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Effect of CPAP treatment on endothelial function and plasma CRP levels in patients with sleep apnea

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Summary

Background: Continuous positive airway pressure (CPAP) is the most effective method for treating obstructive sleep apnea syndrome (OSAS) and alleviating symptoms. Improved sleep quality with effective CPAP therapy might also contribute to attenuated systemic inflammation and improved endothelial function, with subsequent reduction of cardiovascular risk.

The aim of this study was to assess the effect of 3-month CPAP therapy on brachial artery flow-mediated dilation (FMD) and plasma C-reactive protein (CRP) levels in patients with OSAS.

Material/Methods: Our study group consisted of 38 male patients with no prior history of cardiovascular disease. Twenty patients with an Apnea-Hypopnea Index (AHI) ≥15 were assigned to receive CPAP treatment and 18 subjects with an AHI<5 were included in the control group. Six patients failed to comply with the CPAP treatment. Measurement of FMD and blood analysis was performed at baseline and 3 months after CPAP therapy.

Results: Baseline FMD values were negatively correlated with age, BMI, AHI, DSI,% of time <90% Sa02, and CRP ($p<0.05$). Plasma CRP values were positively correlated with BMI, AHI, DSI and% of time <90% Sa02 ($p<0.05$). In the group of patients who complied with the CPAP treatment, there was a significant increase in the FMD values (9.18±0.55 *vs.* 6.27±0.50) and a decrease in the levels of CRP (0.67±0.15 *vs.* 0.84±0.18) ($p<0.05$).

Conclusions: Appropriate CPAP therapy improved both CRP and FMD values, suggesting its potentially beneficial role in reducing cardiovascular risk in OSAS patients.

key words: CPAP • sleep apnea • inflammation

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Background

The obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder characterized by recurrent episodes of upper airway obstruction and subsequent recurrent arousal during sleep [1]. It is estimated that up to 5% of adults in Western countries have OSAS [2].

According to published data, OSAS is an independent risk factor for hypertension and coronary artery disease [3,4]. Emerging studies suggest that the repetitive episodes of hypoxia and reoxygenation, in a manner similar to that of the ischemia/reperfusion injury model, promote the activation of proinflammatory pathways and disrupt normal endothelial function [5,6].

Brachial artery flow-mediated dilation (FMD) is a validated and widely used research tool for the quantification of endothelial function [7,8]. FMD values are diminished in patients with severe OSAS [9–11].

CRP is an acute phase protein and plays an important role in innate immunity. It is a sensitive marker of inflammation and an important marker of future cardiovascular risk [12,13]. Elevated CRP levels have been reported by several researchers in OSAS patients [14–16].

Brachial artery FMD and CRP are valuable markers of the atherogenic process in OSAS. CPAP is the most effective method for treating OSAS and alleviating symptoms [17]. We hypothesized that the proper use of CPAP should also help improve the levels of FMD and CRP and thus reduce the risk for adverse cardiovascular events.

The aim of this study was to assess the effect of 3-month CPAP therapy on FMD and plasma CRP levels in patients with OSAS.

Material and Methods

This study was conducted in the sleep laboratory of the department of clinical therapeutics at Alexandra Hospital; Athens Medical School. Informed consent was obtained from each patient and approval was also obtained for the conduct of this study from the Hospital Ethics Committee.

Male patients with suspected OSAS, receiving no medication, and known not to suffer from diabetes mellitus, arterial hypertension, dyslipidemia, or inflammatory, cardiovascular, neuromuscular or pulmonary diseases were recruited into the study.

All patients underwent full overnight polysomnography. According to the standard criteria of the American Academy of Sleep Medicine: 1) apnea was defined as a complete cessation of airflow for at least 10 seconds; 2) hypopnea was defined as a reduction in airflow of at least 50%, a <50% reduction associated with electroencephalographic arousals, or a >3% decrease in oxygen saturation; and 3) the apnea-hypopnea index (AHI) referred to the average number of apneas and hypopneas per hour of sleep. Subjects with an AHI ⩾15 were assigned to receive CPAP treatment and formed our study group. Subjects with an AHI<5 were defined as not having OSAS and were included in the control group. Patients with an AHI 5–15 were not eligible for CPAP treatment and were excluded from the study analysis.

A high-resolution 12.0-MHz transducer ultrasound was used to measure brachial artery diameter at rest and during reactive hyperemia. All patients fasted for at least 8 hours prior to the measurement. The assessment was carried out in a quiet room, with a stable temperature at 22 to 24°C, by an experienced physician who was blinded to the patient's sleep recordings and blood analysis. Reactive hyperemia was induced by inflation of a blood pressure cuff placed on the lower part of the arm and inflated to 250 mm Hg, followed by release after 5 minutes. Brachial artery diameter was measured 40 and 60 seconds after cuff deflation. Flow-mediated dilation (FMD) was calculated as the ratio of change in diameter (maximum of 2 measurements – baseline) over baseline value. Endothelial function measurements were reassessed after 3 months of CPAP therapy.

