Obesity Hypoventilation Syndrome

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ABSTRACT

The term *obesity hypoventilation syndrome* (OHS) refers to the combination of obesity and chronic hypercapnia that cannot be directly attributed to underlying cardiorespiratory disease. Despite a plethora of potential pathophysiological mechanisms for gas exchange and respiratory control abnormalities that have been described in the obese, the etiology of hypercapnia in OHS has been only partially elucidated. Of particular note, obesity and coincident hypercapnia are often associated with some form of sleep disordered breathing (apnea/hypopnea or sustained periods of hypoventilation). From a conceptual point of view, even transient reductions of ventilation from individual sleep disordered breathing events must produce acute hypercapnia during the period of low ventilation. What is less clear, however, is the link between these transient episodes of acute hypercapnia and the development of chronic sustained hypercapnia persisting into wakefulness. A unifying view of how this comes about is presented in the following review. In brief, our concept is that chronic sustained hypercapnia (as in obesity hypoventilation) occurs when the disorder of ventilation that produces acute hypercapnia interacts with inadequate compensation (both during sleep and during the periods of wakefulness); neither alone is sufficient to fully explain the final result. The following discussion will amplify on both the potential reasons for acute hypercapnia in the obese and on what is known about the failure of compensation that must occur in these subjects.

KEYWORDS: Obesity, obesity hypoventilation syndrome, hypercapnia, sleep disordered breathing

Patients with obesity have been observed to have a variety of nonspecific respiratory complaints, ranging from dyspnea on exertion and orthopnea, to the more recently described excess of asthma associated with obesity.[1] In addition, a minority of obese patients are found, often incidentally, to have chronic hypercapnia.[2,3] The term *obesity hypoventilation syndrome* (OHS) refers to this combination of obesity and chronic hypercapnia. It requires that the hypercapnia not be directly attributable to underlying cardiorespiratory disease.[4]

Despite a plethora of potential pathophysiological mechanisms for gas exchange and control abnormalities that have been described in the obese, the etiology of hypercapnia in OHS has only been partially elucidated. Of particular note, obesity and coincident hypercapnia are often associated with some form of sleep disordered breathing.[5] Thus, almost invariably, patients with OHS show either a significant exacerbation of blood gas abnormalities associated with sleep or may have a dramatic drop in ventilation that is evident only during sleep.[3] Treatment that corrects the specific sleep-related ventilatory disturbance (e.g., obstructive sleep apnea) can sometimes correct the chronic daytime hypercapnia; this highlights the role of sleep as part of

the pathogenesis of the chronic hypercapnic state in these patients.[6–8]

Hypercapnia is by definition associated with alveolar hypoventilation. In the absence of lung disease, this usually implies overall hypoventilation (i.e., ventilation at the mouth/nose is also reduced). From a conceptual point of view, even transient reductions of ventilation (such as from individual sleep disordered breathing events like apnea and hypopnea) must produce acute hypercapnia during the period of low ventilation.[9] What is less clear, however, is the link between these transient episodes of acute hypercapnia and the development of chronic sustained hypercapnia persisting into wakefulness, when the above mechanism of hypercapnia can no longer be invoked. A unifying view of how this comes about is presented in the following review. In brief, we propose that chronic hypercapnia in the obese patient results from an imbalance between short (apnea, hypopnea) or long (sleep hypoventilation) periods of CO_2 loading caused by abnormal ventilation, and failure of the compensatory CO_2 unloading that must occur between these periods of CO_2 loading for homeostasis of CO_2 to persist. The periods of CO_2 loading are typically related to sleep, and the unloading of CO_2 is typically during wakefulness (Fig. 1). Thus our concept is that chronic sustained hypercapnia (as in obesity hypoventilation) occurs when the disorder of ventilation that produces acute hypercapnia interacts with inadequate compensation; neither alone is sufficient to fully explain the final result. The following discussion will amplify both the potential reasons for acute hypercapnia in the obese and on what is know about the failure of compensation that must occur in these subjects.

