





Complex sleep apnoea syndrome

Summary

Complex sleep apnoea syndrome (CompSAS) is a type of central apnoea characterised by the development or persistence of central apnoeas or hypopnoeas during application of continuous positive airway pressure (CPAP; central apnoea index ≥ 5 events·h⁻¹). These patients present with predominantly obstructive apnoeas during diagnostic sleep studies. No clinical characteristics have been identified which can distinguish them from patients with a normal response during CPAP titration. Probably, this pattern is provoked by the application of high CPAP pressures in obstructive sleep apnoea syndrome patients with enhanced chemoreceptor sensitivity, or in patients with pronounced sleep fragmentation. Negative feedback is sent to the respiratory centre, *via* the Hering-Breuer reflex, which can lead to central apnoea. However, these explanations remain hypothetical at present. In a broader perspective, any occurrence of significant central apnoea activity during attempts to restore airway patency could be classified as CompSAS. Treatment modalities consist of prevention on the one hand (avoidance of high pressures and permissive flow limitation), and advanced ventilation techniques (adaptive servo ventilation) on the other hand.

Statement of Interest
None declared.

Introduction

Snoring and obstructive sleep apnoea syndrome (OSAS) are the most common manifestations within a group of disorders described as “sleep disordered breathing”

[1, 2]. To a lesser extent, central sleep apnoea syndrome (CSAS) can also be present, characterised by a decreased central respiratory drive during sleep, resulting in decreased or absent ventilation and disturbed gas exchange [3]. In OSAS, repetitive collapse of the upper airway takes place, which will finally

 ERS 2013

HERMES syllabus link
module: B.19

lead to O₂ desaturation and arousal. Continuous positive pressure ventilation (CPAP) is the standard therapy to keep the airway open. The optimal pressure is determined during a supervised CPAP pressure titration night with polysomnographic monitoring in a sleep centre [4]. In most OSAS patients, CPAP will improve nocturnal breathing pattern. However, a small group of OSAS patients develop central apnoeas during CPAP titration. This category of sleep disordered breathing is currently defined as complex sleep apnoea syndrome (CompSAS) [5].

Definition

CompSAS can be defined as a sleep apnoea syndrome that initially is diagnosed as OSAS, but is characterised by the frequent occurrence of central apnoeas during CPAP therapy, after elimination of obstructive events (fig. 1) [5, 6]. In the literature, CompSAS has been described as CPAP-related periodic breathing [7], complex disturbed breathing during sleep [8], CPAP-related CSA [9], CSA during CPAP: “CPAP-emergent CSA”, *i.e.* was not present on diagnostic polysomnography (PSG); CPAP-persistent CSA (*i.e.* was also present on diagnostic PSG); “CPAP-induced CSA” [6]; refractory sleep apnoea [10]; and residual sleep

apnoea [11]. However, the term “CPAP-resistant CSA” is used in those with pre-existent CSA [12].

Pathogenesis

The pathogenesis of CompSAS is not known and rarely studied, but in general, it is assumed that the presence of upper airway collapse, combined with a heavily disturbed ventilatory control is causative [13, 14].

The first hypothesis claims that an altered CO₂ excretion takes place when upper airway obstruction is released by CPAP. The permanent open upper airway results in an improved gas exchange, which will lead to a decrease in arterial carbon dioxide partial pressure (PaCO₂). When this value drops below the apnoeic threshold, a central apnoea will develop [15, 16].

