Effect of overnight nasal continuous positive airway pressure treatment on the endothelial function in patients with obstructive sleep apnea

Obstrüktif uyku apnesi olan hastalarda bir gecelik nazal sürekli pozitif hava yolu basıncı tedavisinin endotel fonksiyonuna etkisi

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ABSTRACT

Objective: In this prospective study, we aimed to investigate acute effect of nasal continuous positive airway pressure (CPAP) therapy on the endothelial function of patients with obstructive sleep apnea syndrome (OSA) by using brachial artery flow mediated dilatation (FMD) method.
Methods: Newly diagnosed thirty OSA patients with ages between 29 and 72 years were included in this study. FMD and high sensitivity C-reactive protein (hsCRP) values of patients obtained before and after CPAP dose titration test were compared with paired samples t test or Wilcoxon signed ranks test.
Results: With CPAP therapy apnea hypopnea indices were reduced (60.6±24.9/h vs. 9.6±7.9/h; p<0.001) and oxygen desaturation indices recovered (50±27/h vs. 6±7/h; p<0.001). Heart rates of patients decreased after CPAP therapy (80±10/min vs. 73±8/min; p=0.003). FMD values significantly increased after CPAP (8.55±5.82 percent vs. 12.08±7.17 percent; p=0.003). HsCRP values after CPAP were not different from baseline values
Conclusion: Acute improvement of the endothelial function with one night CPAP therapy suggests endothelial dysfunction in OSA patients to be result of acute pathophysiologic factors. In intermediate and severe OSA patients, CPAP therapy may be considered in acute treatment of diseases associated with endothelial dysfunction. *(Anadolu Kardiyol Derg 2012; 12: 560-5)*
Key words: Endothelial dysfunction, obstructive sleep apnea, continuous positive airway pressure, C-reactive protein, flow mediated dilatation

ÖZET

Amaç: Bu prospektif çalışmamızda obstrüktif uyku apneli (OUA) hastalarda endotel fonksiyonuna nazal sürekli pozitif hava yolu basıncı (SPHB) tedavisinin akut etkisini brakiyal arterde akıma bağlı genişleme (ABG) yöntemini kullanarak değerlendirmeyi amaçladık.
Yöntemler: Yeni tanı almış 29 ve 72 yaş arasında otuz OUA hastası çalışmaya dahil edildi. Hastaların SPHB doz titrasyonu öncesi ve sonrasında bakılan ABG ve yüksek duyarlıklı C-reaktif protein (ydCRP) değerleri eşleştirilmiş örneklem t-testi ya da Wilcoxon işaret rank testi ile karşılaştırıldı.
Bulgular: SPHB tedavisi ile apne hipopne indeksleri azaldı (60.6±24.9/st vs. 9.6±7.9/st; p<0.001), oksijen desatürasyon indeksleri düzeldi (50±27/st vs. 6±7/st; p<0.001). Hastaların SPHB tedavisi sonrası kalp hızları azaldı (80±10/dk vs. 73±8/dk; p=0.003). ABG değerleri SPHB sonrası belirgin olarak arttı (%8.55±5.82 vs. %12.08±7.17; p=0.003). ydCRP değeri SPHB sonrası bazal değerlerden farklı değildi.
Sonuç: Bir gecelik SPHB tedavisi ile akıma bağlı dilatasyonun düzelmesi OUA hastalarında endotel disfonksiyonunun akut patofizyolojik mekanizmalar sonucu geliştiğini düşündürmektedir. Orta ve ağır OUA hastalarında SPHB tedavisi endotel disfonksiyonu ile ilişkili hastalıkların akut tedavisinde düşünülebilir. *(Anadolu Kardiyol Derg 2012; 12: 560-5)*
Anahtar kelimeler: Endotel disfonksiyonu, obstrüktif uyku apnesi, sürekli pozitif havayolu basıncı, C-reaktif protein, akıma bağlı genişleme

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Introduction

Obstructive sleep apnea (OSA) is associated with increased risk of myocardial infarction and stroke (1). Long-term outcome studies of patients with coronary heart disease (CAD) have demonstrated higher cardiovascular mortality in patients with coexisting OSA compared with those without, even after controlling for important confounding risk factors such as age, weight, and smoking (2, 3). Continuous positive airway pressure (CPAP) treatment attenuated this risk according to observational studies (4-6). Current management of moderate-to-severe OSA is largely dependent on continuous positive airway pressure (CPAP), which is very effective in eliminating collapse of the airway during sleep, improving sleep fragmentation, and decreasing daytime sleepiness (7). CPAP acts to splint the upper airway open during sleep and thus counteracts the negative suction pressure during inspiration that promotes upper airway collapse in these patients. Nasal CPAP completely controls the condition and has a dramatic effect on the patient's awake performance because of the normalized sleep pattern (8). CPAP corrects pathophysiologic effects of OSA, decrease sympathetic tonus and fluctuations of intrathoracic negative pressure (9). CPAP also prevents blood pressure increase and decrease left ventricular afterload. By decreasing hypoxic episodes, CPAP increases oxygen delivery and decreases oxygen need.