DEFINITION OF OBESITY HYPOVENTILATION SYNDROME

Approximately 50 years ago OHS was described in two separate case reports.[10,11] Burwell et al coined the term *Pickwickian syndrome* and described the constellation of morbid obesity, hypersomnolence, "plethora," and edema.[11] Laboratory examination of this case revealed hypercapnia, hypoxemia, and polycythemia. In these and many subsequent reports the assumption was that there was a fixed primary ventilatory control abnormality that was present and could be evaluated while the subject was awake. Periodic breathing was reported as prominent, described as clusters of breaths alternating with periods of apnea, but the role of upper airway obstruction was only fully appreciated much later.[12–14] Patients were noted to be somnolent, and this was generally attributed to their elevated PCO_2; in these early reports the role of sleep in the etiology of the hypercapnia was mostly unrecognized. Because upper airway obstruction during sleep had not yet been described, it was not appreciated that this might contribute to either the clinical presentation or the hypercapnia of these patients. By the mid-1970s, reports of obstructive sleep apnea hypopnea syndrome (OSAHS) became more common. As attention became focused on the obstructive upper airway dysfunction, confusion developed between the syndromes of OSAHS and OHS, and the importance of hypercapnia in defining OHS was frequently underemphasized. In fact, because "marvelous

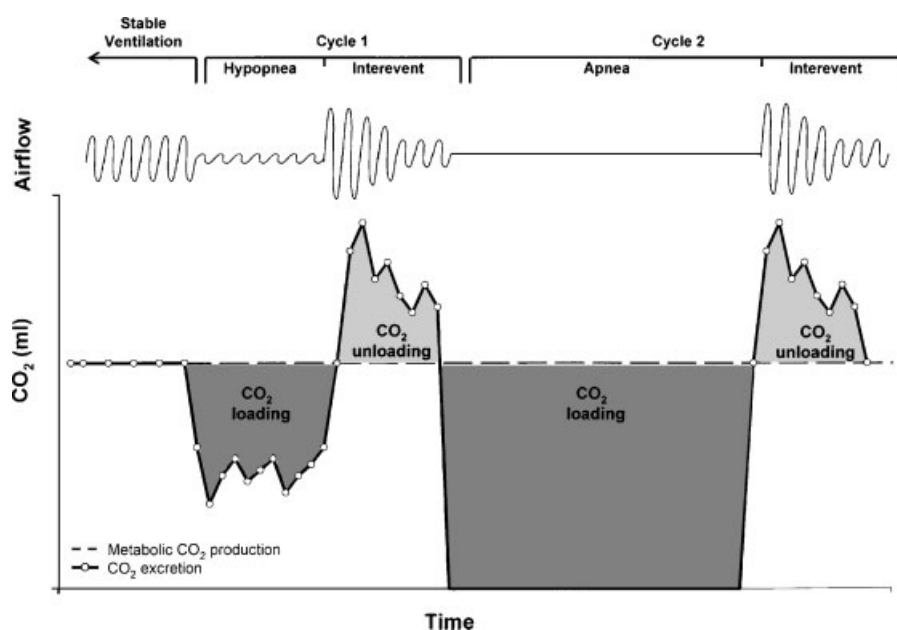**Figure 1** Schema depicting CO_2 loading and unloading during respiratory events.[38] Dark shaded areas depict CO_2 loading due to reduced CO_2 excretion during events. Light shaded areas depict CO_2 unloading due to compensatory hyperventilation between events.

sleepiness" was such a prominent component of Charles Dickens's description of "Joe, the fat boy" in the *Pickwick Papers*,[15] the term *Pickwickian* came to be used by some authors to describe *all* patients with OSAHS independent of hypercapnia provided they were hypersomnolent. At the present, it is well recognized that the majority of patients with OSAHS do *not* have chronic sustained hypercapnia[2,3,16,17]; however, confusion about the nomenclature has persisted, and for the sake of clarity several authorities have suggested the term *Pickwickian* be avoided.[4] To this day there is debate as to whether OHS should be considered part of the spectrum of OSAHS.