A second hypothesis is that over-titration with CPAP will lead to the development of central apnoeas [9, 17]. How this process exactly takes place is not well understood, but a potentially important factor could be the activation of stretch receptors in the lungs. When these receptors are activated due to an excessive expansion of the lungs, they send signals to the breathing centre along the vagal nerve, which inhibits the central motor output. Hence, this will result in an interruption of

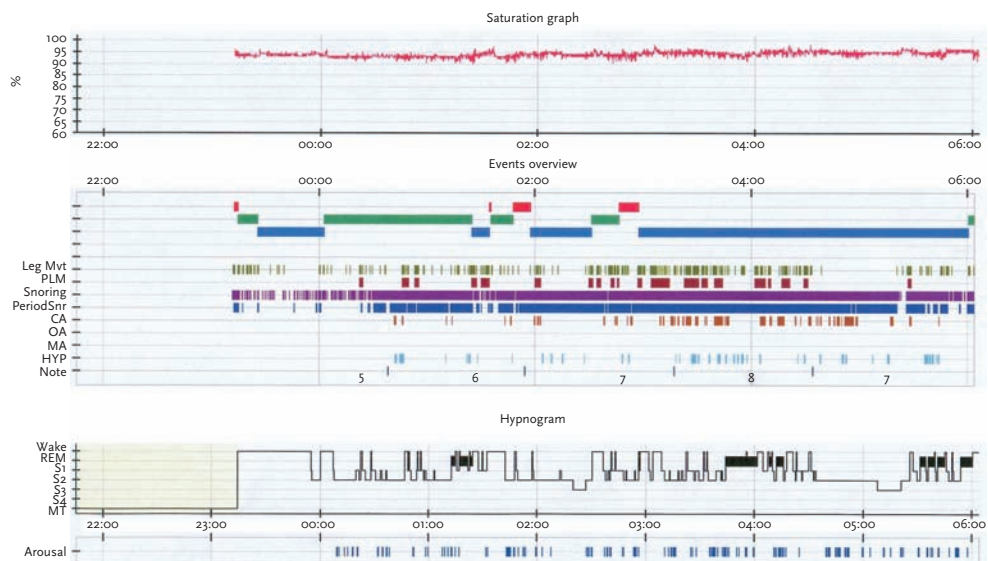


Figure 1

Overview of a CPAP titration night in an OSAS patient that develops central apnoeas. From top to bottom: oxygen saturation, sleep position, heart frequency, leg movement (Leg Mvt; PLM: periodic leg movement), snoring intensity, apnoeas (CA: central apnoea; OA: obstructive apnoea; MA: mixed apnoea), hypopnoeas (HYP), hypnogram.

inspiration. This mechanism protects the lungs against overexpansion, and is called the Hering–Breuer reflex.

A final hypothesis is based on the fact that CPAP will worsen sleep quality in some patients [16, 18, 19]. The frequent changes from sleep to wake and from wake to sleep lead to instability in the ventilatory control system. This leads to oscillations in the PaCO_2 values that can lead to a decrease in PaCO_2 below the apnoeic threshold, with inherent central apnoeas as a consequence. It remains unclear to what extent sleep impairment is the cause or the effect of CompSAS [20]. It was suggested that an elevated nasal resistance might relate to frequent arousals, which could presumably contribute to an increase in central apnoeas [21]. This argues for a causal relationship.

A counter-argument could be that sleep in OSAS is already fragmented, even before CPAP is initiated, but that CPAP probably leads to an increase in the hypoxia-induced hyperventilation, through a decrease in pharyngeal resistance and an increase in ventilatory response on arousals. However, there are indications that sleep fragmentation in untreated CompSAS is more pronounced than in conventional OSAS [6]. This finding favours a predetermined as opposed to an iatrogenic cause for the development of CompSAS. Although the exact mechanism of CompSAS is unknown, probably several mechanisms operate together to produce the CompSAS phenotype. This multitude of factors contributing to CompSAS is the probable reason for variable behaviour of CompSAS patients during acute testing and longitudinal therapy with CPAP in different patient populations [22]. The use of bilevel continuous airway pressure (BiPAP) can also lead to CompSAS [23]. BiPAP can be used as an alternative for CPAP, in case of CPAP intolerance, or when CompSAS is observed during a CPAP titration night. The inspiratory positive pressure can lead to increased tidal volumes, which leads to a decrease in PaCO_2 . As mentioned earlier, central apnoeas will develop when PaCO_2 is rendered below the apnoeic threshold.

