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Original Article

Obstructive sleep apnea-hypopnea syndrome is correlated with higher risk of cardiovascular and cerebrovascular mortality in elderly patients with heart disease

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Abstract: Obstructive sleep apnea-hypopnea syndrome (OSAHS) is considered an independent risk factor for hypertension and heart disease. The current study aimed to explore the correlation between OSAHS with cardiovascular and cerebrovascular outcomes in patients with heart disease. In this prospective cohort study, OSAHS in elderly (age >60) patients with heart disease were assessed with polysomnograms. Patients were divided into an OSAHS group (AHI≥15) and a control group (AHI<15). Cardiovascular and cerebrovascular death, as well as coronary revascularization in a 3 year follow up period were recorded and compared between the two groups. Correlation between OSAHS with cardiovascular/cerebrovascular disease-free survival was analyzed with multivariable COX regression. As resulted, all of total 196 patients were enrolled and 179 were included in the final survival analysis. The OSAHS patients were found with significantly increased obesity parameters as well as abnormal blood glucose and lipid profiles. There were 21 (17 in the OSAHS group and 4 in the control group) patients who died of heart disease, stroke, or underwent coronary revascularization in the follow up period. COX regression analysis showed that OSAHS was significantly correlated with cardiovascular/cerebrovascular disease-free survival after adjustment for age, height, weight, and body mass index. In conclusion, OSAHS and age were associated with higher risk of cardiovascular and cerebrovascular death in elderly patients with heart disease.

Keywords: Obstructive sleep apnea-hypopnea syndrome, mortality, elderly, heart disease

Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a sleep disorder characterized by recurrent upper airway obstruction which causes a long pause in breathing. Apnea is defined as a cessation of respiration for at least 10 seconds during sleep; while hypopnea refers to a more than 50% decrease of respiratory airflow, accompanied by >3% decrease of oxygen saturation. OSAHS is diagnosed as having >30 times recurrence of apnea during a 7-hour nighttime sleep, or when the average number of apnea and hypopnea occur each hour (sleep apnea and hypopnea index, AHI >5) [1]. The prevalence of OSAHS is estimated to be 10% to 17% in the U.S. population. Incidences of OSAHS increase with age, and it is more common in adults older than 60 years old [2]. Recurrent apnea and hypopnea during night sleep result in intermittent hypoxia and hypercapnia, causing dysregulation of neural-endocrine system characterized by increased serum levels of catecholamine, renin angiotensin and endothelin. The imbalanced endocrine system may cause further microcirculation abnormalities and hemodynamic alterations, resulting in tissue ischemia, hypoxia and organ damage. Therefore, OSAHS is implicated as an independent risk factor for multiple systematic diseases [3].

OSAHS has been associated with the risk as well as prognosis of cardiovascular disease in many studies. It shows that OSAHS was associated with endothelial dysfunction and subclini-

cal atherosclerotic coronary artery disease (CAD) [4], and blood pressure was elevated in the subjects with severe OSAHS [5]. The rate of myocardial infarction in OSAHS patients was found to be four times higher than healthy people, and the incidence of hypertension and heart diseases were two and three times higher respectively [6]. In addition, the prevalence of OSAHS in patients with cardiovascular disease is also higher in the population [7], and associated with adverse outcomes of these patients [8, 9]. The rate of mortality and cardiovascular events are higher among OSAHS patients than in normal cohorts [10, 11]. Furthermore, OSAHS can increase the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) significantly in patients with coronary artery disease (CAD) [12]. Recent studies and meta-analysis have further demonstrated OSAHS is an independent risk factor of cardiovascular events, screening and therapy for OSAHS may improve health outcomes in patients with CAD [13-16]. However, the association of OSAHS with risk of cardiovascular events varies in the population. For example, age and ethnicity have shown to affect the association between OSAHS and the risk of cardiovascular events. Studies focusing on elderly patients with heart disease have rarely been reported. Therefore, a prospective cohort study was designed to determine the association of OSAHS with cardiovascular and cerebrovascular death in elderly patients with heart disease.

