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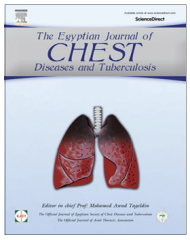

ORIGINAL ARTICLE

Can continuous positive air way pressure reverse carotid artery atherosclerosis in obstructive sleep apnea?

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KEYWORDS

Continuous positive airway pressure;
Obstructive sleep apnea;
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Abstract *Background:* Data from epidemiological studies and randomized clinical trials strongly suggest that obstructive sleep apnea (OSA) is associated with elevated risk of cardiovascular events. Although OSA and cardiovascular diseases share many risk factors, studies have demonstrated that OSA is an independent risk factor of arterial hypertension and atherosclerosis.

Objective: To determine the impact of treatment with continuous positive airway pressure (CPAP) on carotid artery intima-media thickness (CIMT) in patients with OSA.

Methods: 40 newly diagnosed OSA patients were assigned into two groups. Conservative treatment group (CT, $n = 20$) which refused CPAP treatment, and CPAP group (CPAP, $n = 20$) which received CPAP treatment. CIMT was determined at baseline and after 6 months.

Results: Mean follow-up time was 6.1 ± 2.1 months. At baseline, all measurements were similar in both groups and did not change significantly in CT group after 6 months. In contrast, a significant change occurred in CIMT in CPAP group (8 (20) vs. −115 (10) μm, $p = 0.03$) from baseline.

Conclusion: CPAP significantly reduced CIMT in OSA patients.

Introduction

OSA is a common sleep related breathing disorder characterized by repetitive upper airway collapse during sleep resulting in intermittent hypoxia, sleep fragmentation and sympathetic over-activity. The condition affects all age groups and is prevalent across different populations globally [1].

Although OSA and cardiovascular diseases share many risk factors, studies have demonstrated that OSA is an independent risk factor of arterial hypertension and atherosclerosis [2].

The mechanisms of this relationship are incompletely understood. However, the evidence suggests that intermittent hypoxia and the arousal response are likely the main pathophysiologic factors associated with oscillation of systemic and pulmonary arterial blood pressures, heart rate, and cardiac function. These factors expose the heart and circulation to a

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cascade of noxious stimuli that, over time, may initiate or contribute to the progression of most cardiovascular disorders [3].

In everyday practice, attention is usually paid to atherosclerotic plaques in the vessels, typical of advanced atherosclerosis with organ dysfunction. However, atherosclerosis is a chronic, progressive, pathological process with a long asymptomatic subclinical phase [4]. In recent years, CIMT has been well accepted as a non-invasive tool which may predict the likelihood of acute coronary events and stroke in asymptomatic healthy subjects [4,5]. Therefore, assessment of CIMT as an early predictor for atherosclerotic changes seems to be a much better approach.

Ultrasonography—a noninvasive, quick, and reproducible technique—can be used to evaluate the atherosclerotic process at an early stage. CIMT correlates well with anatomic measurements and is a marker of both structural vascular damages and in prediction of the cardiovascular risk in asymptomatic healthy subjects [2]. Epidemiological and interventional studies frequently use CIMT as a surrogate marker for subclinical or early atherosclerosis [3].

CPAP is the treatment of choice for patients with symptomatic OSA, as it has been shown to improve daytime sleepiness, alertness and quality of life and to decrease blood pressure [6–8]. Whether CPAP treatment is effective in counteracting the autonomic imbalance and increased arterial stiffness in patients with OSA remains a matter of debate [9].

Aim of the present study

The aim of the present study is to evaluate the effect of CPAP vs. conservative treatment on CIMT over a period of 6 months in OSA patients.

Patients and methods

The present study was conducted as prospective observational study for the treatment effects on CIMT in 40 newly diagnosed OSA patients. OSA was defined by an overnight portable sleep study showing apnea–hypopnea index (AHI) $\geqslant 5$/h of sleep plus excessive daytime sleepiness or two of the following symptoms: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, and impaired concentration [10,11].

The exclusion criteria included patients known to have coronary artery disease or receiving lipid-lowering agents for dyslipidemia or previously diagnosed to have OSA.

