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Influence of lung function and sleep-disordered breathing on stroke: a community-based study

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Abstract

Background—Impaired lung function is regarded as a risk factor for stroke in patients with chronic obstructive pulmonary disease. However, the association between reduced lung function and incident stroke in a community-based population with sleep-disordered breathing (SDB) remains unknown.

Methods—We performed a prospective study within the Sleep Heart Health Study cohort. Full montage home sleep testing and spirometry data on 2082 and 2072 individuals with and without SDB, respectively, were analysed. Cox proportional hazards regression models were used to estimate the association between lung function and incident stroke.

Results—Over 11.7 years, 183 cases of stroke were identified in participants without pre-existing cardiovascular diseases, including 71 and 112 with an AHI < 5 events/hour and ≥ 5 events/hour, respectively. In the entire population, lung function was inversely associated with incident stroke (hazard ratio (HR): 0.913 [95% confidence interval (CI): 0.839–0.994] for every 10% increase in percentage of predicted FVC). When the population was divided according to the presence/absence of SDB, the association of lung function with incident stroke became stronger in individuals with SDB (HR: 0.899 [0.822–0.984] for every 10% increase in percentage of predicted FEV₁; HR: 0.881 [0.787–0.987] for every 10% increase in percentage of predicted FVC) but not in individuals without SDB.

Conclusions—Lung function may serve as a risk factor for incident stroke in a community-based population, especially in those with SDB. Spirometry may help improve the risk management for primary care in community-based populations.

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Keywords

Lung function; Sleep-disordered breathing; Community; Stroke; Cohort study

Introduction

An association between reduced lung function and stroke is commonly observed in patients with clinically established lung diseases, as well as in healthy individuals who exhibit lung function within the normal range during examination [1–4]. In addition to forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁), sleep-disordered breathing (SDB) is another important risk factor of stroke [5,6]. Although the clinical importance of the co-occurrence of SDB and chronic obstructive pulmonary disease (COPD) is increasingly being recognised [7,8], the influence of reduced lung function on incident stroke has not been well studied in community-based populations with SDB.

It has been suggested that participants with SDB and impaired lung function, especially those with COPD, have more pronounced nocturnal hypoxaemia than do those with one disorder alone [9]. The synergistic effect promotes the activation of the sympathetic nervous system, oxidative stress, and systemic inflammation, which collectively contribute to vascular injuries and cardio-cerebral vascular incidents [3]. However, Putcha *et al.* demonstrated that the incremental contribution of lung function to mortality is attenuated with increasing SDB severity [10]. The aim of the present study was to investigate the influence of impaired lung function on incident stroke in a population of individuals with and without SDB from the Sleep Heart Health Study (SHHS), a large community-based perspective cohort. We hypothesized that reduced lung function with SDB may be associated with stroke in this study.

Methods

Study Design and Participant

The SHHS (registration number: NCT00005275) is a community-based, multi-centre, prospective cohort study designed to establish the cardiovascular outcomes of SDB among individuals in the population who are aged 40 years or older [11]. Of the 11,145 eligible people who were eligible for recruitment into the SHHS, 5804 ultimately agreed and provided informed consent to complete the baseline interview and health examination (1995–1998) [12]. The adjudicated heart health outcomes, including stroke, heart attack, heart failure, and other cardiovascular events, were followed until 2011. The protocol was approved by the Institutional Review Board of each participating institution (Boston University, Case Western Reserve University, Johns Hopkins University, Missouri Breaks Research, Inc., New York University Medical Center, University of Arizona, University of California at Davis, University of Minnesota–Clinical and Translational Science Institute, University of Washington). The data were accessed based on a signed agreement with the Brigham and Women's Hospital, Boston, MA.

Polysomnography

Participants in the SHHS underwent in-home polysomnography with the Compumedics P-series portable monitor (Abbotsford, Victoria, Australia). Details regarding the polysomnographic equipment, hook-up procedures, scoring, and quality assurance and control have been described elsewhere [11,13]. Apnoea was defined as the complete or near-complete cessation of airflow for at least 10 s. Hypopnoea was defined as airflow or thoracoabdominal movements that were at least 30% below the baseline values for at least 10 s. The apnoea-hypopnoea index (AHI) was defined as the average number of apnoeas and hypopnoeas, each associated with a 4% decrease in oxygen saturation, per hour of sleep [13]. SDB was defined when an individual had an AHI of ≥ 5 events/h based on in-home polysomnography [14].

