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Treatment Options for Central Sleep Apnea: Comparison of Ventilator, Oxygen, and Drug Therapies

Josef Yayan and Kurt Rasche

Abstract

Central sleep apnea (CSA) is a sleep-related disorder characterized by pauses in breathing during sleep when the brain respiratory network momentarily interrupts transmission of impulses to the respiratory musculature. CSA presents significant problems being an independent risk factor for cardiovascular events and death. There are several available treatment options according to CSA severity. Currently, adaptive servo-ventilation is considered best for CSA patients. The goal of the present study was to retrospectively investigate different treatment methods employed for CSA, such as different modes of ventilation, oxygen therapy, and drugs to determine the most effective one. Data were obtained from hospital records during 2010–2015. The diagnosis of CSA and the optimal treatment method were supported by polysomnography examinations. Devices used during sleep to support breathing included continuous positive airway pressure, bi-level positive airway pressure, or adaptive servo-ventilation. We classified 71 (2.9 %) patients as having CSA from 2,463 patients with sleep-disordered breathing. Of those 71 patients, 54 (76.1 %, 95 % CI 66.2–86.0 %) were male and 17 (23.9 %, 95 % CI 14.0–33.8 %) were female, and they had a mean age of 67.1 ± 14.1. Four (5.6 %) patients underwent a combination therapy, 39 (54.9 %) received a ventilator in proper ventilation mode, 25 (35.2 %) received oxygen therapy, 7 (9.9 %) received medication, and 4 (5.6 %) received no treatment. We conclude that although the majority of patients needed treatment for central sleep apnea, a clear advantage in using ventilators when compared to oxygen therapy or drug therapy could not be found.

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Keywords
Central sleep apnea • Continuous positive airway pressure • Bi-level positive airway pressure • Adaptive servo-ventilation • Oxygen therapy • Drugs

1 Introduction

Central sleep apnea (CSA) is a sleep disorder characterized by the occurrence of apneas of more than 10 s during sleep as a result of reduced or absent stimulation from the respiratory center in the brain. There are different clinical presentations of CSA, and symptoms may include daytime sleepiness, repeated awakenings, and insomnia (Muza 2015).

The gold standard in the treatment of sleep disorders is continuous positive airway pressure (CPAP). The different forms of treatment for central breathing disorders include CPAP, bi-level positive airway pressure (BPAP), and adaptive servo-ventilation (ASV). ASV represents the most modern method of treatment for Cheyne-Stokes respiration and ventilation support, with variable airflow through the respiratory tract that changes depending on synchronization with the respiratory rate of the patient. ASV has the most favorable impact on the long-term prognosis of sleep disorders (Kazimierczak et al. 2013).

Oxygen therapy is an alternative therapy for CSA (Momomura 2012). In cases where CPAP fails, drug therapy is also recommended for the treatment of CSA according to the International Classification of Sleep Disorders, Third Edition (ICSD-3) (AASM 2014). Medicinal treatment with acetazolamide and theophylline has restricted supporting evidence but may be considered for the treatment of CSA related to congestive heart failure if standard medical therapy has not been effective. Zolpidem or triazolam may be prescribed for the management of CSA after the exclusion of causal risk factors for respiratory depression (ICSD-3) (AASM 2014). However, clear, evidence-based recommendations for the treatment of CSA have not been published in the most recent issue, and the suggestions given as to the most effective treatment options of CSA were relative.

The aim of present study was to seek the best method of treatment for CSA by comparing the influence on the apnea-hypopnea index (AHI) of different ventilation modes, oxygen therapy, and drug therapy. Starting the optimal form of treatment as early as possible can enhance effectiveness of therapy and reduce patients' suffering.

2 Material and Methods

2.1 Setting and Patients

Patients' data were anonymized prior to analysis. The Ethics Committee of the University of Witten-Herdecke in Germany approved the study. The requirement for written, informed consent of the patients was waived by the Ethics Committee because of the retrospective nature of the study.

