

Influence of obstructive sleep apnoea on coronary artery disease in a Chinese population

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Abstract

Objective: This study aimed to investigate the correlation between obstructive sleep apnoea (OSA) and the severity of coronary artery disease (CAD) assessed by angiography.

Methods: This prospective study screened 273 patients diagnosed with CAD by coronary angiography. The severity of CAD was assessed by SYNTAX score. A total of 255 subjects were enrolled of whom 161 were diagnosed with OSA, with an apnoea–hypopnoea index ≥ 5 /hour. Ninety-four CAD patients without OSA were used as controls. The relationship between OSA and CAD was analysed by multiple linear regression.

Results: The prevalence of OSA in CAD patients was 63.1%. The prevalences of single-vessel, two-vessel, and three-vessel disease were similar in the two groups. However, CAD was significantly more severe in patients with OSA, measured by SYNTAX score, than in those without OSA. OSA was independently associated with CAD after adjusting for traditional risk factors.

Conclusions: OSA is relatively common among patients with CAD in China. The independent association between OSA and CAD, even after adjusting for traditional confounders, suggests that OSA should be taken into account when considering the risk factors for CAD. The present findings highlight the important adverse influence of OSA on the severity of CAD.

Keywords

Obstructive sleep apnoea, risk factor, coronary artery disease, SYNTAX score, polysomnography, coronary angiography

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Introduction

Coronary artery disease (CAD) is widely accepted to be related to high mortality. It is predicted that there will be increases of approximately 21.3 million cardiovascular events and 7.7 million cardiovascular deaths from 2010 to 2030 in China.¹ Male sex, diabetes mellitus, hypertension, hypercholesterolemia, obesity, and smoking are all traditionally considered as risk factors for CAD. Although recent progress in the prevention and treatment of traditional cardiovascular risk factors has helped to decrease CAD-related morbidity and mortality, the condition remains a major public health challenge worldwide. Investigation of other potential risk factors for CAD may thus aid the development of additional preventative strategies and further reduce the incidence and mortality of CAD.

Obstructive sleep apnoea (OSA) is a common disorder characterised by repetitive partial (hypopnoea) or complete (apnoea) occlusion of the upper airway during sleep, caused by collapse of the pharyngeal airway and resulting in sleep fragmentation and oxyhaemoglobin desaturation.² It affects an estimated 9% of adult women and 24% of adult men.³ Previous studies have shown prevalences of OSA as high as 30% to 69% in patients with CAD.⁴⁻⁶ However, there is a lack of epidemiologic data on OSA in Chinese patients with CAD. Changing lifestyles, rapid economic growth, an increased prevalence of obesity, and an aging population all indicate that the prevalence of OSA in China is bound to increase. OSA has been considered as an independent risk factor for cardiovascular disease,^{7,8} and OSA has been shown to significantly increase cardiovascular morbidity and mortality, especially in patients with pre-existing cardiovascular disease.⁹ However, the association of OSA with serious morbidity has raised few concerns because untreated OSA is a substantial but underappreciated public

health threat. OSA thus remains largely underdiagnosed and consequently undertreated in clinical practice.^{10,11}

Several cross-sectional studies have reported an association between OSA and coronary heart disease,^{4,5,12} although most of these were small hospital- or clinic-based case-control studies that often lacked adjustments for important cardiovascular risk factors. Other studies including patients with CAD have yielded conflicting data regarding the relationship between OSA and CAD in patients with and without sleep apnoea.^{13,14} However, data regarding the prevalence and influence of OSA in Chinese patients with CAD patients are scarce. The SYNTAX score was introduced to evaluate the severity of complex CAD, combining anatomic and clinical coronary factors and predicting long-term mortality.¹⁵ Further data are needed to clarify the reasons for the prevalence of OSA in CAD populations. The present study aimed to determine the prevalence of OSA in patients with CAD in China, and to evaluate the association between OSA and CAD assessed by SYNTAX score.

