

Study on Relationship Between Carotid Intima-Media Thickness and Inflammatory Factors in Obstructive Sleep Apnea

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Purpose: The purpose of this study was to explore the change of carotid intima-media thickness (IMT) and its correlation with inflammatory markers in patients with different degrees of obstructive sleep apnea (OSA).

Methods: One hundred hospitalized patients were selected and were divided into the normal control group (21 cases), the mild-moderate group (39 cases) and the severe group (40 cases) according to their apnea hypopnea index (AHI). Carotid IMT of all registered patients was studied with ultrasound, and serum levels of high-sensitivity C-reactive protein (hs-CRP), Lipoprotein-associated phospholipase A2 (Lp-PLA2) and tumor necrosis factor- α (TNF- α) were measured. Pearson correlation analysis and multiple stepwise regression analysis were used to analyze the correlation between carotid IMT and inflammatory factors.

Results: Patients with mild, moderate and severe OSA Carotid IMT had significantly higher levels of serum hs-CRP, Lp-PLA2 and TNF- α compared with the normal control group ($P < 0.001$). The levels of carotid IMT, serum protein hs-CRP, Lp-PLA2 and TNF- α in the severe OSA group were significantly higher than those of the mild-moderate OSA group, with P values being less than 0.001. Carotid artery IMT was positively correlated with serum hs-CRP ($r = 0.83$, $P < 0.001$), Lp-PLA2 ($r = 0.58$, $P < 0.001$), and TNF- α ($r = 0.69$, $P < 0.001$). hs-CRP, TNF- α and AHI were independent factors affecting carotid artery IMT. In addition, AHI was an independent indicator of carotid atherosclerosis ($P = 0.0012$).

Conclusion: Increased inflammatory factors in OSA patients might cause the progression of atherosclerosis, which might increase the risk of cardiovascular and cerebrovascular diseases in OSA patients.

Keywords: atherosclerosis, intima-media thickness, inflammation, obstructive sleep apnea

Introduction

In recent years, with the socioeconomic development and the accelerated population aging, China has carried an increasingly heavy burden of cerebrovascular diseases, which far exceeds the global average. Sleep breathing disorders (SBD) is a common disease that is characterized by recurrent apnea and apnea during the quality sleep periods, including the central nervous system sleep apnea and the obstructive sleep apnea,¹ and the most common type is OSA.² Studies have shown that the obstructive sleep apnea is closely associated with an increased risk of stroke,³⁻⁸ and it proved to be an independent risk factor for stroke. However, the exact mechanism is still unclear, and current research shows that it is likely to have multiple pathways. Repeated apnea and hypopnea during the night lead to chronic intermittent hypoxia, carbon dioxide (CO₂) retention, and the increased sympathetic excitability, resulting in an increased systemic inflammatory response, oxidative stress, endothelial dysfunction and metabolic abnormalities.⁹⁻¹² More and more clinical evidence indicates that serum inflammatory mediator levels in OSA patients are significantly raised and are positively correlated with OSA severity, which confirms that local and systemic inflammation exists in OSA patients.¹³⁻¹⁶

Atherosclerosis is the main pathophysiological basis of cerebrovascular diseases, and the continuous inflammatory response severely affects atherosclerosis^{17,18} as it aggravates atherosclerosis occurrence and progression. It is not hard to see that inflammation is a common feature of OSA and atherosclerosis, and that it plays an important role in linking them. Oxidative stress in OSA produces a variety of inflammatory mediators, and atherosclerosis may be a local response to systemic inflammation which further increases the risk of stroke. Carotid IMT is a useful marker of subclinical and early atherosclerosis for scientific research.¹⁹ Ultrasound, as a non-invasive, rapid and repeatable technique, can assess the course of atherosclerosis by measuring carotid IMT and plaque properties. A series of recent studies have linked OSA to subclinical atherosclerosis, but the exact mechanism remains unclear, and clinical data on OSA and carotid atherosclerosis remain controversial. OSA and atherosclerosis share many common risk factors, thus it is not clear whether their association is unique or mainly driven by confounders. In addition, data on inflammatory markers that could elucidate the relationship among OSA, inflammation and atherosclerosis in detail were not included in most studies. Therefore, the purpose of this study was to evaluate the correlation between the inflammatory markers and the non-invasive measurement results of subclinical atherosclerosis, so as to analyze the correlation between OSA and atherosclerosis and study the correlation between IMT of cervical vessels and the serum protein level of these inflammatory markers. By doing so, the correlation between OSA and atherosclerosis and the role of inflammation can be elaborated.