In 1999 the American Academy of Sleep Medicine (AASM) published guidelines and diagnostic criteria for the various sleep related breathing disorders.[4] The AASM guidelines state that several different breathing disorders *may* be associated with chronic hypercapnia during wakefulness, including OSAHS and sleep hypoventilation syndrome (SHVS). They state that, whereas OSAHS is characterized by intermittent upper airway obstruction during sleep, SHVS is characterized by episodes of alveolar hypoventilation sustained over several minutes and is not generally due to upper airway obstruction. Neither OSAHS nor SHVS requires the presence of obesity. Despite this, the majority of patients with obesity and chronic hypercapnia have some degree of OSAHS.[17–20] The AASM statement asserts that chronic hypercapnia can be due to either SHVS (predominant hypoventilation) or hypercapnic OSAHS (predominant upper airway obstruction), and these have a common clinical presentation. Both hypercapnic syndromes are often (but not invariably) associated with obesity (at which point they are synonymous with OHS) and may only be distinguished based on results of nocturnal polysomnography and response to treatment.[8] Based on these considerations, is it apparent that for subjects with chronic hypercapnia due to OSAHS, daytime PCO_2 may normalize with relief of upper airway obstruction, and that this indicates that the chronic hypercapnia is dependent on the presence of the apnea/hypopnea phenomenon per se. In contrast, for subjects with SHVS, the relative absence of obstructive sleep apnea–hypopnea and the failure of the hypercapnia to disappear with treatment of the upper airway obstruction indicate the importance of sustained hypoventilation independent of sleep.[8]

CLINICAL SPECTRUM OF OHS

Most, but not all, patients with OHS will have some daytime respiratory complaints and some degree of excessive daytime somnolence.[3] However, the spectrum of severity of these complaints is quite extreme and may not relate to the severity of the hypercapnia.[3,5,21,22] All the other complaints seen in the more typical eucapnic patient with OSAHS may also be present, including fatigue, somnolence (which can be mild or severe), mood disturbance, impaired concentration and memory, sleep disruption with snoring and choking, and morning headaches. On physical exam there are few specific findings that distinguish OHS from OSAHS. However, several things may suggest hypercapnia and cor pulmonale in the former, including injected sclera (thought to be related to elevated PCO_2 and cerebral vasodilation), massive peripheral edema, and signs of cor pulmonale on cardiac and hepatic exam. Although subtle (echocardiographic) evidence of right ventricular dysfunction is seen in some series of patients with OSAHS uncomplicated by hypercapnia, overt cor pulmonale is extremely uncommon in OSAHS in the absence of hypercapnia. In contrast, most patients with OHS (hypercapnia) will eventually show signs of circulatory congestion and cor pulmonale. Although massive obesity may increase the risk of hypercapnia in OSAHS, there is only a modest correlation between body mass index (BMI) and PCO_2.[2,9,17,23–25] Similarly, the severity of the OSAHS (by AHI [apnea-hypopnea index] or degree of transient O_2 desaturation on polysomnography) is not a good predictor of hypercapnia.[26] Some studies have suggested that reduced forced vital capacity on pulmonary function testing carries some risk for hypercapnia, but again there is much overlap with the general (non-OHS) obese population.[9,27]

The "typical" presentation of patients with OHS falls into two main patterns that differ primarily in the route by which the patient comes to clinical attention.[3,5,21] Patients either present as part of the general OSAHS population or after an episode of severe respiratory failure, often precipitating a stay in the intensive care unit (ICU). Published series of OHS have tended to show different findings depending on which of these groups predominated.

The patient with OHS who first presents to the sleep laboratory or clinic for evaluation of a sleep complaint is clinically nearly indistinguishable from the typical obese, snoring, sleepy patient with OSAHS who is generally eucapnic while awake. The hypercapnic patient who presents in this way will frequently be unrecognized initially if blood gases are not drawn; it is only on careful analysis of the sleep study that hypoventilation will be suspected from the prolonged, rather than intermittent, desaturation pattern seen during the night. Whereas in the past, arterial blood gases were routinely drawn on all patients presenting for evaluation of OSAHS, the present practice is to rely on noninvasive oximetry. Thus hypercapnia often remains untested and unrecognized in the clinic due to the mistaken impression that evaluation of hypoxia by oximeter fully replaces the need for an arterial blood gas sampling. An elevated serum bicarbonate on the venous blood is often the only hint that an arterial PCO_2 needs

