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SCIENTIFIC INVESTIGATIONS

Central Sleep Apnea on Commencement of Continuous Positive Airway Pressure in Patients With a Primary Diagnosis of Obstructive Sleep Apnea-Hypopnea

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Introduction: Central sleep apnea (CSA) may occur in patients with snoring and obstructive sleep apnea-hypopnea (OSAH) during commencement of continuous positive airway pressure (CPAP) therapy. The presence of CSA may limit the effectiveness of CPAP therapy. The aims of this study were to assess the prevalence of CSA amongst patients starting CPAP for OSAH and to identify possible predictors of this condition.

Methods: We reviewed the polysomnograms (PSGs) and clinical records of 99 consecutive patients with a primary diagnosis of OSAH who were referred for an in-laboratory CPAP titration study. Patients with a CSA Index of ≥5 per hour at or near (±1 cm H_2O) prescribed CPAP level formed the CSA-CPAP group. The remaining patients made up the noCSA-CPAP group. Demographic, baseline and CPAP titration PSG variables were compared between the 2 two groups.

Results: 13 subjects (13.1%) had CSA-CPAP. Patients with and without CSA-CPAP did not differ with respect to age or body mass index. 46% of patients with CSA-CPAP had CSA on their baseline PSGs compared with 8% in the noCSA-CPAP group (p <0.01). CSA-CPAP patients also had a higher apnea-hypopnea index (72.1 vs. 52.7 p = 0.02), a higher arousal index (43.3 vs. 29.2 p <0.01), and a higher mixed apnea index (6.8 vs. 1.3 p = 0.03), on their baseline PSGs. Therapeutic CPAP could not be determined in 2 CSA-CPAP patients due to a very high frequency (of severe) central apneas. In the remaining 11, the CPAP prescription to eliminate obstructive events was higher than in the noCSA-CPAP group (11.0 vs. 9.3 p = 0.08). AHI was greater both at or near prescribed CPAP (48.8 vs. 6.7 p <0.01) and overall (47.4 vs. 14.9 p <0.01). A history of ischemic heart disease or heart failure was more frequent amongst patients with CSA-CPAP than those without (p = 0.03).

Conclusion: A significant minority of patients with a primary diagnosis of OSAH have either emergence or persistence of CSA on CPAP. Risk factors include male sex, history of cardiac disease, and CSA on baseline PSG.

Keywords: Central sleep apnea, obstructive sleep apnea-hypopnea, continuous positive airway pressure

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INTRODUCTION

Sleep disordered breathing has 2 basic mechanisms: upper airway narrowing and neural dysfunction of ventilatory control.[1,2] Obstructive sleep apnea-hypopnea (OSAH) is characterized by episodes of complete or partial upper airway obstruction during sleep.[3] Conditions associated with worsening severity of events include supine body position and rapid eye movement (REM) sleep. The therapeutic response to continuous positive airway pressure (CPAP) is usually complete.

Central sleep apnea (CSA) syndrome is characterised by recurrent episodes of apnea in the absence of upper airway obstruction during sleep[1] which can occur in association with alveolar hypoventilation (i.e., hypercapnic), or it can be normocapnic or hypocapnic.[4,5] Normocapnic or hypocapnic central sleep apnea can occur in a number of forms, including idiopathic central sleep apnea, Cheyne-Stokes respiration, and high altitude sleep apnea. Treatment of CSA is challenging because the therapeutic response to CPAP is usually incomplete, with significant residual periodic breathing and sleep fragmentation. Other than CPAP,[6] various therapeutic options have been studied including theophylline,[7] acetazolamide,[8] atrial overdrive pacing,[9] cardiac resynchronization,[10] inhaled carbon dioxide,[11] bilevel positive airway pressure, and adaptive seroventilation.[12,13] These studies have been predominantly conducted in patients with congestive cardiac failure and Cheyne-Stokes respiration and have had variable results.

A new category of sleep disordered breathing has recently emerged, which appears to belong to neither obstructive nor central sleep disordered breathing groups. Some patients exhibit predominantly mixed apneas, while others exhibit obstructive apneas that seem to change to central events by alterations with body position or application of CPAP.[14] Little is known about this group of patients who lack a common syndromic definition or clinical and pathophysiological description. The condition has