Materials and Methods

This study explored the relationship between carotid IMT and inflammatory factors of patients with different degrees of OSA through the analysis of carotid IMT and serum inflammatory markers of these patients. A total of 100 patients who met the enrollment conditions received overnight PSG monitoring and were divided into the control group, the mild-moderate OSA group and the severe OSA group according to their AHI. The general clinical data and relevant laboratory indicators of the study subjects were collected, the carotid IMT of the patients was detected by ultrasound, and the serum hs-CRP, Lp-PLA2, TNF- α levels were detected by enzyme-linked immunosorbent assay. The experimental data were analyzed by SPSS22.0 statistical software.

Patients

From February 2017 to February 2021, 79 patients with untreated obstructive sleep apnea syndrome diagnosed by the Department of Neurology of the Third People's Hospital of Zhengzhou City were randomly selected. 21 patients with normal polysomnography (PSG) monitoring were randomly selected as the control group. We excluded the following subjects: patients previously diagnosed with SBD; patients under 18 years old; patients having acute cardiovascular and brain disease, severe liver, kidney, or lung diseases; patients unable to provide informed consent. The study was approved by the author's Medical Ethics Committee and all subjects signed the informed consent.

Polysomnography (PSG)

All enrolled patients were monitored by night PSG. The patients were not allowed to drink, smoke or take sedative or sleeping pills 1 day before the examination. The total number of patients with apnea and hypopnea during sleep in the night was recorded and the AHI was calculated. AHI is the sum of the mean number of apnea and hypopnea events per hour of sleep. Central or mixed apnea hypopnea syndrome is considered as a complication of stroke, thus stroke patients with central or mixed apnea hypopnea syndrome were excluded. The AHI over 5/ hour together with sleep related disorders was considered as a diagnosis indicator of OSA, so subjects whose AHI was less than 5/ hour were selected for normal control experiments. According to the significant level of OSA in patients, the OSA patients were reclassified as follows: patients with AHI 5 ~ < 30 was in the moderate-severe OSA group, and patients with AHI >30 was in the severe OSA group.

Measurement of Carotid IMT and Plaque

All patients were diagnosed by the color Doppler ultrasound of the carotid artery. The instrument was a Siemens ACUSONS2000 color ultrasound system, and the frequency of the probe was 10 MHz. During the examination, each patient lay in the supine position and tilted his or her head back to fully expose the neck. The probe was placed on the neck for longitudinal and lateral scanning examinations to explore the proximal end of the bilateral common carotid artery near the bifurcation and the bilateral neck intima-media thickness of the artery. The distal wall of the superior and

inferior carotid arteries and the bifurcation of the carotid arteries were examined carefully. Mean IMT was calculated as the mean of the six accurate measurements (excluding plaque location) on both sides of the left ventricle at the late stage. Data including the presence or absence of plaques and the location of plaques were recorded. All the subjects were examined by the same analyst who did not understand the clinical medical characteristics.

Measurement of hs-CRP, Lp-PLA2 and TNF- α

All subjects went to bed at 10 pm and woke up at 6 am. Peripheral venous blood samples were collected at 6 am. Samples were stored at -80°C until their profiling was performed. According to the manufacturer's instructions, hs-CRP, Lp-PLA2 and TNF- α were measured by enzyme-linked immunosorbent assay.

