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Original Article

Impact of different hypopnea definitions on obstructive sleep apnea severity and cardiovascular mortality risk in women and elderly individuals

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ABSTRACT

Objective: To assess the impact of three hypopnea definitions on the severity classification of obstructive sleep apnea (OSA) and its association with cardiovascular mortality risk in women and elderly individuals.

Methods: We analyzed two Spanish clinical cohorts (1116 women and 939 elderly individuals) who were studied for suspicion of OSA between 1998 and 2007. A calibration model was used to apply different definitions of hypopnea to our two cohorts. Hypopnea was defined as a 30–90% reduction in oronasal flow for ≥10 s followed by (1) ≥4% fall in oxyhemoglobin saturation—$AHI_{4\%}$; (2) ≥3% fall in oxyhemoglobin saturation—$AHI_{3\%}$; or (3) ≥3% fall in oxyhemoglobin saturation or an event-related arousal—$AHI_{3\%a}$.

Results: In both cohorts, the prevalence of an AHI ≥30 events/h increased by 14% with $AHI_{3\%a}$, compared to $AHI_{4\%}$ criteria. The percentage of women with an AHI <5 events/h decreased from 13.9% with $AHI_{4\%}$ to 1.1% with the $AHI_{3\%a}$ definition. In fully adjusted multivariable analyses, AHI ≥30 events/h was associated with increased cardiovascular mortality risk in women, regardless of the hypopnea definition, and in elderly individuals diagnosed using the $AHI_{4\%}$ and $AHI_{3\%}$ but not the $AHI_{3\%a}$ definition.

Conclusions: Our findings suggest that hypopnea definitions substantially influence OSA prevalence and severity classification, and also affect the association with cardiovascular outcomes. With the currently recommended criterion ($AHI_{3\%a}$), a threshold of 30 events/h is appropriate to identify women, but not elderly individuals with increased risk of cardiovascular death.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder characterized by repetitive episodes of complete or partial upper airway obstruction during sleep. The apnea–hypopnea index (AHI), that is, the sum of apneas plus hypopneas per hour of sleep, is the conventional metric used to diagnose and to classify the severity of OSA. A precise definition of the events that compose this index is therefore of the utmost importance. Although the definition of apnea is clear and has not changed over the years, the scoring of hypopneas depends on several factors, such as the degree of the accompanying oxyhemoglobin desaturation (SaO_2), the degree of airflow reduction, and the occurrence of an arousal. Furthermore, the criteria for scoring hypopneas have varied with successive updates from the American Academy of Sleep Medicine (AASM) [1,2]. These modified criteria may lead to significant changes in estimates of the AHI, which, in turn, will alter disease prevalence and possibly even therapeutic decisions. Specifically, less stringent criteria would result in a higher prevalence of moderate-to-severe

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OSA and increase the potential number of patients requiring active treatment, particularly in the presence of associated symptoms. For example, the use of the 2012 AASM criterion for hypopnea, which requires at least a 30% decrease in oro-nasal airflow accompanied by either a three percent decrease in SaO_2 or an event-related arousal, implies that almost one-third of the subjects analyzed in a recent study could be reclassified between non-OSA and OSA categories, compared to former, more restrictive criteria (AASM 2007) [3,4]. Recent studies conducted in either population-based or small clinical cohorts have confirmed that these changes in the hypopnea definition have led to a higher prevalence of OSA [3,5–8]. However, the impact of different hypopnea metrics on population subsets is unknown. Another concern is that variability in defining hypopneas could influence the association with cardiovascular outcomes [6]. The aim of this study was to investigate the impact of three different definitions of hypopnea on the classification of OSA severity and its association with cardiovascular mortality risk in two large clinical cohorts of women and elderly individuals.

2. Methods

2.1. Design, settings, and patients

We have analyzed two large clinical cohorts composed of 1116 women and 939 elderly individuals (≥65 years of age) who were consecutively studied for suspicion of OSA between 1998 and 2007 in two Spanish sleep clinics and were followed up until December 2009. The two cohorts were originally assembled to investigate the association between OSA and cardiovascular mortality, as well as the effect of continuous positive airway pressure (CPAP) on this association. Exclusion criteria were age <18 years, central sleep apnea syndrome (>50% of apneic events were central), and previous CPAP treatment. Characteristics of the two patient cohorts, recruitment methodology, and results from the original studies have been described in detail elsewhere [9,10].

