10–20% of patients referred to sleep laboratories with obstructive sleep apnea syndrome (OSAS) (38, 54, 56) with the prevalence increasing to almost 50% of super-obese individuals (BMI > 50 kg/m²) who are hospitalized (60).

The mechanisms underlying the selective development of awake hypoventilation in some morbidly obese individuals has been the subject of clinical interest for more than 50 years (6, 9, 54, 67, 78). It appears that for most individuals with morbid
obesity, various compensatory mechanisms operate to maintain eucapnia despite the ventilatory limitations imposed by excess weight (8, 46). The appearance of daytime hypercapnia arises under conditions where some aspect of this compensation fails or is inadequate (6, 46, 81).

**RESPIRATORY FUNCTION IN OBESITY HYPOVENTILATION**

The respiratory impairments related to simple obesity have been well described (36, 72) and include reduced lung volumes, decreased chest wall compliance, increased respiratory resistance, and increased work of breathing. Spirometric values from OHS individuals usually demonstrate a reduction in forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) compared with normal-weight controls and SO eucapnic persons, while the FEV₁/FVC ratio in both OHS and eucapnic SO persons remains within the normal range (28, 39, 54, 72). While the same restrictive pattern in pulmonary function is seen in those with OHS and eucapnic SO, the changes in functional residual capacity (FRC) and expiratory reserve volume (ERV), and to a lesser extent total lung capacity (TLC), are usually more pronounced in OHS persons even at similar levels of BMI (28, 72) (Fig. 1).

The effects of obesity on pulmonary function are influenced by both the quantity and distribution of excess adipose tissue (16, 40). Previous work has shown that a central pattern of fat distribution, as measured by waist:hip circumference ratio, is associated with a greater reduction in respiratory mechanics than excess weight around the hips (peripheral obesity), independent of BMI (16, 40). Individuals with OHS demonstrate a central pattern of obesity, with a higher prevalence of the disorder seen in men (54, 68), who generally have a higher waist:hip ratio than women (40).

Obesity-related changes in lung volumes impair pulmonary mechanics and are more marked in OHS than equally obese eucapnic individuals (36). Early studies demonstrated that respiratory system compliance of eucapnic SO subjects was ~20% less than that measured in normal-weight subjects, while in OHS it was reduced by almost 60% (57, 84). Most of the reduction in total respiratory system compliance appears to be due to reduced compliance of the chest wall, although the reduction in lung volumes associated with severe obesity, especially FRC, can also increase small airway and respiratory resistance (99).

These alterations in the compliance and resistance of the respiratory system increase both the work and the energy cost of breathing. In early work, Sharp and colleagues (84) found that the work of breathing was ~30% above normal in obese subjects and almost three times normal in those with OHS. Similarly, Pankow and colleagues (64) showed that the pressure-time product of the diaphragm in individuals with SO and eucapnic OSAS was similar during breathing at rest but was significantly greater in those with OHS. In SO individuals, expiratory flow limitation and intrinsic positive-end expiratory pressure have been shown to occur during tidal breathing, especially in the supine position (21, 65, 86), contributing to an increased work of breathing by imposing an additional load on the inspiratory muscles. A positive relationship between the increased work of breathing and an elevation in $P_{ACO_2}$ has been reported (34, 78). The oxygen cost of breathing is also increased substantially by obesity (37, 78). In circumstances where this load on the respiratory system exceeds capacity, hypoventilation occurs.

Respiratory muscle strength in obesity has been variously reported as normal (15, 34, 48, 78, 86, 97) or reduced (39, 78, 82), although the latter is generally only seen in very severe obesity or in those with OHS (15, 39, 52, 78). Although inspiratory muscle strength may be normal when measured in the upright position, this may not be the case when the individual is supine, where the efficacy of the diaphragm has been shown to be reduced in the morbidly obese (86), and maximal inspiratory pressures can fall significantly (83). The degree of deterioration in diaphragmatic function in the supine position is greater in those with OHS compared with eucapnic SO subjects (83), and this is thought to arise from a mechanical overstretching of the diaphragm due to the increased abdominal mass (83), or as a consequence of air trapping, which places the inspiratory muscles at a mechanical disadvantage (79).