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therefore previously been referred to as "complex sleep apnea syndrome."[14] Frequent central apneas or a Cheyne-Stokes respiratory pattern after initial application of CPAP, often causes sleep to remain severely fragmented.[11,14,15] Thomas et al reported that it was often difficult to find a satisfactory CPAP pressure and, at best pressures, mean apnea-hypopnea index was 60 per hour.[15] In most patients, CSA was unmasked only after application of CPAP.[14] In a recent retrospective review of 223 consecutive split sleep studies that showed a sleep-related breathing disorder,, Morgenthaler et al estimated the prevalence of complex sleep apnea syndrome (central apneas > 5/hr on CPAP) to be 15% while primary CSA was rare (0.4%).[16] As with earlier reports of complex sleep apnea syndrome, while CPAP suppressed obstructive episodes, the residual apnea-hypopnea index remained high, due mostly to central apneas. The investigators found no clinical risk factors for complex sleep apnea syndrome apart from male gender. Treatment for CSA in such patients has only recently begun to be systematically investigated.[17]

Risk factors for OSAHS and CSA are well established. Male gender and body mass index are the main risk factors for OSAHS; whereas male gender, age greater than 65, lower left ventricular ejection fraction on echocardiogram, and atrial fibrillation are risk factors for CSA.[18] The early identification of patients with complex sleep apnea is important because this group does not respond well to CPAP. Although the best treatment option is still not known,[17] the early introduction of alternative treatment modalities has the potential to improve patient outcomes. Identifying the clinical profile of patients with complex sleep apnea may help in the understanding of the pathophysiology of this syndrome.

There were 2 aims in this study: firstly, to assess the prevalence of CSA upon commencement of CPAP, and secondly, to determine clinical factors that may help predict those at risk of complex sleep apnea.

METHODS

The Research and Ethics Committee of the Repatriation General Hospital approved the study protocol. A retrospective review was undertaken of the polysomnographies and clinical records of 99 consecutive patients with a primary diagnosis of OSAH who were referred for an in-laboratory CPAP titration polysomnographic study at the Adelaide Institute for Sleep Health, Repatriation General Hospital. Separate baseline and titration PSGs as well as split studies were included in the study.

Patient characteristics, including age, gender, body mass index (BMI), comorbidities and medications, were obtained. Comorbidity data were either obtained from the case notes or reported by patients at the time of sleep study. A history of 3 specific comorbidities of potential relevance to CSA was sought: ischemic heart disease (IHD), congestive heart failure (CHF), and cerebrovascular accident (CVA). For the diagnosis of CHF, formal echocardiography was not requested, and only reviewed if available. Patient medication histories were specifically reviewed for opioids, benzodiazepines, and antidepressants.

Standard PSG montages were used as follows: Electroencephalography (EEG, C3/C4, C2/C5 lead placements), electro-oculograms (EOG), submental electromyogram (EMG), nasal cannula to measure nasal pressure, limb movement sensors, inductive plethysmography for thoraco-abdominal motion, electrocardiography and arterial oxygen saturation (SpO_2, finger pulse oximetry). The signals were digitized and stored using a Compumedics-E Series sleep system (Melbourne, Australia). Sleep and sleep arousals were scored using standardized methods. Apneas and hypopneas were scored according to internationally agreed criteria.[19] Hypopnea was defined as (i) >50% from baseline reduction in the amplitude of nasal pressure signal, or, if this signal was absent or of poor quality, the sum of noncalibrated thoracic and abdominal plethysmography signals; OR (ii) a clear amplitude reduction in one of these parameters that was <50% from baseline but associated with either oxygen desaturation >3% or arousal. The central apnea index (CAI) and apnea-hypopnea index (AHI) were computed as the number of central apnea events, and the number of apneas plus hypopneas, respectively, per hour of sleep. CAI and AHI were also calculated at the closest available pressure to that prescribed by the reporting physician to abolish obstructive breathing events. This was achieved by summing all relevant events for each available epoch of sleep in which the CPAP pressure was closest to prescribed pressure ± 1 cm H_2O, and dividing by the corresponding sleep time.

Diagnosis of CSA was made on the diagnostic polysomnogram if the central apnea index was ≥5 per hour and at least 50% of all apneas were purely central in origin, that is, without obstructive components.[16] Patients were considered to have emergence or persistence of CSA on CPAP if the residual CAI at or near the prescribed CPAP level was ≥5 per hour. These patients formed the CSA-CPAP group. The remaining patients formed the noCSA-CPAP group.

The variables that were compared between CSA-CPAP and noCSA-CPAP groups included anthropomorphic variables, comorbidities, medications, and characteristics of baseline and titration PSGs. The Student *t*-test and chi-squared test were used to compare the 2 groups. A p-value of ≤0.05 was considered statistically significant. Non-normally distributed variables (average awake SpO2 and average desaturation) were compared between the CSA-CPAP and noCSA-CPAP groups using Mann-Whitney U tests.

RESULTS

Of the 99 patients who had CPAP titration study performed for OSAH, 13 (13.1%) had either emergence or persistence of CSA at or near prescribed CPAP.

