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Morbidity and Predicted Mortality in Older Adults with Central Sleep Apnea

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Abstract

Objectives: To assess cardiovascular morbidity and prognostic mortality risk in older patients with CSA in comparison to those with OSA and without any SDB (apnea-hypopnea index <15/hour).

Background: Sleep-Disordered Breathing (SDB), including both Central Sleep Apnea (CSA) and Obstructive Sleep Apnea (OSA), is a prevalent condition in older adults. In contrast to OSA, the information concerning the morbidity and mortality associated with CSA is scarce and inconsistent.

Methods: We analyzed a prospectively collected database of consecutive patients aged 70 and over referred for suspicion of SDB. All patients underwent an overnight polysomnography and a clinical assessment. Cardiovascular morbidities and prognostic index for 4-year mortality (PIM) were abstracted from patient records.

Results: The data derived from 207 patients (79.7 ± 5.7 years) was divided into three groups according to the apnea classification (20 CSA, 121 OSA, and 66 no-SDB). Stroke (7/20, p= 0.02) and hypertension (19/20, p=0.003) were more frequent in CSA patients than OSA and no-SDB patients. The mean PIM score of patients with CSA (10.7 ± 3.3) was higher than those with OSA (7.8 ± 3.1) and no-SDB (8.4 ± 2.9), even after adjustment for potential confounders including gender and SpO_2 (p <0.001).

Conclusion: CSA is associated with stroke and hypertension and an increased prognostic mortality risk compared to OSA and no-SDB in older patients. The knowledge of morbidities and mortality risk associated with CSA may help in planning preventive and therapeutic strategies to improve patients' global health status and quality of life.

Keywords: Central sleep apnea; Obstructive sleeps apnea; Sleep-disordered breathing; Mortality; Older adult

Brief Summary

Current knowledge/study rationale

Sleep-Disordered Breathing (SDB) in general and Central Sleep Apnea (CSA) in particular are known to increase with advancing age. The information concerning the morbidity and mortality associated with CSA in older populations is scarce and inconsistent. It is not known if CSA-related mortality is greater than Obstructive Sleep Apnea (OSA) related mortality in the elderly.

Study impact

Our study using a prognostic mortality risk index demonstrates that CSA diagnosed by full polysomnography is a major and independent risk factor for mortality in older adults. Untreated CSA compared with OSA is also significantly associated with stroke and hypertension.

Introduction

The prevalence of Sleep-Disordered Breathing (SDB), defined as an Apnea-Hypopnea index (AHI) of 15 or greater, is 23% in the community-dwelling older over the age of 70 [1]. Central Sleep Apnea (CSA), a form of SDB, can affect more than one third of these elderly patients with SDB [1]. The prevalence, severity and costs of CSA will likely escalate as the older adult population increases in number and lives longer.

CSA is characterized on the polysomnogram by recurrent cessation of respiration during sleep with no associated ventilatory effort. In contrast obstructive sleep apnea (OSA) is defined as repetitive episodes of upper airway obstruction with ongoing respiratory efforts [2]. In OSA patients the repetitive upper airway collapse occurs during sleep because negative pressure generated during inspiration is not effectively counteracted by splinting by pharyngeal dilators, especially when narrowing occurs as a result of excessive soft tissue (e.g. obesity, loss of soft tissue elasticity related to age) or vulnerable craniofacial anatomy (e.g. edentulous older adults). In both cases, the Continuous Positive Airway Pressure (CPAP) is the most widely used treatment even in older adults. Furthermore, bilevel positive airway pressure (BiPAP) in a spontaneous-timed mode and Adaptive Servo-Ventilation (ASV) which generates positive airway pressure with variable pressure in response to a patient's expiration are increasingly recommended in order to ameliorate central respiratory events related to chronic heart failure.

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There is a limited body of information concerning the morbidity and mortality associated with CSA in older populations. In previous cohort studies concerning older patients, chronic heart failure is mentioned as the most common comorbid condition, yet the specific mortality rate associated with untreated CSA or untreated OSA is not well understood [3,4]. Since there is a high prevalence of CSA in the elderly, we can expect that CSA may increase the risk of both cardiovascular morbidity (not only chronic heart failure) and mortality risk in that age group.

We hypothesized that in older patients, CSA is associated with increased cardiovascular morbidity and mortality risk when compared to OSA and no-SDB, independent of potential confounders. To address this hypothesis, we conducted a cross-sectional study in 207 consecutive older adult patients seen in our geriatric sleep disorders center that underwent an in-hospital polysomnography and clinical assessment.