Maximum voluntary ventilation, a reflection of respiratory muscle endurance, decreases as BMI increases (39) and is more commonly reduced in those with OHS compared with eucapnic SO (36, 78, 79), being around 55% of normal in OHS and 80% of normal in SO (36). The reduction in endurance is thought to be related to reduced chest wall compliance or breathing at low lung volumes (95), although it may also reflect changes in the structure of respiratory muscles themselves. In an animal model of obesity, the diaphragms of obese Zucker rats were found to undergo remodeling such that the cross-sectional area of type I and type IIa fibers significantly increased, and the diaphragm thickened (20). Such changes could contribute to enhanced force generation and maintenance of ventilation despite added chest wall load (20). Powers et al. (70) showed that obesity produced a fast-to-slow shift in myosin heavy chain phenotype with an increase in the oxidative capacity of the respiratory muscles in obese Zucker rats, a change that would promote fatigue resistance in the face of a high work of breathing. While there are currently no data on diaphragm morphology in human obesity, if similar changes are present, the reduced respiratory muscle endurance identified in OHS could reflect compensatory mechanisms are either.
overwhelmed by the increased load of massive obesity or the shift to fatigue-resistant fibers is incomplete.

UPPER AIRWAY CHANGES

Excessive fat accumulation also compromises the upper airway. Using impulse oscillometry during wakefulness, Lin et al. (45) showed that, compared with morbidly obese eucapnic OSAS subjects and normal controls, those with OHS have increased upper airway resistance (UAR) in sitting and supine postures. In contrast, in controls and those with eucapnic OSAS, UAR was normal in sitting but increased in the latter group when supine. It is likely that this increase in UAR could be another factor contributing to the increased work of breathing seen in OHS (45). Support for this is provided by other work showing that in normal-weight controls and eucapnic obese OSAS patients, the work of breathing was normal in the sitting position, but increased during wakefulness and sleep in the obese subjects when they were supine. By comparison, hypercapnic obese subjects had an abnormally high work of breathing sitting and lying, irrespective of whether they were awake or asleep (41).

GAS EXCHANGE

Gas exchange is also significantly affected by obesity hypoventilation. Individuals with OHS are more hypoxemic and by definition more hypercapnic than those with SO. Some degree of hypoxemia is common in morbid obesity, and is related to ventilation perfusion (V/Q) inequality. Low lung volumes, in particular ERV, favor small airway closure (31), with tidal breathing occurring closer to residual volume. Since those with OHS have lower ERV compared with individuals with SO (28, 72), the degree of hypoxemia is more marked in this former group. Waist-to-hip ratio has been shown to be more closely associated with pulmonary gas exchange than weight or BMI, with 36% of the variance in PaO2 and 20% of the variance in PaCO2 explained by this parameter (98). In addition, individuals with OHS adopt a pattern of breathing that is characterized by a lower tidal volume and higher respiratory rate than that seen in simple obesity (64). The increased dead space ventilation arising out of such a breathing pattern would promote further worsening of gas exchange, with potential implications for endothelial function (44). This appears to be borne out clinically where, compared with eucapnic SO individuals with or without OSAS, individuals with OHS are more likely to be hypertensive (77), have significant pulmonary hypertension (35, 88), and have a higher incidence of cardiovascular disorders, including congestive heart failure, angina, and cor pulmonale (3).

VENTILATORY CONTROL, SLEEP, AND OHS

Individuals with severe obesity need to generate higher levels of minute ventilation to maintain eucapnia as basal oxygen consumption (VO2) (8, 37) and CO2 production (VCO2) (73) are higher, and work of breathing is increased (84). Central respiratory drive has been shown to be substantially increased in eucapnic morbidly obese individuals compared with normal-weight subjects (23, 46, 81, 86). This higher drive would assist in maintaining ventilation despite severely abnormal chest wall mechanics (8, 19). In contrast, individuals with OHS lack this augmented drive (46, 81), which would increase their vulnerability to developing worsening respiratory failure in times of increased load (81).