Baseline Characteristics

Table 1 summarizes the demographics and physical findings of the patients in the CSA-CPAP and noCSA-CPAP groups. Consistent with previous studies in OSAH populations,[20,21] patients were on average middle-aged and obese and were predominantly male. There was no difference between the 2 groups in age or BMI, but the proportion of males was higher in the CSA-CPAP group.

Diagnostic PSGs

The findings of the diagnostic PSGs are shown in table 2. The average AHI in both groups was within the severe range for OSAH. Patients with CSA-CPAP had more severe sleep disordered breathing and disturbed sleep than those in the noCSA-CPAP group. The average frequency of mixed and central apneas during the diagnostic PSGs was higher in the CSA-CPAP group

than in the noCSA-CPAP group. Almost half the patients in the CSA-CPAP group had significant CSA (i.e., ≥5 central sleep apneas per hour of sleep) on their diagnostic PSGs, whereas this was the case in <10% of those in the noCSA-CPAP group.

Titration PSGs at or Near Prescribed CPAP

The findings of titration PSGs at or near prescribed CPAP are shown in Table 3. In 2 patients in the CSA-CPAP group, optimal CPAP pressures were not achieved because of severe persistence of CSA or emergence of CSA. The remaining 11 patients had significantly higher total AHI and CAI at or near prescribed CPAP levels, compared with corresponding results in the noCSA-CPAP group. This finding occurred in spite of a trend toward higher final prescribed CPAP levels.

Titration PSGs, Overall

Table 4 summarizes the data over the entire CPAP-titration period (i.e., not confined to the optimized CPAP levels). In keeping with the results reported in the previous section, the CSA-CPAP group had significantly higher total AHI and CAI over the entire CPAP-titration PSGs, compared with the noCSA-CPAP group.

There was no significant difference between the 2 groups with regard to average awake oxygen saturation (SpO_2). However, the CSA-CPAP group had significantly higher maximum oxygen desaturation during their titration PSGs, compared with the noCSA-CPAP group.

Comorbidities

A diagnosis of either IHD or CHF was recorded in a higher proportion of patients in the CSA-CPAP group than the noCSA group. No other significant difference for comorbidities or medications was found between the 2 groups.

DISCUSSION

In this retrospective study, the prevalence of either emergent or persistent CSA on CPAP was 13.1%, which is consistent with the only previously reported prevalence of 15%.[16] Three differences were noted when comparing the CSA-CPAP group with the noCSA-CPAP group: a higher proportion of men, more disturbed sleep both on baseline and titration studies and a higher prevalence of CHF and/or IHD.

There are a number of potential explanations for CSA-CPAP and the male preponderance of patients manifesting this problem. Ventilatory control instability has been proposed as a mechanism underlying sleep disordered breathing.[22] Loop gain refers to chemoresponsiveness or the hypoxic and hypercapnic ventilatory responses, and a high loop gain system is destabilizing to ventilation. Wellman and colleagues measured both loop gain and passive pharyngeal closing pressures in a group of patients with apnea during stable, supine NREM sleep.[23] Loop gain correlated loosely with apnea severity for the entire group. The relationship was much tighter in patients with moderately collapsible airways. It has been shown that men and patients with cardiac failure have higher loop gain. This could explain ventilatory instability, periodic breathing and CSA on CPAP in these patients. Men have higher awake hypercapnic ventilatory

Table 1—Baseline Characteristics of Patients with Sleep Disordered Breathing

Characteristics	CSA-CPAP n = 13	noCSA-CPAP n = 86	p-value
Age, yr	55.2 ± 16.0*	57.4 ± 10.6	0.53
Sex	Male 12 (92%)	Male 68 (79.1%)	<0.01
BMI, kg/m^2	33.4 ± 7.9	33.1 ± 5.8	0.90

Abbreviation: BMI: Body Mass Index
* Mean ± Standard deviation

Table 2—Diagnostic Polysomnography

Variables	CSA-CPAP n=13	noCSA-CPAP n=86	p-value
AHI, events per hr	72.1 ± 32.0	52.7 ± 28.1	0.02
ArI, events/hr	42.3 ± 20.8	29.2 ± 16.1	<0.01
MAI, events/hr	6.8 ± 19.7	1.3 ± 5.1	0.03
CAI, events/hr	12.4 ± 23.9	1.2 ± 2.3	<0.01
No of subjects with CSA (proportion of group with CSA)	6 (46%)	7 (8%)	<0.01

Abbreviations: AHI: apnea-hypopnea index, ArI: arousal index, MAI: mixed apnea index, CAI: central apnea index.