Methods

Design and setting

We performed a prospective case-control study including outpatients or inpatients who were habitual snorers and who underwent coronary angiography at Harbin Medical University from February 2019 to December 2021. The study was approved by the ethics committee of Harbin Medical University (no. HMUIRB2019 0117) and was conducted in accordance with the Second Declaration of Helsinki. All patients provided written informed consent and all patient-related information was de-identified. The reporting of this study conforms to the STROBE guidelines.¹⁶

Patient selection

Consecutive outpatients or inpatients of either sex with habitual snoring who underwent coronary angiography were recruited into the study. The inclusion criteria were Chinese nationality, age 35 to 75 years with CAD verified by coronary angiography, and ability to give informed written consent. Subjects were excluded if they were classified as New York Heart Association Class III–IV with ejection fraction <45% or had severe pulmonary disease, central sleep apnoea, significant psychiatric disease, a history of pharyngeal surgery for OSA, or current use of continuous positive airway pressure (CPAP) treatment for OSA. Patients were also excluded if they declined to participate or were unable to provide informed consent.

Data collection

Before initiating the study, all potential subjects were invited to attend an educational program that explained the purpose and methodology of the study. After obtaining informed consent, the patients' demographic data, including age, sex, medical history (including comorbidities and risk factors), current medicines, lifestyle habits, height (cm), and weight (kg) were recorded, and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The included subjects were required to undergo transthoracic echocardiography or an echocardiographic examination within 1 month. CAD diagnosis was determined based on the results of the coronary angiography, using 50% stenosis as a cut-off for the presence of CAD. CAD severity was calculated using the SYNTAX score, measured by an interventional cardiologist who was blinded to the patient's OSA status.

Risk factor definitions

Hypertension was defined as current use of antihypertensive medications and/or resting

blood pressure >140 mmHg systolic and/or >90 mmHg diastolic, measured with a mercury manometer with an appropriate cuff size on 2 different days, after the participant had been seated in a chair with their feet on the floor and arm supported at heart level for at least 10 minutes. Hyperlipidaemia was defined as current use of cholesterol-lowering medications and/or a total cholesterol value >5.18 mmol/L (200 mg/dL), triglycerides >1.70 mmol/L (150 mg/dL), and low-density lipoprotein cholesterol >3.37 mmol/L (130 mg/dL) in a plasma sample drawn after overnight fasting. Diabetes mellitus was diagnosed when a patient was receiving insulin and/or oral antidiabetic agents or had a history of fasting blood glucose >125 mg/dL. Smoking only included current smokers. Excess weight was defined as a BMI >25 but $\leq 30 \text{ kg}/\text{m}^2$ and obesity as a BMI >30 kg/m^2 .

Sleep evaluation

The self-administered sleep questionnaire included questions with yes/no alternatives concerning history of snoring, witnessed apnoea, sleep fragmentation, nocturia, and night sweating, as well as excessive daytime tiredness before the present study. Subjects with suspected OSA underwent overnight polysomnography (PSG) in a sleep centre using an Embletta X100 (Medcare Flaga, Reykjavik, Iceland), including oximetry, airflow measurements (oronasal thermistor and pressure cannula), and measurements of the rib cage and abdomen during breathing, as described previously.¹⁷ PSG was performed from 10:00 pm to 6:00 am when the patient was in a stable clinical condition (at least 4 weeks after coronary angiography and hospital discharge). No sedative medication was given. Apnoea was defined as complete cessation of airflow lasting at least 10 s and hypopnoea was defined as a decrease in the amplitude of respiratory flow signal of at least 50% for a minimum