Endothelium is necessary for maintaining the health of vessel wall, local regulation of vascular tonus and structure, and homeostasis. Endothelial dysfunction specifies disequilibrium of these functions and predicts vascular events in patients with or without established vascular disease (10). Endothelial dysfunction occurs in the presence of atherosclerosis or its risk factors and contributes to both initiation and progression of atherosclerotic lesions (11). Endothelial dysfunction may be a plausible link between OSA and cardiovascular diseases.

Endothelial dysfunction occurs as a result of either acute or chronic endothelial damage. OSA may lead endothelial dysfunction in both mechanisms. Recent studies on OSA, which have documented that CPAP therapy varying from 1 week to 6 months could improve endothelial function, provide data for chronic effects (12-16). However, endothelial effects of single CPAP therapy have not been investigated well. Although increase in plasma nitrite and nitrate levels after two nights of CPAP therapy was recently reported (17), an acute clinical effect of CPAP has not been studied.

We aimed to determine effects of overnight nasal CPAP (nCPAP) therapy on endothelial function and inflammation to discriminate presence of acute treatable unfavorable effects of OSA on endothelium.

Methods

Study design

This study protocol was based on a single-centered prospective nonrandomized study design.

Patient population

Between March 2009 and November 2009 consecutive subjects admitted to the Sleep Laboratory at Kırıkkale University Department of Pulmonary Diseases for overnight polysomnography were enrolled. Patients with untreated moderate to severe OSA, defined as an apnea/hypopnea index (AHI) ≥15 events/h and arterial oxygen desaturation to <90% at least once per night on the polysomnographic study, were included in the study. Patients with lung disease [forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and/or diffusing capacity of lung for carbon monoxide (DLCO) less than 80% of predicted on respiratory function testing], central sleep apnea, renal failure and history of cerebrovascular or cardiovascular event were excluded. All consenting subjects underwent electrocardiography and 2D Doppler echocardiography to exclude underlying heart disease including left heart outflow obstruction, left ventricular systolic dysfunction (ejection fraction <50%) or severe valvular heart disease.

The study was approved by the local ethics committee and all patients gave informed written consent.

Study protocol

Initial evaluation of patients with moderate or severe OSA included collection of demographic and anthropometric measurements. Fasting venous blood samples and blood pressures of patients were measured on the morning before CPAP titration analysis. Patients were asked about their regular medication and medical history with special reference to arterial hypertension, hypercholesterolemia, diabetes mellitus and their smoking habits and underwent baseline (pre-CPAP) forearm vascular reactivity studies. Blood samples on the mornings before and after overnight CPAP therapy were drawn from patients for CRP measurements. Endothelial functions of patients were measured by flow mediated dilatation (FMD) of brachial artery on the mornings before and after overnight CPAP therapy. The results were assessed to elucidate effects of overnight CPAP therapy.

Polysomnography

Basal diagnostic polysomnographies were performed by an experienced technician using portable device (SleepScreen Jaeger®, Taipei, Taiwan) with video recorder. Electroencephalography, bilateral electrooculography, submental electromyography, nasal airflow, electrocardiography, thoracoabdominal motion and oxygen saturations were recorded. The AHI was defined as the number of apneas plus hypopneas per hour of sleep. Apnea was defined as a decrease in airflow amplitude to <25% of baseline lasting for at least 10 s; hypopnea was defined as a decrease in airflow or chest wall movement amplitude to less than 60% of baseline lasting for at least 10 s, with both apneas and hypopneas requiring an associated ≥4% oxyhemoglobin desaturation. Oxygen desaturation index (ODI) was calculated as the number of oxygen desaturations (≥4%) per hour of sleep.

Patients underwent overnight CPAP dose titration protocol with autoCPAP device (AutoSet Spirit, ResMed, Sydney, Australia) to determine minimum effective pressure to abolish apnea, hypopnea, and oxygen desaturation. Both of basal and dose titration polysomnography analysis were interpreted by the same experienced chest physician.