to be sampled.[17] Although the awake oxygen saturation may be low in patients with hypercapnia, it is often only modestly reduced until sleep. Unfortunately, noninvasive measurement of hypercapnia by end tidal CO_2 has proven difficult and inconsistent for technical and clinical reasons, and we feel it is not useful for screening. Our practice is to obtain blood gases (specifically arterial PCO_2) in any patient presenting with a history suggesting OSAHS who also has either an elevated venous bicarbonate level and/or associated chronic obstructive pulmonary disease (COPD) or predisposition to respiratory depression (e.g., drugs). If associated disease or respiratory depression are present, there is a potential for interaction with OSAHS that makes hypercapnia much more likely, but whether this should be considered part of OHS is debatable. Thus significant COPD, untreated hypothyroidism, use of opiates (including methadone), and use of sedating or psychoactive medications are, in our experience, often found in patients with hypercapnia and OSAHS. Unfortunately, as the drugs frequently are hard to discontinue it is difficult to prove their role in the hypercapnia other than conceptually.

In contrast to the patient presentation described earlier, some patients with OHS present with a much more severe form of respiratory failure.[5] These patients frequently come to the attention of the clinician after an episode of severe acute respiratory decompensation or an intercurrent unrelated hospitalization leading to iatrogenic suppression of ventilation with oxygen, sedatives, or overdiuresis. Although it is not clear that the chronic symptoms of these patients are very different from those of the first group, the hypercapnia and hypoxia are usually much more severe on presentation. Patients with acute or chronic respiratory failure due to OHS tend to deteriorate when given O_2 and respond dramatically to assisted ventilation. Often these patients are treated in an ICU and their hypercapnia may have been mistaken for severe COPD. Evidence of right and occasionally suspected left heart failure are often prominent. On careful history and physical examination there is little support for the diagnosis of COPD. Pulmonary function tests will show absence of significant airways disease and either normal or reduced lung volumes as the predominant finding rather than obstructive physiology. The major physical findings will relate to fluid overload (peripheral edema), but classical signs of pulmonary edema due to low cardiac output will usually not be found as might happen in more typical congestive heart failure due to cardiac disease. A useful bedside test is to show that the patient voluntarily can easily and rapidly hyperventilate and within a minute normalize oxygenation and produce a PCO_2 below 40 mm Hg.[28] This is rarely seen in hypercapnic COPD without extreme effort on the part of the patient.

In summary, because the key to the diagnosis of OHS is the hypercapnia, this should be considered whenever evaluating an obese patient. In many patients measurement of venous bicarbonate concentration is sufficient to exclude hypercapnia. Irrespective of symptoms, the presence of hypercapnia or an elevated venous bicarbonate in an obese patient should be sufficient to begin an evaluation for the diagnosis of OHS.

DIAGNOSIS AND TREATMENT OF CHRONIC HYPERCAPNIA IN PATIENTS WITH OBESITY HYPOVENTILATION SYNDROME

Once diagnosis of OHS has been established by finding sustained awake hypercapnia, a combined diagnostic/treatment algorithm can be used during nocturnal polysomnography to identify the specific respiratory sleep disturbances in a given patient.[8] Because multiple types of respiratory abnormalities may coexist, the algorithm is designed to sequentially eliminate the different disorders to uncover the full spectrum of abnormality. The stepwise elimination of disorders is accomplished by the application of therapy.

