

Complex sleep apnea syndrome

Anuja Sharma

Pulmonary and Critical Care Associates, 225 North Smith Avenue, Suite 300, St Paul, Minnesota, USA

Indian J Sleep Med 2010; 5.3, 81-83

Definition

Complex sleep apnea syndrome (CompSAS) is a form of sleep apnea specifically identified by the presence or emergence of central apneas or hypopneas upon exposure to continuous positive airway pressure (CPAP) or a Bi-level positive airway pressure (BiPAP) device when obstructive events have disappeared. These patients have predominantly obstructive or mixed apneas during the diagnostic sleep study occurring at greater than or equal to 5 times per hour. With the use of CPAP or BiPAP they show a pattern of apneas and hypopneas that meets the definition of Central sleep apnea (CSA). As central hypopneas are rarely scored in clinical practice, the definition requires the occurrence of central apneas that make up more than 50% of all scored respiratory events, a threshold that could miss clinically significant non obstructive events.¹

Another definition based on pathophysiology of concomitant upper airway obstruction due to respiratory control dysfunction. Comp SAS is associated with a typical polysomnographic pattern, specific therapeutic response to positive pressure (improvement of obstruction but worsening of periodic breathing with or without induction of central apneas) and a sensitivity to direct or indirect manipulations of carbon dioxide (CO₂) levels (by decreasing hyperventilation with adaptive forms of positive airway pressure, exogenous CO₂ or allowing rebreathing of CO₂)².

Address for correspondence

Dr Anuja Sharma, MD
 Pulmonary and Critical Care Associates
 225 North Smith Avenue, Suite 300
 St Paul, Minnesota, USA
 tele : 651 726 6200
 email: asharma@pccaonline.com

Studies show that after optimal CPAP titration, patients with CompSAS have moderate to severe sleep disordered breathing and sleep fragmentation. Allam et al described 63 patients with baseline apnea-hypopnea index (AHI) of 30/hr (15-54), who developed central apneas after application of optimal CPAP [AHI at optimal CPAP of 30/hr (16-42), central apnea index (CAI) at optimal CPAP of 14/hr (7-28) and arousal index (AI) at optimal CPAP of 35/hr (26-44)³]. Kuzniar et al described 13 patients with baseline AHI of 35/hr (22-40), AHI at optimal CPAP of 24/hr (23-35), CAI at optimal CPAP of 18/hr (9-31)⁴. Similar findings have also been reported in other studies⁽⁵⁻⁷⁾.

Prevalence

Morgenthaler et al provided the first ever estimate of the prevalence in 2006⁸. It was a retrospective review of 223 adults consecutively referred over one month and 20 consecutive patients diagnosed with central sleep apnea (CSA). Study excluded all patients with a clinical history of congestive heart failure or left ventricular ejection fraction of 40% or less, leaving 219 patients for analysis. Prevalence of CompSAS, Obstructive sleep apnea-hypopnea syndrome (OSAHS) and CSA was 15%, 84% and 0.4% respectively. Eighty one percent of CompSAS patients were males compared with 61% of OSAHS patients. Diagnostic AHI for CompSAS, OSAHS and CSA was 32.3 +/- 26.8, 20.6 +/-23.7 and 38.3+/-36.2 respectively. Residual AHI in patients with CompSAS, OSAHS and CSA was 21.7+/-18.6, 2.14+/-3.14 and 32.9+/-30.8 respectively. Overall, clinical risk factors did not predict emergence of CompSAS. Other studies since have quoted a prevalence of 13-20%.

Jahaveri et al provided another estimation of prevalence in 2009. It was a retrospective study of 1286 patients over one year⁹. CSA on CPAP was noted with a frequency of 3-10%/month with an average of 6.5%

(84 patients). Demographically there was no difference between patients who developed CSA on CPAP and those who did not do so. Only 42 of the 84 patients returned for a second CPAP titration and CSA was noted to have been eliminated in 33 patients. The authors concluded that CPAP emergent CSA was “transitory” and persisted in only 1.5% at eight weeks after CPAP therapy. Persistence correlated with severity of OSAHS at baseline. The study was criticized because half the patients with CSA on CPAP were lost to follow up. Technically, thermistors were used for airflow monitoring. The 42 patients who were restudied had persistent sleep fragmentations suggesting that “all was not well”. Strength lay in the number of patients.

