CLINICAL RESEARCH STUDY

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Sleep Apnea and Risk of Deep Vein Thrombosis: A Non-randomized, Pair-matched Cohort Study

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ABSTRACT

BACKGROUND: Patients with sleep apnea have been reported to be associated with increased prevalence of deep vein thrombosis (DVT) in some papers, which were criticized for either a small sample size or lack of a prospective control. Our study strived to explore the relationship of sleep apnea and the subsequent development of DVT using a nationwide, population-based database.

METHODS: From 2000 to 2007, we identified a study cohort consisting of newly diagnosed sleep apnea cases in the National Health Insurance Research Database. A control cohort without sleep apnea, matched for age, sex, comorbidities, major operation, and fractures, was selected for comparison. The 2 cohorts were followed-up, and we observed the occurrence of DVT by registry of DVT diagnosis.

RESULTS: Of the 10,185 sampled patients (5680 sleep apnea patients vs. 4505 control), 40 (0.39%) cases developed DVT during a mean follow-up period of 3.56 years, including 30 (0.53%) from the sleep apnea cohort and 10 (0.22 %) from the control group. Subjects with sleep apnea experienced a 3.113-fold (95% confidence interval, 1.516-6.390; $P = .002$) increase in incident DVT, which was independent of age, sex, and comorbidities. Kaplan-Meier analysis also revealed the tendency of sleep apnea patients toward DVT development (log-rank test, $P = .001$). The risk of DVT was even higher in sleep apnea cases who needed continuous positive airway pressure treatment (hazard ratio 9.575; 95% confidence interval, 3.181-28.818; $P < .001$).

CONCLUSION: Sleep apnea may be an independent risk factor for DVT.

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KEYWORDS: Deep vein thrombosis; Intermittent hypoxia; Sleep apnea; Sleep-disordered breathing

Sleep apnea (SA) is a disorder characterized by apnea during sleep, resulting either from repetitive collapse of the upper airway (namely, obstructive sleep apnea [OSA]) or from loss of respiratory effort due to a central neurologic etiology (central sleep apnea [CSA]). The majority of SA patients presenting for polysomnography have OSA, accounting for more than 90%, whereas CSA makes up <10%.[1] OSA affects 24% of men and 9% of women of the middle-aged population in the US[2] and has been reported to be associated with a variety of cardiovascular diseases.[3-6]

A growing amount of evidence suggests a hypercoagulable state in OSA patients, supporting an inclination toward thrombogenesis.[7,8] In contrast to abundant reports elucidat-

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ing the great impact of SA on arterial thrombotic events such as coronary artery diseases and cerebrovascular accidents,[3,5,6] few clinical studies have addressed the relationship between SA and deep vein thrombosis (DVT). In a cross-sectional study, Arnulf et al[9] first surveyed 68 patients with pulmonary embolism and DVT, among which 43 patients (63.2%) had moderate-to-severe OSA. Another prospective observational study enrolling 89 OSA patients disclosed a higher incidence of DVT (2.2%) during a 3-year follow-up period, compared with the control group.[10] Despite indicating a possible link of OSA and DVT, these 2 studies were criticized for limited sample size and lack of a prospective control.

CLINICAL SIGNIFICANCE

- Sleep apnea, female sex, and hypertension are independently associated with increased risk of deep vein thrombosis.
- Risk of deep vein thrombosis is higher in patients who use continuous positive airway pressure, suggesting an increased risk with increasing severity of sleep apnea.

We hypothesized that SA may contribute independently to the development of DVT. Utilizing a nationwide database, we conducted this nonrandomized, pair-matched cohort study to investigate the relationship between SA and the subsequent development of DVT.

MATERIALS AND METHODS

Database

The National Health Insurance program in Taiwan has been operating since 1995 and 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 National Health Insurance claims database, and it has published numerous extracted datasets for researchers. The NHRI released a cohort dataset comprising 1,000,000 randomly sampled people who were alive during 2000 and collected all the records of these individuals from 1995 onwards. The database has been confirmed by NHRI to be representative of the Taiwanese population.[12] It also is one of the largest nationwide population-based databases in the world, with more than 270 scientific articles published using its data.[13] In this cohort dataset, each patient's original identification number has been encrypted to protect privacy. Of note, the encrypting procedure is consistent such that the linkage of claims belonging to the same patient is feasible within the NHIRD datasets.

