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Continuous positive airway pressure therapy improves arterial elasticity in patients with obstructive sleep apnea

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Obstructive sleep apnea syndrome;
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Summary
Background: Reduced arterial elasticity is an important mediator of accelerated atherogenesis and consequent increased cardiovascular morbidity in obstructive sleep apnea (OSA). The aim of our study was to investigate whether continuous positive airway pressure (CPAP) therapy may improve arterial elasticity in subjects with OSA.
Methods: In 44 subjects with OSA, we measured arterial elasticity by applanation tonometry before and after 6 months of treatment with CPAP. Nine OSA+ subjects withdrew from the study.
Results: The 35 patients with OSA who completed the 6-month CPAP treatment showed a marked reduction in both the large artery (LAEI, $P = 0.001$) and small artery (SAEI, $P = 0.009$) elasticity indices, independent of potential confounders. In OSA+ subjects who withdrew from the study, SAEI and LAEI did not change significantly over time.
Conclusions: Six months of CPAP therapy improves arterial elasticity in subjects with OSA.

Introduction

Multiple studies have demonstrated that obstructive sleep apnea (OSA) is strongly associated with known vascular risk factors and increased cardiovascular morbidity.[1,2] Of note, OSA itself may act as an independent risk factor for hypertension, ischemic heart disease, stroke, and arrhythmia.[3–5] Although the exact mechanisms by which OSA may be linked to increased vascular risk are not entirely understood,[6–8] it has been recently suggested that endothelial dysfunction and arterial elasticity may represent a pivotal link.[9] Arterial compliance is defined as the ability of an artery to expand and recoil with cardiac pulsation and relaxation.[10,11] Measurements of arterial elasticity, using

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applanation tonometry,[12] provide useful information regarding vascular health and a decrease in arterial compliance can be regarded as a valid marker of early vascular dysfunction. Of great interest, estimation of arterial elasticity may serve not only as cardiovascular risk assessment but also as a surrogate marker of treatment benefits.[13,14]

Nasal continuous positive airway pressure (CPAP) has become the gold standard of treatment of sleep-disordered breathing.[15] When worn during sleep, CPAP effectively reduces or eliminates most sleep-disordered breathing events, resulting in a global improvement in sleep architecture.[16] Evidence also suggests that CPAP may results in positive cardiovascular and metabolic effects in patients with OSA, ultimately leading to an improvement in the cardiovascular risk profile.[17,18] Previous studies have shown that CPAP therapy can improve microvascular endothelial function and decrease stiffness of the central to middle-sized arteries.[19,20] However, data on the long-term impact of CPAP on measures of arterial elasticity in patients with OSA are lacking. The aim of our study was to fill this gap and to evaluate the changes induced by CPAP on large and small arterial elasticity indices (LAEI and SAEI, respectively). The analysis of LAEI and SAEI allows an evaluation of the elasticity of the large conduit arteries and the small microcirculatory arteries. Although LAEI and SAEI measure different aspects of arterial elasticity, a reduction of both indices has been linked to an increased vascular risk.[13]

Methods

Study participants and diagnostic polysomnography

We initially considered for our study 97 consecutive subjects referred to our laboratory because of symptoms of OSA for diagnostic polysomnography. Exclusion criteria were as follows: use of immunomodulatory drugs; history of coronary artery disease, peripheral artery disease, or cerebrovascular disease according to medical history and clinical examination; transplantation; alcohol and drug abuse; HIV infection; significant medical illnesses (active infections, autoimmune disorders, malignancy, liver disease, chronic obstructive pulmonary disease, asthma, neuromuscular disorders).

In all participants, overnight polysomnography was performed with a Compumedics Sleepwatch System (Compumedics p-series: Compumedics, Melbourne, Australia). The study subjects reported to the sleep laboratory at approximately 8:30 p.m., and polysomnography was started at approximately 10:30 p.m. Polysomnographic recordings included two electroencephalography channels (C3/A2 and O2/A1), two electrooculogram channels, one submental electromyogram channel, and one electrocardiography channel. Ventilatory monitoring included recording of oronasal airflow (with an oronasal thermistor), hemoglobin oxygen saturation by pulse oximetry (SaO_2 was measured via a finger oximeter), respiratory movement of the chest (with inductive plethysmography), and abdomen and body posture. Sleep staging was performed according to the standard criteria of Rechtschaffen and Kales.[21] Nasal airflow was carefully analyzed in order to assess ventilation during sleep. Apnea was defined as an episode of airflow cessation lasting at least 10 s. Hypopnea was defined as an episode of reduced thermistor signal amplitude of at least 50% and an associated drop in oxygen saturation of at least 3% or an arousal lasting 10 s or longer. The sum of the time elapsed in periods of apnea and hypopnea was divided by the total sleep time to obtain the Apnea-Hypopnea Index (AHI). OSA was diagnosed when the patient's AHI was more than or equal to 5. The Epworth Sleepiness Scale (ESS) was used to measure excessive sleepiness.[22]