Statistical Analysis

SPSS 22.0 statistical software was used to analyze the data. The normally distributed measurement data in this study were expressed as the mean $\pm$ standard deviation ($\bar{x} \pm S$). Pairwise comparisons were performed using independent sample *t*-tests. Comparisons between multiple groups were analyzed by single factor analysis of variance. Data were represented by the number of cases (n%) through the chi-square test; correlation research was performed with the Pearson's correlation analysis; independent correlation factor analysis was conducted by multiple stepwise regression analysis, and a probability of less than 0.05 was considered to be significant.

Results

Baseline Characteristics of Patients

This study included 100 subjects. Characteristics of the OSA group and the normal group, including age, sex, body mass index, neck circumference, previous medical history data, metabolic independent variables and IMT, are shown in Table 1. Low-density lipoprotein (LDL) of patients with severe OSA (3.2 ± 0.3) was higher than that of the normal

Table 1 Baseline Characteristics of the Control Group and OSA Patients

	AHI < 5	5 $\leq$ AHI < 30	AHI $\geq$ 30	P
Sex, male/female	13/8	21/18	24/16	0.789
Age, yr	56.1 $\pm$ 12.4	58.7 $\pm$ 10.1	58.4 $\pm$ 10.9	0.640
BMI, kg/m ²	24.5 $\pm$ 3.1	24.8 $\pm$ 2.5	25.8 $\pm$ 4.0	0.308
Neck, cm	38.3 $\pm$ 1.8	39.0 $\pm$ 2.3	39.2 $\pm$ 2.3	0.306
HTN	5(23.8%)	10(25.6%)	13(32.5%)	0.707
DM	2(9.5%)	5(12.8%)	4(10.0%)	0.920
Dyslipidemia	6(28.6%)	11(28.2%)	10(25.0%)	0.505
AF	4(19.0%)	5(12.8%)	7(17.5%)	0.826
MI	5(23.8%)	7(17.9%)	9(22.5%)	0.856
Stroke or TIA	10(47.6%)	12(30.8%)	18(45.0%)	0.315
Antiplatelets	7(33.3%)	9(23.1%)	13(32.5%)	0.579
Anticoagulants	2(9.5%)	3(7.7%)	5(12.5%)	0.909
Statin	4(19.0%)	10(25.6%)	8(20.0%)	0.818
TC, mmol/L	5.4 $\pm$ 0.7	5.5 $\pm$ 0.6	5.4 $\pm$ 0.7	0.940
HDL, mmol/L	1.3 $\pm$ 0.5	1.4 $\pm$ 0.4	1.4 $\pm$ 0.6	0.349
LDL, mmol/L	3.0 $\pm$ 0.2	3.1 $\pm$ 0.3	3.2 $\pm$ 0.3 ^a	0.036
TG, mmol/L	2.1 $\pm$ 0.5	2.1 $\pm$ 0.4	2.2 $\pm$ 0.4	0.928
HbA1c, %	5.2 $\pm$ 0.96	5.4 $\pm$ 1.12	5.4 $\pm$ 0.99	0.793
Presence of carotid plaque, n	15(71.4%)	27(69.2%)	29(72.5%)	0.949
Carotid IMT (mm)	0.88 $\pm$ 1.18	1.04 $\pm$ 0.14 ^a	1.19 $\pm$ 0.18 ^{bc}	< 0.001
AHI (mean)	2.53 $\pm$ 1.38	17.50 $\pm$ 6.76	41.12 $\pm$ 6.59	< 0.001

Notes: ^aP < 0.05, AHI < 5 versus AHI $\geq$ 30; ^bP < 0.05, AHI < 5 versus 5 $\leq$ AHI < 30; ^cp < 0.05, 5 $\leq$ AHI < 30 versus AHI $\geq$ 30.