Study Sample and Control

We identified patients who were newly diagnosed as cases of SA (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 780.51, 780.53, 780.57) from the 1,000,000 sampling cohort dataset from January 1, 2000.[14] An age-, sex-, and comorbidity-matched control group was selected from those patients without SA throughout the whole course of follow-up. In both groups, subjects with pre-existing DVT (ICD-9-CM codes 453.0-453.9) before enrollment were excluded from this study.

The comorbidities to be matched in the 2 groups included pre-existing (upon enrollment) hypertension (ICD-9-CM codes 401.xx–405.xx), diabetes mellitus (250.xx), chronic obstructive pulmonary disease (491, 494, 492, 496), coronary artery disease (411.xx, 413.xx, 414.xx), dysrhythmia (427.xx, 785.0, 785.1), ischemic stroke (433.xx, 434.xx, 436, 437.1), chronic kidney disease (580.xx-587.xx), cancer (140.0–199.1), hyperlipidemia (272-272.4), fractures (733.10-733.19, 800-829), and major surgery (by procedure codes of NHIRD). History of major surgery, which included all operations requiring general anesthesia and at least 1-day recumbency, was recorded within 1 month before occurrence of events (DVT) or at the end of follow-up. Among female enrollees, history of pregnancy and hormone-related medication also were recorded.

Main Outcome

The end point of the study was defined as occurrence of DVT (ICD-9-CM codes 453.0-453.9). In this database, the ICD codes of SA and DVT did not change throughout the whole follow-up period (2001-2007), assuring the consistency of the disease registry. Continuous positive airway pressure (CPAP) applies a constant level of positive pressure at the airway opening during spontaneous breathing. It is a treatment generally recommended for patients with OSA who have not responded to more conservative therapies (eg, behavior modification, oral appliances) and patients with complex comorbidities, such as congestive heart failure. In order to investigate the association between increasing severity of SA and future risk of DVT, risk of DVT also was analyzed in the sample after stratification for use of CPAP, which we used as a surrogate marker for SA severity.

Statistical Analysis

Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, Wash) was used for data management and computing. Statistical analyses were performed utilizing SPSS software (Version 18.0; SPSS, Inc., Chicago, Ill). All data were expressed as mean ± SD or percentage. Comparisons between the 2 groups were determined by independent Student's t test for continuous variables or Pearson's χ^2 test, Yates' correction for continuity/Fisher's exact test as appropriate for categorical variables. We used Cox propor-

Table 1 Demographic Data for SA Patients and Controls (N = 10,185)

	SA	Control	*P* Value
N	5680	4505	
Age, year	45.18 ± 17.54	44.75 ± 17.57	.213*
Female (%)	37.9	37.5	.699
Pregnancy (% of female)	0.6	0.5	1.000
Hormone-related medication (% of female)	3.9	3.3	.340
Follow-up period (years)	3.07 ± 2.14	4.18 ± 1.92	<.001*
Comorbidities			
Hypertension (%)	34.5	33.2	.182
Diabetes mellitus (%)	18.3	17.2	.159
COPD (%)	23.7	22.7	.253
Coronary artery disease (%)	22	20.4	.05
Arrhythmia (%)	19.9	18.7	.115
Heart failure (%)	6.1	5.3	.115
Ischemic stroke (%)	6.4	5.5	.073
Chronic kidney disease (%)	10.7	10.1	.372
Cancer (%)	7.7	7	.199
Hyperlipidemia (%)	29	20.9	<.001
Fracture (%)	0.6	0.3	.054
Major operation (%)	0.2	0.2	.876
Development of DVT during follow-up	30 (0.53 %)	10 (0.22 %)	.001†

COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; SA = sleep apnea.

Data are given as mean ± SD or percentage. *P* values for comparisons between 2 groups are determined by chi-squared test with Yates' correction for continuity unless mentioned otherwise.

*Independent *t* test.

†Kaplan-Meier analysis.

tional hazards models to test the association of SA with DVT. Survival analysis also was assessed using the Kaplan-Meier method, with the significance based on the log-rank test. Statistical significance was inferred at a 2-sided *P* value of <.05.