Patients' smoking status, body mass index (BMI) (calculated as kilograms per meter squared), arterial blood pressure, and heart rate were recorded at baseline and 3 months after CPAP treatment. Non-smokers were defined as those patients who had never smoked. Furthermore blood analysis including: glucose, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides and CRP, was performed prior and 3 months after CPAP.

A standard statistical software package SPSS (SPSS Inc, Chicago, IL) was used in the analysis. Descriptive statistics were calculated for all variables. Difference regarding smoking status between OSA and control subjects was assessed with the chi-square test. The t test was used to detect differences in age, BMI, blood pressure, heart rate, lipidemic profile, sleep parameters, FMD and CRP values between OSA patients and control subjects. The association between baseline CRP and FMD values with age, BMI, and sleep parameters was assessed with the Pearson correlation test. Paired-samples t test was used for comparison of the patients' FMD and CRP values at baseline and 3 months after CPAP therapy. P values less than 0.05 were considered statistically significant.

Results

A total of 48 patients were recruited during our study period. Ten patients had an AHI between 5 and 15 and were excluded from the study, 18 subjects were included in the control group (AHI<5), and 20 patients with AHI ⩾15 formed the OSAS group in need of CPAP treatment.

Baseline characteristics of OSAS and control subjects are presented in Table 1. There were no significant differences between control subjects and OSAS patients with regard to the mean age, BMI, blood pressure, heart rate, lipid markers, glucose and smoking status. Compared to the controls, the OSAS group had significantly lower FMD values (6.72±0.86 *vs.* 9.59±1.15) and higher plasma CRP levels (0.82±0.16 *vs.* 0.29±0.14) (p=0.00).

Baseline FMD values were negatively correlated with age, BMI, AHI, DSI,% of time <90% Sa02, and CRP (p<0.05). Plasma CRP values were positively correlated with BMI, AHI, DSI, and% of time <90% Sa02 (p<0.05) (Table 2). After adjustment for age and BMI, FMD values retained

Table 1. Baseline characteristics of control subjects and patients with OSAS.

	Control (N=18)	OSAS (N=20)	P-Value
Age(years)	48.33±7.67	54.30±10.84	0.06
Smoking(N/%)	14 (77.80%)	15 (75.00%)	0.67
BMI	30.00±2.14	31.30±2.00	0.06
Systolic BP(mmHg)	126.57±10.64	124.35±4.84	0.40
Diastolic BP(mmHg)	78.03±5.86	77.02±5.90	0.60
Heart rate/min	79.57±7.83	77.49±8.90	0.45
Cholesterol (mg/dl)	204.67±47.49	225.50±43.52	0.17
LDL(mg/dl)	134.00±33.36	142.75±29.78	0.40
HDL(mg/dl)	48.17±5.09	51.25±9.93	0.23
Triglycerides (mg/dl)	145.83±64.97	146.80±60.50	0.96
Glucose (mg/dl)	97.33±9.24	97.10±12.89	0.95
AHI	2.67±1.41	25.35±15.05	0.00
DSI	1.50±0.51	21.80±11.28	0.00
% of time <90% Sa02	0.67±0.49	7.40±4.62	0.00
CRP(mg/dl)	0.29±0.14	0.82±0.16	0.00
FMD	9.59±1.15	6.72±0.86	0.00

Table 2. Association between baseline CRP and FMD with age, BMI, and sleep parameters.

		FMD	CRP
Age	r	–0.38	0.16
	P-value	0.02	0.32
BMI	r	–0.47	0.52
	P-value	0.00	0.00
AHI	r	–0.81	0.77
	P-value	0.00	0.00
DSI	r	–0.83	0.80
	P-value	0.00	0.00
% of time <90% Sa02	r	–0.82	0.77
	P-value	0.00	0.00
CRP	r	–0.79	1.00
	P-value	0.00	.

their correlation with AHI (B=–0.08, p=0.00), DSI (B=–0.10, p=0.00) and% of time <90% Sa02 (B=–0.28, p=0.00). After adjustment for BMI, CRP values also retained their correlation with% of time <90% SaO_2 (B=0.04, p=0.00), DSI (B=0.01, p=0.00) and AHI (B=0.01, p=0.00).

Out of 20 patients in the OSAS group, 6 failed to comply with the CPAP treatment and returned the devise within 2 weeks. During the study period, patients' BMI and smoking status did not change. In the group of patients who complied with the CPAP treatment, there was a significant increase in the FMD values (9.18±0.55 *vs.* 6.27±0.50) and a decrease in the levels of CRP (0.67±0.15 *vs.* 0.84±0.18) (p=0.00). No changes were detected in the group of patients who failed to comply with CPAP (Figures 1, 2).

