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APNEA IN HEART FAILURE

Central sleep apnea in patients with congestive heart failure

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Abstract Central apnea during sleep represents a manifestation of breathing instability in many clinical conditions of varied etiologies. Central apnea is the result of transient cessation of ventilatory motor output, which represents that inhibitory influences favoring instability predominate over excitatory influence favoring stable breathing. This article will review the determinants of central apnea, the specific features of CHF-related central apnea, and outline a management approach

Keywords Cheyne–Stokes respiration · Ventilatory control instability · Heart failure

Determinants of central apnea during NREM sleep

The removal of the wakefulness "drive to breathe" renders respiration during sleep (specifically non-rapid eye movement or NREM sleep) critically dependent on chemical influences, especially PCO_2. NREM sleep unmasks a highly sensitive, hypocapnic apneic threshold; accordingly, central apnea occurs if arterial PCO_2 is lowered below the "apneic threshold" [1, 2]. This can be induced experimentally via passive nasal mechanical ventilation resulting in hypocapnia of varied degrees.

Hypocapnia is the most ubiquitous and potent influence favoring inhibition of ventilatory motor output in sleeping humans. However, some types of hyperventilation, including brief and active hyperventilation, may not result in apnea. Hypoxic hyperventilation, and possibly other forms of active hyperventilation, may be associated with activation of an excitatory neural mechanism referred to as short-term potentiation (STP) [3–5]. This neuronal phenomenon may preserve rhythmic respiration despite transient hypocapnia. In fact, termination of brief hypoxia or transient arousals from sleep rarely lead to central apnea despite hypocapnia at or below the apneic threshold [5, 6]. However, prolonged hypoxia may abolish STP, which may explain the development of periodic breathing after 20–25 min of hypoxia and the occurrence of central apnea upon termination of prolonged hypoxic exposure [5, 7]. Likewise, central apnea does not usually occur following brief episodes of hyperventilation in sleeping humans [8] or dogs [9] possibly due to insufficient reduction in PCO_2 at the level of the central chemoreceptors.

Central apnea can also occur through non-chemical pathways; for example, application of negative pressure and subsequent deformation of the upper airway lead to central apnea in a canine model [10]. Likewise, central apnea is more frequent in the supine position [11–13] and may respond to nasal continuous positive airway pressure therapy (CPAP) [14]. In fact, the lateral position may lead to amelioration of severity of central apnea and Cheyne–Stokes respiration [11–13].

Apnea does not occur as an isolated event but in clusters of breaths separated by intervals of apnea or hypopnea. This has given rise to the maxim: apnea begets apnea. Patients with CHF and central apnea often display the typical crescendo-decrescendo pattern of Cheyne–Stokes respiration. This form of periodic breathing represents a cumulative effect of physiologic ventilatory responses aiming to minimize the fluctuation in arterial blood gases. Changes in PCO_2 and PO_2 produce proportional counteracting changes in ventilation; however, a delayed or exaggerated response produces periodic rather than stable breathing.

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The properties of the ventilatory control during sleep underpin the notion that physiologic responses lead to pathologic instability. The ventilatory control system operates as a negative-feedback closed-loop cycle to maintain homeostasis of blood gas tensions within a physiologic range. Many authors have adopted the engineering concept of "loop gain" (GL) as a measure of ventilatory stability or susceptibility to central apnea and recurrent periodic breathing [15]. Loop gain represents the overall response of the plant (representing the lung and respiratory muscles), the controller (representing the ventilatory control centers and the chemoreceptors), and the delay, dilution, and diffusion inherent in transferring the signal between the plant and the controller. There are several excellent reviews discussing the dynamics of ventilatory control in humans [16–18].