Assessment of Lung Function

Lung function was measured using spirometry. Spirometry was performed during the baseline examination according to previously published parent study protocols [9]. The three most common lung function indices, including forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and the FEV_1 /FVC ratio, were employed in our study. The FEV_1 as a percentage of the predicted value (FEV_1 PP) and FVC as a percentage of the predicted value (FVCP) were calculated according to each individual's age (in years) and height (in metres) using the following formulas:[15]

Women:

$$\text{predicted } FEV_1 = 2.72 + 3.50 \times (\text{Height} - 1.65) - 0.025 \times (\text{Age} - 45)$$

$$\text{predicted } FVC = 3.54 + 4.53 \times (\text{Height} - 1.65) - 0.024 \times (\text{Age} - 45)$$

Men:

$$\text{predicted } FEV_1 = 3.63 + 3.62 \times (\text{Height} - 1.75) - 0.032 \times (\text{Age} - 45)$$

$$\text{predicted } FVC = 4.84 + 5.83 \times (\text{Height} - 1.75) - 0.025 \times (\text{Age} - 45)$$

Ascertainment of Outcomes—The primary outcome is stroke in the present study. Data on incident stroke were extracted from the discharge information at local hospitals according to cohort-specific protocols between the date of the baseline polysomnogram and the end of follow up [16,17]. Specifically, stroke was defined as a series of neurologic symptoms with a sudden onset that lasted at least 24 h or until death, usually along with the support of brain images.

Covariates

During the SHHS home visit, a study technician collected each participant's health history using a standardised questionnaire before polysomnogram monitoring. Smoking status was classified as "never" (if the participant reported smoking fewer than 20 packs of cigarettes during their lifetime), former, or current. Participants' body mass index (BMI), and blood lipid measurements were obtained using a standardised protocol at the SHHS baseline examination [11]. History of hypertension was identified based on the second and third blood pressure readings, or if the participant was being treated with hypertension agents. History of diabetes mellitus was ascertained based on the report of a physician-administered diagnosis, or on the reported use of insulin or oral hypoglycaemic medication.

Statistical Analysis

Participants were followed up until a first stroke occurred between the date of the polysomnogram and the final censoring date. Individuals who did not develop a stroke were censored at the date of death or last contact. Descriptive statistics are presented in the entire population and subgroups established via AHI dichotomisation. Values represent the mean $\pm$ standard deviation for continuous variables or number (percentage) for categorical variables. Cox proportional hazards regression modelling was used to examine the association between baseline lung function and incident stroke in this study. Multivariate models were adjusted for the following factors: (1) age, sex, and BMI in Model 1; (2) Model 1 plus smoking status and AHI (continuous), which are recognised as important risk factors of cardiovascular events; (3) Model 2 plus total cholesterol, triglycerides, high-density lipoprotein, history of diabetes mellitus, and history of hypertension. The interactions of AHI and lung function parameters are tested based on Model 3 to examine whether additional interference exists within the associations with stroke. *P* values <0.05 were considered to be statistically significant. All statistical analyses were performed with the SPSS software package version 22.0 (IBM Corp., Armonk, NY).

Results

Among 5804 participants, 600 had a medical history of cardiovascular diseases before baseline (including myocardial infarction, heart failure, stroke, and revascularisation), 762 were without follow-up data, 281 lacked baseline FEV1 or FVC values, and 7 were missing height data, ultimately leaving an analytical sample size of 4154 participants. Participants were divided into two groups according to the presence/absence of SDB, as follows: 2072 participants with an AHI of ≥ 5 events/h in the group with SDB and 2082 individuals with an AHI of < 5 events/h in the group without SDB (Figure 1).