RESULTS

A total of 5680 newly diagnosed SA patients (mean age 45.18 ± 17.54 years) were identified from the 1,000,000 sampling cohort dataset between January 2000 and December 2007. Another 4505 subjects without SA (mean age 44.75 ± 17.57 years) were matched for age, sex, comorbidities, major operation, and fractures, serving as the control group. The demographic parameters of study subjects are listed in **Table 1**. At the end of the study period (December 31, 2007), most enrollees in both groups (96.6% in SA cohort and 95.3% in the control group) remained active and were followed through the end of the study (**Figure 1**).

During an average of 3.56 ± 2.12 years' follow-up period, there was a significantly higher incidence of DVT development among SA patients, compared with the control group (30 [0.53%] vs 10 [0.22%], *P* = .001). **Figure 2** outlines the results of a Kaplan-Meier analysis, and the log-rank test, which showed that SA patients had a significantly higher incidence of DVT than those patients without SA (*P* = .001).

Comparison between patients with and without DVT was shown in **Table 2**. Patients with DVT were older, more likely to be female, and more likely to have the comorbidities of hypertension, diabetes mellitus, coronary artery disease, ischemic stroke, chronic kidney disease, cancer, hyperlipidemia, and SA. The Cox proportional hazards regression model was used to determine the factors independently associated with the development of DVT. After

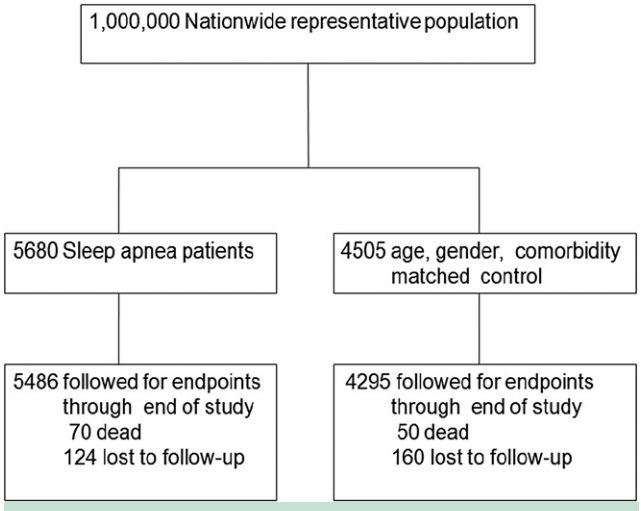

Figure 1 Study profile.

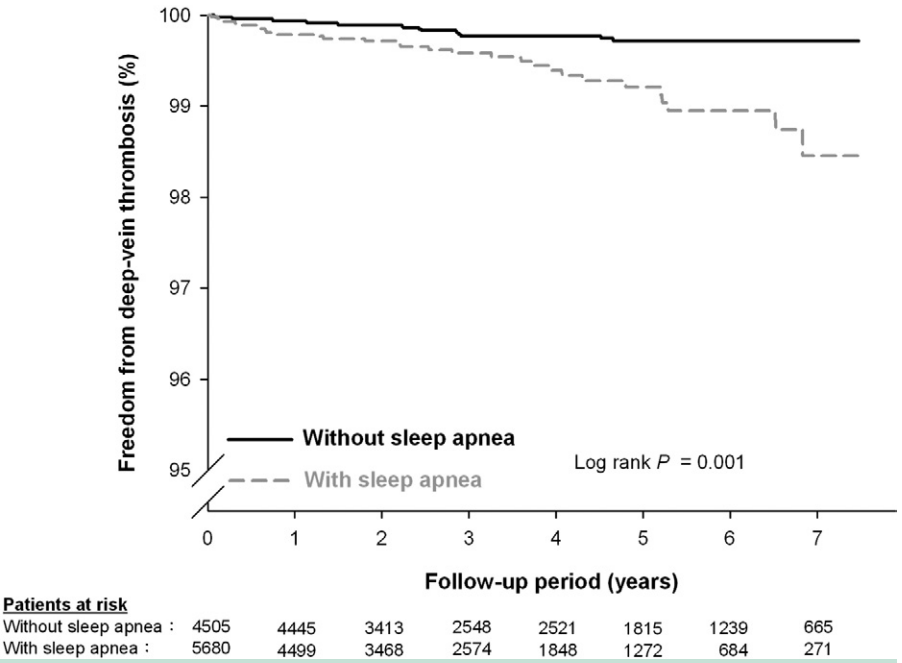

Figure 2 Kaplan-Meier curves of freedom from deep vein thrombosis in patients with and without sleep apnea. There was a statistically significant difference between the 2 curves (log-rank test, $P = .001$).

