Incidence and Risk of Atrial Fibrillation in Sleep-Disordered Breathing Without Coexistent Systemic Disease

– Nationwide Longitudinal Cohort Study –

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Background: Although the link between sleep-disordered breathing (SDB) and atrial fibrillation (AF) has been reported, a population-based longitudinal cohort study was lacking. The goal of the present study was to investigate the AF risk carried by SDB, using the National Health Insurance Research Database in Taiwan.

Methods and Results: From 2000 to 2001, a total of 579,521 patients who had no history of cardiac arrhythmias or significant comorbidities were identified. Among them, 4,082 subjects with the diagnosis of SDB were selected as the study group, and the remaining 575,439 subjects constituted the control group. The study endpoint was the occurrence of new-onset AF. During a follow-up of 9.2 ± 2.0 years, there were 4,023 patients (0.7%) experiencing new-onset AF. The occurrence rate of AF was higher in patients with SDB compared to those without it (1.3% vs. 0.7%, $P < 0.001$). The AF incidences were 1.38 and 0.76 per 1,000 person-years for patients with and without SDB, respectively. After an adjustment for age and sex, SDB was a significant risk factor of AF with a hazard ratio of 1.536. The AF risk increased with increasing clinical severity of SDB, represented by the requirement of continuous positive airway pressure use.

Conclusions: SDB itself, without the coexistence of other systemic diseases, was a risk factor of AF. (*Circ J* 2014; 78: 2182–2187)

Key Words: Atrial fibrillation; Incidence; Sleep-disordered breathing

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with marked morbidity, mortality, and socioeconomic burden.^{1,2} The age-adjusted incidence of AF significantly increased from 3.04 to 3.68 per 1,000 person-years in the USA.³ The incidence of AF is lower in Asia.⁴ In a nationwide cohort of 702,502 participants in Taiwan, the AF incidence was around 1.5 per 1,000 person-years, and was much lower in patients with a CHADS₂ (Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack) score of zero (0.77 per 1,000 person-years).⁵ Traditional risk factors for AF include advanced age, male gender, hypertension, diabetes mellitus, heart failure and end-stage renal disease.^{5–7} Recently, some novel predis-

posing factors for AF were identified, such as obesity, metabolic syndrome and use of steroids or non-steroidal anti-inflammatory drugs.^{8–10}

Sleep-disordered breathing (SDB) has been reported to be associated with various cardiovascular diseases, including hypertension, coronary artery disease, heart failure, ventricular arrhythmias, stroke and sudden cardiac arrest.^{11–14} In recent years, there has been increasing awareness of the possible link between SDB and AF.^{15–18} A previous study, however, showed that SDB was not a risk factor of AF in patients without evident cardiovascular diseases,¹⁶ raising the question of whether SDB alone is a predisposing factor for AF. Also, the temporal relationship between SDB and AF has not been studied in a population-

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based longitudinal cohort, which would have less selection bias and could more accurately represent the real-world condition. Therefore, the goal of the present study was to investigate the risk of AF carried by SDB in a nationwide database, and to determine whether SDB is a novel risk factor for AF in a population without significant comorbidities.

Methods

Database

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes (NHRI). The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The NHIRD is a cohort dataset that contains all the medical claims data for 1,000,000 beneficiaries, who were randomly sampled from the 25.68 million enrollees under the NHI program. These random samples have been confirmed by the NHRI to be representative of the Taiwanese population. In this cohort dataset, the patients' original identi-

fication numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient is feasible within the NHI database and can be followed continuously. The database, with its large sample size provided an excellent opportunity to study the relationship between SDB and AF.