Flow mediated dilatation

Flow-mediated dilatation of the brachial artery was noninvasively examined by 2D high-resolution ultrasound machine (GE Medical Systems Vivid 7 Pro, GE Vingmed AS, Horten, Norway) with a 12-MHz linear array transducer in Echocardiography Laboratory of Department of Cardiology. All subjects fasted from midnight before the procedure and were studied in the morning in supine position. Patients were encouraged to take their regular medications and were asked to avoid alcohol, tobacco or caffeine use before FMD measurements. A sphygmomanometric cuff was first placed above the antecubital fossa. After baseline longitudinal image of brachial artery is acquired, cuff was inflated to at least 50 mmHg above systolic pressure to occlude brachial artery for 5 minutes. Brachial artery diameter was measured 1 minute after cuff deflation. Brachial artery diameter percent change was calculated and recorded as the FMD of the patient. The variability of the diameter measurement was minimized by calculating the average derived from three diameter measurements determined along the longitudinal segment of brachial artery. All measurements were done by the same physician.

High sensitivity C-reactive protein

Blood samples for hsCRP assay were obtained from the cubital vein of patients into EDTA tubes. The samples were then analyzed by chemiluminescence method using a fully automatic immunoassay analyzer (PATHFAST, Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany).

Statistical analysis

The SPSS statistical software (SPSS 15.0 for Windows Inc, Chicago, IL) was used for all statistical calculations. Data are expressed as mean±SD and median (minimum-maximum) for continuous variables and number and percent for categorical variables. The Kolmogorov-Smirnov test was used as test of normality. Parameters before and after CPAP treatment were compared with paired samples t test or Wilcoxon signed ranks test as appropriate. Relationships between variables were assessed with Pearson or Spearman correlation test. Pearson correlation coefficient was used for analysis of intraobserver variability of brachial artery diameters. A 2-sided $p<0.05$ was considered statistically significant.

Results

Study group consisted of 30 patients (8 women and 22 men), with mean age of 51.73±10.46 years. Demographic characteristics of patients are summarized on Table 1. Thirteen patients were under antihypertensive medication, 7 patients were diabetic, 12 patients had hypercholesterolemia and 8 patients were smokers.

OSA indices

Waist circumference was positively correlated with AHI and ODI (r=0.518, p=0.003, r=0.500, p=0.005 respectively), though hip circumference, waist/hip ratio or body mass indices were not correlated with either AHI or ODI. The correlation between baseline brachial artery FMD and AHI did not reach statistical significance (r=-0.310 p=0.09). Baseline systolic blood pressure was correlated with AHI and ODI [r=0.440 (p=0.015), r=0.475 (p=0.008), respectively]. The hsCRP was not correlated with either FMD or OSA indices.

Effects of CPAP on clinical and laboratory variables

Results on the impact of CPAP treatment on clinical and laboratory variables are summarized in Table 2. CPAP treatment was well tolerated by every patient. Nocturnal breathing parameters of all patients were below clinically relevant cut-off values. After CPAP treatment AHI and ODI and heart rate significantly decreased and brachial FMD significantly increased ($p<0.05$ for all). Correlation coefficient for intraobserver variability of brachial artery diameter measurements was 0.964 ($p<0.001$). The hsCRP level did not differ before and after CPAP treatment.

Table 1. Demographic and biochemical characteristics of patients

Age, years	51.73±10.46
Waist circumference, cm	112.57±11.48
Hip circumference, cm	115.97±11.81
Waist/hip ratio	0.97±0.08
Body mass index, kg/m^2	32.47±6.69
Systolic BP, mmHg	121.50±14.69
Diastolic BP, mmHg	79.67±8.80
Total cholesterol, mg/dL	208.93±32.01
LDLc, mg/dL	120.40±36.60
HDLc, mg/dL	46.96±8.89
Triglyceride, mg/dL	207.77±114.10
Fasting blood glucose, mg/dL	119.93±65.13
Urea, mg/dL	30.71±9.19
Creatinine, mg/dL	0.98±0.15
Leukocytes, 10^3x/l	8.46±1.84
Na^+, mmol/L	139.17±2.58
K^+, mmol/L	4.43 ±0.33
Hemoglobin, g/dL	14.95±1.52
TSH, uIU/mL	1.98±1.22