In general, the ventilatory response to hypercapnia has been shown to be reduced in both eucapnic SO and OHS compared with normal controls (8, 81, 100), and lower again in OHS compared with SO individuals (18, 23, 81). Chouri-Pontarolo et al. (13) characterized two groups of individuals with OHS: those in whom the response to CO2 fell within the normal range and those who were low responders. While age, BMI, and awake arterial blood gases did not differ between these two groups, those with blunted responses were objectively sleepier and demonstrated more severe REM hypoventilation than those with more normal responses. Hypoxic ventilatory drive is also markedly depressed in OHS compared with eucapnic SO (100). While depressed chemosensitivity may have a genetic basis (91), other factors such as sleep disordered breathing (6, 30) and neurohormonal influences (61, 92) potentially play a substantial role in the blunting of ventilatory responses to chemical and mechanical stimuli.

Recent work, primarily from animal models, has identified leptin, a protein produced by adipose tissue and involved in appetite regulation and energy expenditure, as a potential link between obesity, respiratory depression, and the development of awake hypercapnia. The leptin-deficient (ob/ob) mouse shares many similarities to humans with OHS including obesity, daytime hypercapnia, and a blunted ventilatory response to CO2 during wakefulness and sleep (69, 91, 92). Leptin replacement in the mouse model improves lung mechanics (92), increases ventilation, and improves ventilatory responsiveness to CO2 during wakefulness and sleep (61). In contrast to the ob/ob mouse, in human obesity serum leptin levels are increased (33). As leptin increases ventilation during sleep it has been speculated that elevated leptin levels in obese humans may act as a compensatory mechanism to maintain an adequate level of ventilation despite the increased ventilatory load (61, 62). However, fasting serum leptin levels are higher in obese hypercapnic individuals than in those who are able to maintain eucapnia (66), implying that eventually in some patients there is a resistance to the ventilatory stimulatory effects of leptin. This is supported by data from severely obese individuals, where an association between higher concentrations of serum leptin and reduced respiratory drive and hypercapnic ventilatory response has been reported (10). In another study, excluding individuals with severe obesity, patients with sleep apnea and hypercapnia had significantly lower hypercapnic ventilatory responses compared with eucapnic patients despite similar serum leptin levels, BMI, and lung volumes (49). This is consistent with the hypothesis that insensitivity to the stimulating effects of leptin could blunt any respiratory stimulatory effects of this protein (66). Unfortunately, the lack of agents that could be used in humans to overcome leptin resistance, or maybe more correctly “central leptin insufficiency,” limits pivotal research in this area (33).

Other adipokines, reactive oxygen species, altered sympathetic nerve activity, or the hypothalamic-pituitary axis may also be activated by hypoxia and hypercapnia, further influencing respiratory control. However, more data are required to determine the extent to which these factors impact ventilation in obesity hypoventilation.
SLEEP-BREATHING DISORDERS AND OHS

Patients with OHS also have significantly greater degrees of oxyhemoglobin desaturation during sleep than those with eucapnic obesity (2, 32, 74), and this recurrent nocturnal hypoxemia may blunt hypoxic ventilatory drive (32, 46, 100), predisposing the individual to hypoventilation. Although the impact of sustained hypoxia on ventilatory control has not been extensively studied in humans, in animal models hypoxia has been shown to interfere with the synthesis and turnover of a wide range of neurotransmitters including γ-aminobutyric acid (96), dopamine (58), and adenosine (42). In a recent study of nonobese men during sleep, sustained hypoxia was shown to delay arousal from sleep in response to external loading (30). By increasing the arousal threshold, sustained nocturnal hypoxemia may delay the normal compensatory mechanisms that operate to minimize the impact of abnormal sleep breathing on gas exchange (30).

Obstructive sleep apnea (OSA) is associated with excess weight, so it is not surprising that this disorder is a common clinical finding in both eucapnic SO individuals as well as part of the sleep-breathing disorder in OHS (2, 13, 32, 35). Studies of consecutive patients with severe obesity recruited from obesity outpatient, sleep, and bariatric surgical clinics have identified that as many as 70–80% of these individuals are affected by OSA (17, 22, 76), which is moderate to severe in 25–40% of cases (51, 75). Most patients with OHS also demonstrate obstructed breathing during sleep (35, 54, 56, 63), with only ~10% of cases showing isolated sleep hypoventilation (35, 63).