Prevalence

In recent years, different studies have reported the prevalence of CompSAS to be between 0.56 and 18%. High prevalences were reported

by an Italian [7] and two US studies [5, 24] in which 15% and 18% of the patients developed central apnoeas. The highest prevalence (18%) was reported in series of patients with chronic heart failure and OSAS [24]. The lowest prevalence (0.56%) was reported in a German study measuring brain natriuretic peptide (BNP) as an additional marker for the exclusion of possible confounding Cheyne–Stokes respiration cases [25].

An Australasian study [6] reported 13.1%, while two Japanese studies reported a prevalence of 5% [18, 19]. In a Belgian study, CompSAS was found in only nine (2.9%) out of 349 CPAP titration nights for OSAS [26]. A US study reported CompSAS in 6.5% of their patients in an extensive series of 1286 CPAP titrations [12], while a German study reported a prevalence of 12.4% during titration, and 6.9% during follow-up (3.2% in those with initial CompSAS and 3.7% *de novo* CompSAS) [20]. Differences in prevalence data are attributed to fast CPAP titration (that may lead to higher pressures and induce central apnoeas), supine position [27], sleep duration, use of split-night designs [5], intake of opioid medication [5], ethnic differences [28] and presence of predisposing factors for chronic heart failure [5]. The exclusion of these factors is especially important for patients with a history of coronary heart disease, hypertension, and/or atrial fibrillation [29]. It must also be emphasised that airway obstruction, especially in the supine position, can mimic central apnoea [30], while the high prevalence of supine dependency of CompSAS by THOMAS *et al.* [27] was intended, as patients were examined predominantly in the supine position [27]. Overall, the prevalence of CompSAS in clinical settings remains somewhat hazy, while the multitude of pathways leading to CompSAS results in a dynamic phenotype, with the improvement or disappearance of CompSAS activity in some patients, and *de novo* appearance in others.

Diagnostics

CompSAS is diagnosed based on PSG. The first condition is the presence of OSAS, based on a minimal apnoea–hypopnoea index (AHI) of 5 events per hour of sleep with a majority of obstructive events. If during CPAP titration, a reduction is obtained of the number of obstructive events to <5 events per hour of

sleep, while the central apnoea index (CAI) is ≥ 5 events per hour sleep, the diagnosis of CompSAS can be established [6, 31]. Research has indicated that CompSAS can be distinguished from OSAS by means of an automated electrocardiography-based method during a diagnostic sleep study. This application is however not yet available in the routine setting [32].

Clinical presentation

Most studies show that more than 80% of CompSAS patients are male. An explanation could be that males have a higher hypercapnic ventilatory response, and are therefore more predestinated to develop CompSAS. Not all studies came to the same conclusion [19]. In general, patients with OSAS or CompSAS do not show statistically significant differences in age, level of sleepiness (based on Epworth scale) [5, 9, 11, 31], lung function parameters (*i.e.* forced expiratory volume in 1 s) [9] or arterial blood gases. One of the characteristics of OSAS patients is an elevated body mass index (BMI), which is also observed in CompSAS [5, 6, 9, 18], although some authors have found a somewhat lower BMI [31]. One study reported a BMI higher than in conventional OSAS patients [19]. Different studies also reported the severity of OSA as one of the risk factors for long-term CPAP-persistent central apnoeas [12, 33].

Given the frequent association of central apnoea and chronic heart failure (CHF) [3], the prevalence of CHF and ischaemic heart disease (IHD) has also been studied in CompSAS. However, no consistent findings were reported [6, 9, 19, 31]. Recently, it was reported that only one-third of patients with CompSAS had any risk factor of CompSAS (arterial hypertension, coronary artery disease, CHF) prior to sleep testing [28]. Last but not least, elevated nasal resistance was also associated with CompSAS [21].