Data are presented as mean±SD
BP - blood pressure, HDLc - high density lipoprotein cholesterol, K^+ potassium, LDLc - low density lipoprotein cholesterol, Na^+ sodium, TSH - thyroid stimulating hormone

Subgroup analyzes

Effect of one night CPAP therapy on FMD in respect to age and cardiovascular risk factors are summarized in Table 3. When the patients were analyzed according to their gender; there was a negative correlation between FMD and AHI in male patients (r=-0.474, p=0.026). Similarly FMD was negatively correlated with ODI (r=-0.550, p=0.008). In women, abovementioned relations were not observed. Although heart rate and OSA severity were not found to be correlated among men; in female group, heart rate was strongly associated with both AHI and ODI (r=0.754, p=0.031 and r=0.807, p=0.014 respectively). Heart rate decrease after CPAP therapy was significant in both women and men. FMD significantly increased with CPAP therapy from 7.72% to 11.21% in men (p=0.011). FMD increase in women from 10.84% to 14.46% was not statistically significant (p=0.149).

We also considered the results in respect to the patients' risk factors. Among nonsmokers FMD and CRP were not correlated with OSA indices. However CRP of smokers were positively correlated with AHI (r=0.820, p=0.013). In non-diabetic group FMD was negatively correlated with both OSA and AHI (r=-0.493, p=0.013, r=-0.537, p=0.008 respectively). However, in diabetic population no significant relation was observed. In hypertensive patients, neither FMD nor CRP was correlated with OSA indices. However normotensive patients had negative correlation between FMD and OSA indices (r=-0.539 with AHI, p=0.026 and r=-0.573; p=0.016). FMD or CRP was not correlated with OSA indices when patients were grouped according to hypercholesterolemia.

FMD improved significantly in nonsmoker, smoker, non-diabetic, normotensive or normolipidemic subgroups. However, in diabetic, hypertensive or hypercholesterolemic subgroups FMD changes were not significant.

Table 2. Comparison of parameters before and after CPAP therapy

Variables	Baseline	Post-CPAP	*p
FMD, %	8.5±5.8	12.0±7.1	0.003
AHI	60.6±24.9	9.6±7.9	<0.001
ODI	50.3±27.3	5.7±6.6	<0.001
hsCRP, mg/L	4.8±4.7	5.0±5.2	0.44
Heart rate, beats/min	79.8±10.3	73.5±8.1	0.003

Data are presented as mean±SD
*Paired samples t-test
AHI - Apnea/hypopnea index, CPAP - continuous positive airway pressure, FMD - flow mediated dilatation, hsCRP - high sensitivity C - reactive protein, ODI - oxygen desaturation index

Table 3. Comparison of flow mediated dilation before and after CPAP therapy when patients are grouped according to gender or presence of risk factors

Grouping variable (number of patients)	FMD (pre-CPAP)	FMD (post-CPAP)	*p
Female (8)	10.84±8.97 8.52 (1.29-22.56)	14.46±8.84 12.4 (3.36-27.41)	0.123
Male (22)	7.72±4.16	11.20±6.48	0.011
Normotensive (17)	9.62±6.01 7.55 (2.50-22.56)	12.84±7.62 11.69 (2.35-27.41)	0.013
Hypertensive (13)	7.15±5.47 5.94 (1.29-21.96)	11.08±6.71 11.42 (2.28-22.99)	0.064
Nonsmoker (22)	8.09±6.42	11.22±8.04	0.039
Smoker (8)	9.82±3.79 9.39 (5.31-17.07)	14.41±3.26 15.05 (9.87-20.13)	0.012
Nondiabetic (23)	8.53±5.57	12.71±7.48	0.002
Diabetic (7)	8.61±7.07 6.33 (1.29-21.96)	9.98±6.09 11.93 (2.66-17.93)	0.398
Normocholesterolemic (18)	8.11±6.00 6.52 (1.29-22.56)	12.64±7.48 10.51 (3.36-27.41)	0.004
Hypercholesterolemic (12)	9.20±5.73 6.99 (2.33-21.96)	11.22±6.91 12.44 (2.28-20.56)	0.239

Data are presented as mean±SD and median (min-max) values
*Paired samples t-test or Wilcoxon signed ranks test
Pre-CPAP - before continuous positive airway pressure therapy, post-CPAP - after continuous positive airway pressure therapy, FMD - flow mediated dilatation

Discussion

We demonstrated that overnight CPAP treatment significantly improved endothelium dependent FMD of OSA patients and did not change CRP levels. This study supports presence of acute reversible unfavorable effect of OSA on vascular endothelium, which is ameliorated by overnight CPAP therapy.

