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Review Article

Hypercapnia in Obstructive Sleep Apnoea

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Abstract

There is a tendency for Carbon Dioxide (CO_2) to accumulate during sleep but mechanisms exist to bring CO_2 levels to the normocapnic range during the awake state. Sleep disordered breathing increases the likelihood of inadequate CO_2 unloading which may translate to persisting hypercapnia during waking hours. Hypercapnia is seen in Obstructive Sleep Apnoea (OSA) in the presence of obesity and/or Chronic Obstructive Pulmonary Disease (COPD), but also in the absence of either. Daytime hypercapnia in OSA per se is not associated with severity of Sleep Disordered Breathing (SDB) and the underlying pathophysiologic principles involved are complex. It is unclear to date if hypercapnia represents a complication, a marker of poorer prognosis, or a compensatory mechanism, as it is currently likely to be underdiagnosed in OSA. An Arterial Blood Gas (ABG) to diagnose hypercapnia is relatively invasive and not deemed necessary in all patients investigated for SDB. Furthermore, it is a measure of CO_2 at one point in time. Less invasive means of monitoring, such as transcutaneous CO_2 ($tcCO_2$) or end-tidal CO_2 ($etCO_2$) monitoring is acceptable to patients, and provides a more continuous assessment of CO_2 levels in sleep.

Keywords: Hypercapnia; Obstructive sleep apnoea; Sleep disordered breathing

Abbreviations

OSA: Obstructive Sleep Apnoea; COPD: Chronic Obstructive Pulmonary Disease; SDB: Sleep Disordered Breathing; ABG: Arterial Blood Gas; CO_2: Carbon Dioxide; $tcCO_2$: Transcutaneous Carbon Dioxide; $etCO_2$: End Tidal Carbon Dioxide; SWS: Slow Wave Sleep; REM: Rapid Eye Movement; NREM: Non Rapid Eye Movement; $PaCO_2$: Arterial Partial Pressure of Carbon Dioxide; RTN: Retrotrapezoid Nucleus; NTS: Nucleus Tractus Solitaries; AT: Arousal Threshold; V_E: Minute Ventilation; HCVR: Hypercapnic Ventilatory Response; AHI: Apnoea Hypopnoea Index; CPAP: Continuous Positive Airway Pressure; CSF: Cerebrospinal Fluid; HCO_3: Bicarbonate; OSAS: Onstructive Sleep Apnoea Syndrome; OHS: Obesity Hypoventilation Syndrome; FEV_1: Forced Expiratory Volume in One Second.

Introduction

Respiratory control and function is an integrated and complex system comprised of metabolic, biochemical and neurobehavioural components. These serve to maintain blood gas tensions and acid-base homeostasis in the awake state. In the sleep state, this regulatory system is altered, and becomes sleep stage-dependent. Due to the complexities of respiratory regulation, which in itself, varies within and between individuals, the mechanisms that underlie ventilation and arousal responses to hypercapnia and hypoxia in sleep are not completely understood. Nonetheless several theories exist which are consistent with contemporary physiological principles, and contribute to unveiling of the likely mechanisms involved.

Acute Hypercapnia in Sleep in Normal Individuals

Acute hypercapnia occurs in normal individuals, as there is a natural tendency for CO_2 to accumulate in sleep, due to (i) reduced ventilatory responses, (ii) decreased chemosensitivity, (iii) decreased respiratory muscle effectiveness, and/or (iv) a reduced arousal response, in the sleep state when compared to the awake state, leading to a reduction in minute ventilation and tidal volume.

Reduced ventilatory responses

CO_2 is a major breathing stimulus, but basal respiration and respiratory reflex regulation changes significantly in different states of consciousness [1]. Tidal volume (which is equal to minute ventilation divided by breathing frequency), decreases modestly in Slow Wave Sleep (SWS) and declines further during Rapid Eye Movement (REM) sleep [2]. Also, the slope of the ventilatory response curve decreases modestly during NREM (non REM) sleep, and there is a greater reduction in this slope during REM sleep [3]. Hence, despite the sleep-related increase in $PaCO_2$, minute ventilation does not increase in NREM and REM sleep, as much as would occur in the awake state, resulting in a mild elevation of $PaCO_2$ in NREM and REM sleep. Minute ventilation decreases in adolescents and adults by about 8-15% in sleep, compared with wakefulness [4]. $EtCO_2$ rises by 2-3mmHg during NREM sleep, with a further 2-3mmHg increase during REM sleep [5].