Discussion

The measurement of endothelium-dependent dilation in response to reactive hyperemia is a non-invasive and validated

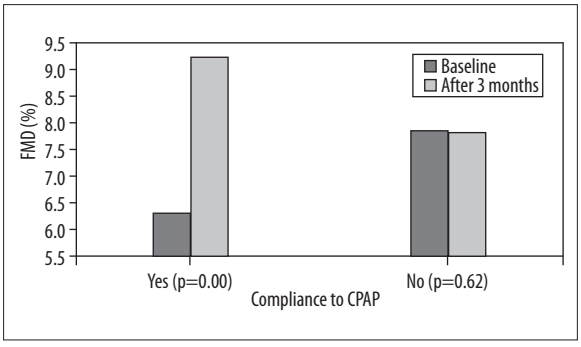

Figure 1. Bar charts represent mean value of FMD at baseline and 3 months after in OSA patients compliant and none compliant with CPAP.

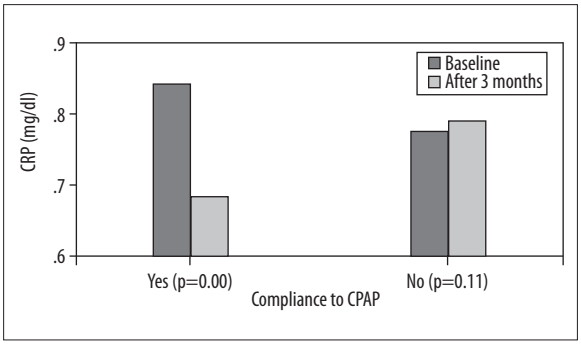

Figure 2. Bar charts represent mean value of CRP at baseline and 3 months after in OSA patients compliant and none compliant with CPAP.

method for the assessment of the endothelial function [18]. Alterations in endothelium dependent dilatation have been documented in patients with coronary artery disease and diabetes and, recently, OSAS [19–22]. The regulation of vasomotor tone, as measured by the change in the forearm blood flow after transient ischemia, appears to be regulated by the availability of nitric oxide. Researchers have shown that in the OSAS the pathophysiologic stressors resulting from repetitive episodes of hypoxemia/reoxygenation downregulate the activity of the endothelial nitric oxide synthase and upregulate the expression of various vasoactive substances such as endothelin-1 and angiotensin II [23–25].

In this study, FMD values appeared to be significantly higher in the control group compared to the OSAS patients, and were negatively correlated with the AHI, DSI and% of time <90% Sa02. In accordance with our results, previous studies have also shown that endothelial dysfunction, as measured by FMD, was correlated with the severity of OSAS [9–11]. Furthermore, FMD values were negatively correlated with age. In a recent study by Yim-Yeh et al., age proved to be an independent predictor of FMD [10].

Recently, data have emerged regarding the potential beneficial effects of CPAP on endothelial function. A study by Ip et al. demonstrated that FMD was significantly improved after 4 weeks of CPAP treatment, while Bayram et al. found that the improvement in the endothelial function was sustained after 6 months of treatment in complaint patients [26,27]. Our results also confirm the beneficial role of CPAP on FMD values after 3 months of treatment.

Recently, a large amount of evidence has demonstrated the pivotal role of inflammation in cardiovascular disease. In view of this, C-reactive protein has gained increasing attention as an independent risk factor for coronary disease [28]. In patients with OSAS, circulating levels of inflammatory markers appeared to be elevated, suggesting the presence of systemic inflammation [29,30]. In agreement with previous reports, we showed that CRP levels were positively correlated with the OSAS severity [14–16]. Furthermore, CRP was correlated with BMI, an observation consistent with the ability of adipose tissue to release certain cytokines, including Interleukin-6, and to stimulate CRP synthesis [31].

Although both FMD and CRP are involved in the pathophysiology of cardiovascular complications, the association between these 2 parameters in OSAS remains elusive. Two separate studies by Chung et al. and Verma et al. failed to find a relationship between FMD and CRP in healthy subjects [32,33]. Nevertheless, a study by Nystrom et al in patients with coronary artery disease revealed a correlation between endothelial dysfunction (measured with FMD) and the levels of CRP [34]. This study demonstrated a negative correlation between CRP and FMD. These discrepancies may be attributed to differences in methodology and inclusion criteria among published studies.

This study also demonstrated that appropriate use of CPAP therapy can significantly decrease the levels of CRP. Previous studies have also presented similar results, thus denoting the possible beneficial role of CPAP in reducing systemic inflammation and cardiovascular risk in OSAS patients [35–39].

Conclusions

The limitations of this study should be noted. The study population consisted of patients with no prior history of cardiovascular or pulmonary disease, thus the study results should be interpreted with caution in patients beyond this particular group. Furthermore, female patients were excluded from the study analysis to avoid potential sex-based differences in hormone secretion that could affect both CRP and endothelial function.

This single-center study demonstrated that male OSAS patients with no prior history of cardiovascular disease had significantly higher CRP levels and lower FMD values compared to control subjects – a finding indicative of the possible presence of subclinical atherosclerosis and subsequent increased risk for developing cardiovascular disease. Appropriate CPAP therapy improved both CRP and FMD values, suggesting its potentially beneficial role in reducing cardiovascular morbidity and mortality in OSAS patients. Further well-designed prospective studies are needed to elucidate the effect of CPAP on the reduction of cardiovascular risk.

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