Our approach first addresses identification and treatment of upper airway obstruction by applying increasing continuous positive airway pressure (CPAP) to obliterate apnea and hypopnea. If persistent flow limitation is identified by a flattening of the inspiratory portion of the flow–time waveform, CPAP should be increased further until the inspiratory flow contour normalizes. This ensures that obstruction of the upper airway is no longer contributing to a mechanical load on the respiratory apparatus. If O_2 saturation is adequate with CPAP therapy alone (i.e., saturation >90%), the patient is diagnosed with OHS due to OSAHS and treatment is prescribed at the pressure determined by the algorithm. Hypoventilation is most likely not present, and daytime blood gases after several nights of therapy will probably show hypercapnia has resolved. If persistent O_2 desaturation is noted despite treatment for upper airway obstruction, central alveolar hypoventilation is presumed and the patient is diagnosed with OHS due to SHVS. Treatment with nocturnal bilevel ventilation should be initiated. The expiratory airway pressure is set equal to the CPAP required for treatment of the upper airway obstruction, and the inspiratory airway pressure is increased until the O_2 saturation is >90%. A backup respiratory rate is often required to prevent sustained hypoventilation despite an increased tidal volume because of a falling respiratory rate. If coexisting lung disease or cardiopulmonary congestion is not present, it is rarely necessary to provide supplemental O_2 to keep the O_2 saturation above 90%. A review of our laboratory's experience utilizing this algorithm in patients with chronic daytime hypercapnia has been recently published and showed that ~50% of hypercapnic patients with OSAHS required only CPAP, whereas the remainder

were diagnosed with SHVS and required therapy with noninvasive bilevel ventilation in addition to CPAP.[8]

PATHOPHYSIOLOGY

Several prior reviews of the respiratory physiology of obesity and specifically of OHS have listed a multitude of mechanisms through which obesity could impair lung function and contribute to hypercapnia.[3,5,21,22,29] These include altered lung volumes due to direct mass loading,[27,30,31] increased work of breathing,[32,33] and abnormal gas exchange due to altered ventilation/perfusion matching from basilar atelectasis and altered pulmonary blood flow due to pulmonary congestion from an increased central blood volume.[34] However, the primacy of the foregoing mechanisms is called into question by the ease that patients with OHS have in transiently returning their blood gases to normal by voluntary hyperventilation and the marked effect that sleep has on worsening or causing the hypercapnia.[28] Similarly, resolution of daytime hypercapnia with treatment of the nocturnal abnormality alone (whether by correction of obstruction or by intermittent ventilation) strongly suggests that a fixed pathophysiological abnormality does not underlie the hypercapnia. Our view is that there is an interaction between the cause of transient hypercapnia and other factors that convert it into a more chronic phenomenon lasting into wakefulness. Clearly, any factor that impairs lung function (like those listed earlier and associated with obesity, as well as coexistent independent lung disease like COPD) will predispose to hypercapnia, but it is important also to consider the role of compensatory mechanisms responding to acute changes in ventilation. Whereas at least one paper suggested that hypercapnia in OSAHS was often due to coexisting COPD,[35] our own experience and subsequent series[9,17] suggest significant COPD is found in only a small part of the hypercapnic population where this is not a dramatic clinical entity. In this regard, it is interesting to note that when respiratory drive is high (e.g., in congestive heart failure and diabetic metabolic or ketoacidosis), patients with hypercapnia and OHS often show reversion of PCO_2 to the normal range despite worsening of their intrinsic lung disease (unpublished observations).

There has recently been some suggestion that humoral factors related to obesity, particularly leptin, ghrelin, and others, may play a role in suppressing ventilatory drive in the obese. Some support for this is found in animal models,[36] but data in humans suggest this is not an important mechanism in the typical obese patient.[37]

The foregoing arguments have led us to develop the following perspective on how OHS develops, which emphasizes the role of the compensatory mechanisms responding to the initial inciting period of hypoventilation that must be present.

Many respiratory events include a transient decrease in ventilation. By definition these must be associated with transient acute hypercapnia (CO_2 loading) during the event. Typically such events occur during sleep and include apnea, hypopnea, and longer periods of sustained hypoventilation. Maintaining overall CO_2 homeostasis will require a compensatory response that increases ventilation during the period between the events. Any underlying disorder of gas exchange (such as COPD) will only intensify the effect by limiting CO_2 elimination. Breath-by-breath measurements of whole-body CO_2 balance during sleep (see Fig. 1) have shown several effects of periodic breathing on acute CO_2 loading. These include measurements of the magnitude of compensation for CO_2 accumulated during apnea/hypopnea and show this is ultimately limited by the duration available and magnitude of ventilation during the compensatory phase between events (e.g., between apneas). Thus, when apneas become three times longer than the breathing interval, CO_2 tends to accumulate despite maximal tidal volume because there is insufficient time for adequate hyperventilation between the events.[23,38] In addition, modeling studies show that to maintain full CO_2 unloading during periodic ventilation, there is a requirement for an overall average ventilation that is higher than the average minute ventilation required to maintain PCO_2 during nonperiodic breathing.[39] This further stress on the ventilatory load imposed by apneas is a consequence of the temporal dissociation between oscillating ventilation and continuous perfusion [temporal ventilation/perfusion (V/Q) mismatch]. It is mathematically similar to the effect of classical V/Q mismatch from spatially nonuniform lung disease.