The occurrence of apnea leads to several consequences that conspire to promote further breathing instability. The first is the inertia of the ventilatory control system that prevents the return of rhythmic breathing until $PaCO_2$ increases by 4–6 mmHg above eupneic arterial PCO_2 [19]. In addition, central apnea is associated with narrowing or occlusion of the pharyngeal airway [20]. Thus, resumption of ventilation requires opening of a narrowed or occluded airway and overcoming tissue adhesion forces [21] and cranio-facial gravitational forces. Termination of central apnea is associated with variable asphyxia (hypoxia and hypercapnia) and transient arousal, resulting in ventilatory overshoot, subsequent hypocapnia, and further apnea/hypopnea. This sequence explains the overlap between central and obstructive apnea (upper airway obstruction often follows central apneas upon resumption of respiratory effort, i.e., mixed apnea).

Pathophysiologic classification of central sleep apnea

The classification of central apnea as hypercapnic or non-hypercapnic (based on the level of daytime $PaCO_2$) does not capture the continuum of ventilatory abnormalities in clinical conditions. Physiologically, central apnea could be caused by reduced alveolar ventilation or by hypocapnia following alveolar hyperventilation.

Central sleep apnea, in its hypercapnic form, is caused by removal of the wakefulness stimulus to breathe in patients with neuromuscular hypoventilation disease or severe abnormalities in pulmonary mechanics [22]. Therefore, it is a form of nocturnal ventilatory failure in patients with marginal ventilatory status or worsening of existing chronic ventilatory failure. Arousal from sleep restores alveolar ventilation to a variable degree; resumption of sleep reduces ventilation in a cyclical fashion. This type of central apnea does not necessarily meet the strict criteria of "central" or of "apnea". Consequently, the presenting clinical picture includes both features of the underlying ventilatory insufficiency and features of the sleep apnea/hypopnea syndrome. This type of central apnea is uncommon in patients with CHF unless a concomitant neuromuscular disease of chest wall deformity is present.

Hypocapnia secondary to hyperventilation is the most common underlying mechanism of central apnea and the most relevant mechanism in patients with CHF. This type of apnea occurs in the absence of daytime alveolar hypoventilation; in fact, common features include hyperventilation and hence hypocapnia, even during wakefulness [23] with no evidence of a neuromuscular disorder, abnormal lung mechanics, or impaired responses to chemical stimuli. Oscillating sleep state at sleep onset [24] or transient hypoxia possibly due to reduced lung volumes in obese supine patients may trigger the "first" apnea and set in motion the process of apnea-hyperapnea and leads to sustained breathing instability, manifested as periodic breathing (see above).

Central apnea risk factors

Several physiologic or pathologic factors influence the susceptibility to central apnea including sleep state, age, gender, sleep state, and several medical conditions.

Sleep state exerts a major influence on breathing during sleep. Breathing instability is likely to occur at sleep onset as sleep state oscillates [24–27], with reciprocal oscillation in $PaCO_2$ around the hypocapnic apneic threshold. Consequently, central apnea may occur if sufficient hypocapnia occurred; recovery from apnea is associated with transient wakefulness and hyperventilation. The subsequent hypocapnia elicits apnea upon resumption of sleep. Consolidation of sleep stabilizes $PaCO_2$ at a higher set point above the apneic threshold. Interestingly, central apnea may occur without preceding hyperventilation at the transition from alpha to theta sleep in normal subjects and is associated with prolongation of breath duration [28]. Post-hyperventilation central sleep apnea is uncommon during REM sleep, suggesting that REM sleep is impervious to chemical influences owing to increased ventilatory motor output [29, 30].

Aging is associated with increased prevalence of central sleep apnea [31–33]. Possible causes include age-related sleep state oscillations [24, 34]; co-morbid conditions such as thyroid disease [35], congestive heart failure [36], atrial fibrillation [37], and cerebrovascular disease [38], or that aging per se may contribute to increased susceptibility to develop central apnea in older adults [32].