CPAP treatment is associated with improved signs of atherosclerosis, particularly endothelial functions in OSA patients (12). Effective 4 -week CPAP therapy of OSA patients exerted beneficial effects on endothelial repair capacity (18). In a recent study CPAP treatment for 8 weeks reduced circulating endothelial cells, this is correlated with improvement in endothelium-derived vasodilatation (19). Treatment with CPAP for 3 months improved baseline endothelial NO release and stimulated endothelium dependent vasorelaxation in the systemic circulation (15). In compliant patients, improvement in FMD was consistent after 6 months of CPAP therapy (13). Ip et al. (14) demonstrated improvement of FMD after 3 months of CPAP therapy. As an interesting point, improvement in endothelial function was not sustainable after stopping CPAP treatment for 1 week. The authors suggested that recurrent hypoxia-reoxygenation triggered endothelial dysfunction.

In order to prove effect of acute pathophysiologic mechanisms for endothelial dysfunction in OSA improvement in endothelial function after one night CPAP treatment needs to be demonstrated. Only in a recent study 2 nights of CPAP therapy was associated with an increase in plasma nitrite and nitrate levels which might represent acute improvement in endothelial functions (17). However, their study subjects did not adhere low nitrite/nitrate diet. Circulating nitrite and nitrate levels are not expression of nitric oxide pathway only, indeed. FMD is a feasible, accurate and reproducible technique in order to assess vascular endothelial response to a stimulus (20). Improvement of endothelial function after single CPAP therapy in our study supports central role of acute pathophysiologic changes on endothelial dysfunction.

From the present study, it is not possible to explain the mechanism of improvement in FMD after CPAP. Endothelial dysfunction in OSA is believed to be initiated mainly by hypoxia, inflammation, or oxidative stress (21). Not only reduction in vasodilator substances, but also elevated vasoconstrictor substances in OSA play role in the development of endothelial dysfunction. Underlying mechanisms of early beneficial effects of CPAP treatment on endothelial function might be improved oxygenation, decreased sympathetic activity, decreased oxidative stress or inflammation or decreased blood pressure surges. Although it is reported that hsCRP levels decreased in OSA patients who were treated with CPAP for 1-4 weeks (22) in our study unchanged hsCRP level, as a marker of inflammation, may suggest that acute improvement may not be associated with an anti-inflammatory effect.

A recent study suggested that waist circumference is more reliable than BMI in stratifying mortality in CAD patients (23). Concordantly, waist circumference but not BMI was significantly correlated with OSA indices in our study. Blood pressure increases in concordance with OSA severity (9). The correlation we found between baseline systolic blood pressure and OSA severity is compatible with the literature (3). Furthermore, it is known that CPAP therapy also may lead improvement in baroreflex response (24). In a previous study, 4 weeks of CPAP therapy decreased heart rate variability (25). In another study, nocturnal mean and maximal heart rates are increased with severity of OSA (26). These results point the influence of sympathetic hyperactivity. Although we did not measure sympathetic activity, observation of heart rate decrease suggests that single CPAP therapy might attenuate sympathetic hyperactivity.

Study limitations

One may suggest that presence of cardiovascular risk factors might be associated with an established endothelial dysfunction, which did not improve with one night CPAP therapy. However, when classified in respect to cardiovascular risk factors, the subgroups were not large enough to make a conclusion with their data. Small sample size and heterogeneous patient distribution and absence of control group are limitations of our study.

Mean FMD of the present study population was higher than most of the previous studies on OSA (14, 16, 19, 27-29), although studies with similar FMD results exist (13, 30). Therefore, the present study might probably be composed of subjects with less endothelial damage. A recent study revealed gradual attenuation of the inverse relation between FMD and cardiovascular risk (31). Thus low risk patients may be more prone to changes in FMD caused by acute effects, as observed in our study. Although the precise mechanisms of improvement in endothelial function remain to be clarified, potential benefit of one night CPAP treatment in OSA patients with higher cardiovascular risk needs to be investigated.

Blood samples after CPAP therapy were drawn in the morning shortly after awakening. Half-life of CRP is approximately 19 hours (32), thus there were not enough time windows to expect hsCRP decrease. Therefore, further prospective studies are needed to demonstrate acute effects of CPAP therapy on inflammatory parameters.

Conclusion

Endothelial dysfunction in OSA may be result of acute pathophysiologic changes and may improve with one night CPAP treatment.

Conflict of interest: None declared.

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