Pathogenesis

The pathogenesis of Comp SAS is unclear and inadequately studied. Theories are largely based on speculation. The predominant pathophysiology is felt to be dysregulation of CO₂ homeostasis. It is felt that correction of upper airway obstruction with CPAP leads to decreased resistance, decreased dead space, increased ventilation and consequent hypocapnia. Over titration can cause washout of CO₂ from anatomical dead space and worsen sleep quality. The arousals related to the latter can lead to hyperventilation with consequent inhibition of ventilation. On the other hand activation of stretch receptors because of over titration with CPAP can cause inhibition of ventilation. It appears that, in some patients, this and the delay in controller response can cause breathing instability and generation of apneas and hypopneas¹⁰.

Features

Patients with CompSAS are more likely to be males, have a lower BMI and have more frequent events in NREM sleep. There may be a suggestion of central events at baseline as events attenuate in REM sleep. However, risk factors typically associated with CSA such as cardiomyopathy, atrial fibrillation, stroke and old age are absent. Allam et al described 63 patients with mean age of 71 years (mean +/-SD 59-78) and males 84% and BMI 29-34%³. Kuzniar et al described 13 patients with a mean age of 65 (69+/-10), males 85% and BMI 32 (30-35)⁴.

At this time, it is not possible to predict development of CompSAS on clinical basis. However, in a

retrospective study by Thomas et al in 2007, ECG based spectral analysis was able to predict development of predominantly central sleep apnea with a sensitivity of 95.2% and specificity of 85.7%².

Relevance

In a case series described by Pusalavidyasagar et al in 2006, 87.9% were treated with CPAP despite persistence of central events. There was no significant difference in CPAP compliance or change in Epworth Sleepiness Scale between two groups¹¹.

In a 2008 retrospective study by Pusalavidyasagar et al, patients with CompSAS who had undergone two therapeutic polysomnograms (PSGs) at least one month apart in 2003-05, thirteen patients who met the criteria were identified. Repeat PSGs had been ordered for evaluation of abnormal overnight oximetry on CPAP or CPAP intolerance. AHI on CPAP decreased from 26 to 7 with AHI<10 in 7 patients. CPAP “nonresponders” were sleepier and tended to have a lower BMI. CPAP compliance was the same. The authors maintained that AHI in CompSAS patients did tend to improve with time on CPAP, but nearly half maintained an elevated AHI. They recommended prospective studies to define therapy¹².

Based on scant data, it appears that CompSAS does improve on CPAP with time. However, the studies are inadequate because of small numbers, loss to follow up and no long term evaluations of other endpoints such as cardiovascular morbidity and mortality.

Treatment

The goals of treatment include normalization of AHI and sleep architecture. There are no predictors to suggest which patients will respond to CPAP alone with time. This may be speculated to be secondary to heterogeneous nature of the syndrome and factors governing adaptation. The principles of treatment include support of ventilation during apneas and prevention of swings in pCO₂.

CPAP stabilizes the upper airway but has no effect on central events. Oxygen may improve CompSAS by affecting the hypoxic drive but data is limited. A note of caution is appropriate- CPAP nonresponders may prematurely discontinue treatment with subsequent bias against acceptance.

Standard Bi-level device is contraindicated. Adaptive servo ventilation (ASV) strategies are recommended. The algorithm automatically adjusts the magnitude of pressure support, breath by breath, to provide minimal, comfortable support during over breathing phase or during normal breathing. It increased support during under breathing. It creates a target minute ventilation. The algorithm monitors patient ventilation, compares it to the target ventilation and adjusts pressure support up or down as needed to achieve target. Allam et al in 2007 described the first 100 patients at Mayo clinic to use adaptive servo ventilation. CompSAS accounted for 63% of patient, CSA 22% and CSR 15%³. The median diagnostic AHI was 48/hr (range 24-62). With CPAP, AHI was 31/hr (range 17-47). With Bi-level in spontaneous mode the AHI worsened with median of 75/Hr (range 46-111). Use of ASV improved the AHI dramatically to a mean of 5/hr (range 1-11). Overall mean AHI was <10/hr in 64 patients. However, of the 44 successful patients contacted, 32 reported improvement in sleep quality³.