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; AF, atrial fibrillation; MI, myocardial infarction; TIA, transient ischemic attack; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; IMT, intima-media thickness.

control experiment (3.0 ± 0.2), and their difference was statistically significant. The difference of IMT among the three groups was statistically significant ($P < 0.001$). Pairwise comparison showed that IMT of the normal group (0.88 ± 1.18) was lower than that of the mild-moderate OSA group (1.04 ± 0.14) and the severe OSA group (1.19 ± 0.18). IMT (1.04 ± 0.14) in the mild-moderate OSA group was significantly lower than that of the severe OSA group (1.19 ± 0.18).

Serum Levels of hs-CRP, Lp-PLA2 and TNF- α

By the principle of $AHI < 5$, $5 \sim 30$, and ≥ 30 , AHI was divided into three groups: the normal group, the mild-moderate group, and the severe group (Figure 1). Serum hs-CRP, Lp-PLA2, and TNF- α levels (20.23 ± 5.36 mg/L, 194.88 ± 17.29 ng/mL, and 1.92 ± 0.34 μ g/L) of patients with severe OSA increased significantly compared with patients with mild-moderate OSA (10.34 ± 4.80 mg/L, $P < 0.0001$; 180.49 ± 18.11 ng/mL, $P < 0.0001$; and 0.94 ± 0.42 μ g/L, $P < 0.0001$) or patients in the normal group (4.66 ± 3.58 mg/L, $P < 0.0001$; 163.10 ± 17.58 ng/mL, $P < 0.0001$; and 0.37 ± 0.27 μ g/L, $P < 0.0001$). In addition, serum hs-CRP, Lp-PLA2 and TNF- α levels (10.34 ± 4.80 mg/L; 180.49 ± 18.11 ng/mL; and 0.94 ± 0.42 μ g/L) of the mild-moderate OSA group were higher than those of the normal group (4.66 ± 3.58 mg/L, $P < 0.0001$; 163.10 ± 17.58 ng/mL, $P < 0.0001$; and 0.37 ± 0.27 μ g/L, $P < 0.0001$).

Correlation Between Carotid Artery IMT and Serum Inflammatory Mediators

Pearson correlation analysis was used to test whether the level of serum inflammatory mediators was correlated with carotid IMT. Analysis found carotid IMT and serum hs-CRP levels ($r = 0.83$, $P < 0.001$; Figure 2A), Lp-PLA2 ($r = 0.58$, $P < 0.001$; Figure 2B) and TNF- α ($r = 0.83$, $P < 0.001$; Figure 2C) were positively correlated.

Multiple Stepwise Regression Analysis of Independent Correlation Factors Affecting Carotid IMT

In this study, carotid IMT was used as the dependent variable, and hs-CRP, TNF- α , Lp-PLA2, LDL, and AHI were used as independent variables. Multiple stepwise regression analysis was performed on the patients included in this study. The results showed that hs-CRP, TNF- α , and AHI were included in the regression equation of carotid IMT and they were