of 10 s, followed by either a decrease in oxygen saturation of 4% or signs of physiological arousal. Central sleep apnoea was defined as at least 50% of respiratory events showing a pattern of apnoea or hypopnoea without thoracic or abdominal movement. The apnoea-hypopnoea index (AHI) was calculated as the total number of apnoea and hypopnoea episodes occurring per hour of sleep. The minimal diagnostic criterion for OSA was an AHI ≥ 5 /hour. The disease was classified as mild, moderate, or severe, based on AHI values of 5 to <15 , 15 to <30 , and ≥ 30 events/hour, respectively.¹⁸ PSG data were scored manually by trained personnel. All patients self-completed the Epworth Sleepiness Scale (ESS), a previously validated questionnaire¹⁹ used as a measure specific to symptoms of daytime sleepiness in various daytime situations; patients also self-reported habitual snoring.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean \pm standard deviation and categorical variables were presented as absolute numbers and percentages. Normally distributed variables were analysed using the independent samples *t*-test and categorical variables were compared using the χ^2 test. Correlations between variables were analysed using Pearson's test. Multiple linear regression analysis was used to assess the relationship between AHI and SYNTAX score, adjusted for the effects of age, sex, BMI, smoking, hypertension, hyperlipidaemia, and diabetes mellitus. Multiple stepwise linear regression analysis was also performed to identify which variables best explained the variance in the SYNTAX score. Statistical analyses were performed using SPSS for Windows (version 18; SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.

Results

We initially recruited 273 newly diagnosed CAD patients with habitual snoring and clinical suspicion of OSA. Thirteen of these patients declined to participate in the study and five were excluded (2 severe heart failure, 1 history of pharyngeal surgery for OSA, and 2 concomitant central sleep apnoea). A total of 255 screened patients thus met the inclusion criteria and were enrolled in the study (Figure 1), of whom 161 (63.1%) participants presented with OSA. The baseline characteristics are summarised in Table 1. Most subjects were men (82.6%). The mean ages of CAD patients with and without OSA were similar. However, CAD subjects with OSA had significantly higher BMIs and ESS scores and higher prevalences of DM and hypertension than those without OSA (all $P < 0.05$). There were no significant differences in sex, hyperlipidaemia, and smoking history between the two groups.

The coronary angiography findings in CAD subjects with and without OSA are shown in Table 2. There was no significant difference in the prevalence of single-vessel, two-vessel, or three-vessel disease between the two groups. However, CAD was significantly more severe in patients with OSA, measured by SYNTAX score, than in those without OSA ($P < 0.05$).

Univariate linear regression analysis showed that AHI, diabetes mellitus, age, sex, and BMI ($P < 0.05$), but not hyperlipidaemia and hypertension, were significantly correlated with the severity of CAD. Diabetes mellitus, age, and AHI all remained independently associated with CAD in a multiple linear regression analysis model (Table 3).

Discussion

In the present study, we investigated the correlation between OSA, estimated by

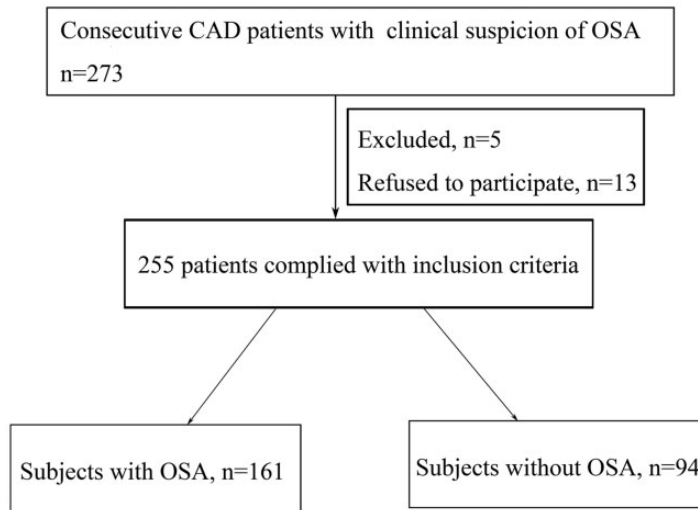


Figure 1. Flow diagram of the study.
CAD, coronary artery disease; OSA, obstructive sleep apnoea.