Sleep assessment

Overnight diagnostic portable sleep study (Embletta gold, level III) was performed for every subject recording chest and abdominal wall movement by inductance plethysmography, airflow measured by a nasal pressure transducer [11,12]. Apnea was defined as cessation of airflow – or its reduction by 90% – for >10 s and hypopnea as a reduction of airflow of $\geqslant 30\%$ for >10 s plus an oxygen desaturation of $>3\%$. Following confirmation of OSA, all patients were arranged to undergo overnight autoCPAP titration. All patients were given a basic CPAP education program by a respiratory technician supplemented by education booklet [11,12]. The technician would fit a comfortable CPAP mask from a wide range of selection for every patient, who was then given a short trial of CPAP therapy with the Autoset (ResMed, Sydney, Australia) CPAP device for 3 days. Following the overnight autoCPAP titration study, each patient was interviewed and invited to participate in the serial CIMT study.

Conservative treatment group (CT, n = 20)

After confirmation of significant OSA and completion of overnight autoCPAP titration, 20 patients who were not keen to start CPAP yet were encouraged to (a) avoid sleep deprivation by having sufficient hours of sleep every night; (b) sleep in lateral positions; (c) avoid sedatives and alcohol consumption; and (d) lose weight by exercise and diet [13]. This group was labeled as conservative treatment group (CT).

CPAP group (CPAP, n = 20)

In addition to the usual advice as given to CT group, 20 patients had agreed to commence CPAP treatment for >5 h/night after completing an overnight autoCPAP titration. They were subsequently prescribed CPAP device with a time counter recording machine run time. The CPAP pressure for each patient was set at the minimum pressure needed to abolish snoring, obstructive respiratory events, and airflow limitation for 95% of the night as determined by the overnight AutoSet CPAP titration study [11,12]. This group was labeled as CPAP group (CPAP).

Carotid artery intima-media thickness (CIMT)

CIMT was measured at baseline and 6 months for patients in both groups. The patients were followed up at the Respiratory clinic monthly whereas objective CPAP usage was measured from the time counter for CPAP group. CIMT was assessed by B-mode ultrasound scanning with compound and harmonic imaging to reduce the near field artifacts [14]. Bilateral CIMT measurements were obtained at the distal 10 mm of common carotid artery [15,16]. The CIMT was defined as the distance between the leading edge of the luminal echo to that of the media/adventitia echo (only the intima "echogenic layer" and the media "echo-poor layer" are included), and analyzed with a computerized edge-detection system. Carotid artery IMT was assessed by B-mode ultrasound scanning with a 12-MHz linear phase array transducer. Carotid IMT measurement by ultrasound was done using a semiautomated border detection program with validated accuracy. Three end-diastolic frames were selected, digitized, and analyzed for the mean IMT, and the average reading from these 3 frames was calculated for both right and left carotid arteries. The sole carotid scan operator was blinded to the clinical treatment status of the studied subjects and was not involved in the clinical assessment. Blood pressure (BP) was measured in the right arm after at least 15 min of rest using a standard sphygmomanometer before PSG and at clinic visits at 6 months.

Statistical analysis

The sample size was estimated by the Power Analysis and Sample Size for Windows software (PASS 2000, NCSS,

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Table 1 Comparisons between CT and CPAP groups regarding different variables.

Characteristics	CT group (n = 20)	CPAP group (n = 20)	p Value
Age	49 (12)	51 (11)	0.21
Sex, male/female	17/3	15/5	0.50
Smoking: yes/no	8/12	7/13	0.51
HTN: yes/no	14/6	12/8	0.31
DM: yes/no	7/13	8/12	0.27
Systolic blood pressure (mmHg)	142.3 (5.1)	139.5 (6.1)	0.38
Diastolic blood pressure (mmHg)	82.5 (3.2)	85.8 (2.7)	0.75
BMI (kg/m^2)	32.2 (0.3)	33.7 (1.2)	0.47
Neck circumference (cm)	37 (9.1)	39 (2.8)	0.09
Waist circumference (cm)	94.6 (2.1)	97.4 (1.7)	0.62
Hip circumference (cm)	105.1 (1.9)	101.3 (1.2)	0.41
Fasting plasma glucose (mg/dl)	95 (10)	102 (3)	0.67
Total blood cholesterol (mg/dl)	235 (31)	241 (42)	0.34
Blood triglyceride (mg/dl)	167 (61)	173 (49)	0.51
CIMT (μm)	693 (30)	702 (30)	0.47

Data expressed as mean (SE); CT, conservative treatment; CPAP, continuous positive airway pressure; HTN, hypertension; DM, diabetes mellitus; BMI, body mass index; μm, micrometer; p value > 0.05 is statistically insignificant.