Materials and methods

Study design and settings

A prospective cohort study enrolled consecutive patients diagnosed with coronary heart disease, ischemic cardiomyopathy and hypertension at The Second Xiangya Hospital of Central South University, Changsha, Hunan Province, China, from March 2002 and October 2004. Sleeping status and blood biochemical characteristics were assessed for all patients. Existence and severity of OSAHS were diagnosed with polysomnogram, and the patients were assigned into an OSAHS group (severe and moderate OSAHS) and a control group (mild or no OSAHS). Cardiovascular/cerebrovascular disease-free survival of the study subjects in a 3 year follow up period were recorded and compared as primary outcomes.

Written consent was obtained from all subjects before the study. The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The research protocol was approved by the institutional review board of the Second Xiangya Hospital of Central South University, and adhered to STORBE guidelines [17]. Written consent was obtained from all subjects before the study.

Patients

Consecutive patients admitted to the hospital for suspicion or treatment of heart-related diseases were selected. The inclusion criteria were being older than 60 years of age, and diagnosed with coronary heart disease, ischemic cardiomyopathy or hypertension by EGG, dynamic EGG, Doppler echocardiography, or coronary angiography. The exclusion criteria were severe heart failure (according to NYHA heart failure classification grade III or IV), tumor at advanced stages, severe liver or kidney dysfunction, severe pulmonary diseases, hypothyroidism, difficulty in communication, and ongoing coronary reconstruction.

Assessment of OSAHS

Polysomnogram is considered the gold-standard for diagnosis of OSAHS [3]. All patients in the current study underwent a 7-hour polysomnogram (Somnostar-α, Sensor Medics, USA) with EEG montage and cardiorespiratory parameters as follows: EEG, EOG, EMG, ECG, snoring level, oronasal airflow, thoracoabdominal motion, and fingertip blood oxygen saturation. Then, the diagnostic criteria were adopted from the American Sleep Disease Association (ASDA): Sleep apnea is defined as a cessation of mouth and nose airflow for over 10 seconds during sleep. Obstructive sleep apnea is defined as a pause of mouth and nose airflow, accompanied by paradoxical respiratory movement of the chest and abdomen. Hypopnea is defined as a reduction of mouth and nose airflow at least 50% of baseline for more than 10 seconds, accompanied by a 3% decrease of oxygen saturation (SaO_2). AHI refers to the average time of apnea and hypopnea in 1 hour. OSAHS is defined as AHI score ≥5; mild OSAHS is considered as 5≤AHI<15; while moderate OSAHS is about 15≤AHI<30; and severe OSAHS is AHI≥30. The scale system of the micro-

arousal index (MAI) was adopted from 1992 Atlas criteria of ASDA. Microarousal refers to a shift to α waves lasting >3 seconds in the sleep brain waves. MAI >10 times/hour indicates sleep fragmentation and disorder of sleep pattern. Oxygen saturation (SaO_2) is the oxygen concentration in the blood, and SaO_2 <90% is considered hypoxia. The ratio of SaO_2 <90% is the percentage of total sleep time that SaO_2 is <90%.

Patients with AHI≥15 were (moderate and severe OSAHS) assigned to the OSAHS group, while patients with AHI<15 (mild and no OSAHS) were assigned to the control group.

Biochemical assays

Peripheral blood samples were obtained the next morning following polysomnogram test and subjected to the following tests: liver and kidney function, blood lipids, and blood cell count. Fasting and postprandial (2-hour) blood glucose levels were measured using an automatic biochemical analyzer (Olympus Corporation, Japan).