The demographic and clinical information of the participants is shown in Table 1. In this study, the longest follow-up time is 15.8 years, and the shortest is 3.7 years, and the average is 11.7 years. Most of the study population was Caucasian (87.9%), 63.44 ± 10.94 years for the average age, 28.27 ± 5.02 kg/m² for BMI and 9.71 ± 12.89 events/h for AHI in the entire population. Compared to the AHI < 5 group, the AHI ≥ 5 group was significantly more likely to be male (55.5% vs. 33.5%), current smokers (55.3% vs. 33.5%), and older (65.57 ± 10.43 vs. 61.33 ± 11.03 years) ($P < 0.001$ for all). The AHI ≥ 5 group also had a

significantly higher BMI (29.66 ± 5.27 vs. 26.88 ± 4.33 kg/m²), and higher prevalence of hypertension and diabetes mellitus compared to the AHI < 5 group ($P < 0.001$ for all).

In the entire population, for each 10% increase in FEV₁PP and FVCPP, the risk of stroke decreased by 13.2% and 25.6%, respectively. After adjusting in Model 1, the influence of lung function on stroke was modestly diminished, with a hazard ratio (HR) of 0.912 (95% CI: 0.856–0.971) for every 10% increase in FEV₁PP, and 0.890 (95% CI: 0.822–0.964) for every 10% increase in FVCPP. Further adjustment in Model 2 decreased the intensity of the prediction, although it was still statistically significant ($P = 0.021$ for FEV₁PP and $P = 0.006$ for FVCPP). With the additional adjustment in Model 3, the relationship still remained statistically significant, with an HR of 0.913 (95% CI: 0.839–0.994) for every 10% increase in FVCPP ($P = 0.036$) (Table 2).

The interaction analyses were examined between AHI and lung function measurements ($P_{\text{interaction}} = 0.011$ for each 10% increase in FEV₁PP; $P_{\text{interaction}} = 0.032$ for each 200 mL increase in FEV₁; $P_{\text{interaction}} = 0.001$ for each 10% increase in the FEV₁/FVC ratio), which revealed the associations with stroke could be modified by AHI. To diminish the interference of AHI in the association between lung function and incident stroke in individuals with and without SDB, analyses were also conducted in the AHI ≥ 5 and AHI < 5 groups. In the model that was adjusted for all variables, FEV₁PP and FVCPP were significantly associated with incident stroke in the AHI ≥ 5 group, but not in the AHI < 5 group (Figure 2). In the AHI ≥ 5 group, the HR for incident stroke was 0.889 (95% CI: 0.882–0.984) for every 10% increase in FEV₁PP and 0.881 (95% CI: 0.787–0.987) for every 10% increase in FVCPP after multivariable adjustment. However, the FEV₁, FVC, and FEV₁/FVC ratio, regardless of whether AHI was dichotomised at a cut-off point of 5, were not significantly associated with stroke after adjusting for all potential covariates (Supplementary Table 1).

Discussion

Two of the most prevalent chronic respiratory disorders in clinics, COPD and SDB, are commonly complicated by cardiovascular events. The two disorders co-exist in approximately 1% of adults, while asymptomatic lower lung function combined with SDB is even more prevalent [18]. In the present study, impaired lung function was associated with a high risk of stroke in the entire population, consistent with the findings of previous studies [19]. Besides, lung function, as assessed by the FEV₁PP or FVCPP, was inversely associated with incident stroke in participants with SDB but not in those without SDB. Our findings confirmed that impairments in lung function, even if they fail to reach the clinical diagnosis standard of pulmonary diseases, are nevertheless associated with a higher risk of stroke.

Other studies have also reported an inverse association between lower-lung function and incident stroke [2,19]. For instance, Portegies *et al.* noted that the risk of stroke significantly increased in a large perspective cohort of patients with COPD, even reached to 6.66-fold within the acute severe exacerbation of COPD [20]. Truelsen and colleagues also found that reduced lung function, as measured by FEV₁PP, was a predictor of first-time stroke and fatal stroke even in individuals who had no respiratory symptoms [2]. The findings of these prior studies are in accordance with our overall results. However, considering the interaction

between SDB and lung function and SDB-induced cardiovascular comorbidity [21], further prospective studies are needed to clarify the synergistic effects of SDB and reduced lung function.