Reduced chemosensitivity in sleep

The reduction in central chemosensitivity in sleep is poorly understood. The exact interaction and coordination of various brainstem nuclei in producing the final response to CO_2 is unknown, but three such sites exemplify the complexity of this interaction: the Retro Trapezoid Nucleus (RTN), medullary raphe, and the Nucleus Tractus Solitarius (NTS). Data predominantly from animal models indicates that the RTN provides the ventilatory drive in the awake state [6]. The NTS has chemoreceptor action in sleep and wakefulness [7], whilst the firing rate of medullary raphe nuclei is highest in wakefulness lower in NREM sleep and lowest in REM sleep [8].

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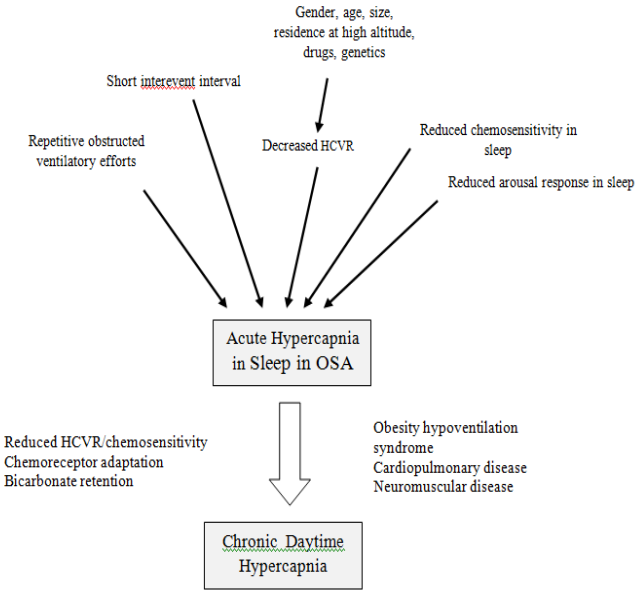

Figure 1: Summary of contributing factors for acute hypercapnia in OSA, and the transition to daytime hypercapnia.

These and other sites have varying thresholds, sensitivity and arousal dependence. It is proposed that a hierarchical arrangement exists and the combination and coordination of their responses provide control and stability to breathing in sleep and wakefulness [6].

Decreased respiratory muscle effectiveness

Peripherally, airway resistance increases during SWS due to decreased upper airway muscle tone and this is further amplified during REM sleep [1]. These upper airway muscles maintain airway patency, and include the genioglossus, the sternohyoid and the tensor palatine. They have a reduced contractile response to increasing CO_2 levels in NREM sleep in humans, [9] as well as in REM sleep in an animal model [10]. Further, the activity of accessory muscles of respiration is inhibited during REM sleep and the chest wall becomes more compliant. In essence, there is an increase in the work of breathing due to the mechanical load from increased upper airway resistance, and a reduction of inspiratory force [5]. These in turn, increase the potential for the accumulation of CO_2 and the development of acute hypercapnia in NREM and REM sleep.

Reduced arousal response to acute hypercapnia

Arousal from sleep as a response to hypercapnia sustains airway patency and allows adequate gas exchange, thereby achieving normal blood gas tensions. Hypercapnia is a more potent arousal stimulus than hypoxia [3,11]. The arousal response to hypercapnia occurs at higher CO_2 levels in SWS compared with REM sleep and stages 1 and 2 sleep [3]. There is significant inter-individual variation in the Arousal Threshold (AT) for hypercapnia, and AT also depends on the method used to induce hypercapnia [5,12]. For instance, arousal secondary to hyperoxic hypercapnia tends to occur when the end tidal $PaCO_2$ reaches 10-15mmHg above the baseline waking level [12]. On the other hand, the combination of hypercapnia and hypoxaemia has a lower arousal threshold, being a more potent arousal stimulus than hypoxia or hypercapnia alone.

Acute Hypercapnia during Sleep in OSA

Transient periods of hypoventilation occur in sleep disordered breathing resulting in acute hypercapnia. Recovery from this occurs through an increase in minute ventilation and/or arousal. Acute hypercapnia develops when there is an imbalance between abnormal ventilatory patterns during apnoeas and hypopnoeas, and the compensatory ventilatory response in the inter-apnoea or inter-event period [13,14]. Surprisingly, the type, duration or frequency of apnoeas, does not relate to hypercapnia in patients with OSA [15]. However, either a short inter-apnoea period [16] or an increased apnoea to inter-apnoea duration ratio [13], can result in inadequate unloading of CO_2, leading to the development of acute hypercapnia in sleep in OSA. Similarly, calculated measures of $etCO_2$ were observed to correlate inversely with mean post-apnea duration [17]. Furthermore, wake $etCO_2$ was found to be correlated inversely with post- to pre-event breath amplitude, and positively with the ratio of mean event to mean inter-event duration [18].

