Central Sleep Apnea in Patients with Congestive Heart Failure

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KEYWORDS

• Central sleep apnea • Congestive heart failure • Loop gain • Peripheral chemoreceptors
• Central chemoreceptors • Rostral fluid shifts

KEY POINTS

- Central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR) are common in congestive heart failure (CHF).
- Common risk factors for CSA/CSR in patients with CHF are male gender, older age, hypocapnia, and the presence of atrial fibrillation.
- CSA arises from perturbations in the control of $Paco_2$ during the night.
- Augmented peripheral and central chemoreceptor activity is common in CHF and thought to underlie the perturbations in control of $Paco_2$ during sleep.
- Other important contributors to CSA/CSR in patients with CHF include rostral fluids shifts, diminished cerebrovascular activity, and prolonged circulation time.

Central sleep apnea (CSA) and Cheyne-Stokes respiration (CSR) during sleep are common in patients with congestive heart failure (CHF), representing a manifestation of breathing instability. This article reviews the determinants of CSA, the specific features of CHF-related CSA, and the underlying mechanisms.

DETERMINANTS OF BREATHING INSTABILITY DURING NON–RAPID EYE MOVEMENT SLEEP

Determinants of Central Apnea During Sleep

Breathing during wakefulness is influenced by both metabolic and behavioral factors. The sleep state (specifically non–rapid eye movement [NREM] sleep) is associated with loss of the wakefulness drive to breathe, rendering respiration critically dependent on chemical influences, especially $Paco_2$. Accordingly, a change in arterial $Paco_2$ leads to a corresponding change in ventilation to maintain the prevailing $Paco_2$ within a narrow physiologic range. However, CSA occurs if the arterial $Paco_2$ decreases below a reproducible sensitive hypocapnic apneic threshold.[1] Thus, hypocapnia is an important inhibitory factor during NREM sleep and is a key reason for the genesis of CSA and CSR in patients with CHF.[2]

CSA is common at sleep onset as the electroencephalogram oscillates between wakefulness and light sleep, with reciprocal changes in the $Paco_2$ around the apneic threshold. Thus, sleep state and breathing continue to oscillate until sleep is consolidated, a higher $Paco_2$ set point is established, and $Paco_2$ is maintained above this level.

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CSA at sleep onset is described as physiologic; however, it is not universal. Thus, it is unclear whether CSA at sleep onset is a physiologic phenomenon or a subclinical marker of increased propensity to hypocapnic CSA.

CSA is uncommon during rapid eye movement (REM) sleep relative to NREM sleep. REM sleep may be impervious to central hypocapnic disfacilitation because central respiratory activity is increased during REM sleep,[3] suggesting that REM sleep is similar to wakefulness in terms of hypocapnic ventilatory response. Although post-hyperventilation CSA is rare in REM sleep, transient hypoventilation secondary to REM-induced loss of intercostal muscle activity in patients with neuromuscular disease may appear as CSA morphologically.

Determinants of Periodic Breathing During Sleep

CSA rarely occurs as a single event; instead, it occurs in cycles of apnea or hypopnea, alternating with hyperpnea, a reflection of the negative feedback closed-loop cycle that characterizes ventilatory control. Specifically, a transient change in chemical stimuli leads to a corresponding change in ventilation to correct the initial perturbation. Likewise, a transient increase in minute ventilation results in increased alveolar P_{O_2} and decreased P_{CO_2} and a subsequent ventilatory response, opposite to the initial perturbation. The overarching goal is to preserve ventilation and chemical stimuli within a narrow range, while responding to changes in sleep state or gas exchange, under a variety of physiologic or pathologic conditions. This process is often described using the engineering concept of loop gain, combining the response of the ventilatory system to changing partial pressure of end-tidal CO_2 (P_{ETCO_2}) (the controller), and the effectiveness of the lung/respiratory system in lowering P_{ETCO_2} in response to hyperventilation (the plant).[4] Changes in either parameter change the requisite magnitude of hypocapnia to reach CSA (termed the CO_2 reserve; a lower CO_2 reserve is associated with an increased tendency to CSA). Loop gain is a useful concept in understanding control of breathing; however, the applicability of loop gain clinically is limited in part because arousals and upper airway obstruction can abruptly alter the responsiveness of the system to a perturbation in chemical stimuli.

Plant gain is the relationship between Δ Pa_{CO_2} versus minute ventilation (Δ VE). It measures the efficacy of the system to change arterial Pa_{CO_2} in response to a change in ventilation. Thus, low Pa_{CO_2}, for a given metabolic rate, promotes ventilatory stability by requiring a larger increase in VE for a given reduction in arterial Pa_{CO_2}, whereas high Pa_{CO_2} promotes instability. Steady state hyperventilation, and hence hypocapnia, promotes stability by decreasing plant gain. The controller gain is the ventilatory response for a given change in chemical stimuli (Δ VE vs Δ Pa_{CO_2}). When CSA is induced by passive mechanical hyperventilation, the controller gain represents the slope of CO_2 chemoreflex sensitivity below eupnea in response to induced hypocapnia. A high controller gain is associated with ventilatory instability, whereas a low controller gain is associated with ventilatory stability. As the blood leaves the pulmonary capillaries, the chemical stimuli are diluted by the systemic circulation and delayed by the obligatory transit time; the cerebral circulation adds further delay and dilution. Thus, Pa_{CO_2} does not necessarily reflect the chemoreceptor P_{CO_2}. This point may be particularly relevant in patients with CHF and low ejection fraction who have prolonged circulation time.

Role of Central Apnea in the Development of Obstructive Sleep Apnea

A less recognized phenomenon is that CSA may also influence the development of obstructive sleep apnea (OSA) (**Fig. 1**). It has been shown that pharyngeal obstruction develops when ventilatory drive reaches a nadir during induced periodic breathing.[5,6] In studies using upper airway imaging, the authors have shown that CSA results in pharyngeal narrowing or occlusion in normal individuals and patients with sleep disordered breathing.[7,8] Patients with unfavorable upper airway anatomy may be particularly dependent on ventilatory motor output to preserve upper airway patency.[7] Pharyngeal collapse combined with mucosal and gravitational factors may impede pharyngeal opening and necessitate a substantial increase in a drive that perpetuates breathing instability.

PATHOPHYSIOLOGIC CLASSIFICATION OF CENTRAL SLEEP APNEA

The classification of CSA as hypocapnic or nonhypocapnic (based on the level of daytime Pa_{CO_2}) is traditionally used. However, this classification does not capture the continuum of ventilatory abnormalities in clinical conditions.

Nonhypocapnic CSA is caused by removal of the wakefulness stimulus to breathe in patients with neuromuscular disease or severe abnormalities in pulmonary mechanics. Therefore, it is technically a form of sleep-related ventilatory failure in patients with marginal respiratory status. Hypoventilation is terminated by arousal, only to recur