The Effects of Obstructive Sleep Apnea on Risk factors for Cardiovascular diseases

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Abstract

Introduction: Obstructive sleep apnea (OSA) is known to cause variety of cardiovascular diseases. Objective: The aim of this study was to examine the correlation between polysomnography (PSG) and risks factor for coronary heart disease in patients suspected to have OSA. Methods: A total of 108 consecutive adult habitual snorers underwent PSG. We assessed patients using the respiratory disturbance index (RDI), the Epworth sleepiness scale (ESS), body mass index (BMI), fasting serum total cholesterol, triglycerides (TGs), and C-reactive protein (CRP). Results: Mean RDI scores were 0.53, 10.6, 27.3, and 45.1 in the control group (n = 21), mild (n = 29), moderate (n = 31), and severe (n = 27), respectively. Partial correlation analysis showed that patients’ RDI score was significantly correlated with CRP after adjustment for BMI. Partial correlation analysis showed that the mean ESS score correlated significantly with the CRP level after adjustment for BMI. Partial correlation analysis showed that the mean least oxygen saturation was significantly correlated with CRP after adjustment for BMI. Pearson’s correlation coefficients examining the relationship between BMI and total cholesterol; TG and CRP were found to be 0.531, 0.401, and 0.321. The correlation of CRP levels with disease severity as assessed by RDI, ESS, and least oxygen saturation was significant after adjustment for BMI. Conclusions: Patients with OSA have elevated serum levels of high-sensitivity-CRP, a marker for inflammation and an independent risk predictor for cardiovascular morbidity.

Keywords
obstructive sleep apnea, high-sensitivity c-reactive protein, cardiovascular disease, cerebrovascular diseases, polysomnography

Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disease that affects 4% of the entire population. It induces frequent partial or total obstruction of the upper airway during sleep, which decreases oxygen saturation and disrupts sleep.1,2

Obstructive sleep apnea triggers the activation of sympathetic nerves, high blood pressure, and oxidative stress through repetitive apnea and hypopnea, leading to cardiovascular diseases such as atherosclerosis.3

According to recent studies, OSA is related to several factors that injure vascular endothelial cells and lead to atherosclerosis. In addition, hypoxia and systemic inflammation triggered by OSA are related to the progression of atherosclerosis and act as risk factors for cardiovascular and cerebrovascular diseases. Moreover, other studies have indicated that these risk factors increase the incidence of atherosclerosis, hypertension, and cerebral infarction.2,4

It is known that hypoxia and reoxygenation, which are physiological factors associated with OSA, trigger the activation of inflammatory cells as well as hyperlipidemia. Several studies have shown that this inflammatory process increases serum total cholesterol and triglyceride (TG) levels while also decreasing low-density lipoprotein.5

C-reactive protein (CRP) is the most important predicting factor of cardiovascular disease and is known to be related to vascular endothelial cell dysfunction, which is one of the pathophysiologic factors associated with coronary artery disease.4,5

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Repetitive hypoxia and reoxygenation in patients with OSA increase proinflammatory mediators such as CRP. Increased CRP due to chronic inflammation is known to be an independent risk factor for peripheral vascular disease, myocardial infarction, and cerebral infarction.\(^5\,6\)

In addition, OSA is closely related to obesity, an important cause of metabolic disease. Regardless of obesity status, OSA is known to be related to risk factors of several cardiovascular diseases.

However, the exact OSA risk factors that induce cardiovascular diseases have not yet been investigated; therefore, examining the risk factors related to the development of cardiovascular disease and death is of clinical importance.\(^5\)

In this study, we researched the relationships between several polysomnography (PSG) variables as clinical indicators of OSA severity and risk factors of coronary heart disease.

### Patients and Methods

This study examined 108 patients who visited an ENT center for habitual snoring from February 2008 to June 2010 and underwent PSG. The ratio of men to women was 80:20, and we excluded patients with cardiovascular disease, chronic heart failure, or chronic kidney disease as well as those who have taken Nonsteroidal anti-inflammatory drugs, hyperlipidemia medications, or steroid hormones. Patients were also excluded if they had previously undergone an operation or had continuous positive airway pressure.

For 108 patients, we measured the respiratory disturbance index (RDI), mean oxygen saturation, least oxygen saturation, age, the Epworth sleepiness scale (ESS, Figure 1), body mass index (BMI, kg/m\(^2\)), fasting total cholesterol and TG (mg/dL), and CRP. We diagnosed OSA for the patients with an RDI higher than 5, whereby the RDI classified patients with 5 < RDI ≤ 15 as mild, 15 < RDI ≤ 25 as moderate, and 25 < RDI ≤ 35 as severe. Patients with RDI < 5 were used as the control group, and patients were divided into a total of 4 groups.

