REVIEW ARTICLE

Complex sleep apnea: An overview

Dhrubajyoti Roy[1], Arup Halder[2]

1. Consultant Pulmonologist and Director, PULSAR, Kolkata, West Bengal, India
2. Pulmonologist-Kolkata, West Bengal, India

DOI No:10.5958/0974-0155.2014.01110.3 *Indian J Sleep Med 2014; 9.3, 102-106*

Abstract

Complex sleep apnea is increasingly recognized as an emerging entity with improved awareness and treatment of obstructive sleep apnea (OSA). This condition may cause continuous positive airway pressure (CPAP) intolerance and persistent symptoms of sleepiness. An high index of suspicion is required to diagnose these subset of patients both during titration and on CPAP therapy. Early recognition of the condition and institution of proper treatment and follow-up measure will improve the CPAP therapy in OSA.

Keywords: Obstructive sleep apnea, central sleep apnea, Central Apnea Index, sleep-disordered breathing, excessive daytime sleepiness, partial pressure of carbon dioxide, partial pressure of oxygen.

Introduction

Sleep-disordered breathing (SDB) is a common disorder of the general populationsimilar to asthma, diabetes, hypertension, ischemic heart disease, hypothyroidism, etc., with obstructive sleep apnea (OSA) affecting approximately 15% men and 5% women between the ages of30 and 60 years[1]. The cardiovascular morbidity and mortality of untreated OSA is significant[2].

In OSA, a repetitive collapse of the upper airway takes place that may lead to oxygen desaturation and arousal with sleep fragmentation. This clinically manifests with loud snoring, witnessed apnea, choking, and excessive daytime sleepiness. The conventional wisdom in SDB is that, it is because of anatomical problems such as a small upper way airway (oropharynx) in mostly obese, male subjectsin the presence ofaggravating factors such as smoking, alcohol, and sedatives. Splinting the airway with continuous positive airway pressure (CPAP)/bilevel positive airway pressuretherapyalmost always succeed when the patient is compliant(although the compliance can be as low as 30%).The conventional wisdom is also that CPAP may be difficult and uncomfortable to use in many patients (although different interfaces are available now). The patients CPAP educational support system is not just enough, and perhaps, all these might be the reasons for CPAP failure in diagnosed OSA.

The central sleep apnea (CSA) is another less common form of SDB, which is diagnosed in about 5% of those who undergo a sleep disorder study. The sensitive chemo regulatory center in the brain stem,the medulla, controls breathing to maintain partial pressure of oxygen (PO_2) and partial pressure of carbon dioxide (PCO_2) within normal limits. PCO_2 changes are more dangerous and important than PO_2 changes. PCO_2 is the most important determinant of blood pH and should be within limits. The CSA may primarily be related to the dysfunction of medullary,chemo regulatory, and respiratory centers, resulting in central apnea/periodic breathing. While obstructive events in OSA respond well to CPAP therapy, the response of central events is often incomplete, not sustained overtime and may be a cause of CPAP failure[3–5]. CPAP treatment of obstructive events

Address for correspondence
Dhrubajyoti Roy
Consultant Pulmonologist and Director, PULSAR
264C, Rashbehari Avenue
Kolkata, West Bengal700019, India

in OSA itself can lead to the development of new CSA and Cheyne–Stokesrespiration (CSR) pattern in a subset of patients with OSA. This syndrome of obstructive events occurring mainlyduring non-rapid eye movement (NREM) sleep, with an incomplete response to positive airway pressure(PAP) has been labeled as complex sleep apnea.[6–8].

In a clinical review of patients evaluated over 1 month for suspected SDB, 15% (34/223) presentedcomplex sleep apnea syndrome (CompSAS), compared with 84% and 0.4% patients being diagnosed with OSA and CSA, respectively[9]. So, there is a need for a diagnostic category ofpatients with treatment emergent central apneas—especially wherecentral apnea does not correct with continuous CPAP use.