Subjects

From 1 January 2000 to 31 December 2001, 670,731 patients who were aged ≥ 20 years and had no past history of cardiac arrhythmias or rheumatic heart disease were identified from the NHIRD. A total of 579,521 patients who were younger than 75 years old and had no significant comorbidities, including hypertension, diabetes mellitus, congestive heart failure, ischemic stroke or transient ischemic attack, ischemic heart disease, chronic kidney disease, chronic pulmonary disease (asthma or chronic obstructive pulmonary disease), peripheral arterial disease, malignancy and systemic autoimmune diseases, were selected. From them, 4,082 subjects who had the diagnosis of SDB were enrolled as the study group, and the remaining 575,439 subjects constituted the control group. SDB was diagnosed using

Table 1. Age and Gender vs. Presence of SDB

Variables	Study group (with SDB) (n=4,082)	Control group (without SDB) (n=575,439)	P-value
Mean age (years)	43.6±12.6	38.9±13.1	<0.001
Age distribution (years)			<0.01
20–40	1,610 (39.4)	324,163 (56.3)	
40–60	1,959 (48.0)	199,145 (34.6)	
60–74	513 (12.6)	52,131 (9.1)	
Male	2,604 (63.8)	294,458 (51.2)	<0.001

Data given as mean ± SD or n (%). SDB, sleep-disordered breathing.

Table 2. Risk of AF vs. Presence of SDB

Variable	All (n=579,521)	SDB	
		Yes (n=4,082)	No (n=575,439)
AF			
Yes	4,023 (0.7)	53 (1.3) [†]	3970 (0.7)
No	575,498 (99.3)	4,029 (98.7)	571,469 (99.3)
Crude HR (95% CI)		1.815 (1.384–2.380); P<0.001	
Adjusted HR (95% CI) [‡]		1.536 (1.171–2.014); P=0.002	

Data given as n (%). Mean follow-up was 9.2±2.0 years. [†]P<0.001 in comparison with patients without SDB. [‡]Adjustment for age and gender.

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio. Other abbreviation as in Table 1.

Figure 2. Cumulative frequency curve for new-onset atrial fibrillation (AF). Patients with sleep-disordered breathing (SDB) had a higher rate of new-onset AF during the follow-up period.

the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (780.51, 780.53, and 780.57), which theoretically represent an apnea-hypopnea index >5.^{19–22} A flowchart of the enrollment of study patients is shown in **Figure 1**.

The study endpoint was the occurrence of new-onset AF (ICD-9-CM code 427.31) during the follow-up period. To ensure accuracy of diagnosis, we defined patients as having AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department.²³ The diagnostic ac-

Table 3. Incidence of AF vs. Presence of SDB

	Groups	
	Study group (with SDB)	Control group (without SDB)
No. new-onset AF	53	3,970
No. patients	4,082	575,439
Person-years	38,371	5,236,495
Incidence [†]	1.38	0.76

[†]AF cases per 1,000 person-years of follow-up. Abbreviation as in Tables 1,2.

Table 4. Severity of SDB and Risk of New-Onset AF

Groups	HR [†]	95% CI	P-value
Without SDB (reference group)	1	—	—
SDB, CPAP not indicated	1.457	1.099–1.932	0.009
SDB, CPAP indicated	4.507	1.691–12.010	0.003

[†]Adjusted for age and gender.

CPAP, continuous positive airway pressure. Other abbreviation as in Tables 1,2.

curacy of AF using this definition in NHIRD has been validated previously.^{24,25} In the Chang et al study, which reviewed the medical records of 660 patients who fitted the diagnosis of AF defined by ICD-9-CM codes, the diagnostic accuracy of AF was around 90%.²⁵

Continuous positive airway pressure (CPAP) applied a constant level of positive pressure at the airway opening during spontaneous breathing, and represented a treatment indicated for patients with SDB who have not responded to conservative therapies, such as behavior modification and oral appliances. In order to understand the relationship between the clinical severity of SDB and the risk of AF, we analyzed whether CPAP was used for patients with SDB, and regarded it as a proxy of disease severity.

Statistical Analysis

The data are presented as mean $\pm$ SD for normally distributed continuous variables and as proportions for categorical variables. The differences between continuous values were assessed using an unpaired 2-tailed t-test. The chi-squared test was used for comparisons of nominal variables. The AF-event curve was plotted and the statistical significance was examined using log-rank test. The risk of patients with or without SDB in developing AF is expressed as the hazard ratio (HR), which was analyzed using Cox regression analysis. Statistical significance was set at $P < 0.05$ and all statistical analysis was carried out using SPSS 17.0 (SPSS, Chicago, IL, USA).