The study examined optimal treatment methods in patients with CSA using records gathered at the Department of Pneumology, HELIOS Clinic, University of Witten/Herdecke, in Wuppertal, Germany over the period 1 January 2010 – 20 July 2015. The Clinic is the largest university hospital in the Bergisch Land, which is a low mountain range region within the state of North Rhine-Westphalia in Germany and has 967 beds and 26 departments. The hospital treats approximately 550 inpatients in the sleep lab each year. The records concerned patients with CSA according to the International Classification of Diseases (ICD) G47.30 (WHO 2015), examined in the sleep lab.

Three study groups were formed relating to the severity of CSA according to the AHI. The

patients were over 18 years old, but their age varied. The presumption of CSA arose from the patients' history and information from their partners, and the diagnosis of CSA was made principally by a pronounced daytime sleepiness and a number of other symptoms and secondary diseases.

2.2 Cumulative Impact Case Study

The case definition included those with clinical symptoms of CSA, such as excessive daytime sleepiness, snoring, episodes of breathing cessation during sleep witnessed by another person, abrupt awakenings accompanied by shortness of breath, awakening with a dry mouth or sore throat, morning headache, difficulty staying asleep, or concentration problems, who tested positive for CSA by polysomnography. The selection of cases was made independently using hospital chart data; individual matching was not undertaken.

CSA was defined by a tendency to experience apnea during sleep due to insufficient activity of the respiratory center, weak respiratory muscle activity, and failure of the diaphragm and lungs. A clinically relevant CSA was diagnosed if more than 55 % of the total number of respiratory events were central (White 1985). The symptoms of sleep-disordered breathing were classified as breathing pauses, snoring, daytime sleepiness, concentration disturbance, performance degradation, insomnia, dry mouth, headache, and dizziness.

2.3 Diagnosis

The diagnosis of CSA included various investigations, with a focus on interviewing the participants regarding their sleep habits, daily condition, and medical histories. In addition, physical examinations that included an examination of the ear, nose, and throat were performed. In the present study, a Masimo Radical^{TM} Signal Extraction Pulse Oximeter with Finger Sensor (Masimo Europe Ltd., Puchheim, Germany) was used through the night to measure and record the patients' blood oxygen saturation levels and pulse rates. A more comprehensive investigation was performed in case of evident pathological findings on these tests.

Polysomnography was performed by standard procedures (Sleep Diagnostic System ALICE 4®, Heinen + Löwenstein, Bad Ems, Germany). The examination by polysomnography was carried out several times until the optimal application of therapy could be found for the patients with CSA.

The AHI, which is used to indicate the severity of CSA (Punjabi 2015), is represented by the number of apnea and hypopnea events per hour of sleep. The apneas must last for at least 10 s and be associated with dips in blood oxygenation. Combining the AHI and oxygen desaturation gives an overall sleep apnea severity score that evaluates both the number of sleep disruptions and the degree of oxygen desaturation. The AHI was calculated by dividing the number of apnea events by the number of hours of sleep. AHI values were categorized as follows: 0–4 was normal; 5–14 was mild sleep apnea; 15–29 was moderate sleep apnea; and 30 or more was severe sleep apnea (Thornton et al. 2012). Three study groups were formed according to the AHI calculation corresponding to the severity of CSA.

The Epworth Sleepiness Scale (ESS 2015) was used to assess daytime sleepiness, which was measured with a short questionnaire (Johns 1991). The questionnaire asked to rate the increasing probability of falling asleep on a scale from 0 to 3 for eight different situations that most people engage in during their daily lives, though not necessarily every day. A total score of 0–9 was considered normal, while that of the 10–24 range indicated that expert medical advice should be sought. Scores of 11–15 were taken as indicators of mild-to-moderate sleep apnea, and above 16 indicated the possibility of severe sleep apnea or narcolepsy.

2.4 Ventilation Therapy

Continuous Positive Airway Pressure (CPAP) was used a breathing method in patients with CSA during sleeping, which supports

spontaneous breathing by positive pressurization in the inspiratory phase. CPAP provides continuity of the functional residual capacity of the lungs to make adequate oxygenation possible. The ratio of ventilation to perfusion is significantly improved, and the work of breathing is reduced.

