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

Athanasios Panoutsopoulos1ABCDEF, Anastasios Kallianos2ABCDEF, Konstantinos Kostopoulos2ABCDEF, Charalampos Seretis3F, Eleni Koufogiorga2DEF, Athanasios Protogerou2ABCDEF, Georgia Trakada2BF, Charalampos Kostopoulos2BF, Nikolaos Zakopoulos2AD, Ioannis Nikolopoulos2AD

1 Department of Internal Medicine, General Hospital of Argos, Argos, Greece
2 Department of Clinical Therapeutics, Alexandra Hospital, University of Athens Medical School, Athens, Greece
3 Department of Emergency Medicine, 401 General Military Hospital of Athens, Athens, Greece

Source of support: Departmental sources

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% SaO2, and CRP (p<0.05). Plasma CRP values were positively correlated with BMI, AHI, DSI and % of time <90% SaO2 (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

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=883603

Word count: 1732
Tables: 2
Figures: 2
References: 39

Author’s address: Charalampos Seretis, Department of Emergency Medicine, 401 General Military Hospital of Athens, Athens, Greece, e-mail: seretismilisurg@gmail.com
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 Alexandria 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% SaO2, and CRP (p<0.05). Plasma CRP values were positively correlated with BMI, AHI, DSI, and % of time <90% SaO2 (p<0.05) (Table 2). After adjustment for age and BMI, FMD values retained...
their correlation with AHI (B=–0.08, p=0.00), DSI (B=–0.10, p=0.00) and % of time <90% SaO2 (B=–0.28, p=0.00). After adjustment for BMI, CRP values also retained their correlation with % of time <90% SaO2 (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

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**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% SaO2  | 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      | P-value=0.02  |
|                      | P-value=0.16  |              |
| BMI                  | r=–0.47      | P-value=0.00  |
|                      | P-value=0.52  |              |
| AHI                  | r=–0.81      | P-value=0.00  |
|                      | P-value=0.77  |              |
| DSI                  | r=–0.83      | P-value=0.00  |
|                      | P-value=0.80  |              |
| % of time <90% SaO2  | r=–0.82      | P-value=0.00  |
|                      | P-value=0.77  |              |
| CRP                  | r=–0.79      | P-value=1.00  |
|                      | P-value=0.00  |              |
The association between FMD and CRP is well documented in patients with coronary artery disease and diabetes and, recently, OSAS [19–22]. The regulation of vaso-motor 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 upregulated the expression of various vasoactive substances such as endothelin-1 and angiotensin II [23–25].

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 compliant patients [26,27]. Our results also confirm the beneficial role of CPAP on FMD values after 3 months of treatment.

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.

**References:**

1. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest, 2007; 132: 525–57
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med, 2002; 165: 1217–29
3. Peppard PE, Young T, Palta M, Skatrud J: Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med, 2000; 342: 1378–84

4. Marin JM, Carroio SJ, Vicente E, Aguili AG: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet, 2005; 365: 1046–53

5. Wang P, Zoeri J: Measurement of nitric oxide and peroxynitrite generation in the postischemic heart. Evidence for peroxynitrite mediated reperfusion injury. J Biol Chem, 1996; 271: 2923–30

6. Liao JK, Zuharta J, Yu FS et al: Regulation of bovine endothelial constitutive nitric oxide synthase by oxygen. J Clin Invest, 1995; 96: 2661–66

7. Santos-Garcia D, Rodriguez-Vazquez M, Arias-Rivas S, Blanco M: Brachial arterial flow mediated dilation: utility in clinical and experimental practice. Rev Neurol, 2011; 53: 351–60

8. Thijsen DH, Black MA, Pyke KE et al: Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol, 2011; 300: H12–12

9. Sert Kuniyoshi FH, Singh P, Gami AS et al: Patients with obstructive sleep apnea exhibit impaired endothelial function after myocardial infarction. Chest, 2011; 140: 62–67

10. Yim-Yeh S, Rahangdale S, Nguyen AT et al: Obstructive sleep apnea and aging effects on macrovascular and microcirculatory function. Sleep, 2010; 33: 1170–83

11. Yim-Yeh S, Rahangdale S, Nguyen AT et al: Vascular dysfunction in obstructive sleep apnea and type 2 diabetes mellitus. Obesity (Silver Spring), 2011; 19: 17–22