Polysomnographic characteristics *a priori*

Based on the diagnostic PSG to establish OSAS, it is not possible to predict whether someone will present with CompSAS. Some evidence has been reported that CompSAS patients might have a higher CAI at diagnosis

than OSAS patients (CAI > 5 events per hour in 46% of CompSAS compared with 8% of OSAS), but this could not be confirmed by others [5, 6, 31]. One study reported a significantly higher CAI in non-rapid eye movement (NREM) sleep and in supine position, but the differences were small and not clinically relevant [19]. During CPAP titration, CompSAS patients present central apnoeas most often during NREM sleep, and certainly much fewer or no apnoeas during REM sleep [9, 34]. A higher arousal index was reported in CompSAS in one study [6], but was not confirmed in other studies [12, 19].

Use of BNP

There are arguments for choosing BNP levels as a criterion for detection or exclusion of heart failure in patients with CompSAS [25]. Concomitant heart failure may trigger susceptibility to central apnoeas (so-called Cheyne–Stokes respiration), and may influence prevalence data. Moreover, the occurrence of Cheyne–Stokes respiration is not dependent on reduced systolic left ventricular function. Cheyne–Stokes respiration can also be seen in patients with diastolic heart failure or only mildly reduced systolic left ventricular function. Therefore, an ejection fraction cut-off of 40% is not sensitive enough to select patients with chronic heart failure and Cheyne–Stokes respiration [29, 35]. Finally, identification of CHF can allow for better tailoring of therapy to pathophysiology involved in an individual patient. Patients with elevated BNP ($> 100 \text{ pg} \cdot \text{mL}^{-1}$) can then be excluded. However, it has to be borne in mind that BNP can also be influenced by other diseases (renal failure, liver cirrhosis), medication or obesity.

Treatment of CompSAS

Prevention

Rather than starting specific treatments, it is useful to consider whether high CPAP pressures are applied (pressure toxicity), provoking CompSAS.

Patients with CompSAS most often respond well to positive airway pressure, but the obstruction cannot always be eliminated without aggravating periodic breathing or provoking

central apnoeas. A possible preventive measure is the so-called permissive flow limitation [8]. The pressure is set on a level that keeps a mild degree of airway obstruction, without disturbing ventilatory control mechanisms. When O_2 desaturations occur with central apnoeas during CPAP application, combined oxygen administration can be considered. Patients report that this helps to improve sleep quality, although this is probably a placebo effect [8]. However, O_2 administration will lead to a decrease of the hypoxic ventilatory response, which stabilises breathing, and CompSAS will disappear [36]. Finally, drugs that induce breathing instability, like methadone and baclofen, have to be avoided [8].

Pharmacotherapy

When prevention is not sufficient, pharmacotherapy can be considered. Theophylline and acetazolamide can contribute to an improvement in periodic breathing. However, these drugs are not used as a single therapy, due to their limited effect and eventual side-effects [37]. Stabilisation of NREM sleep can also be useful by means of adequate sleep hygiene, regular sleep–wake times, and by use of traditional sleeping pills (benzodiazepines) and sleep stabilising antidepressants (trazolan, mianserin) [8].

Expected evolution when CPAP therapy is maintained

A few studies have shown that in the majority of patients with CompSAS, central apnoeas disappear (almost) completely during follow-up PSG [9], with improvement in sleep efficiency, a decrease in wake after sleep onset, and a lower number of arousals in comparison with the baseline diagnostic night. However, a number of studies reported a minor effect of CPAP on sleep and breathing variables [38]. Therefore, CPAP seems effective in some patients, while ineffective in others. CompSAS also seems to develop *de novo* in 4% of OSAS patients during follow up for CPAP therapy [20]. Very few data are available regarding CPAP compliance and clinical improvement. In one study, CompSAS patients demonstrated more dyspnoea, poor CPAP adherence and more often spontaneous removal of the mask [31]. Another study

reported an inferior effect of CPAP on sleep as well as breathing parameters [39].