Central sleep apnea is uncommon in pre-menopausal women [39]. There is evidence that women are less

susceptible to the development of hypocapnic central apnea relative to men following mechanical ventilation. Physiologically, the hypocapnic central apneic threshold is higher in men relative to women [2]. Administration of testosterone to healthy pre-menopausal women elevates the apneic threshold [40]. Conversely, suppression of testosterone with leuprolide acetate in healthy males decreases the hypocapnic-apneic threshold and potentially stabilizing respiration [41]. Thus, male sex hormones are the most likely factor elevating the apneic threshold in men.

Sleep apnea is common after a cerebrovascular accident (CVA) [38, 42, 43], with central apnea being the predominant type in 40% of patients of sleep apnea after a CVA [43]. Likewise, central apnea occurs in 30% of patients stable methadone maintenance treatment [44]. Finally, several medical conditions predispose to the development of central apnea including hypothyroidism, acromegaly, and renal failure [45–49], all of which have an unexpectedly high prevalence of sleep apnea. Nocturnal hemodialysis is associated with improvement in sleep apnea indices [48].

Some patients may manifest central apnea with no apparent risk factor and are considered to have "idiopathic central apnea", associated with increased chemo responsiveness and sleep state instability [50, 51]. Nevertheless, it is possible that these patients will have occult cardiac or metabolic disease. For example, idiopathic central sleep apnea is more prevalent in patients with atrial fibrillation.

Sleep apnea is highly prevalent in patients with CHF [36, 52–54]. Javeheri et al. demonstrated that 51% of male patients with CHF had sleep-disordered breathing, 40% had central sleep apnea, and 11% obstructive apnea. Risk factors for CSA in this group of patients include male gender, atrial fibrillation, age >60 years, and daytime hypocapnia ($PCO_2 < 38$ mmHg) [55]. Risk factors for OSA differed by gender; the only independent determinant in men was body mass index (BMI), whereas age over 60 was the only independent determinant in women.

The presence of pulmonary vascular congestion in patients with central apnea and CHF leads to hyperventilation and hypocapnia [36]. Paradoxically, steady-state hypocapnia is stabilizing by virtue of decreased plant gain [56–58]. In other words, steady-state reduction of $PaCO_2$ is potentially stabilizing rather than destabilizing as is commonly thought. However, the apneic threshold in patients with central apnea and CHF is precariously close to the eupneic PCO_2, because of increased chemoreflex sensitivity or controller gain.

Clinical features and diagnosis

Patients with central apnea may present with the usual symptoms of sleep apnea syndrome, or with insomnia and poor nocturnal sleep. These symptoms may be due to sleep fragmentation secondary to recurrent apnea. In fact, poor nocturnal sleep may be a presenting symptom in patients with central apnea due to CHF. Diagnosis of central sleep apnea requires nocturnal polysomnography and accurate detection of flow, measurement of oxyhemoglobin saturation, and detection of respiratory effort [59].

Accurate detection of respiratory effort is important to distinguish central from obstructive apnea. Cardiogenic oscillations (pulse artifacts) on the flow signal are often used as evidence of central etiology and a patent upper airway. The underlying rationale is the pulse artifacts represent transmission of a pulse waveform from the thorax, and hence indicates a patent upper airway that allows the transmission of cardiogenic oscillation. However, there is evidence that this index is invalid to ascertain upper airway patency. Morrell et al. [60] used fiber optic nasopharyngoscopy to evaluate upper airway patency during central apnea; cardiogenic oscillations were present even when the airway is completely occluded.

Other measurement of effort include measurement of the lapsed time for the pulse signal to reach the periphery, or pulse transit time (PTT) [59]. The technique measures the elapsed time between R wave on the ECG and the arrival of the pulse wave to the finger. The underlying physiologic principle is that blood pressure influences vessel stiffness and hence the speed of the pulse wave. When blood pressure increases during an obstructive apnea owing to increased intra-thoracic pressure swings, the pulse transit time displays parallel swings.