Table 2 Polysomnographic data in CT and CPAP groups.

Characteristics	CT group (n = 20)	CPAP group (n = 20)	p value
AHI	44 (13)	51 (17)	0.37
SpO_2 < 90%	32 (19)	36 (21)	0.61
Lowest SpO_2	77 (11)	72 (13)	0.32
ESS	14 (3)	13 (4)	0.27
ODI	55 (17)	61 (19)	0.41

Data expressed as mean (SE); CT, conservative treatment; CPAP, continuous positive airway pressure; AHI, apnea–hypopnea index; SpO_2 < 90%, pulse oximetry <90% during sleep time as percentage of total sleep time; ESS, Epworth sleepiness scale (0–24), ODI, oxygen desaturation events; p value > 0.05 is statistically not significant.

Kaysville, Utah). The primary end-point was the change in CIMT. Data are expressed as mean ± standard error (SE) unless stated otherwise. A p-value of <0.05 is considered statistically significant.

Results

40 newly confirmed OSA patients were collected. They had met the study criteria to participate in the serial CIMT study after completing PSG and an overnight autoCPAP titration. However, 20 eligible patients refused CPAP treatment and preferred conservative management (CT group) and 20 patients had agreed to commence CPAP treatment (CPAP group) in addition to the usual advice given to CT group.

Among the 40 studied patients who had completed study, the demographics and CIMT between the two groups were similar (Table 1).

Among the 40 studied patients who had completed study, the severity of OSA between the two groups was similar (Table 2).

Comparison of parameter changes between CT and CPAP

The serial mean CIMT at baseline, and 6 months were 693 (30) and 701 (20) μm for the CT group (Table 3) whereas the serial mean CIMT for the CPAP group were 702 (30), and 587 (30) μm respectively, p = 0.03 (Table 3).

Discussion

In a group of 40 symptomatic patients newly diagnosed with severe OSAS, this prospective observational study has shown that CPAP treatment (CPAP group, n = 20) resulted in a significant reduction in carotid artery IMT compared to those who had preferred conservative treatment (CT group, n = 20) over a study period of 6 months.

Data from epidemiological studies and randomized clinical trials strongly suggest that OSA is associated with elevated risk of cardiovascular events [17]. Although OSA and cardiovascular diseases share many risk factors, studies have demonstrated that OSA is an independent risk factor of arterial hypertension and atherosclerosis [3,18].

There are several proposed published mechanisms that linked OSA and stroke. Sahlin et al. stated that patients with stroke and OSA have an increased risk of early death over 10 years [19], whereas sleep apnea is significantly associated with increased risk of stroke among patients with coronary artery disease over a follow-up period of 10 years [20]. Kohler and his colleges assessed cardiovascular risk of OSA and CPAP effect in males. After 4 weeks of therapeutic CPAP, a significant reduction was seen in sympathetic activity (evaluated by urine normetanephrine excretion), arterial stiffness (evaluated by augmentation index), mean ambulatory arterial blood pressure and significantly improved baroreflex sensitivity. They suggested that treatment of OSA with CPAP may lower cardiovascular risk [9]. Likewise data from the Sleep Heart Health Study (SHHS) have shown that modest to severe levels of OSA are associated with an approximately threefold increased risk of ischemic stroke in community-dwelling men [21]. In an observational sleep clinic study, Yaggi et al. [22]

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Table 3 Comparisons between CT and CPAP regarding mean CIMT at baseline and after 6 months (μm).

CT group (n = 20)				CPAP group (n = 20)			
Baseline	6 months	Change	p value	Baseline	6 months	Change	p value
693 (30)	701 (20)	8 (20)	0.45	702 (30)	587 (30)	−115 (10)	0.03

Data expressed as mean (SE); p value ≤ 0.05 is statistically significant.

have shown that OSA significantly increases the risk of stroke or death from any cause and the increase is independent of other known risk factors.