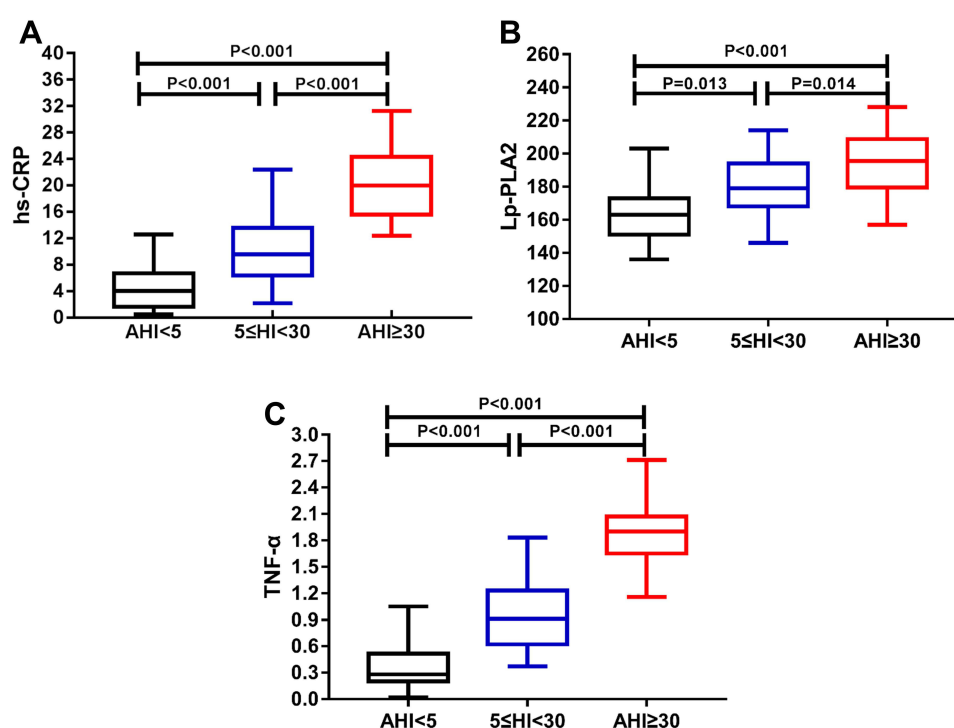


Figure 1 (A) hs-CRP levels stratified by AHI. (B) Lp-PLA2 levels stratified by AHI. (C) TNF- α stratified by AHI Level. The horizontal line indicates the average value; Block limits and minimum values indicate the 25th and 75th percentiles; The beard represents the 10th and 90th percentiles.

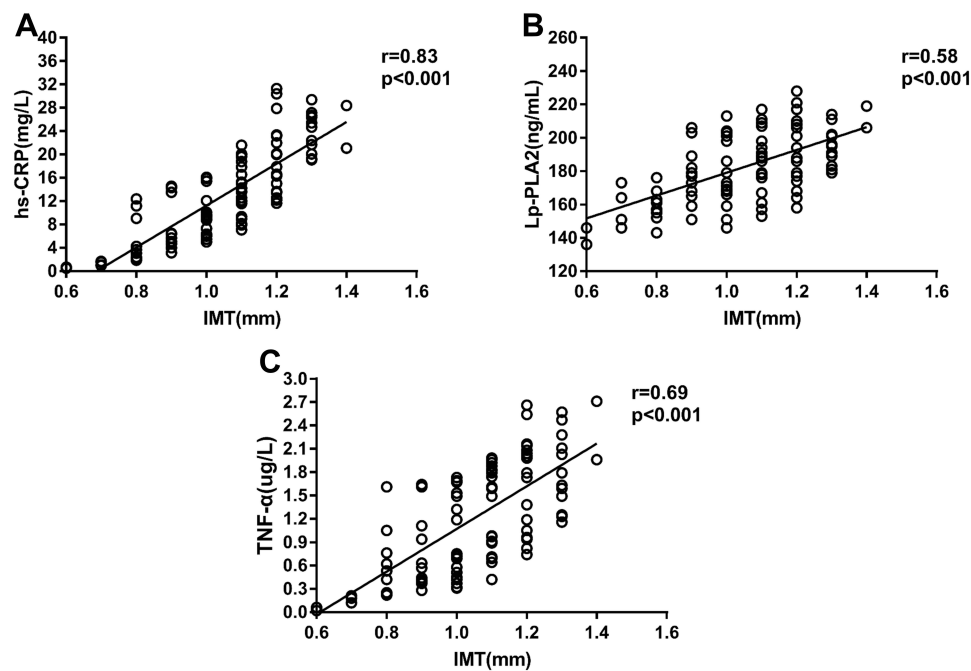


Figure 2 Correlation between carotid IMT and serum levels of hs-CRP (A), Lp-PLA2 (B), and TNF- α (C) in patients with OSA.

independent factors that affected carotid IMT. According to the standard regression coefficient, hs-CRP ($\beta' = 0.349$, $P < 0.001$) was the strongest indicator of carotid IMT (Table 2).