Daytime sleepiness evaluation

The Epworth Sleepiness Scale (ESS) score was utilized for daytime sleepiness evaluation. The ESS is a questionnaire including eight questions which need to be filled out by patients [18]. Sleepiness under various stimulations was scored on a 0-24 scale: 0 means no sleepiness and 24 indicates extreme sleepiness. A score >10 was considered as notable sleepiness.

Follow-up

Follow-up in the study was conducted by a trained specialist through either phone interview or office visit every 3 or 6 months until March 2006. The outcomes recorded including heart feailure and death, stroke and death, or coronary revascularization (coronary artery bypass grafting or coronary stenting). Causes and times of death were further confirmed with death records.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0.0 (IBM Corporation, Armonk, NY, USA). Measurement data were presented as mean ± SD. The Student t test was used to compare normally distributed data between the two groups, and the Mann-Whitney U test was used to analyze non-normally distributed data, Student t test and Mann-Whitney U test were used to analyze the study parameters and sleep characteristics of patients in control and OSAHS groups. Categorical data was expressed as frequency and percentage, the associations of OSAHS, gender and smoke or not were evaluated with Pearson's Chi-squared test. A survival curve was then generated using the Kaplan-Meier method. Non-cardiovascular deaths were considered as loss of track. Log-rank test was applied to compare cardiovascular/cerebrovascular disease-free survival between the two groups. Independent risk factors of cardiovascular/cerebrovascular disease-free survival were analyzed using multivariable COX regression. All tests were two-tailed, and $P<0.05$ was considered as statistically significant.

Results

Clinical results

A total of 196 patients diagnosed with heart disease underwent polysomnogram testing from March 2002 to October 2004, including 175 males and 21 females with an average age of 70.87±7.12 (range 60-88). As shown in **Table 1**, there were 128 patients diagnosed with moderate to severe OSAHS (OSAHS group) and 68 with mild to no OSAHS (control group). Compare to the control group, OSAHS patients were significantly younger age ($P=0.004$). Obesity seems to be associated with OSAHS, indicated by the increased weight ($P<0.001$), BMI ($P<0.001$), neck circumference ($P=0.001$), and abdominal circumference ($P<0.001$). ESS sleepiness score is higher in patients with greater severity of OSAHS ($P=0.001$). Interestingly, several biochemical parameters detected are different in the two groups. Compared to the control group, OSAHS patients have higher blood glucose levels (fasting blood glucose, $P=0.002$; 2 h postprandial glucose, $P=0.045$), higher triglyceride levels ($P=0.024$), lower levels of HDL ($P=0.016$), HD/CD ($P=0.047$), but higher Apolipoprotein B levels ($P=0.027$). In addition, patients in the OSAHS group have slightly larger diameter of the posterior left ventricle ($P=0.012$).