The study protocol was approved by the Ethics Committee of the Uludag University Medical School. A written informed consent was obtained from all participants.

Definition of cardiovascular risk factors

Age was analyzed as a continuous variable. Body mass index (BMI) was calculated by taking the weight (in kilograms) over the height (in meters-squared). The use of cardiac drugs (β-blockers, statins, calcium antagonists, angiotensin-converting enzyme inhibitors, aspirin) was recorded in all participants. In our study, smoking was defined as regular smoking of cigarettes. Diabetes mellitus was diagnosed on the basis of fasting blood glucose concentrations $\geq$126 mg/dL or current use of antidiabetic medications. Arterial hypertension was defined as active treatment with antihypertensive medications or documentation of systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg on at least two separate occasions. Serum samples were measured for lipid variables using commercially available kits on a Hitachi 7350 Autoanalyzer (Hitachi Ltd., Tokyo, Japan).

Measurements of arterial elasticity

All measurements of arterial elasticity were performed on the radial artery using the noninvasive technique of arterial applanation tonometry. The PulseWave Sensor HDI (Hypertension Diagnostics, Eagan, MN, USA) was used to determine LAEI and SAEI. Applanation tonometry is based on the principle that when the curved surface of a rounded pressure-containing chamber (in this case, an artery) is partially flattened, pressures are normalized and a sensor placed on the flattened surface can record the pressure in the chamber.[12,23] This technique, which analyzes the signal-averaged radial artery waveform based on a modified Windkessel model, correlates well with other methods that measure hemodynamic parameters in humans.[13]

Data analysis

Continuous variables are presented as means $\pm$ standard deviation. Categorical variables are reported as counts and compared using the χ^2-test. Differences between subjects with and without OSA were evaluated by the unpaired *t*-test. Within-group comparisons were performed using the paired Student's *t*-test. Correlations among the study variables were examined by Pearson's correlation. Simple linear regression analysis was used to assess whether changes in SAEI and LAEI were independent of potential confounders, including age, gender, BMI, blood pressure values, heart rate, lipid parameters and the use of cardiac drugs. All statistical analyses were performed using the

SPSS 13.0 software package (SPSS Inc., Chicago, IL, USA). A two-tailed P value < 0.05 was regarded as significant.

Results

General characteristics of the study participants

OSA was diagnosed in a total of 66 subjects. Twenty-two individuals with OSA did not receive CPAP treatment and were excluded from the analysis. A total of 44 subjects with OSA (OSA+) and 31 subjects without OSA (OSA−) were finally included. The baseline characteristics of subjects with and without OSA are depicted in Table 1. There were no significant differences between the two groups in terms of age, BMI, blood pressure parameters, diabetes, and lipid profile. In addition, the use of cardiovascular drugs (statins, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers) did not differ in the two groups (data not shown). Compared with the OSA− group, OSA+ subjects showed higher ESS scores, systolic blood pressure, diastolic blood pressure, and mean arterial pressure. LAEI and SAEI values at baseline showed a trend toward lower values in OSA+ subjects compared with OSA− individuals; this difference, however, failed to reach statistical significance probably due to the small sample size.

Polysomnographic measures

The polysomnographic measures of nocturnal sleep in the two study groups are shown in Table 2. As expected, the two groups differed for a number of polysomnographic parameters, the only exceptions being the time of REM sleep and the average oxygen saturation while awake.

Baseline determinants of arterial elasticity in the OSA+ group

Pearson's correlation coefficients were determined to assess whether baseline measures of arterial elasticity were associated with the general or the polysomnographic characteristics of the OSA+ group. Both SAEI and LAEI were negatively correlated with systolic blood pressure ($r = -0.463$, $P = 0.05$ and $r = -0.483$, $P = 0.03$, respectively). In addition, SAEI showed an inverse correlation with diastolic blood pressure ($r = -0.422$, $P = 0.01$). No other significant correlation was found.