AutoSet CS™ Pace Wave™: Adaptive Servo-Ventilator (ASV) for patients with CSA. This technology continuously monitors the ventilation of patients with CSA and automatically adapts to the exact volume of required pressure support and expiratory positive airway pressure (EPAP) in response to the patient's needs stemming from episodes of apnea, respiratory flow limitations, and snoring in order to stabilize the upper airway.

Bi-level positive airway pressure S/T (BPAP S/T) is a method of pressure-controlled ventilation combined with spontaneous breathing through a respirator. This breathing method allows for the spontaneous breathing of a patient without interrupting the set ventilation rate. BPAP S/T is suitable for the treatment of CSA at a medium pressure level. In central apnea, the device switches to ventilation mode and thus ensures the necessary supply of air. BPAP S/T provides two different pressure levels for inhalation and exhalation.

Oxygen therapy was used with either 1 or 2 L of oxygen per minute through a nasal cannula, nasogastric tube, or a mask. The medications used for the treatment of CSA were L-dopa (100 mg) + benserazide (25 mg), prothipendyl (40 mg), mirtazapine (15 mg), tilidine (50 mg), tilidine (50 mg) + naloxone (4 mg), zopiclone (7.5 mg), and clozapine (6.5 mg). The length of patients' hospital stay was compared between the different forms of CSA.

2.5 Statistical Analysis

Data were expressed as proportions, and means ± standard deviations (SD) wherever appropriate. We calculated 95 % confidence intervals (CI) for the total number of patients with CSA. Fisher's exact test for three independent standard normal variables of two probabilities was used to compare associations among the three study groups between sex difference, treatments by breathing apparatus, oxygen therapy, number of patients using medications, and the number of patients who did not receive treatment. One-way analysis of variance (ANOVA) for three independent samples was performed to compare the number and severity of CSA cases, age difference, and duration of hospital stay, ESS, and AHI among the study groups. Two-tailed tests were performed, and a p value of < 0.05 was considered statistically significant.

3 Results

We found 71 (2.9 %) patients with CSA among 2,463 patients with sleep apnea who had been treated in the sleep lab. The mean age of CSA patients was 67 ± 14 years, of whom 54 (76.1 %, 95 % CI 66.2–86.0 %) were males and 17 (23.9 %, 95 % CI 14.0–33.8 %) were females. The male sex was significantly more likely to suffer from CSA ($p = 0.034$). No significant difference in age were found between the three study groups ($p = 0.168$). Severe CSA cases predominated (Table 1; $p < 0.0001$).

Although more than half of the CSA patients were prescribed a ventilator, a clearly advantageous ventilatory mode could not found (Table 1). Only were small proportions of patients treated with oxygen therapy for sleeping at night or with drugs. There was a significant difference in the AHI ($p < 0.0001$), but no difference in the length of hospital stay among the three groups (Table 1; $p = 0.453$).

4 Discussion

Although every year a relatively large number of patients were examined for sleeping disorders, CSA was seen in only 2.9 % of those who had been identified with sleep apnea. CSA was a rare sleep disorder. However, different CSA prevalence is quoted in the literature. The prevalence may be up to 5 % of all patients examined in the sleep lab (Inönü et al. 2014) and it is believed that CSA most often affects men (Sinn et al. 1999).