Table 1. Anthropometric and clinical characteristics of study subjects with and without obstructive sleep apnoea.

Variable	CAD with OSA (n = 161)	CAD without OSA (n = 94)	P
Age, years	58.1 ± 9.8	55.9 ± 10.9	0.150
Sex, male	133 (82.6%)	74 (78.7%)	0.444
BMI (kg/m ²)	27.1 ± 3.5	25.0 ± 3.0	<0.001
AHI (events/h)	26.3 ± 17.9	2.7 ± 1.2	<0.001
ESS score	5.8 ± 4.6	4.0 ± 2.9	0.006
Hypertension	127 (78.9%)	63 (67.0%)	0.036
Hyperlipidaemia	123 (76.4%)	65 (69.1%)	0.205
Diabetes mellitus	59 (36.6%)	17 (18.1%)	0.002
Smoking history	94 (58.4%)	44 (46.8%)	0.073

Data presented as the mean ± standard deviation or number (percentage).

OSA, obstructive sleep apnoea; CAD, coronary artery disease; BMI, body mass index; AHI, apnoea/hypopnoea index; ESS, Epworth sleepiness scale.

AHI, and the severity of CAD, measured by SYNTAX score. To the best of our knowledge, this is the first study to evaluate this relationship. We found that the SYNTAX score was significantly higher in CAD patients with OSA compared with those without OSA. In addition, multiple regression analysis of coronary risk factors showed that OSA was independently

associated with CAD, even after adjusting for traditional risk factors.

Increasing evidence links OSA with the development and progression of certain cardiovascular conditions, such as hypertension, CAD, stroke, congestive heart failure, preoperative assessment of anaesthetic management, and cardiac arrhythmias.^{8,20,21} The well-known major risk

Table 2. Coronary arteriography findings in patients with and without obstructive sleep apnoea.

Variable	CAD with OSA (n = 161)	CAD without OSA (n = 94)	P
Single-vessel disease	29 (18.0%)	25 (26.6%)	0.106
Two-vessel disease	53 (32.9%)	29 (30.9%)	0.733
Three-vessel disease	79 (49.1%)	40 (42.6%)	0.314
Left main lesion	17 (10.6%)	7 (7.4%)	0.412
SYNTAX score	17.7 ± 9.9	11.6 ± 6.5	0.003

Data presented as means ± standard deviation or number (percentage).
OSA, obstructive sleep apnoea; CAD, coronary artery disease.

Table 3. Explanatory variables associated with the severity of coronary artery disease measured by SYNTAX score.

Variable	Model 1		Model 2		Model 3	
	Univariate (r)	P value	Multivariate (β)	P value	Multivariate (β)	P value
Age, years	0.292	<0.001	0.400	0.012	0.199	0.003
Sex	0.252	<0.001	0.231	0.152		
BMI (kg/m ²)	0.141	0.025	0.058	0.396		
Hypertension	0.118	0.059	0.016	0.796		
Hyperlipidaemia	0.076	0.227	0.037	0.538		
Diabetes mellitus	0.263	<0.001	0.193	0.002	0.196	0.001
Smoking	0.199	0.766	-0.028	0.641		
AHI	0.291	<0.001	0.143	0.062	0.146	0.032

Model 1: unadjusted estimate of SYNTAX score; Model 2: adjusted for age, sex, BMI, hypertension, hyperlipidaemia, diabetes mellitus, smoking, and AHI; Model 3: multiple stepwise linear regression to identify the best variables explaining the severity of CAD.