Effect of CPAP therapy on arterial elasticity in the OSA+ group

In the 44 subjects in the OSA+ group, we measured arterial elasticity before and after 6 months of treatment with CPAP. Nine OSA+ subjects withdrew from the study. Table 3 shows the changes in LAEI and SAEI in completers and noncompleters. After 6 months of CPAP treatment, the completer group ($n = 35$) showed a marked reduction in both the LAEI ($P = 0.001$, Fig. 1) and SAEI ($P = 0.009$, Fig. 2) indices. In OSA+ subjects who withdrew from the study ($n = 9$), SAEI and LAEI did not change over time.

Multivariable analysis

We used simple linear regression analysis to determine whether the magnitude of changes in SAEI and LAEI (ΔSAEI and ΔLAEI) in the completers were independent of potential confounders. Results showed that both ΔSAEI ($\beta = -0.41$, $t = -2.9$, $P = 0.009$) and ΔLAEI ($\beta = -0.38$, $t = -2.7$, $P = 0.01$) were not influenced by the confounding effect of other clinical and demographic variables.

Discussion

This study examined the effect of CPAP therapy on arterial elasticity in OSA+ subjects. We found that six months of 6 months of CPAP therapy significantly improved arterial elasticity of large and small arteries in patients with OSA, independent of potential confounders.

Table 1 General characteristics of subjects with and without OSA.

	OSA+ ($n = 66$)	OSA− ($n = 31$)	P
Age, years	52 ± 10	50 ± 9	ns
Sex, males/females	54/12	20/11	ns
Smoking, yes/no	12/54	5/26	ns
Hypertension, yes/no	25/41	10/21	ns
Diabetes mellitus, yes/no	10/56	2/29	ns
Epworth scale	13 ± 4	10.3 ± 4	0.04
BMI, kg/m^2	32 ± 5	31 ± 5	ns
SBP, mm Hg	142 ± 16.7	132 ± 16	0.04
DBP, mm Hg	84 ± 10	77 ± 9	0.05
MBP, mm Hg	106 ± 16	97 ± 11	0.05
Total cholesterol, mmol/L	5.2 ± 0.9	4.9 ± 0.6	ns
HDL cholesterol, mmol/L	1.1 ± 0.3	1.1 ± 0.2	ns
Triglycerides, mmol/L	1.8 ± 0.7	1.7 ± 0.7	ns
LAEI, mL/mm Hg $\times$ 10	13 ± 4	14 ± 5	ns
SAEI, mL/mm Hg $\times$ 100	5 ± 3	6 ± 3	ns

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure, HDL: high-density lipoprotein; LAEI: large artery elasticity index, SAEI: small artery elasticity index, ns: not significant.

Table 2 Polysomnographic data of subjects with and without OSA.

	OSA+ ($n = 66$)	OSA− ($n = 31$)	P
Time of REM sleep, min	58 ± 30	58 ± 36	NS
Time of sleep stage 3—4, min	28 ± 25	58 ± 34	<0.001
Sleep efficiency, %	84 ± 9	76 ± 14	0.01
Average O_2 saturation while awake, %	94 ± 3	94 ± 4	NS
Average O_2 saturation during sleep, %	89 ± 6	95 ± 2	<0.001
Average desaturation, %	9 ± 5	4 ± 2	<0.001
Time with oxygen saturation of less than 90%, min	64 ± 94	3 ± 11	<0.001
Time with oxygen saturation of less than 80%, min	17 ± 43	1 ± 1	<0.001
Time of apnea-hypopnea, min	145 ± 86	3 ± 3	<0.001, by design
Apnea-hypopnea index	50 ± 24	2 ± 1	<0.001, by design
Arousal index/h	33 ± 20	18 ± 8	<0.001

ns: not significant.