In the majority of otherwise normal subjects, compensation for the effect of intermittent (periodic) breathing and acute hypercapnia occurs after each episode of apnea, and there is no net CO_2 loading with each cycle and therefore no predisposition to chronic CO_2 retention. The augmented tidal volume that often occurs in the first breath after an apnea in eucapnic patients with obstructive apnea is the most obvious example of this compensation. In an early paper,[6] we demonstrated a relative failure of this augmentation in patients with chronic hypercapnia. In more detailed experiments, we demonstrated that the initial ventilation following apnea is directly related to the volume of CO_2 loaded during the preceding respiratory event and thus represents an index of "CO_2 load response."[40] Hypercapnic patients demonstrate depression of this index of ventilatory compensation as compared with eucapnic patients (Fig. 2A). We have also shown that hypercapnic subjects have a reduced duration of the interapnea ventilation relative to the length of the preceding apnea (Fig. 2B).[23]

At least one study suggests that impaired CO_2 homeostasis after respiratory events (e.g., the relative
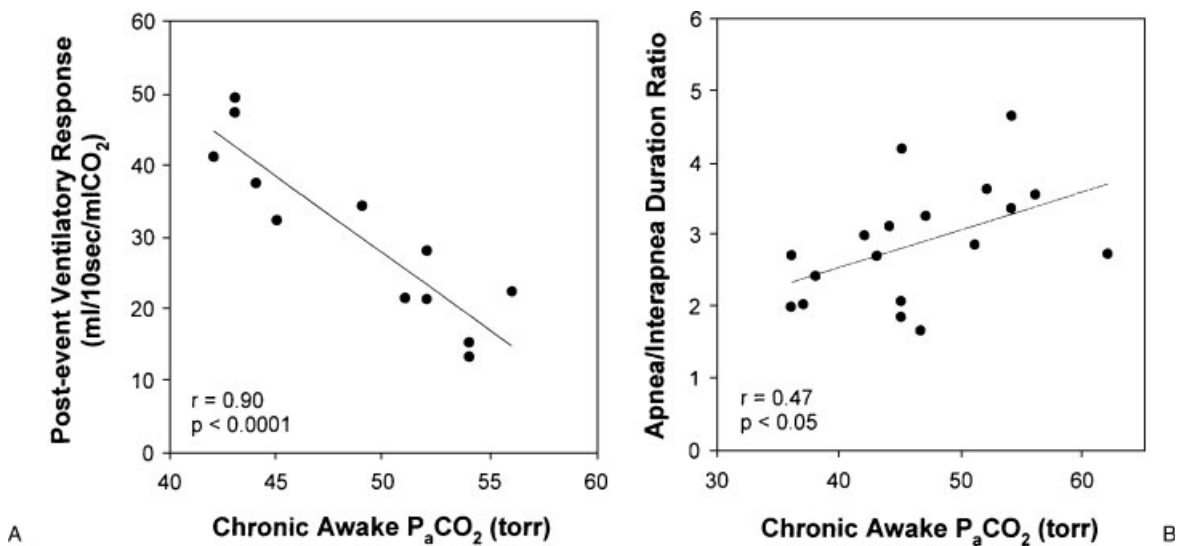
Figure 2   Relationship between compensatory ventilation and chronic awake PCO_2 are illustrated. (A) The post-event ventilatory response to volume of CO_2 loading during preceding apnea is blunted in hypercapnic patients compared with eucapnic patients.[49] (B) The apnea to interapnea duration ratio is greater in hypercapnic patients compared with eucapnic patients.[23] Higher values for this ratio indicate impaired period available for ventilatory compensation (relative to duration of preceding apnea). Figure 2B from Ayappa et al.[23]   Reproduced with permission.

shortening of the interapnea duration and the reduced postevent ventilation) may be mediated by opioids or opioid receptors because endorphin blockade changed this pattern.[41] Increased cerebrospinal fluid (CSF) β endorphin activity with return to normal values following treatment has also been reported in subjects with OSAHS.[42] These observations provide a framework for understanding the facilitating effect that opiates (including methadone) may have on the development of hypercapnia in some patients with OSAHS.