It is known that individuals with lung function impairments are prone to poor sleep quality and experience disturbances in ventilation and gas exchange during sleep; SDB is also very prevalent in these individuals [18]. In their review, Chowdhuri *et al.* demonstrated that reduced lung function and SDB have independently been implicated in cardiovascular diseases, including hypertension, ischemic heart disease, congestive heart failure, arrhythmias, and stroke [22]. However, Putcha and co-workers demonstrated that the incremental contribution of lung function to all-cause mortality decreases as the SDB severity increases [10]. To clarify the influence of reduced lung function combined with SDB on stroke, we carried out the interaction analysis and found that lung function impairment is only associated with a high risk of stroke in individuals with SDB, but not in those without SDB.

Although the underlying mechanisms for this relationship between lung function impairment and risk of stroke in individuals with SDB remain unclear, several potential explanations may be proposed. Prior studies have revealed that both reduced lung function and SDB are associated with vascular endothelial dysfunction and elevated inflammatory mediators, including C-reactive protein, interleukin-6, interleukin-8, and tumour necrosis factor- α , which stimulate and accelerate atherosclerotic plaque formation and rupture, and that these factors are all associated with the cardiovascular events [23,24]. On the other hand, studies have shown that SDB-related stressors may increase the stroke risk by influencing cerebral tissue oxygenation, altering cerebral blood flow and velocity, and modifying cerebral vascular auto-regulation; indeed, cerebral tissue haemoglobin desaturation has been identified in individuals with apnoeas, while tissue deoxygenation has been found in individuals with SDB [25,26]. Notably, SDB may also lead to metabolic dysfunction, which results in insulin resistance, further contributing to the risk of cardiovascular diseases [27]. Therefore, the combination of SDB and impaired lung function may increase the risk of stroke via systemic inflammation and unstable haemodynamics.

Several limitations of this study exist. First, the study was mainly comprised of middle-aged and older Caucasian adults, and might not be generalized to all age and ethnic groups. Second, the calculation methods of the predicted values for lung function vary for different regions and ethnicities, which may lead to different results [15]. In the present study, one optimal prediction method was selected for our study population according to age, sex, and height to avoid potential bias. Third, only the baseline measurement of lung function was available for the individuals in the SHHS; in the future, long-term lung function monitoring should be performed to clarify this association between lung function and stroke. At last, researchers reported that smokers with internal capsule and pontine acute lacunar stroke were prone to severe SDB[28]. Besides, lacunar stroke was regarded as a special subtype with different risk factors [29,30]. Therefore, we will establish a cohort with complete stroke subtypes and topography to facilitate future investigation on the detailed relationships with SDB and lung function in community.

In conclusion, lung function impairment was associated with a high risk of stroke among individuals with SDB from this large community cohort of middle-aged and older adults. This finding might contribute to the management of risk factors for stroke, especially in populations with SDB. More importantly, this result highlights the importance of maintaining lung function within the normal range in community-based populations for stroke prevention and rehabilitation, which warrants further investigation with interventional studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We appreciate the Brigham and Women's Hospital for sharing the Datasets of SHHS. SHHS acknowledges the members of these cohorts who agreed to participate in SHHS. A list of SHHS investigators, staff and their participating institutions is available on the SHHS website, <https://sleepdata.org/datasets/shhs>.

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Figure 1.

Flow chart of participant selection. “Incident cohort” refers to the population being followed up for stroke, which has never been diagnosed before and at baseline.

Figure 2.

The association of stroke and lung function according to AHI categories. Results are presented as hazard ratios (95% confidence interval) for each 10% increase in FEV₁PP and FVCPP.

Model 1: adjusted for age, sex and BMI; Model 2: adjusted for age, sex, BMI, smoking status and AHI; Model 3: adjusted for age, sex, BMI, smoking status, AHI, total cholesterol, triglycerides, high-density lipoprotein, history of diabetes, history of hypertension. FEV₁PP, forced expiratory volume in one second as a percentage of predicted value; FVCPP, forced vital capacity as a percentage of a predicted value.