CAD, coronary artery disease; BMI, body mass index; AHI, apnoea/hypopnoea index.

factors for atherosclerosis are the most likely elements linking CAD to OSA. However, the pathophysiological relationship between OSA and CAD is complex, given that many pathological cardiovascular changes induced by OSA may interact to facilitate the development and/or progression of the different clinical conditions in the spectrum of CAD. The mechanisms leading to the formation and progression of atherosclerotic plaques involve complex interactions among multiple factors, including oxidative stress, endothelial dysfunction, and inflammatory and immunologic factors.²² In patients with OSA, repeated hypoxia and reoxygenation during sleep can increase oxidative stress, leading to

vascular damage. In addition, endothelium-dependent relaxation in other vascular beds is impaired in OSA patients.²³ Namtvedt and colleagues found that endothelial dysfunction in OSA patients was independent of obesity and other traditional risk factors,²⁴ and that CPAP treatment improved these abnormalities.²⁵ Inflammation also plays a key role in the development and progression of atherosclerosis, and increased serum levels of inflammatory factors have been reported in patients with OSA.²⁶ Although CPAP treatment decreased the levels of inflammatory substances,²⁷ a recent study indicated that CPAP did not reduce inflammatory biomarkers in patients with CAD and non-sleepy OSA.²⁸ Notably

however, only 47 patients (44.8%) achieved the target CPAP usage corresponding to ≥ 4 hour/night, and the median CPAP usage was only 3.2 hour/night, which may not be adequate adherence and may have affected the interpretation of the results.

Epidemiological data suggest that OSA is overrepresented in CAD patients, and previous studies have shown prevalences of OSA as high as 30% to 69% in patients with CAD.⁴⁻⁶ However, the prevalence of OSA in the CAD population varies significantly according to variations in diagnostic criteria. OSA can be detected by different methods, including several validated questionnaires and overnight sleep studies. Questionnaire score results obtained on the basis of possible symptoms of sleep apnoea may not be sufficient to predict OSA. To avoid the bias of questionnaire scores, Huang et al. conducted a systemic review and meta-analysis using either PSG or a portable diagnostic device to diagnose OSA.²⁹ They found that the prevalence of OSA was relatively high (69%) using an AHI threshold of >5 , but was slightly lower (58%) using a threshold of >10 . They also found that moderate-to-severe and severe OSA were highly prevalent in patients with acute coronary syndrome (43% and 25%, respectively).²⁹ In the present study, we adopted a questionnaire score for the screening and overnight sleep study for the diagnosis of OSA. Our findings are consistent with reports of a high prevalence of sleep apnoea in subjects with angiographically confirmed CAD (63.1%).⁴⁻⁶ Craniofacial and upper-airway structure also play important roles in the occurrence of OSA, and may be particularly significant in Asian patients.³⁰

The outcome of our study in a Chinese sample was similar to a previous study by Inami et al.,³¹ which revealed a positive correlation between OSA and the severity of CAD. The current results showed no significant difference in single-vessel, two-vessel,

three-vessel, or left main artery CAD in relation to OSA. However, the classification of CAD severity was very crude and may not accurately reflect the severity of CAD lesions,³² and we therefore adopted the SYNTAX score. A multiple linear regression model identified diabetes mellitus, age, and AHI as factors independently associated with CAD. In contrast, Rivera-Pérez et al. found that moderate-severe OSA was associated with the presence of CAD, but found no significant correlation between lesion severity and the AHI.³² Notably however, the proportion of subjects without CAD was up to 61.2% in this previous study, which might have affected the analyses.