Whereas the postevent ventilatory response reflects the output of an integrated control system, this ventilatory response to CO_2 load correlates poorly with the traditional ventilatory response to CO_2 measured during wakefulness. This dissociation suggests that there may be additional inputs to the ventilatory control system present during periodic breathing. These could include the fluctuating hyperoxia/hypoxia and the change in ventilatory control that occurs with sleep/wake alternation.[43] In addition, recent data suggest that a distinct transiently aroused state may exist immediately on arousal that is distinct from sustained wakefulness, and that this state is characterized by enhanced cardiorespiratory activation.[44] Alterations in all of the foregoing could contribute to the altered magnitude of the postevent ventilatory response in hypercapnic sleep disordered breathing but have not been studied directly.

The above observations indicate that there is an integrated ventilatory response to sleep disordered breathing that controls ventilation between events and appears to respond to the volume of CO_2 loaded during the events. This control system appears to be impaired in

patients with established chronic daytime hypercapnia and predisposes these susceptible patients to awakening in the morning with an elevated arterial PCO_2 after multiple inadequately compensated hypercapnic events.

This formulation explains hypercapnia upon awakening after a night of periodic breathing in the susceptible individual. However, it does not explain why a period of wakefulness free of apnea does not result in normalization of PCO_2 before the next period of sleep. Alteration of ventilatory CO_2 drive from changes in blood bicarbonate concentration $[HCO_3^-]$ has been demonstrated in both normal subjects and patients with chronic hypoventilation syndromes,[45] suggesting a role for elevated $[HCO_3^-]$ in sustaining a chronic hypercapnic state.[46] Elevated $[HCO_3^-]$ would blunt the change in hydrogen ion concentration for a given change in PCO_2, in accord with the Henderson-Hasselbalch relationship, thereby further blunting ventilatory CO_2 drive.[47]

Although the magnitude of the bicarbonate retention after a single night is too small to be measured clinically, modeling studies of whole-body CO_2 kinetics that included a renal bicarbonate controller in addition to a ventilatory controller suggest that repetitive nights can produce a cumulative effect sufficient to depress ventilatory control (Fig. 3).[48] In this study, when ventilatory CO_2 response and renal HCO_3^- excretion were normal, increased PCO_2 and $[HCO_3^-]$ did not develop (bicarbonate excretion during the day compensated for that retained during the night). However, when CO_2 response was abnormally low, the model demonstrated a modest rise in awake PCO_2 and $[HCO_3^-]$ over multiple
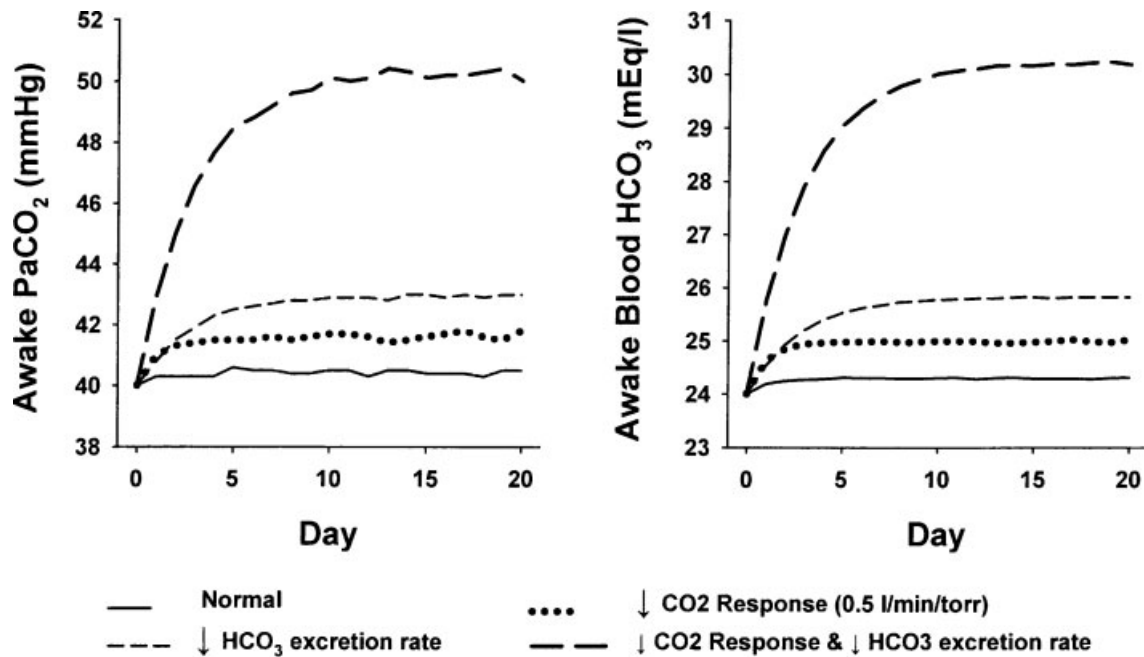
Figure 3   Results from simulations depicting development of chronic hypercapnia model of whole body CO_2 kinetics.[48] The combination of low CO_2 response and low renal HCO_3^- excretion rate produced a synergistic effect on the degree of elevation of awake PCO_2. See text for details.

