Severe Sleep Apnea and Risk of Ischemic Stroke in the Elderly

Roberto Munoz, MD; Joaquín Duran-Cantolla, MD, PhD; Eduardo Martínez-Vila, MD, PhD; Jaime Gallego, MD, PhD; Ramón Rubio, MD, PhD; Felipe Aizpuru, MD, PhD; Germán De La Torre, MD, PhD

Background and Purpose—Convincing evidence of a causal relationship between sleep apnea and stroke has been shown recently in several prospective, well-designed studies. However, these studies have focused on middle-aged people, excluding the elderly population from analysis. To investigate whether sleep apnea represents an independent risk factor in this population, we performed a prospective longitudinal study in a population-based cohort of subjects from 70 to 100 years old.

Methods—Within the context of the Vitoria Sleep Project, a population-based study designed to investigate the prevalence of sleep apnea in the population of Vitoria, Spain, we performed a 6-year longitudinal study in a subsample cohort of 394 noninstitutionalized, initially event-free subjects (70 to 100 years old, median 77.28 years, 57.1% males). Demographic and polysomnographic data and known confounding factors (age, sex, smoking and alcohol consumption status, body mass index, systolic and diastolic blood pressure, total serum cholesterol levels, and the presence or absence of diabetes mellitus, atrial fibrillation, and hypertension) were assessed at baseline. Hazard ratio for developing an ischemic stroke in relation to the apnea–hypopnea index at baseline was calculated.

Results—Over the 6-year follow-up period, 20 ischemic strokes were registered. After adjustment for confounding factors, subjects with severe obstructive sleep apnea hypopnea (defined as apnea–hypopnea index ≥30) had an increased risk of developing a stroke (hazard ratio = 2.52, 95% CI = 1.04 to 6.01, P = 0.04).

Conclusions—This study shows that severe obstructive sleep apnea hypopnea (defined as apnea–hypopnea index ≥30) increases the risk of ischemic stroke in the elderly population, independent of known confounding factors. (Stroke. 2006;37:2317-2321.)

Key Words: elderly | population | risk factor | sleep apnea | stroke

Stroke is a frequent disease, a leading cause of death, and generates high healthcare costs. Several modifiable risk factors have been defined in stroke. However, these traditional risk factors do not fully explain the occurrence of stroke and new risk factors have been proposed.1

In this sense, obstructive sleep apnea hypopnea (OSAH) is emerging as an important risk factor. Since the first reference published in 1985,2 multiple studies have added evidence of this relationship. Initially, several articles focused on snoring.3–9 Later, the apnea–hypopnea index (AHI) was used as a gold standard for OSAH diagnosis.10–15 Recently, we have obtained convincing data of a causal relationship with well-designed prospective studies. First, Marin et al10 showed that in men, severe OSAH (defined as AHI >30) significantly increases the composite risk of fatal and nonfatal cardiovascular events, including stroke and, more important, that continuous positive airway pressure (CPAP) therapy could reduce that risk. Later, Arzt and colleagues,17 based on data from the Wisconsin Sleep Cohort Study, demonstrated that a moderate OSAH (defined as AHI ≥20) was associated with an incremental risk of 3.0 times of developing a stroke. Finally, Yaggi and coworkers18 have showed an increment of composite risk (stroke or dead of any cause) in any degree of OSAH (AHI >5) of ≈1.97 times. However, two of these studies have used stroke as a composite outcome, adding up a possible confounding factor, and Arzt and coworkers found that the association between OSAH and stroke risk was not statistically significant after adjustment for age, sex, and body mass index. Additionally, previous studies focused on a middle-aged population, whereas it is well-known that the greatest incidence of stroke is found in older people. To our knowledge, no study has prospectively evaluated the risk of first ever stroke in older patients. This is an important population to study because the proportion of elderly individuals is increasing in Western countries, representing a great concern of public health.19
To test the hypothesis that OSAH is an independent risk factor to develop a stroke in the elderly, we have performed an observational prospective analysis based on data from the Vitoria Sleep Project, a cross-sectional study designed to investigate the prevalence of sleep apnea in Vitoria, a little town in the north of Spain.