Definition

The CompSAS is a form of central apnea, which is specifically identified by the persistence or emergence of central apneas/hypopneas upon exposure to CPAP when obstructive events have disappeared with PAP therapy. The central events must comprise more than half of the residual SDB events, and Central Apnea Index (CAI) must be >5 events/hr. In the current definition, CompSAS would include only patients whose central apnea could not be attributed elsewhere in the CSA disorders spectrum (i.e., idiopathic, narcotic induced, and Cheyne–Stokes breathing from systolic heart failure).

Complex sleep apnea has been termed in different ways also such as CPAP-related periodic breathing[10], complex disturbed breathing during sleep[11], CPAP-related CSA[12], and CSA during CPAP[8].

Pathophysiology

During normal eupneic breathing, the medullary respiratory center sends rhythmic stimulus to the muscles of respiration from normal oscillation of PCO_2, which oscillates around the ventilatory threshold. If ventilation increases (hyperpnea and hyperventilation) owing to the disturbance of ventilatory controller input (hypercapnia/hypoxemia) arising out of apnea/arousal, the PCO_2 falls and, if drops below the apneic threshold, apnea ensues and the periodic cycle of apnea–hyperpnea goes on (high loop gain state)(Fig. 1).

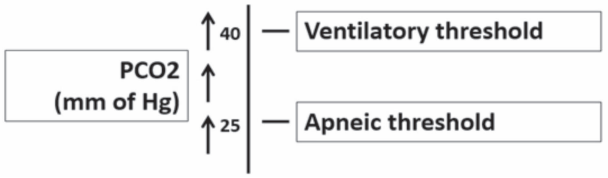

Figure 1: PCO_2 and its effect on ventilatory and apneic threshold (Ventilatory threshold, the PCO_2 level at which ventilation starts; apneic threshold, the PCO_2 level at which ventilation stops)

CompSAS may be a high loop gain state. Loop gain is the ratio of the corrective response and the disturbance:Loop gain= Corrective response (ventilation)/Disturbance (apnea)

If loop gain > 1,that is, if ventilation becomes disproportionately high following apnea, the disproportionate hyperventilation may induce CO_2 level to come below the apneic threshold inducing apnea again. Repeated such cycles of apnea–hyperventilation–apnea with sleep instability and or arousal may lead to self-

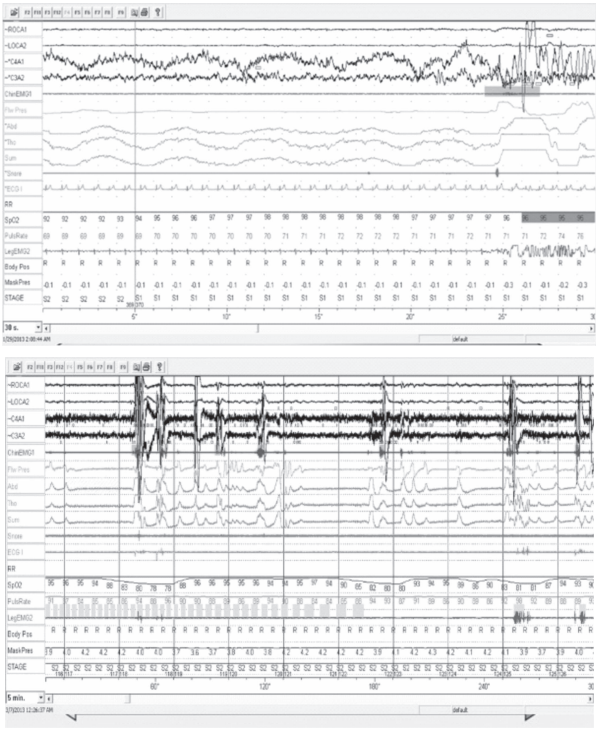

Figure 2: (A) Overnight diagnostic PSG showing OSA event (30-sec epoch). (B) Same patient with OSA showing events of CSA on CPAP titration (5-min epoch)

sustained oscillation in breathing and poor sleep quality (Fig. 2A andB).