Emerging evidence has suggested that arterial elasticity may serve as a surrogate endpoint for estimation of success in patients at high risk for adverse cardiovascular events.[11,14] The sustained improvement of large and small arterial elasticity observed in our study suggests that improved endothelial function may be the predominant mechanism of the changes in LAEI and SAEI.[19] Although the exact mechanisms by which arterial elasticity is improved by CPAP therapy remain to be determined, stimulation of endothelial nitric oxide synthase may play a role.[24]

The results of the present study are of particular interest because all patients underwent polysomnographic measures. Kitahara et al.[25] showed that brachial-ankle pulse-wave velocity (PWV) — an index of arterial stiffness — decreased in patients with moderate-to-severe OSA after four months of CPAP treatment, without significant changes in total serum cholesterol levels, heart rate, systolic and diastolic blood pressures, mean blood pressure, and pulse pressure. These findings are consistent with our results, but the authors failed to include a matched OSA− group or a sham CPAP group. In this study, SAEI and LAEI did not improve significantly in the nine OSA+ subjects who withdrew from CPAP therapy. Nagahama and colleagues[26] reported a significant increase in brachial-ankle PWV in patients with OSA compared with controls, though polysomnography was not performed. Philips et al.[27] assessed arterial stiffness using the aortic augmentation index before and after two months of CPAP therapy, as well as in patients withdrawing from CPAP therapy. The authors found a significant reduction in the aortic augmentation index in the CPAP group, but not in the withdrawal group. Recently, Drager and colleagues[28] demonstrated that four months of effective treatment with CPAP significantly improved carotid intima-media thickness, PWV, levels of C-reactive protein levels, and catecholamines in normotensive middle-aged men with severe OSA without significant comorbidities. On the other hand, our sample included older individuals with a higher frequency of vascular risk factors. Keles et al.[20] have recently shown that CPAP treatment provides improvement in aortic elastic parameters, but the authors failed to report on changes in small artery elasticity. To our knowledge, our study is the first to assess both the LAEI and SAEI compliance parameters in OSA+ patients undergoing CPAP.

Table 3 Changes in arterial elasticity and other clinical parameters after 6 months in completers and noncompleters.

	Completing CPAP therapy ($n = 35$)		*P*	Withdrawn from CPAP therapy ($n = 9$)		*P*
	Baseline	6 months		Baseline	6 months	
Total cholesterol, mmol/L	5.1 ± 0.9	5.1 ± 0.7	ns	5.8 ± 1.1	6.1 ± 1.0	ns
HDL cholesterol, mmol/L	1.1 ± 0.2	1.1 ± 0.3	ns	1.3 ± 0.4	1.2 ± 0.3	ns
Triglycerides, mmol/L	1.8 ± 0.7	1.7 ± 0.6	ns	2.0 ± 0.7	1.8 ± 0.8	ns
BMI, kg/m^2	33 ± 6	33 ± 6	ns	30 ± 3	30 ± 3	ns
SBP, mmHg	141 ± 18	141 ± 18	ns	137 ± 12	137 ± 9	ns
DBP, mmHg	82 ± 14	82 ± 10	ns	82 ± 9	83 ± 9	ns
MBP, mmHg	106 ± 22	102 ± 13	ns	100 ± 11	105 ± 11	ns
HR, beats/min	76 ± 12	71 ± 11	0.01	74 ± 10	78 ± 8	ns
LAEI, mL/mmHg × 10	13 ± 4	17 ± 4	0.001	13 ± 4	12 ± 2	ns
SAEI, mL/mmHg × 100	6 ± 4	7 ± 3	0.009	5 ± 2	5 ± 1	ns

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MBP: mean blood pressure; HR: heart rate, LAEI: large artery elasticity index, SAEI: small artery elasticity index, ns: not significant.