Materials and Methods

Study design and patient population

This is a cross-sectional, observational study using a Lyon University Hospital, Geriatric Sleep Center (Lyon, France) clinic population. Following approval from the Local Ethics Committee, a review of the medical records was performed.

Consecutive patients referred to our sleep center and who met our inclusion criteria (see below) during a three year period were enrolled. Patients were all referred by geriatricians or family physicians because of suspected SDB (either OSA or CSA) with symptoms of snoring, witnessed apneas, excessive daytime sleepiness, or obesity.

Inclusion criteria were: (1) Caucasian men or women (the study sample was limited to Caucasian patients as the prevalence of non-Caucasian patients in our clinic was too low to allow for meaningful subgroup analyses by race/ethnicity), (2) age 70 years and over, (3) hospital based complete polysomnography, (4) extensive geriatric assessment including an evaluation of medical history and comorbid conditions, and (5) stable clinical situation with no medication adjustment for at least 2 weeks prior to the polysomnography.

The exclusion criteria were: (1) acute heart failure, (2) acute respiratory failure, (3) previously diagnosed SDB, (4) currently on CPAP treatment or nocturnal oxygen supplementation.

Polysomnography

Each polysomnography included at least the following recordings: three channel electroencephalography, chin electromyography, bilateral electro-oculography, chest and abdomen respiratory effort, nasal and oral airflow via a thermocouple, snoring, pulse oximetry, ECG and body position. Sleep staging and arousals were scored using standard methods [5].

Apneas were defined as the complete cessation of airflow for at least 10 seconds.

Hypopnoeas were defined as an airflow amplitude reduction of >50% from baseline lasting at least 10 seconds, accompanied by the presence of arousal or oxygen desaturation of at least 4% [6].

Apneas were classified as obstructive if they were associated with continued chest or abdominal movement, or central if there was a cessation of chest and abdominal movement. In addition, mixed apneas were identified if both central and obstructive components were present. The AHI was defined as the total number of apnea and/or hypopnea episodes divided by the number of hours of sleep.

The diagnosis of both CSA and OSA required an AHI of 15 or more events per hour [2]. Patients with AHI<15 were classified as no-SDB. Patients were considered to have CSA or OSA if more than 50 percent of the events determined were central or obstructive events, respectively [7].

Assessment of mortality risk

The potential mortality risk was assessed using the Prognostic Index for 4-year Mortality validated in older adults [8]. An intake form was used to collect information in patient files. The index is composed of 12 independent predictors of mortality: 2 demographic variables (age: 60-64 years, 1 point; 65-69 years, 2 points; 70-74 years, 3 points; 75-79 years, 4 points; 80-84 years, 5 points; ≥ 85 years, 7 points and male sex, 2 points), 6 comorbid conditions (diabetes, 1 point; cancer, 2 points; lung disease, 2 points; heart failure, 2 points; current tobacco use, 2 points; and BMI <25, 1 point), and difficulty with 4 functional variables (bathing, 2 points; walking several blocks, 2 points; managing money, 2 points, and pushing large objects, 1 point). The prognostic index total scores range from 0 (lowest risk) to 26 (highest risk). This prognostic index, incorporating age, sex, self-reported comorbid conditions, and functional measures, accurately stratified community-dwelling older adults into groups at varying risk of mortality: 0 to 5 points predicted a less than 4% risk, 6 to 9 points predicted a 15% risk, 10 to 13 points predicted a 42% risk, and 14 or more points predicted a 64% risk [8].

Abstraction of clinical data

Data on the demographic characteristics, body mass index (BMI, kg/m^2), medical history and cardiovascular comorbidities were extracted from standard medical records at the time of polysomnography. Major sedative drug (e.g. opioid pain relief drugs, sodium oxybate) consumption was checked. In addition, each patient's 4-year prognostic mortality index was calculated based on information available at the time of polysomnography.

Medical history chart abstraction was performed using the following standardized algorithm. Hypertension was defined as a documented diagnosis, treatment of such, or whether the recorded resting blood pressure was ≥ 140/90 mmHg three times in the previous month. Stroke and Transient Ischemic Attack (TIA) were defined as a documented history of stroke or TIA. Ischemic heart disease was defined as a documented history of angina pectoris and/or myocardial infarction and/or coronary angioplasty and/or coronary artery bypass surgery. Atrial Fibrillation (AF) was defined as a documented history of permanent, paroxysmal or persistent AF (at least 2 episodes in the previous 3 months). The diagnosis of chronic heart failure was based on a history of dyspnea and symptomatic exercise intolerance with signs of pulmonary congestion or peripheral edema or documentation of left ventricular enlargement or dysfunction by chest x-ray film, echocardiography, or radionuclide ventriculography. Diabetes mellitus diagnosis was based on a history of diabetes, current treatment (oral therapy and/or insulin) or a fasting glucose value ≥ 7 mmol/l.