BiPAP in the spontaneous-timed mode and adaptive servoventilation

An effective treatment of CompSAS is possible with supporting ventilation during central apnoeas and avoidance of P_{aCO_2} oscillations. This can be realised with the help of BiPAP in the spontaneous-timed (ST) mode or by means of adaptive servoventilation (ASV) [8, 39, 40]. BPAP–ST is a type of noninvasive ventilation that offers a pneumatic splint effect in the airways, supporting ventilation and initiating breathing during episodes of apnoeas. The expiratory positive airway pressure (EPAP) is set to eliminate apnoeas, while the inspiratory positive airway pressure (IPAP) and back-up ventilation frequency (ST mode) are set in order to decrease hypoventilation and prevent overcompensation that leads to hypocapnia and hyperventilation [36].

With ASV, the end expiratory pressure is determined during PSG by evaluating the pressure needed to eliminate obstructive apnoeas. The ASV device automatically determines the extent of the ventilatory support during inspiration (within a set pressure range) based on continuous analysis of the breathing pattern during inspiration [35, 41]. Recently, advanced ASV machines have been developed that include an automatic expiratory pressure adjustment, an advanced algorithm for distinguishing open *versus* obstructed airway apnoea, a modified auto backup rate which is proportional to subject's baseline breathing rate, and a variable inspiratory support [42].

Some trials have evaluated the efficiency of ASV *versus* other treatments in CompSAS. ASV gave a superior decrease of AHI and CAI *versus* CPAP or BiPAP–ST [43, 44]. Moreover, a better sleep quality and symptomatic improvement was reported by 72% during follow-up, as well as a global excellent tolerance for ASV. In a study comparing ASV with BiPAP–ST, both ventilatory modalities resulted in a decrease of the AHI and respiratory arousal index, but only ASV was able to reduce these parameters to almost zero [39]. AHI could be normalised with ASV (<5 events·h⁻¹) in the majority of CompSAS patients. RANDEATH *et al.* [45] evaluated the effect of ASV in

patients with obstructive as well as central apnoeas. The total AHI decreased from 46.8 to 7.8, the central AHI from 25.7 to 7.1 and the obstructive AHI from 14.2 to 0.7. Also sleep quality was significantly better after treatment with ASV. Based on these results, it can be concluded that positive airway pressure, and predominantly ASV, is very effective in CompSAS.

CO₂ administration

A last treatment modality for CompSAS is the combined approach of CPAP or BiPAP with 0.5–1% CO₂, resulting in an immediate (<1 min) decrease of AHI to <5 events·h⁻¹, without complaints of dyspnoea, palpitations or headache [35, 46]. Administration of low concentrations of CO₂ during CPAP or BiPAP therapy therefore seems extremely effective in CompSAS, since administration of CO₂ keeps the prevailing PaCO₂ above the apnoeic threshold. Moreover, increased fractional concentration of inspired CO₂ has an airway resistance-lowering effect in sleeping subjects with high airway resistance, which may minimise the level of CPAP pressure required to ensure airway patency in OSA patients, presumably because of chemoreceptor activation of motor neurons serving both upper airway and pump muscles [47, 48].

Safety concerns of gas application have to be addressed before the application of CO₂ can be considered for clinical use, while increase in sympathetic activity has been observed. Enlargement of dead space or enhanced expiratory rebreathing space in positive airway pressure therapy has been shown to be effective as well in the treatment of CompSAS [49, 50, 51]. A small volume of CO₂ is trapped and inhaled, resulting in a transient increase in inspired CO₂ that ultimately reaches the peripheral and central chemoreceptors.

CPAP-independent CompSAS

Recently, there have been arguments to label this form of sleep disordered breathing as CompSAS in the absence of a CPAP trial, since emerging central apnoeas were also reported after initiation of oral appliance [52], tracheostomy [53], maxillofacial surgery [54] and after surgical relief of nasal obstruction [55].