Results

The mean subject age was 38.9 ± 13.1 years (range, 20–74 years) and men accounted for 51.3% of the patients. Data on age and gender are listed in Table 1. Patients with SDB were older than those without it, and male gender was more prevalent among the study group.

During the period from January 2001 to December 2009 (mean follow-up, 9.2 ± 2.0 years), there were 4,023 patients (0.7%) experiencing new-onset AF. The occurrence rate of AF was higher in patients with SDB compared to those without it (1.3% vs. 0.7%, $P < 0.001$; Table 2). The cumulative frequency curve of incident AF for subjects with and without SDB is shown in Figure 2. The incidence of AF was around 1.38 and 0.76 per 1,000 person-years for patients with and without SDB,

respectively (Table 3). Table 2 also lists the crude and adjusted HR for the development of AF of these 2 groups. After adjustment for age and sex, SDB was a significant risk factor of new-onset AF with a HR of 1.536 (95% confidence interval [95% CI]: 1.171–2.014, $P = 0.002$) on multivariate Cox regression analysis.

In the subgroup analysis of patients with SDB stratified by whether CPAP use was indicated, the adjusted risk of AF was significantly higher in patients who needed CPAP treatment compared to the control group (without SDB) with a HR of 4.507 (95% CI: 1.691–12.010, $P = 0.003$; Table 4). For patients with SDB who did not require CPAP use, the risk of AF was still higher than those without SDB (HR, 1.457; 95% CI: 1.099–1.932, $P = 0.009$).

Discussion

Main Findings

In this large-scale nationwide population-based cohort study, we investigated the association of SDB and AF among healthy subjects who were younger than 75 years old and who had no significant comorbidities. The main findings were as follows: (1) the incidence of AF was around 1.38 per 1,000 person-years for patients with SDB; (2) SDB significantly predisposed patients to develop AF, and was a novel risk factor of new-onset AF; and (3) AF risk increased with increasing clinical severity of SDB, represented by the requirement of CPAP use.

SDB and Risk of AF

The present study has shown that AF incidence was significantly higher in patients with SDB than control subjects (1.38 vs. 0.76 per 1,000 person-years). To the best of our knowledge, this is the first study reporting the incidence of AF in patients with SDB alone in a population-based cohort. But what are the possible mechanisms of the link between SDB and AF? In the Dimitri et al study, which enrolled a total of 40 paroxysmal AF patients receiving catheter ablation (20 subjects had SDB), batrial electroanatomic mapping and electrophysiological study showed that SDB was associated with significant atrial remodeling, characterized by atrial enlargement, voltage reduction, abnormal conductions, and longer sinus node recovery time.²⁶ In a recent animal study from Stanley Nattel's group, intubated rats underwent hemodynamic and echocardiographic studies

after obstructive sleep apnea was mimicked by stopping the ventilator and closing the airway for 40s.²⁷ The results suggested that forced respiration-induced acute left atrial stretch superimposed on left ventricular diastolic dysfunction may be central to AF promotion in SDB. In addition to the left atrial remodeling, Ghias et al reported that SDB-induced AF may be attenuated by ablation of the pulmonary artery-associated ganglionated plexi or pharmacological inhibition of autonomic inputs in an animal model similar to SDB, suggesting that an autonomic link may exist between SDB and AF.^{28,29} Further, the inflammatory responses caused by SDB, which were associated with atrial remodeling,³⁰ arousal responses, the fluctuation of heart rate and hypoxic stress, may also predispose patients with SDB to AF. Taken together, structural and electrical remodeling of the LA due to an increased inflammatory status and repeated atrial stretch and autonomic activation during the apnea episodes may play an important role in the pathogenesis of SDB-related AF.

Previous Studies

In addition to the traditional factors associated with AF, such as hypertension, diabetes and advanced age, many investigators devoted themselves to finding more novel risk factors. Through the identification of more and more predisposing factors to AF, physicians have been able to identify patients at risk of AF more accurately. The present results show that SDB itself is an important risk factor of AF, a finding further supported by the observation that the risk of AF is even higher in patients with SDB with a high clinical severity.