Statistical analysis

Descriptive characteristics and polysomnography measures were compared between patients with CSA, OSA and those without sleep apnea (no-SDB). Means were compared using analyze of variance (ANOVA); the difference in the proportions was tested using the Chi-squared test. The 4-year mortality risk index was compared according to the sleep apnea status using univariate and multivariate ANOVA.

Multiple pairwise comparisons were performed using Scheffe's test, to compare each group with every other one to determine which group differed significantly. Potential confounding covariates were tested in the model: gender, BMI, AHI, SpO_2<90%, hypertension and stroke. Means with their 95% confident intervals (CI), p value of the ANOVA F test and p value of the Sheffe's tests are presented. A p value <0.05 was considered as significant. Statistical analyses were performed with SPSS version 15.0 for Windows (SPSS Software, Chicago, USA).

Results

The study population included 207 patients, grouped by diagnostic status as follows: 20 patients with CSA, 121 patients with OSA, and 66 patients with no-SDB.

Characteristics of the study sample are presented in Table 1. The mean age was 79.7 ± 5.7 years, and there was no significant difference between groups. Patients with CSA had significantly higher proportions of men (90%), stroke or TIA (35%), and hypertension (95%) compared to patients with no SDB (38%, 9% and 56% respectively). BMI was higher among patients with OSA compared to those with no-SDB. No significant differences were observed for age, ischemic heart disease, AF, diabetes mellitus and CHF. In all groups, no patient was identified using chronically or during sleep study opioid pain relief drugs and sodium oxybate which both may contribute to the depression of respiratory drive (Table 1).

Between CSA and OSA patients, no significant differences were noted concerning total AHI, mixed apnea index, hypopnea index, mean SpO_2, lowest SpO_2, and sleep time with SpO_2<90% (Table 2).

Table 3 presents 4-year mortality index univariate and stepwise multivariate analysis. The mean 4-year mortality index was significantly higher among patients with CSA compared to patients with OSA or no SDB (12.0 ± 3.5; 8.1 ± 3.1; 7.1 ± 2.9 respectively; p<0.001). The results remained significant after controlling for gender and SpO_2<90% (p<0.001); no other variables were significant covariates in the multivariate model. There was a trend toward a higher mean of 4-year mortality index among patients with CSA compared to patients with OSA, but the difference did not reach statistical significance.

Discussion

This study highlights two main findings in an older population referred for investigation of SDB. First, patients with CSA had significantly higher proportions of stroke and hypertension compared to patients with no-SDB. Second, there was an association between the CSA and increased prognostic mortality index values. This association remained significant after adjustment for clinical parameters known to affect survival prognosis.

Variables	No-SDB (n=66)	OSA (n=121)	CSA (n=20)	*p* Value
Age, year	79.1 ± 6.0	79.9 ± 4.7	80.7 ± 5.4	0.42
Male gender	25 (38%)	69 (57%)	18 (90%)¶	<0.001
BMI, kg/m²	27.0 ± 5.5	30.8 ± 6.3†	28.5 ± 4.7	<0.001
Stroke or TIA	6 (9%)	23 (19%)	7 (35%)§	0.02
Ischemic Hearth D.	12 (18%)	26 (21%)	6 (30%)	0.52
Atrial fibrillation	7 (11%)	20 (17%)	6 (30%)	0.11
Diabetes mellitus	8 (12%)	29 (24%)	5 (25%)	0.13
CHF	6 (9%)	16 (13%)	6 (30%)	0.06
Hypertension	37 (56%)	87 (72%)	19 (95%)*	0.003

Values are expressed as means ± SD or No. (%) unless otherwise stated. No-SDB, subjects without sleep disordered breathing. CSA, subjects with central sleep apnea. OSA, subjects with obstructive sleep apnea. BMI, body mass index. TIA transient ischemic attack, CHF chronic heart failure.
¶p < 0.001 (No-SDB subjects vs. patients with CSA)
†p < 0.001 (No-SDB subjects vs. patients with OSA)
§p = 0.02 (No-SDB subjects vs. patients with CSA)
*p = 0.003 (No-SDB subjects vs. patients with CSA)

Table 1: Clinical characteristics and cardiovascular comorbidities.