days. Similarly, when renal HCO_3^- excretion rate was lowered to simulate chloride deficiency, the model demonstrated a modest rise in awake PCO_2 and $[HCO_3^-]$ over multiple days, even with normal CO_2 response. Significantly, the combination of low CO_2 response and low renal HCO_3^- excretion rate produced a synergistic effect on the degree of elevation of awake PCO_2. Thus respiratory-renal interactions may contribute to the development and perpetuation of chronic awake hypercapnia in patients with OHS.

The foregoing considerations support the concept that a common denominator for the development of chronic hypercapnia during wakefulness is failure of compensation for the acute hypercapnia that occurs during sleep. Failure of compensation may occur at two different points in time.

- First, immediate ventilatory compensation is required after each acute hypercapnic insult (apnea/hypopnea or sustained periods of hypoventilation). Ventilatory compensation may be compromised by either reduced ventilatory drive (e.g., reduction in innate ventilatory drive or induced by drug or oxygen) or reduced ventilatory efficiency of CO_2 clearance (e.g., as in underlying lung disease or CHF [congestive heart failure]).
- Second, adequate renal bicarbonate excretion is required during wakefulness to offset the effects of uncompensated cyclical hypercapnia. Renal compen-

satory mechanism may be compromised by diuretic induced chloride deficiency and/or by increased sodium avidity (e.g., CHF, hypoxia, or metabolic syndrome) and contribute to the transition between acute hypercapnia and the chronic hypercapnic state.

SUMMARY

We propose that hypercapnia in obesity hypoventilation syndrome is the final expression of multiple factors, acting alone or in concert, in a susceptible subset of obese individuals. The obesity itself contributes through increased metabolic CO_2 production and mechanical loading of the respiratory system by mass loading and intermittent nocturnal obstruction. These alone do not produce sustained hypercapnia in the majority of obese individuals, but in those with impaired immediate ventilatory compensation may do so. Acute hypercapnia during individual cycles of periodic breathing (hypercapnic OSAHS) and/or sustained periods of hypoventilation (SHVS) then transition into sustained hypercapnia for the entire period and ultimately appear during wakefulness because of the development of an elevated bicarbonate concentration. Persistence of elevated bicarbonate concentration can be potentiated by alteration of renal bicarbonate kinetics, reduction of waking ventilatory drive, or both. Elevated bicarbonate concentration further blunts nocturnal ventilatory CO_2

responsiveness and completes the cycle by reducing the nocturnal compensation to further transient events.

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