Table 1. Study parameters of patients between control and OSAHS groups

	Control group (n=68)	OSAHS group (n=128)	*P* value
Age, y ± SD	72.8±6.3	69.75±7.34	0.004
Gender (No./%)			0.406
Male	59 (86.8%)	116 (90.6%)	
Female	9 (13.2%)	12 (9.4%)	
Height (m)	1.66±0.07	1.67±0.06	0.296
Weight (Kg)	69.7±11.1	75.88±11.08	<0.001
BMI (Kg/m^2)	25.2±3.4	27.19±3.45	<0.001
Neck circumference (cm)	38.3±3.2	39.81±3.04	0.001
Abdominal circumference (cm)	95.8±10.3	101.49±10.66	<0.001
ESS	6.9±4.5	9.5±5.44	0.001
Smokers (No/%)	34 (50.0%)	68 (53.1%)	0.677
Hemoglobin (g/L)	129.8±20.3	132.01±18.27	0.439
Red blood cells (×10^{12}/L)	4.04±0.53	4.16±0.63	0.182
White blood cells (×10^9/L)	6.05±1.72	5.88±1.67	0.503
Platelets (×10^9/L)	159.4±49.5	155.12±75.29	0.634
ALT (U/L)	21.7±17.4	24.93±15.92	0.192
Total bilirubin (μmol/L)	14.3±6.9	15.35±10.16	0.393
Bilirubin direct (μmol/L)	5.3±3.0	5.64±4.44	0.526
Urea nitrogen (mmol/L)	6.75±2.42	6.7±2.7	0.898
Inosine (μmol/L)	124.8±40.6	123.85±83.13	0.915
Uric acid (μmol/L)	401±91	406.98±102.48	0.687
Fasting blood-glucose (mmol/L)	5.40±1.54	6.12±1.54	0.002
2 h-postprandial blood glucose (mmol/L)	8.77±2.63	9.67±3.14	0.045
HbA1c (%)	7.01±2.42	7.62±3.28	0.141
Left atrium diameter (mm)	32.8±5.3	33.05±5.21	0.751
Left ventricle diameter (mm)	46.0±7.3	45.71±6.58	0.778
Interventricular septum diameter (mm)	10.6±1.3	10.77±1.94	0.466
Posterior left ventricle diameter (mm)	10.0±1.7	10.57±1.39	0.012
EF (%)	60.7±7.5	58.6±10.12	0.102
FS (%)	32.7±5.5	34.06±9.78	0.290
Triglyceride (mmol/L)	1.54±0.85	1.88±1.23	0.024
Total cholesterol (mmol/L)	4.76±1.01	4.65±0.97	0.457
High-density lipoprotein (mmol/L)	1.26±0.32	1.15±0.29	0.016
Low-density lipoprotein (mmol/L)	2.84±0.73	2.73±0.81	0.351
HD/CD	0.27±0.06	0.25±0.07	0.047
Lipoprotein a (mg/L)	156±131	213.8±201.3	0.016
Apolipoprotein A1 (g/L)	1.38±0.26	1.37±0.28	0.808
Apolipoprotein B (g/L)	0.78±0.27	0.87±0.27	0.027

OSAHS: obstructive sleep apnea-hypopnea syndrome; BMI: body mass index; ESS: Epworth sleepiness scale; EF: ejection fraction; FS: fractional shortening; HD/CD: High-density lipoprotein (mmol/L)/Total cholesterol (mmol/L).

As shown in **Table 2**, OSAHS patients have significantly higher AHI (40.44±19.22 vs 7.45±4.2, *P*<0.001) and MAI scores (22.77±17.21 vs 8.4±5.2, *P*<0.001). In addition, severe hypoxia is more common in the OSAHS patients, indicated by lower minimum oxygen saturation (71.45±13.4 vs 84.6±6.0, *P*<0.001) and higher percentage of hypoxia time (36.22±30.13% vs 9.5±21.3, *P*<0.001). These results show that OSAHS caused more severe hypoxia which may influence long-term outcomes of patients with heart disease.

Table 2. Sleep characteristics of patients in control and OSAHS groups

	Control group (n=68)	OSAHS group (n=128)	*P* value
AHI (occurrences/h)	7.45±4.2	40.44±19.22	<0.001
MAI (occurrences/h)	8.4±5.2	22.77±17.21	<0.001
Minimum SaO_2 (%)	84.6±6.0	71.45±13.4	<0.001
Phase 3, 4 sleep (%)	5.1±5.9	3.22±4.05	0.021
REM sleep (%)	14.4±7.6	15.6±9.61	0.340
Hypoxia time (%)	9.5±21.3	36.22±30.13	<0.001

OSAHS: obstructive sleep apnea-hypopnea syndrome; AHI: sleep apnea and hypopnea index; MAI: microarousal index; SaO_2: oxygen saturation; REM: rapid eye movement.