Table 1

Baseline characteristic of study cohort by AHI categories

	the entire population (N=4154)	AHI < 5 events/h (N=2082)	AHI ≥ 5 events/h (N=2072)	P value
Age, yr	63.44±10.94	61.33±11.03	65.57±10.43	< 0.001
Male, n (%)	1847 (44.5)	698 (33.5)	1149 (55.5)	< 0.001
Smoking status, n (%)				< 0.001
Never	1992 (47.9)	1039 (52.2)	953 (47.8)	
Current	1764 (42.5)	788 (44.7)	976 (55.3)	
Former	398 (9.6)	255 (64.1)	143 (35.9)	
BMI, kg/m ²	28.27±5.02	26.88±4.33	29.66±5.27	< 0.001
AHI, events/h	9.71±12.89	1.98±1.42	17.47±14.52	< 0.001
Hypertension, n (%)	1504 (36.2)	634 (30.5)	870 (42.0)	< 0.001
Diabetes, n (%)	268 (6.5)	93 (4.5)	175 (8.4)	< 0.001
TC, mg/dL	207.15±38.19	206.45±38.82	207.84±37.56	< 0.001
HDL, mg/dL	51.32±15.89	53.70±16.59	48.94±14.78	< 0.001
Triglycerides, mg/dL	149.87±99.06	141.15±81.33	158.58±113.42	< 0.001
Lung function				
FEV ₁ , L	2.69±0.81	2.66±0.81	2.73±0.82	0.012
FVC, L	3.58±1.05	3.54±1.04	3.61±1.06	0.031
FEV ₁ /FVC ratio	0.75±0.08	0.75±0.08	0.75±0.08	0.058
FEV ₁ PP	2.52±0.63	2.49±0.62	2.55±0.64	< 0.001
FVCP	3.56±0.87	3.47±0.84	3.64±0.89	< 0.001
Stroke, n (%)	183 (4.4)	71 (3.4)	112 (5.4)	0.002
Follow-up time, (days)	3924.17±1123.18	4010.08±1082.12	3837.85±1156.82	< 0.001

BMI, body-mass index; AHI, apnoea-hypopnea index; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FEV₁PP, FEV₁ as a percentage of predicted value; FVCP, FVC as a percentage of a predicted value; TC, Total cholesterol; HDL, high-density lipoprotein

Table 2

Hazard ratio (95% confidence interval) for the association of stroke with lung function in the whole study cohort

Lung Function	FEV ₁ (each 200mL)	FVC (each 200 mL)	FEV1/FVC ratio, (each 10%)	FEV1PP (each 10%)	FVCPP (each 10%)
Univariate Model	0.800(0.767-0.835)	0.839(0.812-0.868)	0.882(0.731-1.063)	0.868(0.809-0.930)	0.744(0.688-0.805)
Multivariate Model 1	0.931(0.878-0.986)	0.942(0.898-0.989)	0.949(0.796-1.133)	0.912(0.856-0.971)	0.890(0.822-0.964)
Multivariate Model 2	0.933(0.879-0.991)	0.944(0.899-0.992)	0.962(0.804-1.151)	0.915(0.857-0.976)	0.893(0.824-0.969)
Multivariate Model 3	0.949(0.892-1.009)	1.001(0.999-1.003)	0.992(0.823-1.196)	0.935(0.873-1.001)	0.913(0.839-0.994)

Results are presented as hazard ratios (95% confidence interval) for each 200 mL increase in FVC or FEV₁, for each 10% increase in FEV₁/FVC ratio, FEV₁PP and FVCPP. FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FEV₁PP, FEV₁ as a percentage of predicted value; FVCPP, FVC as a percentage of a predicted value.

Model 1: adjusted for age, sex and BMI;

Model 2: adjusted for age, sex, BMI, smoking status and AHI;

Model 3: adjusted for age, sex, BMI, smoking status, AHI, total cholesterol, triglycerides, high-density lipoprotein, history of diabetes, history of hypertension.