Table 3—Titration Polysomnography At or Near Prescribed CPAP

Variables	CSA-CPAP n=11	noCSA-CPAP n=86	p-value
CPAP	11.0 ± 2.8	9.3 ± 2.5	0.08
AHI	48.8 ± 32.9	6.7 ± 7.3	<0.01
CAI	26.2 ± 20.3	0.5 ± 1.0	<0.01

Table 4—Titration Polysomnography, All Pressures

Variables	CSA-CPAP n=11	noCSA-CPAP n=86	p-value
AHI	47.4 ± 28.4	14.9 ± 15.9	<0.01
ArI	19.1 ± 9.9	15.5 ± 8.8	0.17
CAI	17.0 ± 14.8	0.6 ± 1.0	<0.01
MAI	1.5 ± 2.5	0.01 ± 0.05	<0.01
SpO_2	95.8 ± 1.4	95.5 ± 1.4	0.5
Max O_2 desat	4.4 ± 2.1	2.7 ± 0.9	0.01

Abbreviations: SpO_2: Average awake oxygen saturation, Max O_2 desat: maximum oxygen desaturation during CPAP titration polysomnography.

Table 5—Comorbidities

Variables	CSA-CPAP	noCSA-CPAP	p-value
CHF/IHD	5 (38%)	12 (14%)	0.03
CVA	1 (8%)	4 (5%)	0.64
Opioid/Benzo	2 (15%)	7 (8%)	0.50
Anti-depressants	6 (46%)	20 (23%)	0.10

Abbreviations: CHF/IHD: congestive heart failure/ischemic heart disease, CVA: cerebrovascular accidents, opioids/benzo: opioids, benzodiazepines.

response than women.[24-26] They also have higher ventilatory response to brief arousals from NREM sleep and develop greater subsequent hypoventilation on resumption of sleep.[27] This ventilatory response combined with the observation that men appear to require a smaller reduction in PET_{CO2} than women to develop central sleep apnea, may contribute to the higher male prevalence of CSA.[28,29] Men also have more disrupted and lighter sleep than women, and central respiratory events tend to occur during lighter stages of sleep.[30]

The average SpO_2 was the same for CSA-CPAP patients and noCSA-CPAP patients. Thus, it would seem unlikely that lower baseline saturation was driving the respiratory instability observed in CSA-CPAP patients. The deeper nadir of SpO_2 observed amongst the CSA-CPAP group while on CPAP is most likely because they experienced many more disordered breathing events.

While none of our patients had overt clinical heart failure at the time of their sleep studies, the CSA-CPAP group did have a greater frequency of past IHD and/ or CHF than the noCSA-CPAP group. Moderate to severe sleep disordered breathing is common in patients with CHF.[31,32] CSA is present in 25% to 40% of such patients.[18,31,33,34] In cardiac failure, the elevated central CO_2 ventilatory response lowers Pa_{CO2} towards the apnea threshold at rest, narrowing the difference between ambient Pa_{CO2} levels and the apnea threshold, thereby predisposing to CSA.[35-37] Moreover, the activity of the faster-acting peripheral CO_2 ventilatory response then oscillates ventilation, and is responsible for the periodicity and severity of CSA in subjects with heart failure.[35] A long circulation time also increases the loop gain.[36,37] Lastly, patients with CHF have hypocapnia secondary to lung edema, which may cause hyperventilation and lead to baseline $PaCO_2$ to be closer to the apneic threshold. A number of the above mechanisms could have been operative in some of our patients who reported a past history of cardiac disease.

Our study had several limitations. Firstly, it was a retrospective study. Specific methods such as esophageal balloon recordings were not employed to categorically differentiate between central and obstructive events (especially hypopneas). However, we based the definition of CSA-CPAP on the presence and frequency of central apneas rather than central hypopneas, to minimize the risk of overreporting cases of complex sleep apnea. Despite review of case notes, data availability was limited. Ideally, all patients included in the study would have been interviewed. This would have improved the accuracy of comorbidity data collected and also given insight into subjective experience with CPAP.

Documentation of left ventricular function by echocardiography in all subjects would also have enhanced the study.

The main implication of this study is that the emergent or persistent CSA on starting CPAP may prevent some patients being successfully treated with CPAP for the obstructive component of their sleep disordered breathing; it may also lead to long-term CPAP failure. Treatment response at best may be suboptimal in view of the underlying CSA. Several questions arise from this study. Are there other predicting factors that will help identify those at risk? In our study, the CSA-CPAP group had significantly higher MAI and CAI on the baseline study. This needs to be verified with a larger patient sample. Also, is emergence of CSA on CPAP a transient or acute phenomenon on first starting CPAP or is it an enduring problem?

Conclusion

CSA on commencing CPAP amongst patients with a primary diagnosis of OSAH appears to be relatively common. Male sex and past history of cardiac disease are potential risk factors. These patients seem to have more disturbed sleep on their baseline studies, are prescribed somewhat higher CPAP pressures and may become long-term CPAP failures. Further studies in this area are indicated.

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