Correction of nocturnal oxygenation and reversal of daytime hypercapnia by effective treatment of obstructed breathing during sleep (4, 55, 68, 71) provide strong clinical support for the notion that upper airway obstruction and flow limitation play an important role in the development of OHS. On the other hand, the frequency and severity of apneic events during sleep are similar in patients with eucapnic OSAS and those with OHS (2, 23). Furthermore, only a minority of patients even with severe OSAS develop daytime hypercapnia. Therefore, factors other than the presence of apnea alone must be operating to permit chronic hypoventilation to develop in patients with OHS.

Early studies suggested there was a difference in ventilatory pattern following apneic events between patients who were able to maintain eucapnia and those who were hypercapnic (23, 71). In the face of apnea, hypopnea, or hypoventilation during sleep, ventilation is reduced, permitting intermittent, acute episodes of CO$_2$ retention to occur (5). However, most obese individuals are able to compensate for this transient hypcapnia by augmenting ventilation in the interapnea period (6, 71), thereby maintaining overall eucapnia. In comparison, hypercapnic patients demonstrate reduced ventilation during this postapneic period for a given CO$_2$ load (5), while also having shorter interapnea duration relative to apnea duration, thereby limiting the ability to eliminate the accumulated CO$_2$ (1). These data underpin a model proposed by Rapoport and colleagues (1, 5, 6, 59) to explain progression from acute intermittent nocturnal hypercapnia to persisting stable daytime hypoventilation in some individuals with OHS. The transient accumulation of CO$_2$ following apneic/hypopneic events permits an elevation in bicarbonate concentration to occur. While the degree to which this would occur during a single night is small, it may not be completely excreted prior to the next sleep period, since the time constant for bicarbonate excretion is longer than that of CO$_2$ (59). This rise in bicarbonate level would blunt ventilatory responsiveness to CO$_2$ (24), thereby perpetuating ongoing hypoventilation. To test this hypothesis, Norman et al. (59) have used a computer model of whole body CO$_2$ kinetics that included a respiratory control center and a renal bicarbonate controller. They were able to demonstrate that under certain conditions repetitive abnormal breathing events produce depression of ventilatory control. Modest rises in CO$_2$ could be induced over time if the ventilatory CO$_2$ response was low or renal bicarbonate excretion inadequate. Importantly, when both circumstances occurred simultaneously, the impact on CO$_2$ rise was synergistic (6, 59). They proposed that in order for OHS to develop, there first had to be factors present that would compromise the acute ventilatory compensation for transient sleep hypercapnia. Chronic daytime hypercapnia would emerge if bicarbonate excretion was compromised, as might be seen under conditions of hypoxia, diuretic therapy, or heart failure (6).

IMPACT OF WEIGHT LOSS ON PULMONARY FUNCTION

Initial therapy for OHS is positive airway pressure, which aims to correct sleep disordered breathing (4). This approach usually produces significant improvements in daytime blood gases even in the absence of changes in lung function or body weight (18). However, one study has shown that 12 mo of noninvasive ventilation markedly improved ERV without an appreciable change in weight (28). It was assumed that this improvement occurred secondary to reversal of microatelectasis and increased lung compliance, although this was not directly measured.

Although positive airway pressure (2, 13, 18, 28) and occasionally, medications to improve respiratory drive (47) are used to improve blood gases, longer term management of these individuals is aimed at weight reduction. If this can be achieved it will ameliorate many of the changes associated with obesity, including improved pulmonary function (72, 89, 95).