2.2. Procedures

We followed the Spanish Society of Pneumology and Thoracic Surgery Guidelines for OSA diagnosis and treatment [11]. Each patient in the two cohorts had a diagnostic sleep study, either by full standard polysomnography (PSG) or respiratory polygraphy (RP) with a validated device. Each sleep study was manually scored by trained staff. In both cohorts, apnea was defined as complete cessation of oronasal flow for ≥10 s and hypopnea as a 30–90% reduction in oronasal flow for ≥10 s followed by a ≥4% decrease in SaO_2 ($AHI_{4\%}$ definition).

In the present study, we have investigated three AHI values computed using different hypopnea definitions. First, the aforementioned $AHI_{4\%}$ criterion, which corresponds to the preferred definition of hypopnea in the 2007 AASM Scoring Manual [1]. To estimate the two other AHI values, the calibration model recently proposed by Ho et al. was applied to compare AHI values obtained based on different hypopnea metrics [3]. With this calibration tool, $AHI_{3\%}$ and $AHI_{3\%a}$ values were determined from the original $AHI_{4\%}$ value. In both $AHI_{3\%}$ and $AHI_{3\%a}$, the definition of hypopnea required a decrease in airflow >30%. The $AHI_{3\%}$ definition also required a ≥3% fall in SaO_2, whereas $AHI_{3\%a}$, which is the current hypopnea definition as recommended by the AASM in 2012, required a ≥3% fall in SaO_2 or an event-related arousal.

2.3. Covariate data and clinical endpoints

The following baseline variables were assessed before the sleep study: age, sex, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, prevalent arterial hypertension, type 2 diabetes mellitus, and documented history of cardiovascular events, including stroke, ischemic heart disease, atrial fibrillation, and heart failure.

Severity of OSA was based on the usual AHI thresholds of 5, 15, and 30 events/h. However, to investigate cardiovascular mortality, we decided to combine the groups of AHI <5.0 events/h and 5.0–14.9 events/h into one group (AHI <15) as the reference group. The decision to use AHI <15 events/h as the reference group was based on the limited number of patients with a low AHI, particularly in the elderly patient cohort.

The two main endpoints investigated were the effects of various hypopnea definitions on the severity classification of OSA in women and elderly individuals and to assess whether varying hypopnea criteria altered the association with cardiovascular death. To analyze the first endpoint, we have used the whole cohorts, whereas for mortality we have restricted the analysis to untreated patients. The reason is that we have previously shown that CPAP treatment reduces cardiovascular mortality in women and elderly individuals with OSA, and thus including treated patients may have biased the results [9,10]. For this study, a patient was considered as untreated if she or he was not prescribed CPAP or refused or did not tolerate the device, or displayed a persistent objective average use of <4 h/day. Vital status at the end of follow-up was thoroughly assessed by using information from medical records and death certificates. When a patient died, information about the cause and date of death was obtained from official death certificates. Cardiovascular death was defined as death from stroke, myocardial infarction, heart failure, or arrhythmia [9,10].

2.4. Statistical analysis

The SPSS 20.0 software package (SPSS Inc, Chicago, IL) was used for the analysis. Continuous variables were expressed as means (standard deviations [SD]) or as medians (interquartile ranges [IQR]), and categorical variables as absolute values and percentages. Analysis of variance with Bonferroni correction were used to compare AHI obtained with the three definitions of hypopnea, in both clinical cohorts. Chi-squared test was used to compare categorical variables across AHI groups. Cumulative cardiovascular survival based on each hypopnea definition was calculated according to the Kaplan–Meier method, and survival curves were compared with the log-rank test.

Associations between cardiovascular mortality and OSA severity, according to the three hypopnea definitions, were estimated using Cox proportional hazards regression models, with adjustment for the following covariates: age, sex, BMI, arterial hypertension, diabetes mellitus, and previous cardiovascular events. The results were expressed as hazard ratio (HR) and 95% confidence interval (CI), and a p value <0.05 was considered statistically significant.

3. Results

The two clinical cohorts were composed of 1116 female and 939 elderly individuals, respectively. Baseline characteristics for each cohort are shown in Table 1. The female cohort was followed up for a median of 72 months (IQR, 52–88 months) and the elderly cohort was followed for 69 months (IQR, 49–87 months). The average AHI was within the severe range with any of the hypopnea definitions used, for both cohorts, but it was significantly higher with the $AHI_{3\%a}$ and $AHI_{3\%}$, compared to the $AHI_{4\%}$ criterion (Table 1).

3.1. Severity classification of OSA

The prevalence of severe OSA varied largely in the cohort of elderly patients, from 62.6% with $AHI_{4\%}$ to 77.3% with $AHI_{3\%a}$