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Original Article

Sleep apnea and risk of aortic dissection: A nonrandomized, pair-matched cohort study

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Abstract

Background: Sleep apnea (SA) was associated with increased prevalence of aortic dissection (AD) in studies that were criticized for either their small sample size or lack of prospective observation. Using a considerably larger nationwide, population-based database and a long-term prospective cohort design, our study strived to explore the relationship between SA and the subsequent development of AD.
Methods: From 2000 to 2007, we gathered a study cohort consisting of 15,848 newly diagnosed cases of SA from Taiwan's National Health Insurance Research Database. For the control group, another 39,826 individuals without SA were matched for age, sex, and comorbidity. The two cohorts were followed-up to observe the occurrence of AD.
Results: During an average 3.59 ± 2.41 years of follow-up, we observed 33 cases of new AD occurrence [non-SA (22, 0.1%) vs. SA (11, 0.1%), $p = 0.669$], and the incidence of AD was similar for both groups. After adjusting for age, sex, and comorbidity, only age [hazard ratio (HR) 1.03; 95% confidence interval (CI), 1.01−1.06; $p = 0.006$], male gender (HR 2.49; 95% CI, 1.07−5.79; $p = 0.034$), and hypertension (HR 6.28; 95% CI, 2.36−16.67; $p < 0.001$) were independently associated with AD diagnosis.
Conclusion: SA was not associated with an increased risk of AD using a large nationwide cohort database. Nonetheless, larger prospective studies or meta-analyses are recommended to confirm our findings.

Keywords: aortic dissection; sleep apnea

1. Introduction

Sleep apnea (SA) is a common disorder characterized by cessation of breath during sleep, resulting from repetitive upper airway collapse [namely, obstructive SA (OSA)].[1] OSA affects ~24% of men and ~9% of women in the middle-aged population of the US[2] and is associated with a variety of

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cardiovascular diseases, such as hypertension, coronary artery disease, stroke, and aortic aneurysm.[3−6] Aortic dissection (AD), a catastrophic illness often presenting as acute hemodynamic compromise, shares some common risk factors with SA. Based on their study showing a high prevalence (13/19, 68%) of SA in patients with AD, Sampol and colleagues[7] recently reported SA as a possible risk factor for AD, in addition to the well-known risk factors of hypertension, male sex, and increasing age. Also, a growing body of evidence supports a tendency toward increased aortic size and aortic dissection events among patients with SA.[7−10] Although taken as indicating a possible link between OSA and AD, these studies have also been criticized for their limited sample size and lack of information from a prospective cohort.

Hypothesizing that SA may contribute independently to the development of AD, we used a nationwide database to conduct a nonrandomized, pair-matched cohort study to investigate the relationship between SA and subsequent development of AD.

2. Methods

2.1. Database

Taiwan's National Health Insurance (NHI) program, in operation since 1995, has enrolled nearly all the inhabitants of Taiwan (21,869,478 beneficiaries out of 22,520,776 inhabitants at the end of 2002).[11] The National Health Insurance Research Database (NHIRD) at the National Health Research Institutes (NHRI; http://w3.nhri.org.tw/nhird/en/index.htm) in Miaoli, Taiwan is in charge of the entire NHI claims database and publishes numerous extracted datasets for researchers. The NHRI released a cohort dataset comprised of 1,000,000 randomly sampled people who had been insured from the start of NHI to 2000, collecting all records of these individuals from 1995 onwards. The database has been confirmed by NHRI to be representative of Taiwan's population.[12] It is also one of the largest nationwide population-based databases in the world, with > 280 published scientific articles using its data.[13] In this cohort dataset, each patient's original identification number has been encrypted to protect privacy. The encrypting procedure is consistent so claims belonging to the same patient can be linked within the NHIRD datasets.

2. 2. Study sample and controls

We identified patients who were newly diagnosed with SA [International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 780.51, 780.53, and 780.57] from a 1,000,000 sampled cohort dataset going back to January 1, 2000. An age-, sex-, and comorbidity-matched control group was selected from the patients without SA throughout the study period. Patients diagnosed with AD (ICD-9-CM code 441.0) before enrollment were excluded from this study.

Comorbidity matched in the two groups included pre-existing (upon enrollment) hypertension (ICD-9-CM codes 401.xx−405.xx), diabetes mellitus (ICD-9-CM code 250.xx), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 494, 492, and 496), coronary artery disease (ICD-9-CM codes 411.xx, 413.xx, and 414.xx), ischemic stroke (ICD-9-CM codes 433.xx, 434.xx, 436, and 437.1), intracerebral hemorrhage [ICD-9-CM codes 430.xx−432.9x], chronic renal disease [ICD-9-CM codes 580.xx−587.xx], and peripheral arterial occlusive disease [ICD-9-CM code 443.9]. Both the SA cohort and the control cohort were followed-up from enrollment to the date of AD diagnosis, death, withdrawal from insurance, or until December 3, 2007; the end of the follow-up period (Fig. 1).

2.3. Main outcome

The end point of the study was defined as diagnosis with AD (ICD-9-CM code 441.0). In this database, the ICD codes for SA and AD did not change throughout the follow-up period (2001−2007), assuring the consistency of the disease registry.

2.4. Statistical analysis

A Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, WA, USA) was used for data management and computing. Statistical analyses were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation or percentage. Comparisons between the two groups were determined by independent Student t test for continuous variables, or Pearson's χ^2 test, Yates' correction for continuity/Fisher's exact test for categorical variables. We used Cox proportional hazard models to test the association between SA and AD. Survival analysis was assessed using the Kaplan−Meier method, with significance based on the log-rank test. Statistical significance was inferred as a two-sided p value < 0.05.

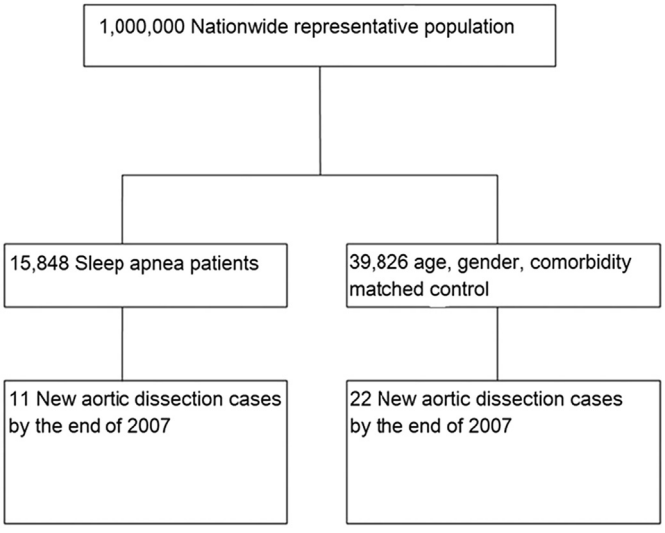

Fig. 1. Flowchart illustrating the follow-up of sleep apnea patients and matched controls.