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**Fig. 2.** Schema outlining some of the potential interactions involved in the development of hypoventilation in a subgroup of individuals with morbid obesity. The plus sign (+) denotes this factor, if normal or increased, has a positive influence on maintaining ventilation. The minus sign (−) denotes factors that, if reduced or blunted, would contribute to lowered ventilation and eventual hypercapnia. HCVR, hypercapnic ventilatory response.
In an early report of the impact of dietary weight loss on gas exchange and pulmonary mechanics, Rochester and Enson (78) found significant differences between patients with OHS and those with eucapnic SO despite similar degrees of weight loss. Maximum voluntary ventilation rose as weight fell in both groups, although the improvement was significantly greater in the OHS group. However, while marked improvements in both \( \text{PaCO}_2 \) and vital capacity with weight loss occurred in those with OHS, only slight changes in these parameters were observed in the eucapnic SO group. In subsequent reports, weight loss following bariatric surgery has been shown to improve lung volumes (72, 89, 93, 95), with the most dramatic improvements occurring in ERV (72, 89, 93, 94), the lung volume most compromised by morbid obesity and OHS (72). Although little data are available, it appears that no significant change in total respiratory compliance occurs with weight loss in OHS, even where clinical and other physiological improvements are seen (84). Respiratory muscle strength and performance are improved by weight loss, with a significant correlation reported between the degree of weight loss achieved and the subsequent improvement in endurance (95). Reversal of gas exchange abnormalities is also achieved with major weight loss. A recent review of 14 studies investigating this question (98) found that after a mean follow up period of 18 mo and a mean weight loss of 44 kg, \( \text{PaO}_2 \) increased by 10 mmHg, \( \text{PaCO}_2 \) fell by 3 mmHg. In studies looking specifically at OHS patients, more marked improvements in \( \text{PaO}_2 \) and \( \text{AaDO}_2 \) were correlated with the improvement in ERV with weight loss (94).

A number of studies have demonstrated significant improvements in sleep disordered breathing following weight loss (7, 26, 89, 90), with a reduction in the use of positive airway therapy postsurgery (7, 50). However, despite improvements in BMI and subjective reports of daytime sleepiness, it has been shown that residual apnea-hypopnea index remains elevated in many individuals following surgery (25, 43), and the actual severity of this is frequently underestimated by clinicians and patients alike (43). Improvements in gas exchange and sleep disordered breathing also result in less polycythemia (89) and pulmonary hypertension (88). However, complete resolution of pulmonary hypertension is uncommon, with improvements appearing to be related to the degree to which OSAS is resolved following surgery (12). This highlights the need to continue to monitor and treat residual sleep disordered breathing to maximize clinical outcomes.

Following weight loss, respiratory drive decreases in eucapnic SO subjects (19) and increases in OHS (78). Likewise, ventilatory responsiveness to \( \text{CO}_2 \) is reduced in eucapnic SO patients following weight loss, but markedly improves in those with OHS (9). In a study of severely obese patients without OSAS who experienced a mean reduction in weight of 16 kg, \( \dot{\text{V}}_{\text{O}_2} \) and \( \dot{\text{V}}_{\text{CO}_2} \) during sleep fell compared with baseline values (29). In OHS, the oxygen cost of breathing during wakefulness has also been shown to reduce with weight loss (78). These findings demonstrate the significant benefits weight loss has on ventilatory control and energy cost of breathing in patients with OHS, reflecting the reduced ventilatory demand and increased ventilatory capacity achieved by a significant fall in weight. Despite the increasing use of surgery to facilitate weight loss among the morbidly obese, there has been surprisingly little systematic objective evaluation of longer term respiratory outcomes, especially in those individuals presenting with OHS.

**CONCLUSIONS**

The emergence of hypercapnia in patients with morbid obesity is a consequence of complex interactions between a number of factors associated with obesity itself, respiratory drive, and sleep disordered breathing (Fig. 2). Adipokines, including leptin, hypoxia, medications, and renal function, are among some of the potential factors that can impact on the various compensatory mechanisms adopted by morbidly obese individuals to maintain eucapnia despite chronically loaded breathing. Treatments directed at correcting sleep disordered breathing (positive pressure therapy), improving respiratory drive (medications such as medroxyprogesterone), and weight loss (diet and surgery) have all been shown to be effective in improving blood gases and subsequent clinical status in individuals with OHS. However, weight loss that is sustained appears to offer the best opportunity to reduce morbidity and mortality longer term. Systematic evaluation of these longer term outcomes is needed, particularly those related to cardiovascular complications.

**REFERENCES**

5. Berger KI, Ayappa I, Sorkin IB, Norman RG, Rapoport DM, Goldring RM. Postevent ventilation as a function of \( \text{CO}_2 \) load during

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