The anatomic and physiologic vulnerabilities for upper airway obstruction or collapse, characteristic of OSA, are always present in CompSAS. The key factors in the pathogenesis ofCompSAS are thought to include the interaction of upper airway obstruction and unstable central ventilatory control factors as mentioned earlierand host conditions and characteristics mentioned later[11,12]. Whileawake, breathing is controlled by the combined behavioral and metabolic factors, in addition to the central and peripheral chemoreceptors (medulla and carotid bodies). During sleep, the absence of behavioral control of ventilation and blunted response to changes in PCO_2,in addition to changes in lung volume and minute ventilation, lead to more variability in PCO_2 levels. In the setting of repetitive upper airway obstruction in OSA, the variability to PCO_2 is even more marked and may lead to a state of loop gain. So, in a subset of OSA patient with high loop gain state, the application of positive airway pressure can produce a ventilatory instability and periodic breathing[13–16]. CompSAS can develop a delay in controller response by medullary respiratory center more during REM, and hence, such breathing abnormalities are found more in NREM than REM and more in lateral than supine position because of more vulnerability of upper airway obstruction in supine state in REM.

Pressure toxicity from CPAP causing Comp SAS (Figure 3) is because of the following factors:

1. Increased ventilation, thereby lowering PCO_2 below apneic threshold precipitating central apnea.
2. Hering–Breuer reflex: lung stretch receptors inhibiting medullary respiratory center.

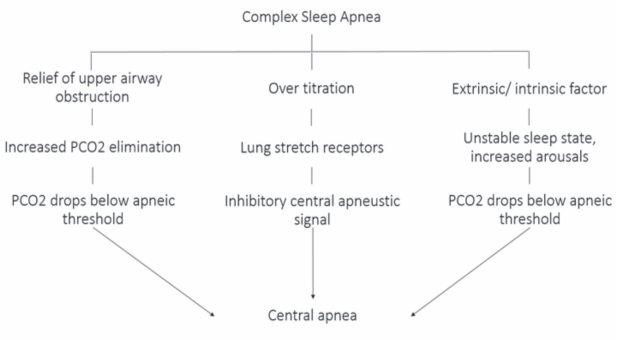

Figure 3: Pathophysiology of complex sleep apnea

3. Poorer tolerance of higher CPAP with sleep fragmentation, arousal.

Clinical characteristics and PSG

None of the clinical markers are absolutely predictive of CompSAS. Only when CPAP therapy is applied, one can identify the condition. A study shows that CompSAS is more common in men thanOSA (81% vs. 60%)[17]. In another study, there was a significant difference in CPAP use anddyspnea in patients with comp SAS when compared with those with OSAS. The same study shows that the treated CompSAS patient reported more CPAP removal during sleep and dyspnea or air hunger at followup.[7] TheCompSAS patient reported more CPAP removal during sleep and dyspnea or air hunger at follow-up[7]. Inadequate clinical response to PAP, persistent hypersomnia, high Apnea–Hypopnea Index (AHI) on PAP compliance track device may be the indicators of the development of CompSAS. In a study by Cassel et al.[15], 2011, de novo appearance of CompSAS in CPAP-treated patients with OSA was observed in 4% patients who did not show CompSAS initially. The severity of sleep apnea present on an 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 to 3 months into ongoing CPAP therapy[18].When compared with those with simple OSAS, patients with CompSAS showed a higher events/hr in NREM than in REM sleep and a higher arousal indexon subsequent CPAP titration study[9]. Sleep laboratories should have a protocol of PAP titration if CompSAS is detected (up titration of CPAP, addition of O_2 to CPAP, bilevel in spontaneous timed mode, and adaptive servoventilation).

Second half of night titrationmay falsely lower the prevalence of CompSAS because of REM protective effect of central apnea. So, the following characteristics help to identify the at-risk individuals: male patients, severe OSA, persistent symptoms with CPAP treatment, noncompliant to CPAP therapy owing to mask problem,anda high arousal index during titration.

Treatment

Treatment of CompSAS is an area of intense debate. The issues of debate are as follows:

1. The disappearance of CompSAS with time with CPAP therapy is observed in a subset of patients,so the high cost of a newer PAP device needs to be considered as the initial mode of therapy.
2. To tailor the therapy to the precise pathophysiology present in a given patient, rather than one size fits for all therapy.
3. All CompSAS have OSAS basically,so the treatment has to overcome nocturnal airway obstruction first and foremost by PAP.
4. Until now, there is no reliable predictor of CompSAS with time; more so, it can develop afterward also.

