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Joint effects of obstructive sleep apnea and resistant hypertension on chronic heart failure: A cross-sectional study

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ABSTRACT

Background: Obstructive sleep apnea (OSA) and resistant hypertension (RHTN) are two major risk factors of chronic heart failure (CHF) and limited information is available about the joint effects of OSA and RHTN on CHF.
Methods: Baseline data of participants who had completed polysomnography were used in the current study. The relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP) were calculated, and RERI > 0 or AP > 0 indicates joint effect of OSA and RHTN on CHF is greater than the sum of estimated effects of OSA alone and RHTN alone. Due to significant interaction between coronary heart disease (CHD) and both OSA and RHTN, participants were stratified into with and without CHD subgroups.
Results: Among 1157 participants, 33.1% had OSA. The prevalence of RHTN in OSA participants was 18.3%. The apnea–hypopnea index (AHI), pulse pressure and CHF were significantly associated with RHTN. In the CHD subgroup, participants with OSA and RHTN were associated with > 3-fold increased odds of prevalent CHF. RERI was 2.66 and AP was 0.75. The odds of prevalent CHF with left ventricular ejection fraction (LVEF) ≥ 45% in participants with OSA + RHTN were > 2-fold higher compared to those without, or with either OSA or RHTN, and RERI was 1.50 and AP was 0.72.
Conclusion: Presence of CHF, increased AHI and pulse pressure are independently associated with RHTN. OSA and RHTN have significant joint effects on CHF, especially in patients with concurrent CHD and preserved LVEF.

1. Introduction

Obstructive sleep apnea (OSA) is highly relevant to blood pressure (BP) elevation [1,2], and numerous observational studies indicate that OSA is the most prevalent secondary cause of treatment resistant hypertension (RHTN) [3,4], which is defined as having clinic systolic and/or diastolic BP ≥ 140 and/or 90 mm Hg despite prescription of ≥ 3 different classes of anti-hypertensive medications, optimally including one diuretic [5].

The concurrence of RHTN and OSA, especially not receiving continuous positive airway pressure (CPAP) treatment, not only makes BP difficult to control but also substantially increases cardiovascular disease risk [6]. OSA is thought to impact cardiac structure and function through various mechanisms, including increased sympathetic output and renin–angiotensin–aldosterone pathway activation [7]. Many of these pathways are biologically relevant to RHTN as well [5], given that RHTN is a risk factor of cardiac dysfunction.

Although the association between OSA and cardiovascular disease is consistently observed in prior observational studies [8,9], this association may vary by RHTN status. For example, a recent observational study suggests that the risk of ischemic heart event and heart failure is higher for sleep apnea patients who had RHTN versus who did not have RHTN [10]. However, this study was limited by lacking data of the apnea–hypopnea index (AHI), and the joint effects on the additive interaction of OSA and RHTN on cardiovascular events had not been well investigated and quantified, too.

In the current study, using baseline data of our ongoing prospective cohort study which is designed to evaluate the prevalence, risk factors and prognostic significance of OSA in hospitalized patients with and without prevalent cardiovascular diseases, we planned to evaluate the prevalence and associated factors of RHTN in participants with newly-diagnosed OSA. In addition, we would investigate and quantify the joint effects on the additive interaction of OSA and RHTN on chronic heart failure (CHF).

2. Methods

2.1. Study design and participant enrolment

This is a prospective cohort study which is designed to evaluate the prevalence, risk factors and prognostic significance of OSA in hospitalized patients with and without

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prevalent cardiovascular diseases. Participants' enrollment initiated from February of 2015 and the recruitment is still ongoing. The present study was approved by the Clinical Research Ethic Committee of Guangdong General Hospital (No. GDREC 2015373H) and all participants were treated in accordance with the Declaration of Helsinki.

Patients with prevalent or suspected cardiovascular diseases were admitted to Guangdong Cardiovascular Institute for further evaluation and management, and the details of the current study were provided to each individual patient before inform consent was obtained. Patients who had a previous diagnosis of OSA, central sleep apnea (CSA), or had received CPAP treatment before were excluded. In addition, participants who were diagnosed as CSA after baseline polysomnography (PSG) assessment were also excluded.