Predictive Value of AHI in Carotid Atherosclerosis

The discriminatory value of AHI score for carotid atherosclerosis was assessed by the ROC curve analysis, which revealed a sensitivity of 93.06%, specificity of 57.16%, and a cut-off value > 5.4 [AUC 0.709; 95% confidence interval (CI) 0.579–0.839; $P = 0.0012$] (Figure 3).

Discussion

OSA is characterized by repeated episodes of complete or partial collapse of the upper airway during sleep, resulting in apnea or hypopnea.²⁰ Data from epidemiological studies and clinical randomized trials indicate that OSA is associated with an increased risk of cardiovascular and cerebrovascular events.⁸ Although OSA and cerebrovascular diseases share many risk factors, studies have shown that OSA is an independent risk factor for atherosclerosis.²¹ The mechanism of this relationship is not completely clear. This study showed that carotid IMT in OSA patients increased, and the thickness of the intima-media increased as sleep apnea became more severe, the increased levels of hs-CRP, Lp-PLA2 and TNF- α was correlated with the severity of OSA, and carotid IMT was positively correlated with the level of hs-CRP, Lp-PLA2 and TNF- α . It was further suggested that the increase of inflammatory factors might enhance the occurrence and progression of atherosclerosis in OSA patients. Previous studies have shown that inflammatory factors such as TNF- α ,

Table 2 Multiple Stepwise Regression Analysis of Independent Correlation Factors Affecting Carotid IMT

	Beta-Coefficient	Standard Deviation	P
hs-CRP	0.349	0.002	0.000
TNF- α	0.093	0.037	0.046
AHI	0.187	0.001	0.007

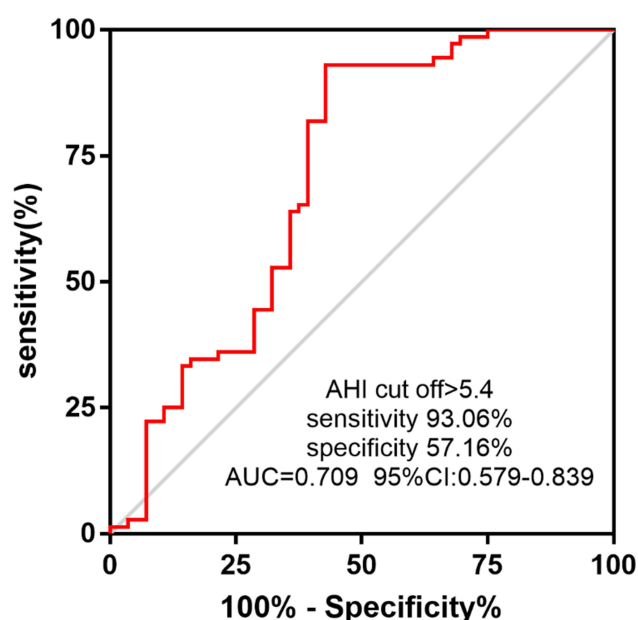


Figure 3 Receiver operating characteristics curve showing the distinguishing ability of AHI score for carotid atherosclerosis.

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristic.