PAP therapy

The basic goal of treatment includes targeting CPAP at the lowest possible pressure that resolves the most obstructive events and avoiding the potential for developing overventilation or hypocapnia that destabilizes the airway or sleep state. In a retrospective review of 1,286 patients receiving PAP therapy, 6.5% of patients developed CompSAS during the initial study; 78.6% of those (*n*=42) who showed CompSAS in the initial study completely resolved the central apnea component after an interval of CPAP therapy for 3 months[18]. In another retrospective study, the central apneas developed de novo in 4% of OSA patients during follow-up for CPAP therapy[15].

Diagnosing CompSAS will become more challenging in limited home-based sleep studies followed by auto-titrating PAP therapy. The clinician's awareness to the condition of limited ability or inability of auto-titrating PAP device to warn for emergent central apnea is highly needed. Poor response or inability to tolerate auto-titrating PAP therapy, persistent hypersomnia, high AHI on PAP compliance track device, more mask problems, or air hunger should raise the suspicion of possibility of CompSAS. This needs for an observed titration testing to confirm CompSAS.

Bilevel ST mode and adaptive servoventilation (ASV) are the devices needed for patients with CPAP failure in CompSAS. They act by breaking the cycle of central apneas leading to arousals and instability in ventilation[8,9] Bilevel STmode splintscollapsing upper airways resolving the obstructive events and, at the same time, stabilizes ventilation during central apneas by forcing breath (timed breath). Introduced in late 1990s, ASV is a bilevel PAP capable of measuring the respiratory output of the patient (tidal breathing, flow and/or minute ventilation). It responds to respiratory output, breath by breath, with a variable amount of pressure support [inspiratory positive airway pressure (IPAP) minus expiratory positive airway pressure (EPAP)]. The response to hypoventilation is by increasing the pressure support while the response to hyperventilation by decreasing the pressure support. The response to central apnea is measured by providing a timed breath. ASV is effective in resolving not only CompSAS but also CSA and CSR.

Drug therapy

The evidence of drug therapy to treat central apneas in CompSAS is highly limited. It includes theophylline, acetazolamide that may improve periodic breathing, or others that increase the NREM sleep that exhibits stable characteristics[8,19].

Other experimental therapy

Experimentally successful treatment of CompSAS with PAP therapy plus controlling inhalation gas blended with 0.5%–1% CO_2 (to resolve central apnea) resulted in an immediate (1 min) decrease in AHI to <5/hr, without complaints of dyspnea, palpitation, or headache[20]. Increasing dead space ventilation or expiratory rebreathing space in PAP therapy may be effective in the treatment of CompSAS. Reports, however, are available for a limited number of patients and for limited duration of therapy, limiting the generalizability and sustainability of this therapy[21,22].

Conclusion

It is clear that CompSAS often has a significant residual SDB even after airway obstruction is relieved (by PAP, oral appliances, or surgery). It is also clear that most patients adapt to these therapies with the resolution of central apneas and hypopneas. Learning to anticipate the responders, the time to response (with regard to long-term treatment adherence), and resolving the importance of control of asymptomatic residual SDB remain as the topics for future research. In the meantime, there appear to be two dominant treatment strategies. One approach is to begin the therapy with CPAP sufficient to eliminate obstructive events and provide follow-up to identify those patients who do not resolve residual central apneas and

periodic breathing. On the basis of current available data, this probably is sufficient for most patients. However, for other patients, the risk of this approach is that they willhave an ineffective and annoying initial experience with PAP. Solution to this potential problem would involve development of improved strategies to delineate the responders from the non-responders. The other approach is to identify those patients with more severe residual SDB at the time of initial management decisions and offer them a successful treatment modality, such as ASV from the outset. The strategy that provides the highest value [(safety +service +outcomes)/cost over time] requires a prospective comparative effective trial.