Morgenthaler et al in 2007 performed a prospective randomized cross over trial comparing NPPV with ASV in patients with CSA/CSR, predominantly mixed apneas and CompSAS in an acute setting¹³. Nine patients had CompSAS. These patients had an initial diagnostic AHI +/-SD of 49.4+/-25.4/hr, Central Apnea Index (CAI) of 5.6+/-4.6, on CPAP mean AHI 41.9+/-28.1/hr and CAI 30.6+/-18.7/hr. Both AHI and CAI were markedly decreased with both NPPV and ASV. On ASV the AHI was 1.6+/-3.6 with a CAI of 0.1+/-0.3. They concluded that both NPPV and ASV are effective in normalizing sleep disordered breathing, with ASV being more effective¹³.

Acetazolamide and theophylline do not have a role. Data suggests that maintaining carbon dioxide levels above apnea threshold by increasing dead space volume, increasing inspired carbon dioxide concentrations and use of sub therapeutic CPAP may have a role in correcting CompSAS. Of course, this is not available for clinical use.

Strong recommendation is made to ensure that appearance of central events on CPAP is true CompSAS. Other reasons for CPAP emergent central events may include inadequate titration, over titration, substantial mask leaks, sleep transition apneas and narcotic induced. Each can be fixed individually without use of ASV device¹⁴.

Future

Further research is definitely needed to define mechanism underlying CompSAS, the role of carbon dioxide and its threshold, adverse clinical consequences and appropriate treatment.

References

1. **Gay PG.** Complex Sleep Apnea: It Really Is a Disease. *J Clin Sleep Med* 2008; 4:403-05.
2. **Thomas RJ, Mietus JE, Peng C et al.** Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep* 2007; 30:1756-69.
3. **Allam JS, Olson EJ, Gay PC, Morgenthaler TI.** Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. *Chest* 2007;132:1839-46.
4. **Kuzniar TJ, Pusalavidyasagar S, Gay PC, Morgenthaler TI.** Natural course of complex sleep apnea- a retrospective study. *Sleep Breath* 2008;12:135-39.
5. **Dernaika T, Tawk M, Nazir S et al.** The significance and outcome of continuous positive airway pressure- related central sleep apnea during split-night sleep studies. *Chest* 2007;132:81-87.
6. **Lehman S, Antic NA, Thompson C et al.** Central sleep apnea on commencement of continuous positive airway pressure in patient s with a primary diagnosis of obstructive sleep apnea-hypopnea syndrome. *J Clin Sleep Med* 2007;3:462-66.
7. **Randerath WJ, Glaetke W, Steiglitz S et al.** Adaptive servoventilation in patients with coexisting obstructive sleep apnoea/hypopnea and Cheyne-Stokes respiration. *Sleep Med* 2008;9:823-30.
8. **Morgenthaler TI, Kagrmanov V, Hanak V, Decker DA.** *Sleep* 2006;29:1203-09.
9. **Javaheri S, Smith J, Chung E.** The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med*; 5:205-11.
10. **Gilmartin GS, Daly RW, Thomas R.** Recognition and management of complex sleep-disordered breathing. *Curr Opin Pulm Med* 2005; 11:485-93.
11. **Pusalavidyasagar SS, Olson EJ, Gay PC, Morgenthaler TI.** Treatment of complex sleep apnea syndrome: a retrospective comparative review. *Sleep Med* 2006; 7:474-79.
12. **Kuzniar TJ, Pusalavidyasagar SS, Gay PJ, Morgenthaler TI.** Natural course of complex sleep apnea- a retrospective review. *Sleep Breath* 2008; 12:135-39.
13. **Morgenthaler TI, Gay PJ, Gordon N, Brown LK.** Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed and complex sleep apnea syndromes. *Sleep* 2007; 30:468-75.
14. **Malhotra A, Bertisch S, Wellman A.** Complex sleep apnea: It isn't really a disease. *J Clin Sleep Med* 2008; 4:406-08.