2.2. Data collection and biochemical measurements

Demographics such as age and gender were collected from medical record. Neck girth and waist and hip circumferences were measured in a standing position in accordance with the World Health Organization recommendation [11] before PSG evaluation. Briefly, neck girth was measured immediately above the thyroid cartilage with participants keeping head up and looking straightforward; waist circumference was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest; and hip circumference was taken around the widest portion of the buttocks. Body mass index (BMI) was calculated by weight in kilograms divided by height in squared meters, and BMI ≥30 kg/m^2 was defined as obesity.

Blood pressure at sitting was measured in accordance with the JNC7 guideline recommendation [12] using an Omron HEM-7051 device (Omron HealthCare, Kyoto, Japan). Participants sit quietly for at least 5 min before measurement. Appropriate cuff which covered at least 80% of circumference was placed on the non-dominant arm and the arm was placed in parallel to the heart level. Two measurements with a 1 minute interval were obtained and averaged. Pulse pressure was calculated by systolic BP minus diastolic BP.

Fasting plasma glucose, lipid profiles, glycated hemoglobin, and serum levels of uric acid, creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured using fasting venous blood in the Central Lab of Guangdong General Hospital.

Participants were placed in the left lateral position, and left ventricular volumes from apical 4 and 2 chamber views were obtained through tracing the endocardial border of the left ventricle using 2D trans-thoracic echocardiography (Philips iE33 xMATRIX system) by experienced physicians, and the machine automatically calculated left ventricular ejection fraction (LVEF) using the biplane Simpson's method.

Comorbidities, including hypertension, diabetes mellitus, coronary heart disease (CHD) and CHF were recorded based on the International Statistical Classification of Diseases (ICD)-9 diagnosis coding. In brief, diagnosis of hypertension was based on previous documented diagnosis or present anti-hypertensive medication usage, and the diagnosis of diabetes mellitus was based on previous documented diagnosis or anti-diabetic medications or insulin usage.

Diagnosis of CHD was based on either coronary computed tomography with contrast or coronary angiography, with at least one major epicardial coronary artery with ≥50% stenosis of lumen. Diagnosis of CHF was based on participants' symptom which was evaluated according to the criteria of the New York Heart Association, clinical manifestations such as orthopnea, LVEF and serum NT-proBNP level. The diagnoses of all comorbidities were verified by an experienced cardiologist.

2.3. PSG evaluation

All participants had been informed of the detailed procedures of PSG evaluation. Participants were allowed to have their regular sleep–wake rhythm, while substances such as alcohol or sleeping medicines were not allowed to be taken during the date of PSG performance. Attended PSG evaluation (PHILIPS RESPIRONICS Alice PDx) was performed in the sleep lab and the AHI as well as the mean and lowest arterial oxygen saturation (SaO_2) levels were obtained. If the participants had airflow complete blockage for >10 s or >50% reduction in respiratory airflow accompanying >3% reduction in SaO_2 for >10 s, the apnea or hypopnea events would be recorded. Participants with central apnea index (CAI)/AHI ≥50% indicative of CSA were excluded [13] and those with the AHI ≥15 events/h were defined as having OSA in the current study.

2.4. Definition of RHTN

Based on the Scientific Statement on the Diagnosis, Evaluation, and Treatment of Resistant Hypertension by the American Heart Association in 2008 [5], the RHTN definition in the current study was systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg despite treatment with ≥3 different classes of anti-hypertensive medications or treatment with ≥4 different classes of anti-hypertensive medications regardless of systolic and diastolic BP levels during indexed hospital admission.

2.5. Statistical analysis

Continuous variables were presented as mean ± SD if normal distribution otherwise presented as median (interquartile range); and categorical variables were presented as number (percentage) of cases. Comparison of RHTN prevalence between different categories of AHI was conducted using the chi-square test. Univariate regression analysis was used to investigate the associated factors of RHTN, and factors in univariate regression analysis with $P < 0.20$ or factors with clinical relevance despite $P > 0.20$ were included in multivariate regression analyses using a forward conditional regression model. The odds ratio (OR) and 95% confidence interval (CI) of RHTN in relation to every 5 events/hour increase in AHI were also evaluated.

The relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP) were calculated and in the absence of additive interaction, RERI and AP should be equal to 0 [14]. RERI >0 or AP >0 indicates the joint effects on additive interaction of OSA and RHTN together are greater than the sum of estimated effects of OSA alone and RHTN alone, and the P value indicates statistical significance of additive interaction. To evaluate and quantify the joint effects, participants were divided into four groups as follows: no-OSA + no-RHTN, no-OSA + RHTN, OSA + no-RHTN, and OSA + RHTN.

In a logistic regression model as to evaluate the odds of OSA and RHTN for CHF, CHD was entered as a covariate. However, a significant interaction between CHD and both OSA and RHTN was observed ($P < 0.001$). Therefore, participants were stratified into with and without CHD subgroups when CHF was set as dependent. In addition, participants with CHF were separated into CHF with LVEF <45% and CHF with LVEF ≥45% subgroups, and the odds of OSA and RHTN for these two subgroups were evaluated, respectively. All the statistical analyses were performed in the SPSS software (IBM 23.0 version).

3. Results

3.1. General characteristics

During February 2015 to September 2016, a total of 1206 participants enrolled and had completed PSG evaluation, and 49 with CAI/AHI ≥50% indicative of CSA were excluded, and the remaining 1157 participants were included into final analysis. As presented in Table 1, overall, the mean age was 56.6 years, male participants accounted for 71.1%, and the prevalence of obesity was 8.6%. The median AHI was 8.6 events/h and the prevalence of OSA was 33.1%. The prevalence of RHTN was 13.0%, with mean systolic and diastolic BP values of 151 ± 20 mm Hg and 87 ± 14 mm Hg respectively, and the mean number of anti-hypertensive medications was 3.5 ± 0.6 in participants with RHTN. The prevalence of CHD and CHF was 45.2% and 21.5%, respectively.

3.2. Prevalence of RHTN by category of AHI values

RHTN prevalence was progressively increased in company with AHI increase. Compared to participants with AHI <5 events/h (7.6%) and AHI 5–14 events/h (12.7%), prevalence of RHTN in participants with AHI ≥15 events/h (18.3%) was significantly higher ($P < 0.001$ for trend), indicating a dose-dependent association of AHI value and RHTN prevalence.

3.3. Associated factors of RHTN

Potential associated factors of RHTN were listed in Table 2. Overall, increased values of AHI (OR 1.049, 95% CI 1.021–1.079, $P = 0.001$) and pulse pressure (OR 1.061, 95% CI 1.033–1.089, $P < 0.001$), and presence of CHF (OR 3.588, 95% CI 1.227–10.489, $P = 0.020$) were independently associated with RHTN after adjusting for covariates including age, male gender, neck girth, BMI, mean SaO_2 level, serum uric acid level, presence of diabetes mellitus and CHD. In addition, linear regression analysis showed that every 5 events/hour increase in the AHI value, in company with the mean SaO_2 decrease by 0.283% and the lowest SaO_2 decrease by 1.705%, was associated with 15.8% (95% CI 10.0%–21.8%) higher odds of prevalent RHTN.

3.4. Comparison of CHF prevalence

There was a slightly, but insignificantly higher prevalence of CHF in the OSA + RHTN group (31.4%) compared to the no-OSA + no-RHTN (20%), no-OSA + RHTN (23.8%) and OSA + no-RHTN (22%) ($P = 0.153$ for trend) groups. Of note, in the CHD subgroup, the prevalence of CHF in the OSA + RHTN group (65.4%) was significantly higher compared to the no-OSA + no-RHTN (32.9%), no-OSA + RHTN (39%) and OSA + no-RHTN (34.2%) ($P = 0.010$ for trend) groups, while in the without CHD subgroup, no significant between-group difference was observed.