Reduced upper airway size during hypopnoeas and apnoeas increases the work of breathing, and there is an increase in the arousal threshold for obstructed inspiratory efforts as the night progresses [19]. This combination of increased work of breathing in OSA and increased AT, is likely to contribute to the development of hypercapnia.

Individual susceptibility to the development of acute hypercapnia in sleep also exists. OSA patients who are obese have an increased baseline production of CO_2 [14,20]. Men have higher metabolic rates and Minute Ventilation (V_E), but women have a greater Hyper Capnic Ventilatory Response (HCVR) and lower $etCO_2$ [20]. Men are also more susceptible to upper airway collapse and hence more vulnerable to increased CO_2 load induced by periods of abnormal breathing in OSA [21]. Hence for each individual, factors that influence the HCVR (eg gender, BMI, age, medication history, and previous residence at high altitude) may determine their ultimate susceptibility to the development of hypercapnia in OSA.

Chronic Daytime Hypercapnia in OSA

Between 11 and 43% of patients with OSA have chronic hypercapnia [22], and not all of these patients achieve normocapnia after correction of the upper airway obstruction [22,23]. Possible mechanisms for the sustained chronic hypercapnia in OSA include: (i) an alteration in the Hypercapnic Ventilatory Response (HCVR), (ii) chemoreceptor and renal adaptation, (iii) and the nature of the obstructive respiratory events observed in these patients.

Alteration in the HCVR

Hypercapnic patients with OSA are said to have reduced ventilatory drive which leads to daytime alveolar hypoventilation. It is still uncertain if the reduced HCVR in hypercapnic patients is due to a congenital abnormality, merely the extreme of the normal spectrum of ventilatory drive [23], or induced by OSA [24]. Nonetheless, to date there are conflicting data regarding the HCVR in OSA in the presence of hypercapnia. Most published studies have shown that HCVR is decreased in hypercapnic patients [15,24,25], and with CPAP therapy, the HCVR recovers, thereby leading to a regression in hypercapnia in some but not all [26-28].

A study of non-obese patients concurs with these findings, and it showed that depressed HCVR and chemo responsiveness contribute to the development of hypercapnia in OSA [29]. Han et al (2001) examined 10 matched eucapnic and hypercapnic subjects with OSA, and found that ventilatory responses to hypercapnia and hypoxia in patients with early morning hypercapnia were lower than those of patients without daytime hypoventilation, independent of age, AHI (Apnoea Hypopnoea Index), and obesity. Moreover, they observed that treatment with CPAP (continuous positive airway pressure) improved alveolar ventilation and chemo responsiveness in hypercapnic OSA patients, with normalisation of daytime $PaCO_2$. This suggests that repetitive episodes of nocturnal hypoxaemia and hypercapnia, and sleep fragmentation, which characterise OSA, can lead to a reduction in ventilatory drive, and there is recovery with treatment.

On the other hand, there are also some patients with pure OSA and daytime hypercapnia with normal or indeed, augmented HCVR [30]. Rapoport et al (1986) showed no difference in HCVR in 8 chronically hypercapnic obese patients following treatment with CPAP or tracheostomy, regardless of $PaCO_2$ levels after treatment. However, in this study, subjects were obese (up to 276% of ideal body weight), making the co-existence of OHS likely. We now know that these patients may require non-invasive ventilation in order to correct their daytime hypoventilation.

Inter-individual variability in the HCVR in normal young adults occurs, as discussed earlier, due to genetic and racial factors, physical traits, sex, age, personality, increased attention during the test, occurrence of psychological disorders and the level of physical training [31]. Men and women probably have different ventilatory control mechanisms [32]. Furthermore, intra-individual variability occurs, within the same day (diurnal), as well as between days, probably due to daily physiologic changes, such as metabolic rate and hormonal fluctuations in women [33]. As such, in order to ascertain the exact role of HCVR in hypercapnic OSA, data where numerous confounders are accounted for, are required. Also it is clear that mechanisms other than decreased HCVR are involved in the pathophysiology of daytime hypercapnia in OSA.