Interleukin-6 (IL-6), Interleukin-8 (IL-8) and C-reactive protein (CRP) significantly increased in OSA patients.²² Similarly, a critical meta-analysis, including 51 scientific studies, found that the level of inflammatory markers in OSA patients increased significantly.²³ The present study confirmed the results of the previous studies, indicating that there was no significant difference in the distribution of other factors (such as sex, age and medical records) in the normal group, the mild-moderate OSA group or the severe OSA group. LDL in the severe OSA group was higher than that of the normal group. In addition, the serum levels of hs-CRP, Lp-PLA2 and TNF- α of the OSA patients were significantly higher than those of the normal subjects. Moreover, serum levels of hs-CRP, Lp-PLA2 and TNF- α significantly increased in patients with severe OSA compared with patients of mild- moderate OSA or the normal group. Most of the previous studies stopped at this point, but we went on to explore the relationship between carotid IMT and inflammatory factors in OSA patients. Therefore, the results in the study expanded the previous findings to show that IMT was also associated with OSA severity, which was similar to the international scientific research of Salepci. Salepci investigated 102 Turkish patients and found that the wall of common carotid artery (CCA) was thicker and OSA patients' IMT was higher than that of the control group. This main parameter was highly correlated with the severity of OSA, indicating that OSA was likely to accelerate the progression of atherosclerosis.²⁴ However, the results of a large and medium-sized multi-ethnic study showed that there was no significant correlation between the carotid atherosclerosis index and the sleep disorders in the entire cohort. However, the association between sleep disorders and carotid atherosclerosis in individuals under the age of 68 was stronger than that of the elderly, and the association in black people was stronger than in other ethnic groups, but the association did not vary by sex.²⁵ OSA is a recognized secondary cause of hypertension that may lead to insulin resistance, diabetes, and dyslipidemia which are all recognized risk factors for atherosclerosis.^{26–28} In order to prevent the influence of these confounding factors, Drager²⁹ scientifically studied a group of young (55 year old) male OSA patients who had no comorbidity such as cardiovascular and cerebrovascular diseases and had never taken any related drugs. The results showed that compared with the control group without OSA, patients with OSA had early signs of atherosclerosis which were significantly affected by the OSA severity. The results further supported the hypothesis that OSA played an independent role in the progression of atherosclerosis. Results of a prospective study showed that the carotid IMT of patients with CPAP treatment for 12 months significantly decreased compared with patients who chose conservative management.³⁰ This scientific research clearly showed that OSA was an independent risk source of atherosclerosis.

Recent studies have shown that the presence and the score of carotid vascular plaque can better help predict cardiovascular and cerebrovascular diseases than IMT^{31,32} does, but our study showed that these three groups of patients had no significant difference in plaque detection rate (71.4% vs 69.2% vs 72.5%, $P = 0.949$). The reason might be that IMT and the plaques reflected the different stages of arteriosclerosis; compared with quantitative plaque measurement, the predictive value of plaque presence was even lower.

