Pathophysiology of Hypoventilation During Sleep

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KEYWORDS

• Carbon dioxide • Hypercapnia • Hypoventilation • Pathogenesis • Sleep
• Sleep-disordered breathing

KEY POINTS

- Alveolar hypoventilation is determined by more than the level of minute ventilation and is defined by an increase in arterial PCO_2.
- Sleep hypoventilation occurs in a variety of disease states with potential carryover to the daytime manifesting as chronic hypercapnia during wakefulness.
- Maintenance of eucapnia during wakefulness requires adequate compensatory mechanisms. Elevation of blood bicarbonate concentration, while appropriate to defend blood pH, provides a mechanism for perpetuation of chronic hypercapnia.

INTRODUCTION

In healthy individuals, the arterial blood gas tensions and pH remain constant within a remarkably narrow range over a spectrum of activities. This stability is maintained by the precise adjustment of alveolar ventilation to metabolic rate. Reduction in alveolar ventilation (ie, hypoventilation) produces an immediate increase in arterial partial pressure of carbon dioxide (P_aCO_2), with a corresponding reduction in arterial partial pressure of oxygen (P_aO_2). For clinical purposes, monitoring of P_aCO_2 is the parameter used to monitor alveolar ventilation; values higher than 45 mm Hg at sea level have been used to define presence of alveolar hypoventilation.[1]

It has been well established that metabolic rate falls during sleep in healthy subjects, with a concomitant reduction in minute ventilation.[2–6] However, in some individuals, an elevation in P_aCO_2 can be detected, defining a state of alveolar hypoventilation.[5,7] The etiology of alveolar hypoventilation can be ascribed to 2 major categories. Alveolar ventilation may fall either because of a reduction in the overall level of ventilation or because of a maldistribution of ventilation with respect to pulmonary capillary perfusion (ie, an increase in anatomic and/or physiologic dead space). This latter mechanism of increase dead space is independent of overall (total) level of ventilation and may occur even in circumstances in which the total ventilation is at an elevated level.

In many disease states, the initial manifestation of alveolar hypoventilation occurs during sleep before development of chronic hypercapnia during wakefulness. Sleep-related hypoventilation events range from short transient to longer sustained events. Regardless of etiology or duration of event,

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maintenance of eucapnia during wakefulness requires adequate compensatory mechanisms. Compensatory mechanisms require an intact integration between respiratory control and acid-base regulatory systems. Because this issue of the journal includes articles for each disease state associated with sleep hypoventilation, this review characterizes the disease states based on pathophysiologic derangements and focuses on the compensatory regulatory mechanisms that would be common to all disorders.

NORMAL SLEEP PHYSIOLOGY AND RELATIONSHIP TO SLEEP STAGE

There are a variety of changes in respiratory mechanics and in the respiratory control system that occur during sleep that predispose subjects to development of reduced minute ventilation. Although a modest degree of hypoventilation with increased P_aCO_2 may occur in healthy subjects,[5,7] this respiratory phenomenon is accentuated in patients with sleep hypoventilation disorders. Regardless of etiology, the severity of resultant hypoventilation and associated CO_2 retention imposes a burden for the CO_2 excretion that is required on awakening to prevent development of chronic hypercapnia during wakefulness.

Respiratory Drive

Alterations in respiratory control during sleep have been well established and may predispose to alveolar hypoventilation. Numerous studies have documented blunted responsiveness to CO_2 during sleep attributable to both an increase in the set point for CO_2 and to a decrease in the ventilatory response slope to increasing PCO_2.[7–11] The precise mechanism for the reduced ventilatory response slope is unclear, and may relate to decreased chemosensitivity, decreased ventilatory output from skeletal muscle hypotonia and/or increased upper airway resistance,[12,13] and to local phenomena in chemosensitive areas.[10,11,14,15] For example, regional PCO_2 at the site of the central chemoreceptors may fall independent of the arterial level when blood flow to the chemoreceptors increases relative to the local metabolic rate.[15] Regardless of the mechanisms involved, the cumulative effect is a modest reduction in CO_2 responsiveness that is most evident during rapid eye movement (REM) sleep. In addition to CO_2 responsiveness, the ventilatory response to hypoxemia also is affected by sleep. Decreased hypoxic response has been demonstrated in both men and women during REM sleep and in men during non-REM (NREM) sleep.[16] Last, sleep has been shown to alter the pattern of breathing; ataxic breathing is commonly observed during phasic portions of REM sleep.[17–19] Although the foregoing alterations are modest in NREM sleep, more profound changes occur during REM, potentially explaining the increased propensity for alveolar hypoventilation to initially manifest during REM in many disease states.

Respiratory Mechanics

Changes in body position may impact gas exchange and respiratory muscle function during sleep. In particular, the supine position is associated with reduction in functional residual capacity (FRC) in all subjects[20,21]; this effect is magnified in obesity due to mass loading on the chest cage. Further reduction in FRC occurs during REM sleep due to hypotonia of the chest wall and accessory muscles.[14] In selected circumstances, the reduction in FRC may decrease resting lung volume to values below the closing volume. For example, in obesity, reduction of FRC is already apparent in the upright position and is exacerbated when patients are supine.[22–26] Alternatively, even in subjects with normal FRC, resting lung volume may fall below closing volume, when the latter is increased due to the presence of underlying diseases (eg, chronic obstructive pulmonary disease [COPD]).[27–29] In either case, persistence of blood flow to regions with airway closure produces shuntlike behavior with resultant hypoxemia. In addition, even in the absence of hypoxemia, reduction in lung volume may predispose patients to develop alveolar hypoventilation due to the increased load on inspiratory muscles in the supine position (eg, obesity).[24,25]

With the onset of sleep, multiple changes occur in the upper airway that ultimately result in an increased resistance to airflow.[13,30–32] First, in the supine position, posterior movement of tongue and soft palate increases upper airway resistance and collapsibility.[33–36] These changes may be responsible for the observation that snoring is generally more prominent in the supine position. Upper airway resistance may be further increased as a result of the reduction in resting lung volume, as reduction in FRC may reduce axial forces along the trachea, thereby reducing that stabilize the pharyngeal airway.[37–40] Second, sleep may be associated with reduced activation of upper airway muscles.[41–48] This effect has been shown to be associated with transient increases in upper airway resistance with a corresponding reduction in ventilation.[32,49] Third, the potential for altered chemical responsiveness of the upper airway has been suggested. Decreased responsiveness of the genioglossus muscle to rising PCO_2 has been