adjusting for age, sex, and the aforementioned significant comorbidities, only SA (hazard ratio [HR] 3.113; 95% CI, 1.516-6.390; $P = .002$), female sex (HR 2.145; 95% CI, 1.143-4.025; $P = .017$), and hypertension (HR 2.510; 95% CI, 1.070-5.889; $P = .034$) were independently associated with DVT development (**Table 3**). Compared with the control group, the adjusted risks of DVT in SA cases who needed and did not need CPAP treatment were 9.575 (95%

Table 2 Characteristics of Patients with DVT and without DVT

	DVT (+)	DVT (−)	*P* Value
n	40	10,145	
Age, year	56.48 ± 14.47	44.94 ± 17.55	<.001*
Female	23 (57.5%)	3819 (37.6%)	.01*
Pregnancy (% of female)	1 (4.3%)	20 (0.5%)	.119†
Hormone-related medication (% of female)	0	141 (3.7%)	1.000†
Comorbidities			
Sleep apnea, n (%)	30 (75%)	5650 (55.7%)	.014*
Hypertension, n (%)	28 (70%)	3427 (33.8%)	<.001*
Diabetes mellitus, n (%)	17 (42.5%)	1795 (17.7%)	<.001*
COPD, n (%)	10 (25%)	2361 (23.3%)	.796
Coronary artery disease, n (%)	19 (47.5%)	2153 (21.2%)	<.001*
Arrhythmia, n (%)	8 (20%)	1965 (19.4%)	.92
Heart failure, n (%)	2 (5%)	581 (5.7%)	1.000
Ischemic stroke, n (%)	7 (17.5%)	603 (5.9%)	.002*
Chronic kidney disease, n (%)	11 (27.5%)	1052 (10.4%)	<.001*
Cancer, n (%)	7 (17.5%)	749 (7.4%)	.026*†
Hyperlipidemia, n (%)	17 (42.5%)	2574 (25.4%)	.021*
Fracture, n (%)	1 (2.5%)	44 (0.4%)	.163†
Major operation, (%)n	1 (2.5%)	19 (0.2%)	.076†

COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis.
*<.05.
Data are given as mean ± SD or percentage. *P* values for comparisons between 2 groups are determined by Student's *t* test for continuous variables or chi-squared test/Fisher's exact test† for categorical variables.

Table 3 Predictor for DVT by Cox Proportional Hazards Regression Analysis

	HR	95% CI for HR	*P* Value
Sleep apnea	3.113*	1.516-6.390*	0.002*
Age	1.007	0.982-1.032	0.579
Female	2.145*	1.143-4.025*	0.017*
Hypertension	2.510*	1.070-5.889*	0.034*
Diabetes mellitus	1.773	0.873-3.598	0.113
Coronary artery disease	1.548	0.746-3.214	0.241
Ischemic stroke	1.593	0.662-3.835	0.299
Chronic kidney disease	1.978	0.949-4.121	0.069
Cancer	1.663	0.719-3.846	0.235
Hyperlipidemia	0.985	0.491-1.975	0.966

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio.
*<.05.

CI, 3.181-28.818; P <.001) and 2.751 (95% CI, 1.317-5.747; P = .007), respectively (**Table 4**).

DISCUSSION

In our current study, we identified SA as an independent risk factor for future development of DVT using a large-scale nationwide database, which supports the concept that SA may contribute to the formation or progression of thrombosis in venous circulation. Additionally, the adjusted risks of DVT in SA patients who needed and did not need CPAP treatment were 9.575 (95% CI, 3.181-28.818; P <.001) and 2.751 (95% CI, 1.317-5.747; P = .007), respectively, suggesting increased risk with increasing severity of sleep apnea.

The mechanism underlying the link of SA and DVT may lie in intermittent nocturnal hypoxia and chronic systemic inflammation, which are characteristic of SA, especially OSA.[15] Short-term hypoxia alone may not induce significant hemostatic derangement in healthy subjects,[16-18] but may provoke coagulation activation and elevation of inflammatory cytokines in subjects with chronic inflammatory lung diseases,[19,20] suggesting the interplay between inflammation and coagulation. For patients with SA, chronic intermittent hypoxia as a result of repetitive apnea/hypopnea events produces reactive oxygen species and activates proinflammatory transcription factor nuclear factor κB and hypoxia-inducible transcription factor-1, thereby increasing the production of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α.[21-24] On the action of these inflammatory cytokines, vascular endothelial cells increase expression and release of tissue factor, triggering the extrinsic coagulation pathway.[25] Platelet aggregation also is enhanced owing to the release of von Willebrand factor by endothelium.[26,27] Endothelial function is further impaired by reactive oxygen species and inflammatory mediators, which reduce nitric oxide availability and repair capacity.[28] On the other hand, these inflammatory mediators also downregulate activated protein C and upregulate plasminogen activator inhibitor, thus suppressing fibrinolysis.[25,29] All the aforementioned factors favor thrombosis formation in patients with SA.

