

Review Article

Complex Sleep Apnea Syndrome

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Complex sleep apnea is the term used to describe a form of sleep disordered breathing in which repeated central apneas (>5/hour) persist or emerge when obstructive events are extinguished with positive airway pressure (PAP) and for which there is not a clear cause for the central apneas such as narcotics or systolic heart failure. The driving forces in the pathophysiology are felt to be ventilator instability associated oscillation in PaCO₂, arterial partial pressure of Carbon Dioxide, continuous positive airway pressure (CPAP) related increased CO₂ carbon dioxide elimination, and activation of airway and pulmonary stretch receptors triggering these central apneas. The prevalence ranges from 0.56% to 18% with no clear predictive characteristics as compared to simple obstructive sleep apnea. Prognosis is similar to obstructive sleep apnea. The central apnea component in most patients on followup using CPAP therapy, has resolved. For those with continued central apneas on simple CPAP therapy, other treatment options include bilevel PAP, adaptive servoventilation, permissive flow limitation and/or drugs.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) affects a growing proportion of general population affecting both men (15%) and woman (5%) and is commonly known as “sleep disordered breathing” [1]. OSAS is linked with significant cardiovascular morbidity and mortality in those untreated [2]. In OSAS, repetitive collapse of the upper airway takes place, which will finally lead to O₂ arterial Oxygen desaturation and arousal. Continuous positive airway pressure (CPAP) is the standard therapy to stabilize the airway preventing repeated collapse. To a lesser extent, central sleep apneas syndrome is diagnosed in about 5% of those who undergo a sleep study. This condition is characterized by diminished respiratory regulation during sleep, resulting in decreased or absent ventilation and disturbed gas exchange [3]. Because the mechanism behind the developing the central events is much more complicated, the response to CPAP is often incomplete and may lead to CPAP failure [4, 5]. For some patients who undergo CPAP treatment for OSAS, CPAP therapy leads to the development of recurrent central apneas or even clear periodic breathing. This phenomenon of obstructive events or mixed central and obstructive events with short

cycles of obstruction and the incomplete response to positive airway pressure (PAP) due to CPAP treatment related central events has been labeled “complex sleep apnea syndrome” (CompSAS) [6–9].

2. Definition

Complex sleep apnea syndrome (CompSAS) is a form of sleep disordered breathing in which central apneas persist or emerge when obstructive events have disappeared with PAP therapy (see Figure 1). By the currently accepted definition, the central events must comprise more than half of the residual sleep disordered breathing events or lead to a periodic breathing pattern which on positive airway pressure therapy becomes predominant and disruptive and the central apnea index (CAI) must be >5 events/hour. Bilevel positive airway pressure ventilation in spontaneous mode may increase the risk of central apneas through augmenting ventilation with a proportionate decrease in carbon dioxide. It is actively being debated whether to include those with central apneas associated with narcotics or Cheyne-Stokes breathing due to systolic heart failure. In the current definition, CompSAS would include only patients whose central apnea could

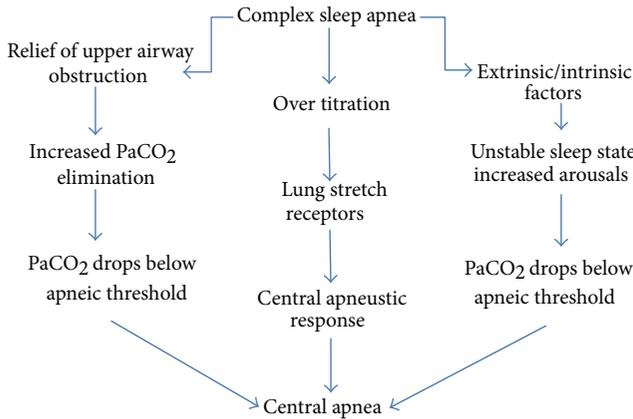


FIGURE 2: Schematic representation of pathogenesis of complex sleep apnea syndrome.

schematic representation of the pathophysiology is illustrated in Figure 2.