Table 1 Comparison of gender, forms of ventilation, oxygen therapy, drug treatment, Epworth sleepiness scale (ESS), and duration of hospital stay in three study groups according to their apnea-hypopnea index (AHI) scores

	AHI 5–14 (%)	AHI 15–29 (%)	AHI > 30 (%)	p-value
Gender				
Male (N = 54)	5 (50)	16 (69.6)	33 (86.8)	0.034
Female (N = 17)	5 (50)	7 (30.4)	5 (13.2)	0.034
Total no. of patients	10 (14.1)	23 (32.4)	38 (53.5)	
Breathing apparatus				
CPAP	0	4 (17.4)	3 (7.9)	0.337
AutoSet CS-A	3 (30)	3 (13.0)	10 (26.3)	0.416
BPAP S/T	1 (10)	1 (4.3)	8 (21.1)	0.169
ASV	0	2 (8.7)	4 (10.5)	0.851
Total N = 39 (54.9 %)	4 (5.6)	10 (14.1)	25 (35.2)	0.126
Oxygen therapy				
Oxygen therapy with 1 liter per minute	0	5 (21.7)	6 (15.8)	0.354
Oxygen therapy with 2 liters per minute	0	7 (30.4)	7 (18.4)	0.137
Total N = 25 (35.2 %)	0	12 (16.9)	13 (18.3)	0.010
Drug treatment				
L-Dopa 100 mg + Benserazide 25 mg	0	0	1 (1.4)	0.999
Prothipendyl 40 mg	1 (10)	0	0	0.141
Mirtazapine 15 mg	0	1 (4.3)	0	0.465
Tilidine 50 mg	1 (10)	0	0	0.141
Tilidine 50 mg + Naloxone 4 mg	1 (10)	0	0	0.141
Zolpidem 10 mg	1 (10)	0	0	0.141
Clozapine 6.5 mg	0	1 (4.3)	0	0.465
Total N = 7 (9.9 %)	4 (5.6)	2 (2.8)	1 (1.4)	0.006
No. treatment N = 4 (5.6 %)	3 (30)	1 (4.3)	0	0.003
ESS (mean score ± SD)	8.4 ± 7.0	9.2 ± 6.3	7.8 ± 5.0	0.639
AHI (mean % ± SD)	9.4 ± 3.6	22.1 ± 6.1	51.9 ± 19.5	<0.001
Duration of hospital stay (mean days ± SD)	2.6 ± 2.3	2.3 ± 1.1	3.5 ± 4.8	0.453

To date, the exact prevalence of people suffering from sleep apnea is unknown (Aurora et al. 2012). Perhaps due to the rare appearance of CSA, no adequate therapies have been developed. In the present study, the male gender was more frequently diagnosed with CSA. CSA occurs due to a disturbance of the brain respiratory network during sleeping, resulting in apnea. The affected people do not realize that their breathing pauses during sleep. Only later, during the day, do the people affected feel the symptoms of CSA, such as sleepiness. This could be one explanation for the late detection and treatment of CSA. While CSA was detected mainly in the elderly in this investigation, the effects of age on the frequency and severity of CSA have not yet been clarified (Bixler et al. 1998).

The gold standard for the examination and diagnosis of CSA is polysomnography (Costanzo et al. 2015). As a baseline control to investigate the relative success of each treatment, all the patients in the present study were subjected to polysomnography, whether being under ventilation, oxygen, or drug therapy. Since the adverse effects of CSA intensify with an increasing number of apneic episodes, reducing the AHI must be the focus of any treatment. The AHI index not only describes the severity of CSA but also serves as an indicator of the success of CSA treatment.

The most frequent recommendation for the treatment of CSA according to the American Academy of Sleep Medicine is CPAP (AASM 2014). This recommendation relates mainly to patients with CSA and heart failure, but other

types of CSA also respond to CPAP treatment (Aurora et al. 2012). However, a definite advantage of CPAP over other treatment modalities was not observed in the present study. That could be explained by the heterogeneity of the various causes of CSA, for which treatment with CPAP would not work equally well. Treatment with CPAP was proposed in patients with mixed CSA and Cheyne-Stokes respiration CSA (Hsu and Lo 2003). Although we did not divide the patients into subtypes of CSA due to a small number of patients, we could find no real advantage of treatment with CPAP in this form of CSA.