Variables	No-SDB (n=66)	OSA (n=121)	CSA (n=20)	*p* Value
Total AHI, No./h	7.6 ± 4.1	42.9 ± 19.6†	47.1 ± 16.6†	<0.001
CSA index, No./h	0.8 ± 1.5	3.3 ± 4.7	25.4 ± 13.6‡	<0.001
OSA index, No./h	2.6 ± 2.5	26.2 ± 17.4§	7.0 ± 5.8	<0.001
MSA index, No./h	0.1 ± 0.4	3.5 ± 6.9†	6.1 ± 6.1†	<0.001
H index, No./h	4.1 ± 3.3	9.9 ± 8.7†	8.5 ± 5.4	<0.001
Mean SpO_2, %	93.4 ± 2.3	92.3 ± 3.2¶	92.5 ± 2.1	0.03
Lowest SpO_2, %	81.9 ± 8.5	72.6 ± 11.5*	75.2 ± 7.8**	<0.001
Time with SpO_2<90%, %	9.1 ± 18.1	17.5 ± 21.3	20.4 ± 17.1***	0.01

Values are expressed as means SD unless otherwise stated.
AHI, apnea hypopnea index. CSA, central sleep apnea. OSA, obstructive sleep apnea. MSA, mixed sleep apnea. H, hypopnea. See Table 1 for abbreviation not used in the text.
†p < 0.001 (patients with OSA or CSA vs subjects with no-SDB)
‡p < 0.001 (patients with CSA vs patients with OSA or no-SDB)
§p < 0.001 (patients with OSA vs patients with CSA or no-SDB)
¶p = 0.03 (patients with OSA vs subjects with no-SDB)
*p < 0.001 (patients with OSA vs subjects with no-SDB)
**p = 0.04 (patients with CSA vs subjects with no-SDB)
***p = 0.02 (patients with CSA vs subjects with no-SDB)

Table 2: Polysomnography Measures.

Mortality Index	No-SDB (n=66)	OSA (n=121)	CSA (n=20)	*p* Value	*p* value No-SDB vs CSA	*p* value No-SDB vs OSA	*p* value CSA vs OSA
Univariate*	7.1 ± 2.9	8.1 ± 3.1	12.0 ± 3.5	<0.001	<0.001	0.1	<0.001
Multivariate†	7.9 ± 2.8	7.9 ± 3.1	10.8 ± 3.3	<0.001	<0.001	0.1	<0.001

*Univariate model for mortality index; R^2=9 %. †Stepwise multivariate model adjusted for gender (p<0.001), and SpO_2 <90% (p<0.001). The other variables (BMI, AHI, hypertension and stroke) were tested in the model and were not significant. The mean age was not significantly different between groups (Table 1), so age was not included in different models. The multivariate analysis contributed significantly to the explanation of the model; R^2=35%.

Table 3: Four-year mortality index univariate and stepwise multivariate analysis in patients with central sleep apnea (CSA), obstructive sleep apnea (OSA) and free of sleep apnea syndrome (no-SDB).

Cardiovascular morbidity

From a pathophysiological point of view, both ventilatory instability and depression of the brainstem respiratory centers may cause central sleep apnea. The ventilatory system is at particular risk of instability when the resting $PaCO_2$ approaches the $PaCO_2$ apneic threshold. In other words, reduction of $PaCO_2$ just a few mm Hg below the $PaCO_2$ set point can result in central apneas. Some other additional factors, such as metabolic alkalosis, low functional residual capacity, upper airway instability, and hypoxia, may further contribute to respiratory instability and CSA [9]. Post-hypocapnia hyperventilation is believed to be the main underlying pathophysiological mechanism for CSA associated with congestive heart failure. CSA associated with long-acting opioid drug use for at least two months [10] or brainstem lesions such as stroke are due to depression of the brainstem respiratory centers or disturbances of peripheral chemoreceptors or both.

We did not observe chronic opioid drug use in our population; however CSA was significantly associated with stroke. According to Bassetti et al. [11] SDB is common particularly in elderly stroke male patients with diabetes, but the authors did not discuss if there was a specific association between CSA and stroke. In a cohort study, among 132 patients who recently had stroke, Sahlin et al. [12] found that 23

OSA patients were at a greater risk of early death, while the 28 with CSA did not have an increased mortality risk. The risk of death was independent of age, sex, BMI, hypertension, diabetes mellitus and AF. In this cohort, the prevalence of CSA was greater than the prevalence of OSA.

CSA was associated with hypertension in our study as well. This may be due to increased sympathetic activity from recurrent apneas and hypoxia, similar to what is seen in obstructive sleep apnea. Of note, other research has shown a limited association between SDB and hypertension in older adults [13].