4. Clinical Characteristics

Clinically speaking, the phenotype of patients with CompSAS is most similar to that of a patient with OSA, and only when CPAP therapy is applied one can identify them (see Figure 1). From those studies we have in selected populations, it appears that those with complex sleep apnea are more often male (>80% versus 60% with OSA). While it is not clear what the exact mechanism is, increased hypercapnic ventilatory response in males could be playing a role [25]. There is slight higher incidence of ischemic heart disease or heart failure compared to those with OSA [26] but this may be due to bias inherent to the populations being evaluated in these studies. The body mass index (BMI) is typically higher than the general population which is typical in OSAS; however, in one study, the BMI with CompSAS was slightly lower than with OSAS [9]. There may be clinically relevant symptoms that leads to detection of CompSAS. In one study, there was a significant difference in CPAP use and dyspnea compared to those with OSA. The treated CompSAS patients reported more CPAP removal during sleep and dyspnea or air hunger at followup [27]. In fact predicting the presence of CompSAS may not be entirely complete after the initial sleep study. One study reported that, if subject had evidence of central events on baseline study (central apnea index > 5), they were more likely to have CompSAS but this was not statistically significant and was not proven by multiple subsequent studies. The severity of sleep apnea present on initial evaluation seems to predict persistent central apneas while on CPAP therapy. Those with severe OSA or CSA on diagnostic study were more likely to have persistent central apneas on subsequent titration studies completed in 2-3 months into ongoing CPAP therapy [28]. The degree of sleep architecture disruption and the hypopnea density in NonREM versus REM sleep may also be predictive. As compare to those with simple OSAS, on subsequent CPAP titration study, those with complex sleep apnea had a higher events/hour index in nonREM sleep

compared to REM sleep and had a more elevated arousal index [9].

5. Treatment

5.1. Positive Pressure Devices. An outline of treatment options is illustrated in Figure 4. Patients with CompSAS can represent a treatment challenge, and the optimal therapeutic approaches remain to be refined. Based on the proposed mechanisms, it appears that the most critical component of any therapy for CompSAS is to minimize potential for developing over ventilation or hypocapnia. This includes targeting CPAP at the lowest pressure that resolves most obstructive events and avoiding modalities that destabilize the airway or sleep state. In a recent retrospective review of 1286 patients receiving PAP therapy, only 6.5% of patients demonstrated CompSAS during the initial CPAP titration study. Of those initially identified with CompSAS, half ($n = 42$) underwent a titration sleep study after an interval of CPAP therapy, and 78.6% (33/42) of those showed resolution of the central apnea component with CPAP [28]. The CompSAS may not be identified on initial sleep studies. The central apneas developed *de novo* in 4% of OSAS patients during followup for CPAP therapy in one retrospective study [29].

Up to this point, CompSAS has been defined by evaluation of an initial sleep study or on followup titration sleep studies. Diagnosing CompSAS will become more challenging as practice protocols are driven out of the controlled environment of the observed sleep study to limited home-based sleep studies followed by autotitrating PAP therapy by the implementation of cost containment in sleep medicine. It is understood that autotitrating PAP devices vary in ability to warn clinician of emerging central apnea. Clinicians will need to be aware of this condition as a possibility in those with either poor response to auto-titrating PAP therapy (lack of improvement in sleep related complaints) or inability to tolerate this type of therapy and champion the need for observed titration testing needed to confirm the presence of CompSAS.

For those with CompSAS who fail CPAP, breaking the cycle of central apneas leading to arousals and instability in ventilation can be achieved with respiratory assist devices designed to better control ventilation. These devices include bilevel PAP in the spontaneous-timed (bilevel PAP-ST) mode and adaptive servoventilation (ASV) [11, 26]. Bilevel PAP-ST is a type of noninvasive ventilation that provides the pneumatic splint effect in the upper airways resolving the obstructive component as well as stabilizing ventilation during central apneas by forcing breaths (timed breath) during episodes of central apneas. The expiratory positive airway pressure (EPAP) is set to eliminate obstructive apneas, while the inspiratory positive airway pressure (IPAP) and backup ventilation frequency (ST mode) are set in order to decrease hypoventilation [30]. Even more refined ventilator support can be found in ASV devices. This type of bilevel ventilator has been shown to be effective in resolving not only CompSAS but also CSA as well as Cheyne-Stokes respiration and can be measurably effective both in the first night of therapy and over long-term management (Figure 3) [26].

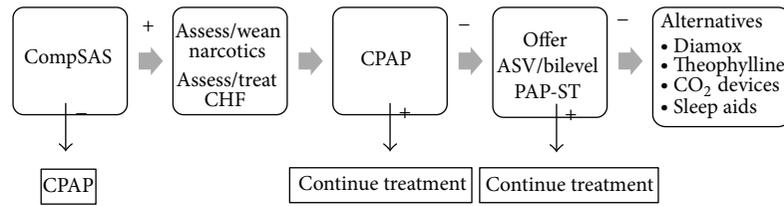


FIGURE 4: A schematic representation of treatment modalities of complex sleep apnea.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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