Management

Central apnea syndrome is a disorder with protean underlying conditions, therefore requiring a full panoply of therapeutic options. Management strategy incorporates underlying conditions, polysomnographic features, and individual factors. Optimal treatment of the underlying condition is a prerequisite component of the management plan in every patient. This is particularly important in patients with CHF where improvement of cardiac function may ameliorate central apnea. Likewise, diuresis may decrease pulmonary vascular congestion, improve oxygenation, and minimize overshoot. Specific therapeutic options include positive pressure therapy, pharmacologic therapy, and supplemental O_2.

Positive pressure therapy

Central apnea may respond to nasal CPAP therapy, especially if it occurred in combination with episodes of obstructive or mixed apnea. Moreover, pure central sleep

apnea may respond to nasal CPAP therapy for several reasons: (i) preventing pharyngeal narrowing during central apnea [14], (ii) improved oxygenation by increased lung volume, and (iii) improving cardiac function by decreasing pre-load and after load. The aggregate of these changes would dampen the ensuing ventilatory overshoot and perpetuation of ventilatory instability [20]. In fact, nasal CPAP is often effective in reversing central sleep apnea, even in the absence of concomitant obstructive apnea [14], possibly by preventing upper airway closure and subsequent ventilatory overshoot [20]. This may also explain the reported increase in PCO_2 after CPAP [61]. Similarly, nasal CPAP therapy in patients with central sleep apnea and CHF produced increased left-ventricular ejection fraction (LVEF) and a reduction of combined mortality-cardiac transplantation risk by 81%, but only in patients with CSA [62].

The exuberance regarding nasal CPAP therapy in patients with central apnea and CHF did not withstand the rigors of controlled clinical trials. The Canadian Continuous Positive Airway Pressure trial, or CANPAP [63], tested the hypothesis that CPAP would improve the survival rate without heart transplantation in patients with heart failure and central sleep apnea. The study enrolled 258 patients who had heart failure and central sleep apnea; participants were randomly assigned to the nasal CPAP treatment group ($n = 128$) or no CPAP (130 patients). Duration of follow up was for a mean of 2 years. There was greater improvement in the CPAP group at 3 months relative to the placebo group as evidenced by greater reductions in apnea-hypopnea index, ejection fraction, mean nocturnal oxyhemoglobin saturation, plasma nor-epinephrine levels, and the distance walked in 6 min at 3 months. Nevertheless, there was no difference in the overall event rates (death and heart transplantation) between the two groups. Thus, nasal CPAP had no effect on survival, despite the effect on the "severity" of central apnea and several intermediate outcome variables. Nevertheless, a post-hoc analysis has shown decreased mortality if CPAP therapy resulted in amelioration of central sleep apnea. Therefore, current evidence does not support the use of CPAP to extend life in patients who have heart failure and central sleep apnea unless evidence of response is demonstrated by polysomnography.

The major finding of CANPAP was the absence of a survival benefit for nasal CPAP therapy. Nasal CPAP therapy had no effect on heart transplant-free survival; however, aggregate data showed only a modest reduction of AHI to 19 events per hour of sleep; a cutoff of 15 events/h was the inclusion threshold for the study and remains a commonly accepted threshold for pathologic AHI. Another limitation of the study was that nasal CPAP therapy was not titrated under polysomnographic monitoring but increased gradually to 10 cm/H_2O or to the highest tolerated number. Optimal CPAP pressure was not determined. In addition, only 100 of the 128 randomized to CPAP underwent repeat polysomnography after 3 months of nasal CPAP therapy [64]. Fifty-seven patients responded to nasal CPAP as evidenced by decreased AHI below 15/h of sleep. Interestingly, the responders (CPAP-CSA-suppressed) group demonstrated a statistically significant increase in LVEF at 3 months ($P = 0.001$) and a higher transplant-free survival than control subjects. Conversely, the non-responders (CPAP-CSA-unsuppressed) group demonstrated no increase in either variable. These findings suggest that improvement in LVEF may be a marker of improved survival. In addition, this study highlights the need to conform optimal response to patients with CHF-CSA. Lowering AHI below 15 events/h of sleep may be suboptimal in terms of improved nocturnal respiration, cardiac function, or mortality.