The ESS classifies the degree of daytime drowsiness in 8 situations using a scale from 0 to 3. We calculated each total score and classified the patients into 4 categories. This study was approved by the institutional review board.

### Polysomnography

We examined each patient’s electroencephalogram, electrooculography, electromyography, and electrocardiogram. We also used a respiratory thermistor to examine the air stream of the nasal and oral cavity and impedance belts on the chest and abdomen to assess respiratory effort. Pulse oximetry was performed, and a tracheal microphone was used to measure snoring. We also performed nighttime PSG and a multisleep latency test, in which a sensor was used to examine the sleeping positions of all patients. The multisleep latency test was conducted according to the guidelines of the American Sleep Association.

We defined apnea as a decreased state of respiration of more than 90% compared with the PSG guideline and a complete block of the airflow through the oral and nasal cavity for at least 10 seconds. We defined hypopnea as a decreased state of oral and nasal cavity airflow of more than 50% compared with normal sleep time. Patients were also classified as having hypopnea if their airflow was decreased to less than 50% and their oxygen saturation decreased more than 3% accompanying their arousal. We defined the respiratory effort-related arousal (RERA) as inspiratory limitation without apnea and hypopnea for 10 seconds or more, triggering arousal and normalization of respiration by arousal. We classified obstructive respiratory disturbance according to these guidelines and defined the RDI as the average rates of apnea, hypopnea, and RERA during the sleeping hours.

### Statistics

We used SPSS 11.5 software to calculate the mean and standard deviations, and we used Pearson correlation coefficient to examine the relationship between the 4 groups’ parameters.

### Results

Table 1 shows the mean age, BMI, RDI, ESS, and the mean and minimal oxygen saturation in the normal and OSA patient groups.

Across the normal, mild, moderate, and severe OSA groups, the mean RDIs (+2.5 standard deviation) were 0.53 ± 0.3, 10.6 ± 3.4, 27.3 ± 2.7, and 45.1 ± 5.7, respectively, and the correlation analysis between RDI and CRP after correcting for BMI indicated a statistically significant relationship (\(P = .05\)). However, no statistically significant relationship was observed between RDI and total cholesterol or between RDI and TG (\(P = .117, P = .231\), respectively).

In the normal, mild, moderate, and severe OSA groups, the mean ESSs (+2.5 standard deviations) were 3.9 ± 1.83, 13.7 ± 2.46, 15.3 ± 2.69, and 17.42 ± 3.51, respectively. The correlation analysis between ESS and CRP after correcting for BMI was statistically significant (\(P = .042\)), but the relationship between ESS and total cholesterol and TG was not (\(P = .807, P = .705\)).
Table 1. Clinical Characteristics of the Patients with OSA and the Control Group.

| Characteristics                  | Control Group | Mild OSA | Moderate OSA | Severe OSA |
|----------------------------------|---------------|----------|--------------|------------|
| Age, years                       | 47.1 ± 2.6    | 45.3 ± 2.9 | 43.8 ± 3.2   | 48.2 ± 3.1 |
| Body mass index, kg/m²           | 27.6 ± 8.1    | 26.8 ± 3.4 | 25.7 ± 2.1   | 26.7 ± 3.1 |
| RDI                              | 0.53 ± 0.3    | 10.6 ± 3.4 | 27.3 ± 2.7   | 45.1 ± 5.7 |
| ESS                              | 3.9 ± 1.83    | 13.7 ± 2.46| 15.3 ± 2.69  | 17.42 ± 3.51|
| Mean oxygen saturation (%)       | 92.2 ± 1.47   | 91.57 ± 0.95| 92.13 ± 0.77 | 88.97 ± 2.82|
| Least oxygen saturation (%)      | 90.06 ± 1.79  | 87.64 ± 2.58| 87.56 ± 3.78 | 80.7 ± 5.67 |

Abbreviations: ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

Table 2. Parameters Measured in the Patients and the Control Group.

| Parameters          | Control Group | Mild OSA | Moderate OSA | Severe OSA |
|---------------------|---------------|----------|--------------|------------|
| Total cholesterol, mg/dL | 199.7 ± 16.08 | 191.9 ± 57.35 | 189.5 ± 39.8 | 203.3 ± 36.1 |
| Triglyceride, mg/dL   | 241.1 ± 177.8 | 164.5 ± 101.3 | 171.4 ± 96.4 | 232.3 ± 97.7 |
| CRP, mg/L             | 0.38 ± 0.33   | 0.34 ± 0.33 | 0.51 ± 0.65  | 0.60 ± 0.74  |

Abbreviations: CRP, C-reactive protein; OSA, obstructive sleep apnea.