One particular strength of this study is the nationwide, cohort study design with age- and comorbidity-matched controls, which allows a powerful conclusion to be drawn. In our study, SA, female sex, and hypertension were identified as independent predictors of DVT development. As aforementioned, OSA was reported to link with a hypercoagulable status. Our current work provides a "bridge" between laboratory hemostatic disturbance and clinical presentation.

In previous studies, female sex seemed to be subject to DVT development due either to pregnancy[30,31] or hormone-related medication.[32,33] As for the characteristics of our study population, among patients with SA there were fewer females and, hence, less pregnancy and hormone-related medication. The odds ratios of these 2 conditions related to female sex may be exaggerated or biased due to few such subjects being enrolled. Despite this, our analysis still revealed that female patients tended to develop DVT, regardless of associated pregnancy or hormone drugs.

With regard to hypertension, it has been shown to be an overlapping risk factor for arterial and venous thrombosis.[34] A meta-analysis by Ageno et al[35] concluded that patients with hypertension were at 1.5-fold higher risk for DVT than were controls. Interestingly, a study by Zamarron et al[36] revealed that OSA patients had higher serum plasminogen activator inhibitor-1 level, which was more pronounced in those with comorbid hypertension, suggesting the possible synergic effect of both factors.

In our current study, we demonstrated the association between CPAP use and the risk of DVT. The data suggest that more severe SA patients who have not responded to more conservative therapies and need CPAP treatment are probably at higher risk of DVT. However, factors associated with increasing severity of SA, such as limitation of patients' movement, obesity, and underlying comorbidities, also may lead to an increased risk for DVT formation. All these factors, as well as increasing severity of SA, may contribute together to an increase in the risk of DVT. Although statistically significant, the clinical relevance of increasing severity of SA and increased risk of DVT needs to be further established.

Table 4 Association between Severity of SA and the Risk of DVT

	HR	95% CI	*P* Value*
Control	Referent		
SA, CPAP not indicated	2.751	1.317-5.747	.007
SA, CPAP indicated	9.575	3.181-28.818	<.001

CI = confidence interval; CPAP = continuous positive airway pressure; DVT = deep vein thrombosis; HR = hazard ratio; SA = sleep apnea.
*Cox proportional hazards regression analysis.

There are some limitations worth noting in this study. Importantly, diagnoses of SA and DVT that rely on administrative claims data registered by physicians or hospitals may be less accurate than diagnoses made according to standardized criteria. Additionally, some personal information, including body mass index and smoking status, was not available in the administrative data, preventing accurate assessment of the contributory and confounding effect of these factors. Most notable among these factors is obesity, which has been reported to increase the risk of DVT.[37,38] Cigarette smoking has been shown, although inconsistently, to have no effect on DVT development, as reported by Ageno et al in a meta-analysis.[35] Of note, CPAP is a treatment generally recommended for patients with OSA who have not responded to more conservative therapies and for SA patients with complex comorbidities such as congestive heart failure. Although we use it as a surrogate marker for SA severity, its use may not necessarily reflect the severity of SA as well as the comorbidity status. Patients' anatomy and preferences also are possible factors in determining appropriate treatment modalities.[39] More research is needed to clarify the issue. Finally, we did not further divide SA into obstructive or central type as the 2001 version of the ICD-9 coding system, which our insurance system adopted, had not done so, either. Nonetheless, the majority of SA patients presenting for polysomnography have OSA, accounting for more than 90%.[1] OSA also was the focus of reports about cardiovascular events associated with SA. Whether OSA or CSA differs in contribution to DVT deserves further exploration.

In conclusion, we identified SA as an independent risk factor for DVT in a large-scale population-based study. The risk was significantly higher in individuals using CPAP treatment, suggesting an increased risk with increasing severity of SA.

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