Chemoreceptor and renal adaptation to hypercapnia

The gradual adaptation of the peripheral and central chemo receptors to the hypercapnia is likely to play a role in sustaining high CO_2 levels during wakefulness, once hypercapnia is established [34]. A compensatory increase in blood bicarbonate concentration (HCO_3) occurs in chronic hypercapnia, which maintains the Cerebrospinal Fluid (CSF) pH and HCO_3 in the normal range. The HCO_3 neutralises the change in pH for a given change in $PaCO_2$. In the presence of HCO_3, a greater degree of hypercapnia (and change in pH) is required to stimulate and initiate the HCVR [35,36] because the central chemo receptors detect changes in CSF pH, which is now buffered by the HCO_3. Persistent elevation of HCO_3- levels can also be potentiated by an alteration of renal bicarbonate kinetics (such as through diuretic use), reduction of the awake HCVR (intrinsic or acquired), or both [37].

Nature of obstructive respiratory events in hypercapnic OSA

The frequency and duration of obstructive respiratory events have not been found to correlate with hypercapnia [15,38]. However, achievement of normocapnia with treatment of OSA with CPAP or tracheostomy in some patients with hypercapnic Obstructive Sleep Apnoea Syndrome (OSAS) indicates that sleep apnoea per se has some contribution to hypercapnia in a subset of patients [39-41]. The variability in return to eucapnia following treatment of hypercapnic OSA with CPAP or tracheostomy may be due to differences in changes in weight, pulmonary function or level of ventilatory chemo responsiveness after therapy for OSAS [23]. Moreover, as the presence of augmented breaths following termination of apnoeas seems to be present in eucapnic but not hypercapnic patients [15], perhaps the nature of the individual response to the apnoeas plays a role in determining the development of hypercapnia. The post-apnoeic hyperpnoea and/or tachypnoea may alleviate the accumulation of CO_2 associated with obstructive apnoeas and hypopnoeas. Whether this is a manifestation of increased chemosensitivity or increased HCVR in sleep remains undefined. Figure 1 summarises the factors that contribute to the development of acute hypercapnia during sleep in patients with and without OSA, and the mechanisms that lead to chronic daytime hypercapnia, including medical conditions that are associated with hypoventilation.

Predictors of Chronic Hypercapnia in OSA

The underlying pathophysiology of daytime hypercapnia in OSA is not totally elucidated, but studies exploring the predictors of hypercapnia provide insight into the likely mechanisms involved. The most consistent clinical predictors of hypercapnia according to these studies are:

1. The presence of hypoxaemia [14,22,29,42-44]. Han and co-workers (2001) found that hypercapnic patients had higher haemoglobin levels, and lower daytime PaO_2. They proposed that hypoxia induces blunted chemoresponsiveness, and treatment with CPAP reverses the cellular effects of hypoxia, thereby improving chemoresponsiveness. However, the follow-up period was brief, the maximum duration being 6 weeks. Data on long term effects of CPAP on ventilatory responses are lacking but necessary, in the context of the acclimatisation period required in the majority of patients commencing CPAP therapy.

2. Obesity [14,22,43] The Obesity Hypoventilation Syndrome (OHS) is defined as chronic hypercapnia (PCO_2 > 45mmHg) associated with obesity, where hypoventilation is not due to cardiopulmonary disease, neuromuscular disease, medication use, chest wall disorder or known congenital or idiopathic central alveolar hypoventilation syndrome [45]. OHS is seen in 10-20% of patients with OSAS referred to a sleep laboratory [43,46].

3. Vital capacity [22,42-44] and FEV_1 [14,43,47]. This exemplifies the influence of airways obstruction in COPD and ventilatory restriction associated with obesity, on gas exchange.

4. Concurrent COPD and neuromuscular disease are other causes of hypercapnia in OSA [23,43,44,48].

5. Measures of CO_2 in sleep include $tcCO_2$, $etCO_2$, and early morning/evening Arterial Blood Gases (ABGs). ABGs are invasive, and give a single measure of $PaCO_2$, but an increased difference in early morning and evening $PaCO_2$ may be a marker for increased mortality [49]. Furthermore, in hypercapnic sleep disordered breathing patients

with OHS or overlap syndrome (OSA and COPD), daytime PCO_2 has been shown to correlate with daytime sleepiness [50]. $TcCO_2$ and $etCO_2$ are both less invasive, and provide a continuous measure of CO_2 throughout the sleep period, and reflect both acute hypercapnia occurring in sleep, as well as chronic hypercapnia. If hypercapnia indeed increases mortality in sleep disordered breathing, the future of CO_2 monitoring is a less invasive means, which continuously measures CO_2 levels in sleep, which will allow CO_2 monitoring to be easily integrated into the routine assessment of patients with suspected sleep disordered breathing.

Conclusion

Hypercapnia in OSA is likely to be a marker of poorer prognosis. Understanding the underlying mechanisms, as well as its diagnosis will, in the future, need to be made through less invasive means which also allows for its continuous monitoring throughout sleep.

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