References

1. **Young T**, Palta M, Dempsey J, Skatrud J,Weber S, Badr S.The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328(17):1230–1235.
2. **Shahar E**,**Whitney CW**,**Redline S**,Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J RespirCrit Care Med* 2001;163(1):19–25.
3. **Naughton MT**.Impact of obstructive sleep apnoea on diabetes and cardiovascular disease. *Thorax* 1998;53:535–540.
4. **Naughton MT**.Pathophysiology and treatment of Cheyne-Stokes respiration. *Thorax* 1998;53:514–518.
5. **Philippe C**, Stoica-Herman M, Drouot X, Raffestin B, Escourrou P, Hittinger L, et al. Compliance with and efficacy of adaptive servo-ventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart* 2006;92:337–342.
6. **Thomas RJ**,**Terzano MG**,**Parrino L**,**Weiss JW**. Obstructive sleep-disordered breathing with a dominant cyclic alternating pattern—a recognizable polysomnographic variant with practical clinical implications. *Sleep* 2004;27(2):229–234.
7. **Pusalavidyasagar SS**, Olson EJ, Gay PC, Morgenthaler TI. Treatment of complexsleepapnea syndrome: a retrospective comparative review.*Sleep Med* 2006;7:474–479.
8. **Gilmartin GS**, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. *CurrOpinPulm Med2005;*11(6):485–493.
9. **Morgenthaler TI**, Kagramanov V, Hanak V,Decker PA. Complex*sleep*apnea syndrome: is it a unique clinical syndrome?*Sleep2006;29*(9):*1203–1209*.
10. **Marrone O**, Stallone A,Salvaggio A,Milone F,Bellia V,Bonsignore G.Occurrence of breathing disorders during CPAP administration in obstructive sleep apnoea syndrome.*EurRespir J 1991;4(6):660–666*.
11. **Marrone O.**Complex sleep apnea and obesity hypoventilation syndrome. Opposite ends of the spectrum of obstructive sleep apnea? *Med Hypotheses*2009;73(4):488-492**.**
12. **Salloum A**, Jaso Mateika H, Chowdhuri S,Omran Q, Safwan B. Increased propensity for central apnea in patients with obstructive sleep apnea-effect of nasal continuous positive airway pressure. *Am J RespirCrit Care Med*2010;181(2):189–193.
13. **Gay P**.Complex sleep apnea: it really is a disease. *J Clin Sleep Med*2008;4(5):403–405.
14. **Malhotra A**,Bertisch S,Wellman A. Complex sleep apnea: it isn't really a disease. *J ClinSleep Med*2008;4(5):406–408.
15. **Cassel W**, Canisius S, Becker HF,Leistner S, Ploch T, Jerrentrup A, et al. A prospective polysomnographic study on the evolution of complex sleep apnoea. *EurRespir J*2011;38(2):329–337.
16. **Nakazaki C**, Noda A, YasudaY,Nakata S, Koike Y, Yasuma F, et al.Continuous positive airway pressure intolerance associated with elevated nasal resistance is possible mechanism of complex sleep apnea syndrome. *Sleep Breath*2012;16(3):747–752.
17. **Lehman S**, Nick A, Thompson C, Peter G,Mercer J,Doug McEvoy R. Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. *J Clin Sleep Med*2007;3(5):462–466.
18. **Javaheri S**, Smith J, Chung E.The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med*2009;5(3):205–211.
19. **Khan A**, Gay P**.** Complex sleep apnea. Sleep Disorders Volume 2014 (2014), Article ID 798487
20. **Thomas RJ**,Daly RW,Weiss JW.Low-concentration carbon dioxide is an effective adjunct to positive airway pressure in the treatment of refractory mixed central and obstructive sleep-disordered breathing. *Sleep*2005;28(1):69–77.
21. **Thomas RJ.** Effect of added dead space to positive airway pressure for treatment of complex sleep-disordered breathing. *Sleep Med*2005;6(2):177–178.
22. **Gilmartin G,** McGeehan B, Vigneault K,Daly RW, Manento M, Weiss JW, et al.Treatment of positive airway pressure treatment-associated respiratory instability with enhanced expiratory rebreathing space (EERS). *JClin Sleep Med*2010;6(6):529–538.