Non-invasive positive pressure ventilation (NIPPV) using pressure support mode (bi-level nasal positive pressure) is a therapeutic option in patients with nocturnal ventilatory failure and central apnea secondary to hypoventilation. However, there is little evidence to support its use in non-hypercapnic central apnea including CHF. In fact, NIPPV in the pressure support, bi-level mode augments tidal volume, leading to hypocapnia and possible worsening of central apnea and periodic breathing during sleep [65]. Meza et al. [66] have shown that application of pressure support ventilation results in periodic breathing in most normal subjects when the pressure gradient is above 7 cm/H_2O.

Recent technological advances allowed for variations in the mode of delivering positive pressure ventilation. One such method is adaptive servo ventilation (ASV) that provides a small but varying amount of ventilatory support against a background of low level of CPAP. Contrary to bi-level, pressure support devices, changes in respiratory effort result in reciprocal changes in the magnitude of ventilatory support. Thus, ventilation remains slightly below the baseline, eupneic average. There is evidence that ASV is more effective than CPAP, bi-level pressure support ventilation, or increased dead space in alleviating central sleep apnea [67].

Pharmacological therapy

Pharmacological therapy is of marginal role in central apnea. Small studies suggest acetazolamide and theophylline may be beneficial in the treatment of central apnea [68]. Acetazolamide is a carbonic anhydrase inhibitor and a weak diuretic that causes mild metabolic acidosis. Acetazolamide ameliorates central sleep apnea when administered as a single dose of 250 mg before bedtime

[69]. Likewise, theophylline ameliorates the severity of Cheyne–Stokes respiration in patients with CHF [70], without adverse effect on sleep architecture. Pharmacologic therapy remains an unfulfilled opportunity that awaits further research.

Several pharmacologic agents may influence the propensity to develop central apnea; therefore, medication use is an important consideration in the management patients with central sleep apnea. For example, the use of beta-blockers in patients with central sleeps apnea and congestive heart failure is associated with reduced apnea index. Conversely, narcotics may worsen central apnea; a change in the pain control regimen may ameliorate the severity of central apnea [44, 71].

Supplemental O_2 and CO_2

Supplemental O_2 therapy may be beneficial in patients with idiopathic central sleep apnea and patients with CHF-CSR [36, 72], most likely by ameliorating hypoxemia and minimizing the subsequent ventilatory overshoot. In addition, supplemental O_2 may alleviate central apnea by increasing cerebral PCO_2 through the Haldane effect. Likewise, supplemental CO_2 abolishes central apnea in patients with pure central sleep apnea. The mechanism of action is by raising PCO_2 above the apneic threshold. However, this therapy is not practical given the need for a closed circuit to deliver supplemental CO_2.

Approach in selected clinical syndromes

1. It is imperative to optimize treatment of the underlying condition such as CHF.
2. Titration of CPAP in the sleep laboratory is beneficial to ascertain response to nasal positive airway pressure therapy. This may determine whether long-term treatment is of benefit.
3. The optimal pressure settings have to be determined in a titration polysomnogram.
4. The use of B-PAP in a pressure support mode may aggravate the severity of central apnea. ASV is a promising therapeutic modality for CHF-CSR.
5. Supplemental O_2 may be beneficial, particularly in patients with CHF-CSR.
6. The use of pharmacologic agents remains uncommon. Additional studies are needed.

Summary

The pathogenesis of central sleep apnea varies depending on the clinical condition. Sleep-related withdrawal of the ventilatory drive to breathe is the common denominator among all cases of central apnea, whereas hypocapnia is the final common pathway leading to apnea in non-hypercapnic central apnea. The pathophysiologic heterogeneity may explain the protean clinical manifestations and the lack of a single effective therapy for all patients.

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