Although the close association between SDB and AF has been discussed and become well-accepted in recent years, we are surprised to find that there have been only several studies investigating whether SDB is a risk factor of AF in the literature, which are summarized in [Table S1](#). It should be noted that most of these studies were cross-sectional observations,^{15,16,18} and may not be able to indicate a temporal relationship between SDB and AF. The Gami et al study, which enrolled a total of 3,542 adults referred for a diagnostic polysomnogram from 1987 to 2003 at the Mayo Clinic, represented the only one longitudinal cohort study investigating this issue.¹⁷ SDB, however, was present in 2,626 subjects (74%) in the Gami et al study, implying that important selection biases could be present and the results may not be generalized to real-world clinical practice. In the present study, we explored the temporal relationship between SDB and AF in a nationwide population-based cohort, which may minimize the risk of significant selection biases and facilitate understanding of the SDB-related incidence of AF. In contrast to the Porthan et al study showing that SDB was not significantly associated with lone AF,¹⁶ the present study indicates that SDB is an important predisposing factor to AF among patients without significant comorbidities, with a HR of 1.536. The negative correlation between SDB and AF in the Porthan et al study may be due to the small sample size, with only 59 AF and 56 non-AF patients, in contrast to the present study, which had a large patient number.

Clinical Applications

The current study has shown that SDB itself can cause AF without the coexistence of other systemic diseases. This finding has not been clearly mentioned before, and provides convincing evidence to support the concept that SDB is a novel risk factor of AF. For patients with SDB who have had ischemic stroke, aggressive examinations should be considered to detect AF even in the absence of any systemic disease. SDB should also be regarded as a potential cause of AF and be routinely

screened for when managing AF patients, especially those without any comorbidity and younger than 75 years old.

Study Limitations

There were several limitations of the present study. First, the occurrence of AF was based on the diagnostic code registered by the treating physicians, and was not further checked externally. This, however, is a common limitation, which was also noted in a previous study,³¹ and the diagnosis of AF in the present investigation was repeatedly confirmed more than twice to minimize diagnostic bias. Second, information on type of SDB (obstructive or central type) was not available in this nationwide registry. Nonetheless, more than 90% of patients with SDB referred for polysomnography had the obstructive type,³² and central sleep apnea was also reported to be associated with AF.³³ Therefore, the type of SDB may not be an important factor that could confound or change the present results. The relationship between AF and central sleep apnea, however, could be bidirectional, with each leading to the other, and further study is necessary to determine whether obstructive or central SDB differs in causing AF. Third, patients enrolled in the present study without significant comorbidity at baseline could have developed new-onset cardiovascular diseases during the subsequent follow-up. Therefore, we were not able to ascertain that the occurrence of AF was solely attributed to SDB. Cardiovascular disease, however, would theoretically develop in both the study and control groups, and may not significantly confound the analysis comparing the risk of AF between patients with or without SDB. Fourth, the diagnosis of SDB was based on the same ICD-9-CM codes as that used in previous studies from Taiwan,^{19–22} and the data on the devices used for diagnosis and the severity of SDB (such as apnea-hypopnea index) were not recorded in this registry database. The diagnostic accuracy of SDB in NHIRD, however, has been validated in a single-center cohort previously, and around 83% of the diagnosis was confirmed on overnight polysomnography, with approximately 90% of them having an apnea-hypopnea index >5.²² Last, we analyzed data on CPAP use only when study subjects were enrolled; whether patients continued to receive CPAP treatment during the follow-up period was uncertain. Consequently, it is unclear whether patients with SDB who received regular CPAP treatment had a lower risk of AF compared to patients with a similar severity of SDB but without long-term CPAP use. Decision-making regarding CPAP was carried out by physicians without a uniform rule, and a selection bias may exist.

Conclusions

The incidence of AF was around 1.38 per 1,000 patient-years among subjects with SDB alone, which was much higher than in those without it (0.76 per 1,000 person-years). SDB itself, without the coexistence of other systemic diseases, is a novel risk factor of AF, and the risk increased with increasing clinical severity of SDB. The important link between SDB and AF should always be kept in mind when managing SDB and AF patients.

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Supplementary Files

Supplementary File 1

Table S1. Studies on SDB and AF

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-14-0222>