12. Madjar M, Willerson JT: Inflammatory markers in coronary heart disease. Br Med Bull, 2011; 100: 23–58

13. Rus H, Niculescu FI: Inflammation, aspirin, and the risk of cardiovascular disease. N Engl J Med, 1997; 337: 423; author reply 423–4

14. Korkuturk O, Ciftci U, Tollareep C, Ciftci B: Elevated C reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. Int Heart J, 2005; 46: 801–5

15. Firat Guven S, Ciftci B, Ciftci B et al: The relationship between high-sensitivity Creactive protein levels and the severity of obstructive sleep apnea. Sleep Breath, 2012; 16: 217–21

16. Liu MM, Lam JC, Mak HK et al: Crohn’s disease is associated with obstructive sleep apnea independent of visceral obesity. Chest, 2009; 135: 250–56

17. Park JG, Raman R, Olson EJ: Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc, 2011; 86: 549–54; quiz 554–55

18. Corretti MC, Anderson TJ, Benjamin EJ et al: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol, 2002; 39: 257–65

19. Simova I, Katova T, Denchev S: Diagnostic accuracy of flow-mediated dilatation of the brachial artery in rat small pulmonary arteries. Br J Pharmacol, 2003; 139: 899–910

20. Phillips BG, Narkiewicz K, Pesek CA et al: Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens, 1999; 17: 61–66

21. Su Y, Liu XM, Sun YM et al: Endothelial dysfunction in impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes mellitus. Am J Cardiol, 2008; 102: 497–98

22. Kato M, Roberts-Thomson P, Phillips BG et al: Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation, 2000; 102: 2607–10

23. Shirai M, Pearson JT, Shimouchi A et al: Changes in functional and histological distributions of nitric oxide synthase caused by chronic hypoxia in rat small pulmonary arteries. Br J Pharmacol, 2003; 139: 899–910

24. Phillips BG, Narkiewicz K, Pesek CA et al: Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens, 1999; 17: 61–66

25. Moller DS, Lind P, Strange B, Pedersen ER: Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. Am J Hypertens, 2003; 16: 754–60

26. Ip MSM, Tie HF, Lam B, Tsang KWT, Lam WK: Endothelial function in obstructive sleep apnea and response to treatment. Am J Respir Crit Care Med, 2004; 169: 348–55

27. Bayram NA, Ciftci B, Keles T et al: Endothelial function in normotensive men with obstructive sleep apnea before and 6 months after CPAP treatment. Sleep, 2009; 32: 1257–65

28. Kaptoge S, Di Angelantonio E, Lowe G et al: C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet, 2010; 375: 132–40

29. Shamuzzaman AS, Winnicki M, Lanfranchi P et al: Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation, 2002; 105: 2462–64

30. Schulz R, Mahmoudi S, Hattar K et al: Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea. Am J Respir Crit Care Med, 2009; 180: 566–70

31. Browning LM, Krebs JD, Magee EC et al: Circulating markers of inflammation and their link to indices of adiposity. Obes Facts, 2008; 1: 259–65

32. Chung S, Yoon IV, Shin YK et al: Endothelial dysfunction and C-reactive protein in relation with the severity of obstructive sleep apnea syndrome. Sleep, 2007; 30: 997–1001

33. Verma S, Wang CH, Lonn E et al: Cross-sectional evaluation of brachial artery flow-mediated dilation and C-reactive protein in healthy individuals. Eur Heart J, 2004; 25: 1754–60

34. Nyström T, Nygren A, Sjöholm A: Persistent endothelial dysfunction is related to elevated C-reactive protein (CRP) levels in Type II diabetic patients after acute myocardial infarction. Clin Sci (Lond), 2005; 108: 121–28

35. Yoko T, Minoguchi K, Matsuo H et al: Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation, 2003; 107: 1129–34

36. Schiza SE, Mermigkis C, Panagiotis P et al: C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy. Eur J Clin Invest, 2010; 40: 968–75

37. Ishida K, Kato M, Kato Y et al: Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. Chest, 2009; 136: 125–29

38. Korostovtseva LS, Sviryaev YV, Zvartau NE et al: Prognosis and cardiovascular morbidity and mortality in prospective study of hypertensive patients with obstructive sleep apnea syndrome in St Petersburg, Russia. Med Sci Monit, 2011; 17(3): CR1–6

39. Zirlik S, Hauck T, Fuchs FS et al: Leptin, obestatin and apelin levels in patients with obstructive sleep apnoea syndrome. Med Sci Monit, 2011; 17(3): 159–64