The exact relationship between OSA and atherosclerosis is still not very clear, but it is undeniable that inflammation is a common feature of OSA and atherosclerosis. To clarify the underlying mechanism of OSA in aggravating atherosclerosis, the relationship between IMT and inflammatory factors were evaluated. The results of the correlation analysis between IMT and inflammatory factors showed that hs-CRP ($r = 0.83$, $P < 0.001$) had a significant correlation with IMT. hs-CRP was an acute nonspecific marker of the systemic inflammatory response in the early stage. As a promoting oxide, hs-CRP could induce the occurrence of lymphocyte adhesion protein 1 and the expression of adhesion molecules (such as ICAM-1 and VCAM-1),^{33,34} and its increase could independently induce the occurrence of atherosclerosis. This study showed that the increase of hs-CRP in patients with OSA was directly proportional to the significant level of OSA and such increase was significantly related to IMT. Therefore, our results suggested that the elevated hs-CRP level might play a major role in the progression of atherosclerosis of OSA patients. TNF- α was caused by cellular immunity, progenitor cells, smooth muscle cells, epidermal cells, etc, and it had universal biological activities. TNF- α could stimulate mononuclear phagocytes and neutrophils, improve their swallowing capability and participate in the whole process of atherosclerosis. Activated immune cells in the atherosclerotic plaques can further secrete TNF- α , which boosts the inflammatory response to continue and gradually aggravate, thus producing the waterfall effect. This study also showed that TNF- α ($r = 0.69$, $P < 0.001$) was obviously related to IMT. Lp-PLA2 was a serine amylase and was mainly caused by active lymphocytes and phagocytes.³⁵ It has been a commonly studied inflammatory marker of atherosclerosis in recent years and has been confirmed in the study. Lp-PLA2 has been shown to upregulate in atherosclerotic plaques and is an independent risk factor for atherosclerotic plaque formation,^{36,37} which was associated with every link of the atherosclerotic plaque formation. Unlike other elements of systemic inflammation, it was highly nonspecific for capillary inflammation. However, so far, very few studies have investigated the role of Lp-PLA2 in OSA. This study showed that Lp-PLA2 increased in the OSA population, and Lp-PLA2 ($r = 0.58$, $P < 0.001$) was weakly related to IMT. A possible mechanism was that OSA patients had continuous and intermittent oxygen deficiency and carbon dioxide storage, which resulted in the air oxidation and antioxidant system out of balance in the body, thus, the role of ATP was jeopardized or damaged, which caused membrane protein damage and released a lot of oxygen free radicals. As a result, Lp-PLA2 was stimulated immediately. In addition, Lp-PLA2 could cause inflammatory phenomena in response to stimulation, such as hypoxia inducible factor 1 and nuclear factors κ B (NF- κ B) that were released and stimulated. Multiple stepwise regression analysis was carried out with carotid IMT as the independent variable. The results showed that hs-CRP, TNF- α and AHI were the independent influencing factors of carotid IMT, as well as, hs-CRP ($\beta' = 0.349$, $P < 0.001$) was also the strongest predictor of Carotid IMT. In addition, Silvana P³⁸ showed that OSA was associated with IMT elevation in a dose-response manner. Mustafa³⁹ showed that the presence of non-calcified /mixed plaques were significantly associated with the severity of sleep-disordered breathing ($P < 0.001$). In the existing studies, the results showed that AHI was an independent indicator of carotid atherosclerosis ($P = 0.0012$). All in all, the results showed that the serum protein hs-CRP, Lp-PLA2 and TNF- α of patients with OSA and their carotid IMT increased. Elevation of carotid IMT and increase of serum hs-CRP, Lp-PLA2 and TNF- α were related. hs-CRP, TNF- α and AHI were independent influencing factors of carotid IMT. Besides, the increase of AHI was likely to have predictive value for carotid atherosclerosis. Recent studies have also shown that OSA-related oxygen deficiency duration was associated with carotid IMT.^{40,41} Since this study is a cross-sectional study, the limitation of the study is that it did not consider the cumulative effect of the OSA duration on IMT. In addition, the study could only determine the correlation between OSA, inflammation and atherosclerosis, and it was not possible to determine the causal relationship between the three, or that how OSA itself increased the risk of these events or the contribution of confounding factors.

In summary, OSA raised the level of inflammatory markers through various pathways, thereby accelerating atherosclerosis and increasing the incidence and mortality of cardiovascular and cerebrovascular diseases. Medical staff should pay a lot of attention to patients with snoring and obstructive pulmonary emphysema apnea in clinical medical work. The

high-risk objects should be screened and timely evaluation and follow-up of the carotid artery of the neck blood vessel should be carried out. For patients with OSA, it is necessary to develop and design various ways to improve hypoxemia, so as to decrease the level of inflammatory mediators during the night and improve the thickness of carotid IMT, thus the prevalence of cardiovascular disease can be reduced.

Data Sharing Statement

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

Ethics Approval and Informed Consent

All research studies on humans have been performed in accordance with the principles stated in the Declaration of Helsinki. Prior to starting the study, ethical approval have been obtained for all protocols from the author's medical (The Third People's Hospital of Zhengzhou) ethics committee to confirm the study meets national and international guidelines for research on humans. And for all studies involving human participants informed written consent to take part in the research have been obtained prior to the commencement of the study.

Consent for Publication

Written informed consent for publication of their details was obtained from the patient.

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Disclosure

The authors declare that they have no competing interests.

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