*Normal range: total cholesterol: 120 to 220 mg/dL; triglyceride: 28 to 200 mg/dL; CRP <0.5 mg/L.

Table 3. Correlation of OSA Parameters With Risk Factors for CHD Before Adjusting for BMI.

| Parameters          | Triglyceride | Total Cholesterol | CRP |
|---------------------|--------------|-------------------|-----|
| RDI                 | 0.118        | 0.217             | 0.004* |
| BMI                 | 0.531        | 0.401             | 0.321 |
| ESS                 | 0.921        | 0.967             | 0.042* |
| Mean O₂ saturation  | 0.307        | 0.203             | 0.074 |
| Least O₂ saturation | 0.076        | 0.103             | 0.001* |

Abbreviations: BMI, body mass index; CHD, coronary artery disease; CRP, C-reactive protein; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

*P-value <0.05.

Table 4. Correlation of OSA Parameters With Risk Factors for CHD after Adjusting for BMI.

| Parameters          | Triglyceride | Total Cholesterol | CRP |
|---------------------|--------------|-------------------|-----|
| RDI                 | 0.117        | 0.231             | 0.005* |
| ESS                 | 0.807        | 0.705             | 0.042* |
| Mean O₂ saturation  | 0.207        | 0.173             | 0.075 |
| Least O₂ saturation | 0.083        | 0.231             | 0.003* |

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESS, Epworth sleepiness scale; OSA, obstructive sleep apnea; RDI, respiratory disturbance index.

*P-value <0.05.

In the normal, mild, moderate, and severe OSA groups, the mean minimal oxygen saturation values (+2.5 standard deviations) were 90.06 ± 1.79, 87.64 ± 2.58, 87.56 ± 3.78, and 80.7 ± 5.67, respectively. In addition, the correlation analysis between the mean minimal oxygen saturation and CRP after correcting for BMI was statistically significant (P = .003); however, the correlations between oxygen saturation and total cholesterol and between oxygen saturation and TG were not significant (P = .083, P = .231, respectively).

Table 2 shows the total cholesterol, TG, and CRP of the OSA and control groups. The prevalence of HTN and DM was not significantly associated with the severity of the RDI (P > .05).

The correlation coefficients between BMI and total cholesterol and between BMI and TG were not statistically significant (P = .401, P = .531, respectively). Moreover, the correlation coefficient between BMI and CRP was also not statistically significant (P = .321). However, the correlations between CRP and each of the RDI, ESS, and mean minimal oxygen saturation scores were statistically significant (P = .004, P = .042, P = .001, respectively; Table 3), even after adjusting for BMI (P = .005, P = .042, P = .003, respectively; Table 4).

When examining the correlations of RDI with TG, total cholesterol, and CRP, only the relationship between RDI and CRP showed a positive correlation (P < .05; Figure 2).

Of the correlation graphs comparing minimal oxygen saturation, TG, total cholesterol, and CRP, only the correlation between the minimal oxygen saturation and CRP was positive (P < .05; Figure 3).

Discussion

Sleep apnea is a common disease with a prevalence of 2% to 26%. In many studies, the risk of cerebrovascular diseases such as hypertension, arrhythmia, night ischemic heart disease, myocardial infarction, and stroke has been shown to be increased in patients with sleep apnea, which is a worldwide health issue.7,8 Thus, the authors endeavored to discover factors that can predict the risk of cardiovascular disease in patients with sleep apnea, while also controlling for BMI (as BMI can influence both diseases) and compare the results.
In this study, RDI, ESS, and the minimal oxygen saturation showed a significant correlation with CRP, which is a risk factor for cardiovascular disease. As the severity of OSA increased, CRP also increased. Total cholesterol and TG showed no significant correlation with these factors.