Table 3. Mortality and major cardiac events for patients in control and OSAHS groups

	Control group (n=68)	OSAHS group (n=128)
Loss, No. (%)	5 (7,4)	12 (9.4)
Cases included No.	63	116
Cases died at end point (No./%)	4 (6.3)	17 (14.7)
Cardiac death (No./%)	4 (6.3)	11 (9.5)
Stroke (No./%)	0 (0)	3 (2.6)
Coronary reconstruction (No./%)	0 (0)	3 (2.6)
Survival rate (%)	93.7	85.3
Follow-up duration (days)	1163±331	1066±401

OSAHS, obstructive sleep apnea-hypopnea syndrome; CPAP, continuous positive airway pressure therapy.

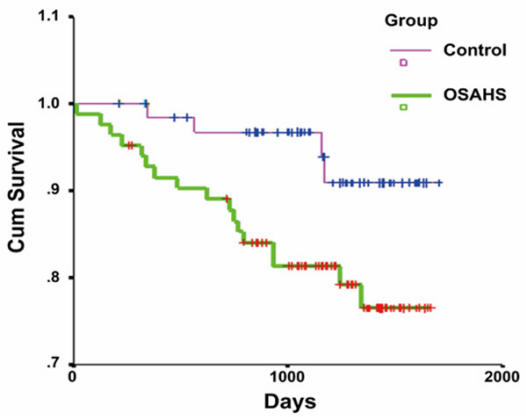

Figure 1. The overall survival curve for OSAHS patients and control.

Follow-up results

As shown in **Table 3**, patient follow up was conducted for an average of 3 years (1112±379 days). There were 17 (8.7%) patients lost to follow-up, including 12 (9.4%) in the OSAHS group and 5 (7.4%) in the control group, ending up with a total of 179 patients included in the final analysis (**Table 3**). A total of 21 patients died of cardiovascular and cerebrovascular diseases, or underwent coronary artery reconstruction, including 17 from the OSAHS group and 4 from the control group. Of the 17 patients from the observation group, 11 patients died of cardiac failure (including 4 sudden deaths), 3 died of stroke, and 3 underwent coronary revascularization (all stent implantation) due to acute coronary syndrome. In the control group, 4 died of cardiac failure. The total cardiovascular/cerebrovascular disease-free survival rate was 88.3%, and the survival rates in the control and OSAHS group was 93.7%, and 85.3% respectively. Kaplan-Meier survival analysis (**Figure 1**) showed significant difference in cardiovascular/cerebrovascular disease-free survival between the two groups ($P<0.05$).

Multivariable COX regression analysis was performed with factors of groups, age, gender, BMI, ESS, and polysomnogram parameters such as OSAHS severity and hypoxia (**Table 4**). The results indicated that the group and age were independent prediction factors for cardiovascular/cerebrovascular death or coronary revascularization.

Discussion

The results of the current study have shown that in elderly patients with heart disease, moderate to severe OSAHS increased the risk of major cardiovascular and cerebrovascular events. OSAHS is associated with various CAD complications including hypertension, heart disease, heart failure, arrhythmia, pulmonary hypertension, and sudden cardiovascular death and stroke. Accumulating evidence from epidemiological studies indicated that OSAHS is strongly associated with hypertension and that at least 30% of hypertensive patients have OSAHS and 40%-60% of OSAHS patients have hypertension [19]. The incidence of hypertension in OSAHS patients was higher than the control group (20% incidence in general popu-

Table 4. The independent prediction factors of cardiovascular/cerebrovascular death or coronary revascularization

	HR value	95% CI	*P* value
Group	12.267	1.032~145.889	0.047
Age	1.135	1.021~1.263	0.019
Gender	0.648	0.132~3.176	0.593
BMI	1.057	0.847~1.319	0.625
ESS	1.085	0.738~1.594	0.679
AHI	1.044	0.897~1.215	0.581
MAI	0.979	0.923~1.039	0.487
Minimum SaO_2	0.986	0.937~1.038	0.588

BMI: body mass index; ESS: Epworth sleepiness scale; AHI: sleep apnea and hypopnea index; MAI: microarousal index; SaO_2: oxygen saturation.