CPAP-independent factors, such as sleep fragmentation induced by (any) therapy, reduction of PaCO₂ and CPAP-independent tendency towards periodic breathing could also be involved in producing the CompSAS phenotype. Consistent with the evolution reported during CPAP therapy in two tracheotomy studies in which OSA patients underwent serial PSGs, it was shown that OSA patients who underwent therapeutic tracheotomy initially had central apnoeas, which decreased later on a repeat PSG [56, 57]. Anyway, obstructive cycles are replaced by central ones with similarly disrupted sleep and poor therapy compliance and clinical outcomes are not surprising.

Conclusion

CompSAS is a disorder in patients with OSAS, who develop central apnoeas during CPAP titration. The pathogenesis is probably based on disturbed ventilatory control. The prevalence of CompSAS varies between 2.6% and 15% and the patients are most often male. There are indications that CompSAS patients have more sleep fragmentation during the diagnostic sleep study, have a higher prevalence of congestive heart failure and/or ischaemic heart disease, but the literature is not conclusive. CompSAS is probably a transient problem, which disappears spontaneously during chronic CPAP therapy. Best treatment results are obtained with ASV.

References

1. Young T, Palta M, Dempsey J, *et al.* The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993; 328: 1230–1235.
2. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22: 667–689.
3. Verbraecken J, De Backer W. Upper airway mechanics. *Respiration* 2009; 78: 121–133.
4. Kushida CA, Littner MR, Hirshkowitz M, *et al.* Practice parameters for the use of continuous and

- bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006; 29: 375–380.
5. Morgenthaler TI, Kagramanov V, Hanak V, *et al.* Complex sleep apnea syndrome: is it a unique clinical syndrome? *Sleep* 2006; 29: 1203–1209.
 6. Lehman S, Antic N, Thompson C, *et al.* 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: 462–466.
 7. Marrone O, Stallone A, Salvaggio A, *et al.* Occurrence of breathing disorders during CPAP administration in obstructive sleep apnea syndrome. *Eur Respir J* 1991; 4: 660–666.
 8. Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. *Curr Opin Pulm Med* 2005; 11: 485–493.
 9. 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.
 10. Badr MS, Grossman JE, Weber SA. Treatment of refractory sleep apnea with supplemental carbon dioxide. *Am J Respir Crit Care Med* 1994; 150: 561–564.
 11. Mulgrew AT, Lawati NA, Ayas NT, *et al.* Residual sleep apnea on polysomnography after 3 months of CPAP therapy: clinical implications, predictors and patterns. *Sleep Med* 2010; 11: 119–125.
 12. Javaheri S, Smith S, Chung E. The prevalence and natural history of complex sleep apnea. *J Clin Sleep Med* 2009; 5: 205–211.
 13. Marrone O. Complex sleep apnea and obesity hypoventilation syndrome. Opposite ends of the spectrum of obstructive sleep apnea? *Med Hypotheses* 2009; 73: 488–492.
 14. Salloom A, Rowley JA, Mateika JH, *et al.* Increased propensity for central apnea in patients with obstructive sleep apnea. Effect of nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2010; 181: 189–193.
 15. Gay P. Complex sleep apnea: it really is a disease. *J Clin Sleep Med* 2008; 4: 403–405.
 16. Malhotra A, Bertisch S, Wellman A. Complex sleep apnea: it isn't really a disease. *J Clin Sleep Med* 2008; 4: 406–408.
 17. Brown LK, Casey KR. Complex sleep apnea: the hedgehog and the fox. *Curr Opin Pulm Med* 2007; 13: 473–478.
 18. Endo Y, Suzuki M, Inoue Y, *et al.* Prevalence of complex sleep apnea among Japanese patients with sleep apnea syndrome. *Tohoku J Exp Med* 2008; 215: 349–354.
 19. Yaegashi H, Fujimoto K, Abe H, *et al.* Characteristics of Japanese patients with complex sleep apnea syndrome: a retrospective comparison with obstructive sleep apnea syndrome. *Intern Med* 2009; 48: 427–432.
 20. Cassel W, Canisius S, Becker HF, *et al.* A prospective polysomnographic study on the evolution of complex sleep apnoea. *Eur Respir J* 2011; 38: 329–337.
 21. Nakazaki C, Noda A, Yasuda Y, *et al.* Continuous positive airway pressure intolerance associated with elevated nasal resistance is possible mechanism of complex sleep apnea syndrome. *Sleep Breath* 2012; 16: 747–752.
 22. Kuzniar TJ, Kasibowska-Kuzniar K, Freedom T. Trials of bilevel positive airway pressure-spontaneous in patients with complex sleep apnoea. *Pneumol Allergol Pol* 2012; 80: 214–219.
 23. Johnson KG, Johnson DC. Bilevel positive airway pressure worsens central apneas during sleep. *Chest* 2005; 128: 2141–2150.
 24. Bitter T, Westerheide N, Hossain MS, *et al.* Complex sleep apnoea in congestive heart failure. *Thorax* 2011; 66: 402–407.
 25. Westhoff M, Arzt M, Litterst P. Prevalence and treatment of central sleep apnoea emerging after initiation of continuous positive airway pressure in patients with obstructive sleep apnoea without evidence of heart failure. *Sleep Breath* 2012; 16: 71–78.
 26. Verbraecken J, Schoonis L, Verplancke B, *et al.* Prevalence of complex sleep apnea (CompSAS) during manual CPAP titration for obstructive sleep apnea. *Eur Respir J* 2009; 34: Suppl. 53, 649s.
 27. 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: 229–234.
 28. Kuzniar TJ, Kasibowska-Kuzniar K, Ray DW, *et al.* Clinical heterogeneity of patients with complex sleep apnea syndrome. *Sleep Breath* 2013 [In press; DOI: 10.1007/s11325-013-0825-4].
 29. Westhoff M, Arzt M, Litterst P. Influence of adaptive servoventilation on B-type natriuretic peptide in patients with Cheyne-Stokes respiration and mild to moderate systolic and diastolic heart failure. *Pneumologie* 2010; 64: 467–473.
 30. Vanderveken OM, Oostveen E, Boudewyns AN, *et al.* Quantification of pharyngeal patency in patients with sleep-disordered breathing. *J Otorhinolaryngol Relat Spec* 2005; 67: 168–179.
 31. Pusalavidyasagar SS, Olson EJ, Gay PC, *et al.* Treatment of complex sleep apnea syndrome: a retrospective comparative review. *Sleep Med* 2006; 7: 474–479.
 32. Thomas RJ, Mietus JE, Peng CK, *et al.* Differentiating obstructive from central and complex sleep apnea using an automated electrocardiogram-based method. *Sleep* 2007; 30: 1756–1769.
 33. Javaheri S. Positive airway pressure treatment of central sleep apnea with emphasis on heart failure, opioids, and complex sleep apnea. *Sleep Med Clin* 2010; 407–417.
 34. Fietze I, Ringel D, Glos M, *et al.* Occurrence and predisposition for complex apneas during CPAP titration in OSA patients. *Eur Respir J* 2008; 32: Suppl. 52, 118s.
 35. Bitter T, Westerheide N, Faber L, *et al.* Adaptive servoventilation in diastolic heart failure and Cheyne–Stokes respiration. *Eur Respir J* 2010; 36: 385–392.
 36. Kuzniar T, Morgenthaler T. Treatment of complex sleep apnea syndrome. *Curr Treatm Options Neurol* 2008; 10: 336–341.
 37. Glidewell RN, Orr WC, Imes N. Acetazolamide as an adjunct to CPAP treatment: a case of complex sleep apnea in a patient on long-acting opioid therapy. *J Clin Sleep Med* 2009; 5: 63–64.
 38. Kuzniar T, Pusalavidyasagar S, Gay P, *et al.* Natural course of complex sleep apnea – a retrospective study. *Sleep Breath* 2008; 12: 135–139.
 39. Morgenthaler TI, Gay PC, Gordon N, *et al.* Adaptive servo-ventilation versus non-invasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. *Sleep* 2007; 30: 468–475.
 40. Brown SE, Mosko SS, Davis JA, *et al.* A retrospective case series of adaptive servoventilation for complex sleep apnea. *J Clin Sleep Med* 2011; 7: 187–195.
 41. Allam JS, Olson EJ, Gay PC, *et al.* Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. *Chest* 2007; 132: 1839–1846.
 42. Javaheri S, Goetting MG, Khayat R, *et al.* The performance of two automatic servo-ventilation devices in the treatment of central apnea. *Sleep* 2011; 34: 1693–1698.