Materials and Methods

Selection of Prospective Cohort

The Vitoria Sleep Project was a two-phase prevalence study started in 1999, which investigated prevalence of OSAH in Vitoria. This population study included noninstitutionalized people from 70 to 100 years of age. A random one-stage cluster sampling stratified by census areas (n=7), age (70 to 80, 81 to 90, >90), and sex was drawn from the sampling frame of households using 1998 census data. Subjects were recruited by mail and by telephone. Exclusion criteria included severe illness (unstable cardiopulmonary or end-stage disease), airway tumors, recent surgery of the upper respiratory tract, tracheostomy, previous diagnoses of sleep-disordered breathing, and serious physical or mental disability of any cause resulting in difficulty completing the study, including major disability resulting from a previous stroke. The study was approved by the Institutional Review Board of the Hospital Txagorritxu and Hospital Santiago and all participants gave written informed consent.

Baseline Evaluation

We divided baseline evaluation in two different phases. The first phase of the study included a comprehensive home-structured interview. Trained interviewers administered the questionnaires, which included a health questionnaire, anthropometric measures (weight, height and neck circumference, and mass body index), and data regarding medications, including any medication for treatment of hypertension, diabetes, arrhythmia, antiaggregants or anticoagulants, and lipid-lowering medications. Blood pressure was measured following the recommendations of the American Heart Association.20 Hypertension was defined as one or more of the following: resting systolic blood pressure of at least 140 mm Hg, resting diastolic blood pressure of at least 90 mm Hg, or treatment with antihypertensive medication. Presence of diabetes mellitus and other prevalent chronic diseases was recorded according to the clinical history and use of specific medication as revealed by the patient or chart review. Prevalence of atrial fibrillation was investigated in medical records from the hospital. Current smoking was defined as daily smoking of any number of cigarettes, cigars, or pipes. Alcohol use was defined as the consumption of an alcoholic beverage (1 U) at least three times per week.

The second phase consisted of an attended polysomnographic study of subjects who had completed the first phase. We carried out continuous polygraphic recordings for an entire night, from 10:30 PM to 7:00 AM, with standardized equipment (Alice 3; Healthdyne Technologies) and the Ultrasom system (Nicolet Biomedical Inc.) recording from surface leads for electroencephalography (C4/A1 and C3/A2 placements), electrocugulography, tibial and submental electromyograms, and electrocardiogram (modified V2 lead). To monitor respiration, we used nasal and oral airway signals recorded by thermistors, tracheal sounds (microphone), and the chest and abdominal effort recorded with two belt sensors (Healthdyne piezoelectric gauge; Healthdyne Technologies). Oxyhemoglobin saturation was recorded by finger-pulse oximeter (model 340; Palco Laboratories), and the body position was monitored by the video component of the Alice 3 or Ultrasom system. Sleep data were staged according to the system described by Rechtschaffen et al.21 A complete cessation of the thermistor signal for at least 10 seconds was defined as apnea. Hypopnea was defined as a discernible reduction around 50% of the thermistor signal for 10 seconds accompanied by a decrease of 3% in oxyhemoglobin saturation and/or an electroencephalographic arousal. An arousal was defined according to the American Sleep Disorders Association.22 AHI was defined as the total number of

apneas and hypopneas per hour of electroencephalographic sleep. At this phase, we determined total cholesterol levels.

Prospective Follow Up

Six years after the beginning of the baseline study, we investigated every medical event in the group of subjects who completed the entire protocol (first and second phase) using the hospital records of Santiago and Txagorritxu’s Hospital, the two local public hospitals. They both have a computer system to encode the diagnosis (International Classification of Diseases, 9th Revision and Diagnosis Related Groups [DRG] codes), recorded by specialized encoders, of every patient who come to our hospitals (inpatient and emergency room cases). Medical records were reviewed by an expert neurologist who was unaware of the patient’s AHI to verify every suspected stroke. Patients with a dubious or incomplete stroke diagnosis were excluded. Diagnoses were determined according to criteria of the National Institute of Neurological Disorders and Stroke for the classification of cerebrovascular events.23