Depending on the population studied, OSA and/or CSA occur in 24% to 82% of heart failure patients [14]. In our study, the association between CHF, OSA and CSA did not reach statistical significance, although it showed a trend towards significance (p=0.06). This finding may be explained by the clinically stable nature of the study patient population, possible unrecognized heart failure or the old age of our sample with possible survival bias. Although CSA is probably a consequence of heart failure, once established it may play an important role in heart failure progression, morbidity, and mortality [15]. As yet, however, causality has not been proven [16].

Our findings were also consistent with previously published work which shows an association between SDB and conditions such as diabetes [17] and atrial fibrillation [18,19].

Mortality

The present study demonstrates that in older adults, CSA is associated with an increased risk of mortality based on a prognostic mortality index scale. This mortality index risk is independent of common confounding factors, such as gender and SpO_2. Our results confirm and extend findings from previous studies performed in younger populations, or samples that may be biased because of CPAP treatment. Of note, the prognostic mortality index is greater in CSA patients compared to OSA or no-SDB patients. According to Lee et al. [8], mortality index scores around 8, similar to those observed in no-SDB and OSA patients are associated with a 15% 4-year mortality risk, and scores around 11 as observed in CSA patients are associated with a 42% mortality risk.

In studies focused on younger adults, CSA has been associated with increased mortality [20,21]. Later research noted that older patients with CSA plus congestive heart failure have a mortality rate greater than those with just congestive heart failure, or CSA or OSA alone [4]. However, investigators of this cohort were not able to determine precisely if any of the patients received oxygen supplementation or CPAP treatment during the 17-year follow up period. Using CPAP to treat OSA in patients with chronic heart failure may also alleviate the heart disease and possibly lengthen survival.

In contrast, other cohort studies, after controlling for common confounding factors in younger patients with CSA and congestive heart failure [22] or CSA and stroke [12] did not observe higher mortality rates in comparison to those with no-SDB. However, in latter cohorts followed for up to 10 years, some CSA patients continued with CPAP therapy at home for up to five years.

Strengths and limitations

The strengths of our study include the availability of hospital-based full polysomnography data, which is the "gold standard" for SDB diagnosis. Previous cohort studies using cardiorespiratory polygraphy to distinguish between OSA and CSA may lead to some inaccuracy and may underestimate the sleep apnea severity due to their inability to distinguish wake from sleep [23].

Our patients were old "old adults" with a mean age of about 80 years. These patients are, on average, about 11 to 14 years older than those in previous studies [3,4]. Some limitations have to be mentioned as well. Patients with unstable clinical conditions were not included. In other words, our sleep center did not recruit patients with acute heart failure or acute ischemic heart disease and, therefore, cannot exclude CSA associated with these comorbid conditions and related mortality. According to Johanson et al. [24], OSA, in persons >75 years does not appear to be associated with cardiovascular disease (CVD) disease or mortality, whereas CSA might be a pathological marker of CVD and impaired systolic function associated with higher mortality. In this cohort of 331 community-dwelling elderly underwent a one-night cardiorespiratory polygraphy (without EEG) and followed-up 7 years, authors did not mention if OSA and CSA patients were treated with CPAP, BiPAP or ASV. The cross-sectional nature of our study precludes inferences about causality between CSA and comorbid conditions. Although our overall sample was large, categorization of CSA, OSA and no-SDB resulted in small groups of CSA, OSA and no-SDB that limited statistical power to determine potential group-related differences in comorbid conditions. Mortality itself was not directly assessed, and was determined instead as a prognostic mortality risk. However, this prediction calculation of the mortality risk [8] has been used in over a dozen research publications, including older adults with diabetes mellitus [25] and functional disability [26]. One benefit of this prognostic mortality risk approach is that it minimizes the potential effect of subsequent SDB treatment on overall survival. In contrast most prior cohort studies have not been able to adequately measure SDB treatment during the period of study follow-up. Clearly, CPAP, BiPAP and ASV treatments can have an impact on study outcomes and may lead to an underestimate of both OSA and CSA effects on mortality.

Conclusions

Previous studies assessing mortality in patients with CSA have been controversial and have had important limitations, including the use of cardiopulmonary polygraphy (instead of complete polysomnography) and unmeasured CSA treatment with CPAP or oxygen therapy during the study follow-up period. In our study, CSA compared to OSA and no-SDB was associated with stroke and hypertension. Furthermore, we noted an increased prognostic mortality risk independent of potential confounders. With regard to increased mortality risk the relative number of co-morbid conditions was also higher in CSA patients, than in patients with OSA or no-SDB. Thus, CSA may be both risk factor and consequence of cardiovascular co-morbidities and vulnerability. Future research is necessary to determine if treatment of CSA in the elderly can lead to reduced morbidity and mortality from these conditions.

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