43. Teschler H, Dohring J, Wang YM, *et al.* Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *Am J Respir Crit Care Med* 2001; 164: 614–619.
44. Becker M, Tröster N, Scheidl S, *et al.* Adaptive servoventilation for complex sleep apnea in patients with different underlying diseases. *Eur Respir J* 2008; 32: Suppl. 52, 743s.
45. Randerath WJ, Galetke W, Stieglitz S, *et al.* Adaptive servo-ventilation in patients with coexisting obstructive sleep apnoea/hypopnoea and Cheyne–Stokes respiration. *Sleep Med* 2008; 9: 823–830.
46. 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: 69–77.
47. Dempsey J, Skatrud J, Smith C. Powerful stabilizing effects of CO₂ during CPAP treatment. *Sleep* 2005; 28: 12–13.
48. Badr MS, Skatrud JB, Dempsey JA. Effect of chemoreceptor stimulation and inhibition on total pulmonary resistance in humans during NREM sleep. *J Appl Physiol* 1994; 76: 1682–1692.
49. Gilmartin G, McGeehan B, Bigneault K, *et al.* Treatment of positive airway pressure treatment associated respiratory instability with enhanced expiratory rebreathing space. *J Clin Sleep Med* 2010; 6: 529–538.
50. Rapoport D. Stabilizing ventilation in OSAHS with CPAP Emergent periodic breathing through the use of dead space. *J Clin Sleep Med* 2010; 6: 539–540.
51. Thomas RJ. Effect of added dead space to positive airway pressure for treatment of complex sleep-disordered breathing. *Sleep Med* 2005; 6: 177–178.
52. Kuzniar TJ, Kovacevic-Ristanovic R, *et al.* Complex sleep apnea unmasked by the use of a mandibular advancement device. *Sleep Breath* 2011; 15: 249–252.
53. Guilleminault C, Cumiskey J. Progressive improvement of apnea index and ventilatory response to CO₂ after tracheostomy in obstructive sleep apnea syndrome. *Am Rev Respir Dis* 1982; 126: 14–20.
54. Corcoran S, Mysliwiec V, Niven AS, *et al.* Development of central sleep apnea after maxillofacial surgery for obstructive sleep apnea. *J Clin Sleep Med* 2009; 5: 151–153.
55. Goldstein C, Kuzniar TJ. The emergence of central sleep apnea after surgical relief of nasal obstruction in obstructive sleep apnea. *J Clin Sleep Med* 2012; 8: 321–322.
56. Guilleminault C, Simmons B, Motta J, *et al.* Obstructive sleep apnea syndrome and tracheostomy. *Arch Intern Med* 1981; 141: 985–988.
57. Coccagna G, Mantovani M, Brignani F, *et al.* Tracheostomy in hypersomnia with periodic breathing. *Bull Physiopathol Respir (Nancy)* 1972; 8: 1217–1227.