Statistical Analysis

For statistical analysis, we dichotomized the variable of interest into two groups according to evidence shown by Marin and coworkers.24 In the first group, we included elderly people with no apnea to mild to moderate (AHI 0 to 29) OSAH, and in the second group, people with severe (AHI ≥30) OSAH. To study any differences in baseline characteristics between patients with and without ischemic stroke, we used the χ² test for categorical variables. We used the Student t test for comparison of continuous variables. In the univariate analysis, we considered the following variables as potential prognostic factors: age, sex, body mass index, systolic and diastolic blood pressure, total cholesterol level, alcohol and tobacco consumption, presence of hypertension, diabetes mellitus, and atrial fibrillation. Survival was calculated by the Kaplan-Meier product limited method as the time from the sleep study to the outcome variable, first-ever stroke. Censored cases were defined as subjects alive at the end of follow up (April 30, 2005) without registered stroke or subjects who died as a result of causes other than stroke. Log-rank test was used to assess differences between groups. Variables with a significant unadjusted association with stroke were entered into a multivariate regression Cox model24 to estimate the hazard ratios and 95% CIs of experiencing an incident stroke. All analyses were performed with the use of SPSS (version 12.0) statistical software.

Results

A total of 2528 participants were selected during randomization, and 1399 entered the inclusion and exclusion criteria. From this eligible population, 1034 accepted to participate in the study, and 810 completed successfully the first phase of the protocol, who were then offered the polysomnographic study. Only 429 subjects agreed. After that, 10 subjects accepted to start CPAP therapy (because they had symptoms related to OSAH and AHI ≥30) and were excluded. Of the remainder, only 405 subjects had a technically correct polysomnography. To carry out the follow-up study, 11 subjects were excluded because, after extensive investigation of medical records, we identified a history of unrelated minor stroke, leaving 394 ischemic event-free subjects. A flow chart of the study population is shown in Figure 1.

Table 1 compares baseline variables among the participants who completed just the first phase with subjects who completed the first and second phases. Participants who completed both phases were younger, the percentage of female participants was slightly lower, and mean diastolic blood pressure and body mass index were significantly higher.
After a follow-up time of 6 years (mean follow-up time = 4.5 years), we verified 20 ischemic strokes representing an annual incidence of 11.28 per 1000 person-years. As expected, mortality was high at the end of the follow-up period (75 subjects [19%]).

Univariate associations of the AHI are shown in Table 2. People who experienced a stroke were more likely to be male and had higher AHI. Additionally, the test for linear trend analysis showed a dose–effect relationship for this association ($P=0.025$). There were no significant differences between other covariates. We used Kaplan-Meier curves (Figure 2) to determine the difference in event-free survival time to a stroke between AHI groups. The event-free survival was lowest in the highest AHI group (log rank test $5.43, P=0.0198$).

As shown in Table 3, the crude hazard ratio for the association between AHI group and incident transischemic attack or ischemic stroke was 2.733 (95% CI = 1.132 to 6.599, $P=0.025$). After adjustment for sex, the hazard ratio decreased slightly to 2.52 (95% CI = 1.044 to 6.1, $P=0.04$) but did not change the association.

**Discussion**

These results shows that the presence of severe OSAH, defined as an AHI $\geq 30$, is an independent risk factor for first-ever stroke in the elderly population.

To date, several studies have examined the relationship between sleep-disordered breathing and cerebrovascular dis-
ease using self-reported snoring or AHI as the primary exposure variable. After adjusting for many potential confounding variables, they signaled OSAH as an independent risk factor to experience a stroke. This is an essential question because OSAH and stroke share many risk factors. However, most of these studies initially were retrospective (mainly case–control or cross-sectional).\textsuperscript{2–14} To establish the causal nature of an association requires an analysis of incident events in prospective cohort studies.\textsuperscript{25} Moreover, most of the mentioned studies included patients with stroke admitted to hospitals and conclusions cannot be applied to a general population. To avoid these drawbacks, we selected a cohort derived from a representative sample of home-living elderly subjects. Because risk factors for OSAH and those for stroke are similar, we considered every potential confounding factor at baseline. After that, we investigated every incident event. For this reason, we are able to presume a causal relationship. Furthermore, as the $\chi^2$ test for linear trend shows, there seems to be a dose–effect relationship for this association, another postulate of causal relationship.\textsuperscript{25} In contrast to previous studies, we did not consider a composite risk.\textsuperscript{16,18} Another improvement from previous studies, which used questionnaires or self-reported diagnoses,\textsuperscript{14,17,18} was that we only recorded as a stroke an event confirmed by a neurologist to avoid recall bias or stroke mimics.