lation) [20]. These results have also shown that the incidence of myocardial infarction was significantly higher in heart disease patients with OSAHS than those without OSAHS, therefore OSAHS was considered as an independent risk factor of myocardial infarction [21]. In addition, AHI is indicated to be an independent predictor of death from heart disease; the 5-year mortality rate increased by 62% in heart disease patients with OSAHS compared with the control group. Meanwhile, the incidence of hypoxia during nighttime sleep significantly increased after myocardial infarction, posing an additional threat for these patients [22]. The association between OSAHS and coronary disease or myocardial infarction has been confirmed by the Sleep Heart Health Study (SHHS) from a large sample size multicenter cohort study [23]. Approximately 50% of OSAHS patients have severe arrhythmias, and most arrhythmias occur during sleep, especially REM sleep with the lowest SaO_2 [24]. Approximately 40%-60% of patients with chronic congestive heart failure had OSAHS [25]. The result of the SHHE shows the incidence of heart failure in the OSAHS population to be 2.38-fold higher than the non-OSAHS population [26].

In this study, we have found that elderly heart disease patients with moderate or severe OSAHS have 3.27 times higher risk of death than those with mild or no OSAHS (control group). Several studies have shown that the major causes of death in patients with moderate or severe OSAHS are cardiovascular events or stroke [27, 28]. In the current study, the 3-year cardiovascular and cerebrovascular death rate was 20.5% in patients with OSAHS, significantly higher than patients without OSAHS (6.4%). Although there were differences among the two groups regarding age, BMI and weight, age and group were found to be associated with survival according to COX regression analysis. Group (severe/moderate vs mild/no OSAHS) showed a correlation to survival rate only after age stratification, which strongly suggests that OSAHS was the factor most influencing cardiovascular and cerebrovascular deaths of elderly patients. Considering our findings, we recommend that OSAHS be considered as a risk factor in elderly heart disease patients. Consistent with other studies, OSAHS has been shown to be an important predictor of heart disease based on differences in age, BMI, hypertension, smoking, and diabetes [29].

The current study was focused on the prognosis of elderly heart disease patients with comorbid OSAHS. A 7-year follow-up study on 308 snoring middle-aged patients without heart disease conducted by Peker et al. [30] reported that the incidence of heart disease was 16.2% for those with OSAHS while it was only 5.4% for those without OSAHS. Peker et al. concluded that middle-aged OSAHS patients were a high-risk population for heart disease and that proactive prevention was needed. Furthermore, the multicenter Sleep Heart Health Study (SHHS) concluded that the risk of hypertension, heart failure, stroke, and ischemic cardiomyopathy were higher in patients with mild OSAHS and were also related to age and BMI [23].

We are aware of several limitations in our study. Selection bias was inevitable during the patient recruitment due to less strict inclusion criteria. Although multivariable COX regression analysis was adopted to reduce bias, the potential influence of more confounding factors could not be eliminated completely. The loss of follow up of some patients may not be totally random therefore this may also have affected the results of the study. In addition, the sample size was relatively small, and the follow-up period may not have been long enough to capture all relevant data. In conclusion, Major cardiovascular and cerebrovascular events were higher in elderly heart disease patients with OSAHS compared with those without OSAHS.

No significant difference was observed between study participants with and without OSAHS in terms of cardiovascular and cerebrovascular mortality. OSAHS and age appeared to be independent risk factors for the death caused by cardiovascular and cerebrovascular events.

Disclosure of conflict of interest

None.

Abbreviations

ASDA, American Sleep Disease Association; CAD, coronary artery disease; ESS, Epworth Sleepiness Scale; MACCEs, major adverse cardiovascular and cerebrovascular events; MAI, microarousal index; OSAHS, obstructive sleep apnea-hypopnea syndrome; SaO_2, oxygen saturation; SHHS, Sleep Heart Health Study.

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