CPAP technology has recently been expanded to provide the ASV ventilation mode for the non-invasive treatment of sleep-disordered breathing. In CSA patients, ASV measurements are collected continuously, and this information is used to continuously adjust the EPAP and the levels of pressure support from the device. ASV is particularly appropriate for patients with heart failure, who are especially prone to developing CSA (Brown and Javaheri 2014). Respiration devices with ASV mode were used in a few patients with CSA in the present study; two out of the six patients who were treated with ASV devices had heart failure. The AutoSet CS-A is a type of ASV that opens the upper airway and automatically adjusts EPAP (Wisskirchen and Teschler 2000). This form of respiration has been increasingly used in patients with CSA in the present study. However, further studies are needed to verify the benefits of the AutoSet CS-A in CSA patients.

Flow-targeted BPAP ventilatory support is designed to normalize breathing in CSA patients, mainly those with Cheyne-Stokes respiration. The flow-targeted dynamic BPAP device offers a minimum EPAP to the upper airway to eliminate obstructive apneas and hypopneas. In addition, the device modulates the inspiratory positive airway pressure to obtain a target intake airflow and eliminate central apneas and hypopneas (Arzt et al. 2008). BPAP was prescribed only for a few patients with severe CSA in the present study. The appropriate ventilation mode for an individual depends on specific needs of each patient.

According to the recommendation of the American Academy of Sleep Medicine, oxygen therapy is designated as a standard treatment for CSA associated with heart failure (AASM 2014). The majority of the patients with CSA in this investigation did not need oxygen therapy. In contrast, nocturnal home oxygen therapy improved the quality of life in patients with CSA and heart failure in a recent study (Nakao et al. 2014).

In the present study, periodic leg movement during sleep was reduced by a combination of L-dopa and benserazide in a patient with CSA and restless legs syndrome who had not tolerated therapy with ventilators. This result and previous publications support the hypothesis that restless legs syndrome and periodic movements in sleep lead to reduced central dopaminergic activity, possibly resulting in reduced sensitivity of postsynaptic dopaminergic receptors (Karatas 2007). This case shows that treatment of polyneuropathy can lead to an improvement in sleep disorders in patients with CSA.

In the absence of non-organic insomnia, we initiated a treatment with the sleep induction medication prothipendyl in a patient with CSA and suspected depression. Controlled studies in patients with CSA and primary insomnia are completely absent; therefore, experts warn against the uncritical and uncontrolled prescription of neuroleptics due to significantly increased mortality rates (Schreinzer et al. 2001).

In the present study we observed a significant reduction of leg movement and good sleep efficiency in a patient with CSA who was treated with tilidine. That patient showed no benefit from ventilation therapy, so after a neurological examination, a therapeutic trial with tilidine was launched yielding a positive therapeutic effect. While tilidine has been previously studied for the management of restless legs syndrome and periodic limb movement disorder (Vignatelli et al. 2006), there has so far been no investigation of tilidine in CSA patients. In another patient zolpidem was used with a significant improvement in sleep as a proportion of sleep pauses to total sleep time was reduced to 6.6 %; thus, central apneas were reduced, although not

significantly. ICSD-3 recommends using zolpidem for treatment of primary CSA only if the patient does not have underlying risk factors for respiratory depression (Aurora et al. 2012). Although an improvement in CSA with the use of zolpidem has also been shown in another study, the drug is generally not recommended due to the current lack of control studies (Quadri et al. 2009). In yet another patient with CSA and Parkinson's disease in the present study, treatment with clozapine accompanied by nightly oxygen therapy was used. Clozapine has been recommended for patients with Parkinson's disease with excessive daytime sleepiness (Askenasy 2003).

A limitation of the present study was that it examined a small number of patients with CSA in one hospital department during a relatively short study period. Further, distinction of CSA in complex or mixed sleep apneas, which could help improve the clarity of study groups was not performed.

Nevertheless, we have shown that none of the ventilation modes, such as CPAP, ASV, AutoSet CS-A, or BPAP shows a clear advantage over another in treatment of CSA patients. We conclude that treatment method for CSA patients should be individually determined after completion of polysomnographic examinations.

Conflicts of Interests The authors report no conflicts of interest in relation to this work.

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