Interestingly, Mo et al. found that severe OSA was associated with significant coronary artery plaque burden, independent of traditional cardiovascular risk factors.³³ Several clinic-based studies also found an association between OSA and the development of CAD, after adjusting for other risk factors.³⁴⁻³⁶ A prospective cohort study of >400 patients with stable angina pectoris and CAD confirmed by coronary angiography followed-up for 5 years found that OSA was associated with higher rates of death, myocardial infarction, and stroke.³⁷ Fernandes et al. also found that symptoms of OSA were associated with an increased risk of long-term adverse cardiovascular outcomes after successful percutaneous coronary intervention.³⁸ We previously showed a tendency towards benefit from long-term CPAP application in patients with uncontrolled hypertension with CAD and OSA, although the results were not significant.³⁹ Notably, some studies indicated that CPAP treatment reduced the harm caused by OSA.^{40,41} Myllylä and colleagues recently reported a beneficial association between CPAP treatment and CVD risk (hazard ratio: 0.64, $P < 0.001$), and CPAP treatment was associated with a decreased risk of nonfatal and fatal CVD events.⁴²

McEvoy and colleagues conducted a randomised controlled trial (SAVE) to evaluate the effects of CPAP therapy in patients with OSA, comparing the effects between patients who received CPAP therapy plus usual care and those who received usual care alone. Surprisingly, they found no significant difference in cardiovascular outcomes between the two groups after a mean follow-up period of 3.7 years.⁴³ However, this finding should be interpreted with caution, given that the mean number of CPAP hours per night (3.3 hours) was relatively low, and many sleep clinicians would not consider this adherence adequate, given that it probably represented less than half the time the patient was asleep. This dose of CPAP may thus not have been adequate to prevent cardiovascular events. Second, the study excluded OSA subjects with ESS scores ≥ 15 , regardless of their symptoms. Although it is uncertain if sleepiness is a marker of susceptibility to cardiovascular risk in OSA, the exclusion of symptomatic patients may limit the ability to detect a cardiovascular benefit of therapy. Third, patients with severe OSA with significant hypoxemia were also excluded from the SAVE study, partly for ethical reasons, and it is possible that the positive effects of CPAP treatment could have been more marked in this group of patients, thus accounting for the lack of association with cardiovascular events. In addition, Peker et al. conducted a randomised controlled trial (RICCADSA) to assess the efficacy of CPAP use in patients with OSA and CAD,⁴⁴ which demonstrated that CPAP therapy did not significantly reduce long-term adverse cardiovascular outcomes in patients with CAD with non-sleepy OSA, using an intention-to-treat analysis; however, adjusted on-treatment analysis showed a significant cardiovascular risk reduction in patients who used CPAP for ≥ 4 versus < 4 hours per night or no treatment.

This study had some limitations that need to be addressed. First, it included a relatively small number of patients. The exclusion of hemodynamically unstable patients avoided resuscitation from being hindered by the monitoring devices but might have introduced bias in this study. Second, it was a prospective case-control study, and no cause-and-effect relationship could thus be inferred, only simple associations. Third, most subjects were male, and it is uncertain if the results can be extended to female populations. However, women are less likely to be referred for revascularisation for acute coronary syndrome than men. Further studies are needed to address this issue. Fourth, some participants with hypertension and hyperlipidaemia may not have received standard medical treatment, which may have influenced the severity of CAD. Fifth, we only included current smokers as smokers, which could also have slightly affected the results. However, the present study also had some strengths. First, all of the participating patients underwent coronary angiography for the diagnosis of CAD and overnight sleep evaluation for sleep-disordered breathing. Second, we investigated the effects of potential confounding factors using multivariate analysis. This study therefore enabled us to address the prevalence of OSA in patients with CAD and to evaluate the association between OSA and CAD in a prospective and controlled manner, taking account of potential confounders.

Conclusions

The present study suggests a high prevalence of OSA in patients with CAD. The independent association between OSA and CAD, even after adjusting for traditional confounders, suggests that more attention should be paid to the screening of OSA when considering the risk factors for CAD. The present findings highlight the

important adverse influence of OSA on the severity of coronary disease. This should alert cardiologists to the implications of the clinical course of OSA.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

Jinghui Shi was responsible for the design of the manuscript and the overall quality of the work. Yufei Liu conducted the study and prepared the manuscript. Yufei Liu and Meitan Wang collected the data.


Declaration of conflicting interests

The authors report no conflicts of interest.

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