Finally, to our knowledge, this is the first study that focuses in the elderly population. We targeted the cluster of people most vulnerable to experience cerebrovascular illnesses. The incidence of stroke increases with age,\textsuperscript{26} and 75% of strokes occur in the elderly.\textsuperscript{27} With the increasing life expectancy, this proportion is likely to rise. Similarly, recent evidence shows that prevalence of OSAH increases with age.\textsuperscript{28} In this study, contrary to previous unconfirmed thoughts\textsuperscript{29,30} that suggest that OSAH lacks relevance in advanced ages, we have found that severe OSAH represents a risk factor for stroke in the elderly.

This study has some potential weaknesses. We could have underestimated the incidence of fatal stroke. Stroke incidence in our cohort is lower than in previous reports.\textsuperscript{31} It is not uncommon that very old people are found dead at home and are not admitted to a hospital, thereby failing to be recorded by our hospital survey. Indeed, like Yaggi and coworkers,\textsuperscript{18} we find a positive association between AHI $\geq 30$ and death (odds ratio = 1.77, 95% CI = 1.02 to 3.07, $P = 0.04$), and this fact minimizes this methodological limitation. As far as nonfatal strokes, we assume that most of subjects would have looked for medical attention in the hospitals surveyed. The reason is that the National Health Service in Spain covers more than 99% of the population. Therefore, most people go to hospitals when they have a serious medical problem.

Another methodological issue is that the characteristics of the subjects who completed both phases of the study differed from the larger group that completed the first phase. For this reason, we assume that our final cohort was not fully representative of the reference population. We think that extreme ages of our subjects could have been an important reason for the high rates of dropout, especially for overnight polysomnography at the sleep unit.

In addition, as happens with most cohort studies, the potential cerebrovascular risk factors were measured at baseline, and changes over time have not been modeled. However, it is unlikely that risk factors changed significantly in 6 years. Somewhat surprising was the observation that classic risk factors such as hypertension, atrial fibrillation, or diabetes did not show an association with stroke. This fact could be explained because, at baseline, practically every subject was being correctly treated for these conditions. That was the case, for example, for atrial fibrillation, the most important single cause of stroke in this age group.\textsuperscript{32} In our cohort, up to two-thirds of people with atrial fibrillation were being treated with anticoagulation, less than one-third was taking antiaggregants, and only $\approx 8\%$ did not have a specific therapy. Adequate treatment should have reduced the effect of atrial fibrillation on the risk of stroke.

Our study is important because, until now, it was believed that OSAH among the elderly was less of a health risk compared with middle-aged people.\textsuperscript{29,30} Nevertheless, following Spanish Respiratory Society guidelines\textsuperscript{33} (that recommend CPAP therapy in subjects with AHI $\geq 30$ and/or subjects with symptoms related to OSAH), we treated a few participants who accepted this therapy, but tolerance was very limited. Obviously, we excluded these subjects from follow-up study.

In conclusion, this study shows that severe OSAH is related to the occurrence of ischemic stroke in the elderly after adjustment for traditional risk factors. We believe that a randomized trial designed to investigate the influence of CPAP therapy on stroke is required to complete the demonstration of a causative relationship.

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**Disclosures**

None.

**References**


**TABLE 3. Cox Regression Model and Hazard Ratio According to AHI**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1</td>
<td>2.73 (1.13 to 6.59)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1</td>
<td>2.52 (1.04 to 6.10)</td>
</tr>
</tbody>
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*Adjusted by sex.


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