Several hypotheses have been suggested regarding the mechanism whereby sleep apnea affects cardiovascular disease. As sleeping affects the whole body, mechanical changes in the pressure between the thoracic cage and airway, effects on the autonomic nerve or vascular interior wall, oxidative stress, inflammation and arrhythmia have been suggested as possible links between sleep apnea and cardiovascular disease. However, according to recent studies, inflammatory materials, oxidative stress, and metabolic factors have also performed an important role.9,10

Yardim-Akaydin et al suggested that repetitive hypoxia/reoxygenation reactions influence systemic inflammation reactions, which was confirmed by increases in CRP and fibrinogen in the blood.11

Repetitive hypoxia/reoxygenation reactions cause a chronic intermittent hypoxia (CIH) state that affects renin–angiotensin activity, production of endothelin, factors involved in peripheral chemical reactions, and autonomic nerve activities.12 In patients with OSA, through the dysfunction of endothelin and lipid peroxidation, levels of inflammation precursors such as tumor necrosis factor, interleukin 1 (IL-1), IL-8, and adhesion molecules increase, resulting in systemic inflammation reactions.13

In previous studies examining sleep apnea and lipid abnormalities, lipolysis, the metabolism of free lipid acids, processing
of TG in the liver, secretion of lipoprotein, and control of lipoprotein expression were shown to cause dyslipidemia.\textsuperscript{14}

Trzepizur et al conducted animal experiments to examine intermittent hypoxia and dyslipidemia. Total cholesterol and LDL levels showed no correlation with oxygen desaturation index; however, nighttime intermittent hypoxia and the severity of sleep apnea showed independent correlations with TG and HDL.\textsuperscript{15} However, in this study, the same correlations among sleep apnea, total cholesterol, and TG were not confirmed.

In this study, as in previous studies, we can confirm a significant correlation between serum CRP and the severity of OSA. Therefore, we suggest that CRP should be used to screen for systemic inflammation in patients with OSA to evaluate their status and degree of risk for developing cardiovascular disease.

In this study, we examined untreated patients with OSA, and we suggest that additional studies assessing the decrease in CRP after CPAP treatments are needed. We believe that CRP can be used to precisely evaluate the status and degree of risk for developing cardiovascular disease; however, future studies should be performed to examine other indicators as well.

**Declaration of Conflicting Interests**
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References

1. Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax. 2007; 62(6):509-514.
2. Guven SF, Turkkani MH, Ciftci B, Ciftci TU, Erdogan Y. The relationship between high-sensitivity C-reactive protein levels and the severity of obstructive sleep apnea. Sleep Breath. 2012; 16(1):217-221.
3. Feng J, He QY, Zhang XL, Chen BY; Sleep Breath Disorder Group, S. o. R. M. Epworth Sleepiness Scale may be an indicator for blood pressure profile and prevalence of coronary artery disease and cerebrovascular disease in patients with obstructive sleep apnea. Sleep Breath. 2012;16(1):31-40.
4. Sharma SK, Mishra HK, Sharma H, et al. Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. Sleep Med. 2008;9(2):149-156.
5. Czerniawska J, Bielen P, Pływaczewski R, et al. Metabolic abnormalities in obstructive sleep apnea patients. Pneumonol Alergol Pol. 2008;76(5):340-347.
6. Kojturm O, Ciftci TU, Mollarecep E, Ciftci B. Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. Int Heart J. 2005;46(5):801-809.
7. Choi JW, Koo SK, Myung NS, Kim YJ, Lee GH, Lee HJ. Analysis of correlation between results of polysomnography and obstructive structure by drug-induced sleep endoscopy in obstructive sleep apnea patients. Korean J Otorhinolaryngol-Head Neck Surg. 2013;56(6):346-353.
8. Zhang M, Li L, Fowler D, et al. Causes of sudden death in patients with obstructive sleep apnea. J Forensic Sci. 2013;58(5):1171-1174.
9. Kasai T, Bradley TD. Obstructive sleep apnea and heart failure: pathophysiological and therapeutic implications. J Am Coll Cardiol. 2011;57(2):119-127.
10. Malhotra A, Lospalzo J. Sleep and cardiovascular disease: an overview. Prog Cardiovasc Dis. 2009;51(4):279-284.
11. Yardim-Akaydin S, Caliskan-Can E, Firat H, Ardic S, Simsek B. Influence of gender on C-reactive protein, fibrinogen, and erythrocyte sedimentation rate in obstructive sleep apnea. Antiinflamm Antiallergy Agents Med Chem. 2014;13(1):56-63.
12. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96(4):1897-1904.
13. Carpio C, Alvarez-Sala R, Garcia-Rio F. Epidemiological and pathogenic relationship between sleep apnea and ischemic heart disease. Pulm Med. 2013;2013:405827.
14. Mirrakhimov AE, Ali AM. Pathobiology of obstructive sleep apnea-related dyslipidemia: focus on the liver. ISRN Cardiol. 2013;2013:687069.
15. Trzepizur W, Le Vaillant M, Meslier N, et al. Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. Chest. 2013;143(6):1584-1589.