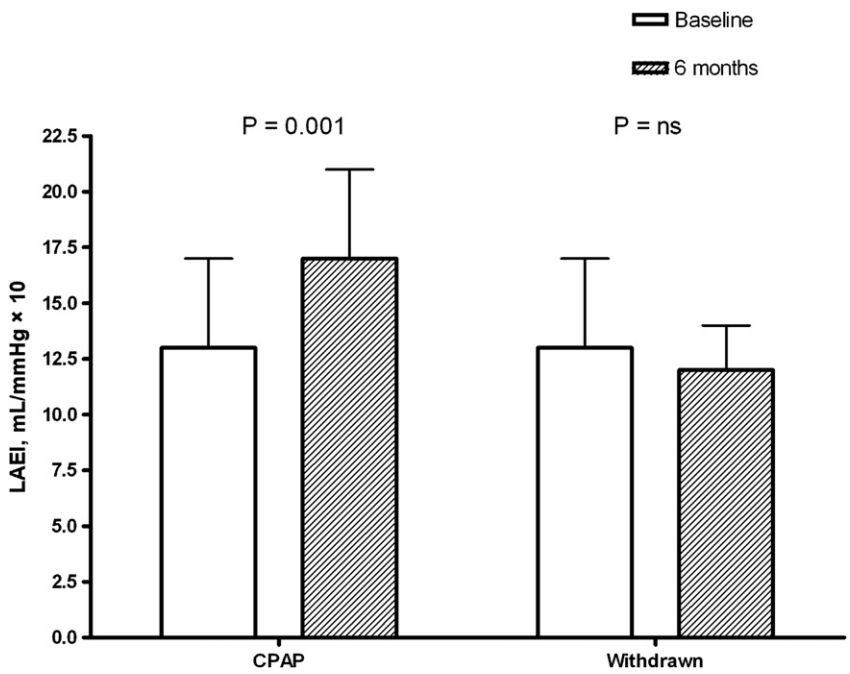

Figure 1 Changes in LAEI observed in OSA+ subjects treated by CPAP for 6 months ($n = 35$) and in subjects who withdrew from treatment ($n = 9$). LAEI: large artery elasticity index, CPAP: continuous positive airway pressure.

Several caveats of this study merit comment. First and foremost, we were unable to measure the changes in LAEI and SAEI at 6 months in subjects without OSA, mainly due to financial and logistic constraints. For similar reasons, we did not measure LAEI and SAEI in the 22 OSA+ subjects who did not receive CPAP treatment. Another limitation is that applanation tonometry is a noninvasive measure of large and small arterial elasticity, and an invasive measure would be more precise. We recognize that the most widespread noninvasive technique to assess endothelial function is flow-mediated dilation (FMD). However, FMD is time-consuming, the equipment is very expensive, and it requires an experienced examiner.[13] Third, the generalizability of our results may be limited by the small sample size. It is noteworthy, however, that two thirds of subjects referred to our sleep laboratory for the evaluation of OSA revealed a pathologic result. This result highlights the need for increased awareness of this frequently neglected pathological condition. Finally, this study was designed as an exploratory pilot project. Although the improvement in large and small arterial elasticity was clear, our data need to be confirmed in randomized, placebo-controlled studies.

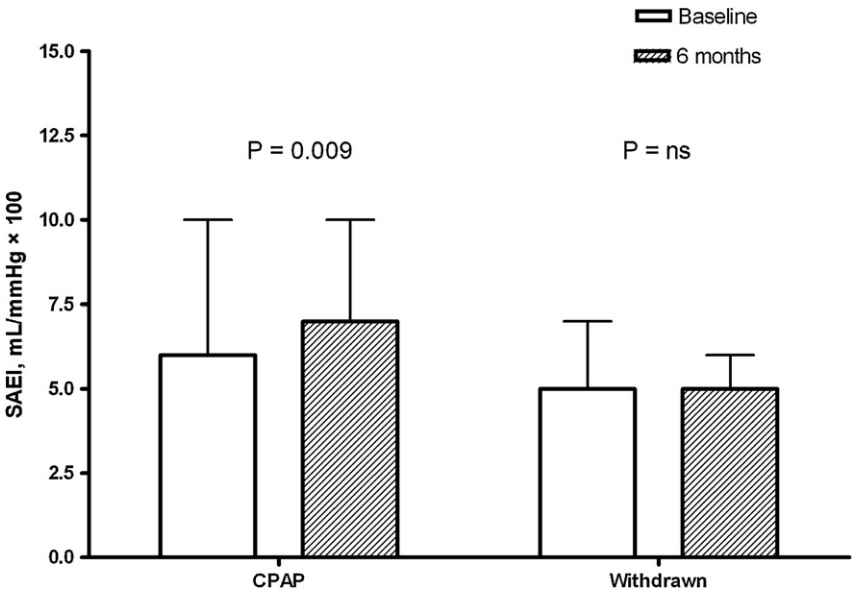

Figure 2 Changes in SAEI observed in OSA+ subjects treated by CPAP for 6 months ($n = 35$) and in subjects who withdrew from treatment ($n = 9$). SAEI: small artery elasticity index, CPAP: continuous positive airway pressure.

The primary outcome measure in this study was arterial elasticity and thus the study was not powered to detect changes in the clinical outcome as a result of CPAP treatment in OSA+ subjects. Greater numbers and longer treatment duration are required to evaluate this possibility fully. However, our findings provide a strong rationale for such a study.

In conclusion, we have shown an increase in arterial elasticity in OSA+ subjects after six months of CPAP treatment. These observations are likely to represent another beneficial vascular effect of CPAP therapy in this patient group.

Conflict of interest

All authors have no actual or potential conflict of interest.

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