Gami et al. stated that there is a strong association between OSA and AF [23]. Many mechanisms have been suggested for this issue. OSA may accelerate atherosclerosis through the effect of hypertension and other mechanisms such as insulin resistance, diabetes, and dyslipidemia. In addition, OSA can induce direct proatherogenic effects through the mechanisms of systemic inflammation, oxidative stress, vascular smooth cell activation, increased adhesion molecule expression, monocyte/lymphocyte activation, increased lipid loading in macrophages, lipid peroxidation, and endothelial dysfunction [24]. Platelet activation [12] and silent brain infarction were also more common in patients with moderate to severe OSA than in controls [25]. Snoring-induced vibrational injury may lead to carotid atherosclerosis [26].

Recently, evaluation of CIMT has been well accepted as a non-invasive tool which may predict the likelihood of acute coronary events and stroke in asymptomatic healthy subjects [4]. CIMT has been applied by several research groups to study different OSA populations.

Data from many studies have suggested that OSA may lead to early atherosclerosis, as reflected by an increase in CIMT and occurrence of plaques, in the absence of any significant comorbidity [27–29]. OSA related hypoxia and systemic inflammation might be associated with progression of atherosclerosis and increased risk of cardiovascular morbidity [29]. Baguet and colleges suggested that severity of oxygen desaturation and blood pressure status were the best predictors for carotid wall hypertrophy whereas plaque occurrence without known cardiovascular disease was also related to the amount of oxygen desaturation regardless of their blood pressure status [28]. Another study by Monneret et al. demonstrated a relationship between lipid peroxidation, carotid artery IMT, and intermittent hypoxia in non-obese OSA patients [30] whereas in patients with minimally symptomatic OSA, diverse properties of endothelial function are impaired and arterial stiffness is increased [31].

In the present study, there were significant differences when comparing the changes in CIMT at 6 months [8 (20) vs. −115 (10) μm] from baseline between CT and CPAP groups. Many published studies suggested this CPAP beneficial effect [32,9,33,34,3]. Dragger et al. randomly assigned 24 patients with severe OSA who were free of comorbidities to receive no treatment (control, n = 12) or CPAP treatment (n = 12) for 4 months. They found a significant reduction in CIMT in CPAP group [32]. Hui and colleges examined a long-term effect of CPAP on CIMT in OSA patients. They observed a significant reduction in CIMT in patients with reasonable CPAP compliance compared to patients who refused this modality of treatment. The beneficial effect of CPAP occurred mostly in the first 6 months and was sustained at 12 months [33]. Agha and Habib assessed CPAP effect on CIMT in OSA patients. They reported a highly significant difference ($p < 0.01$) in CIMT between OSA patients and control group (10 obese non-OSA individuals). They observed a highly significant reduction ($p < 0.01$) in CIMT after 6 months of CPAP usage [34].

Although we did not find any significant correlation between objective CPAP usage and carotid IMT in this study, variability in the individual response may be related to the severity of OSA (AHI, hypoxemia) and CPAP compliance.

In contrast to the present study, Sharma and colleges published a double-blind, placebo-controlled trial. They randomly assigned OSA patients to undergo 3 months of therapeutic CPAP followed by 3 months of sham CPAP, or vice versa, with a washout period of 1 month in between. Results revealed no significant reduction in CIMT with CPAP (n = 43) vs. sham CPAP (n = 43). However, a subgroup analysis among those (n = 51) with CPAP usage at least 5 h/night showed significant reduction in CIMT (34 vs. 14 μm, $p < 0.05$) when comparing CPAP vs. sham CPAP treatment over 3 months [35].

Several limitations to the present study include the following. First, the study had a relatively small sample size. Second, it was not a randomized clinical trial as it would not be ethical to withhold CPAP treatment for symptomatic patients. Third, we did not study any inflammatory markers in blood, OSA severity and its relation to CPAP effect on CIMT. Lastly only baseline data of many variables like glucose and lipids were available and we did not have serial data to assess the treatment effects.

Conclusion

In summary, CPAP treatment resulted in a significant reduction in CIMT over a study period of 6 months, whereas no significant change was noted among those who refused this treatment modality. Newly diagnosed OSA patients should be encouraged to commence CPAP not just to relieve daytime sleepiness but also due to its cardio-protective effects. Further studies are warranted to assess these findings.

Conflict of interest

There was no conflict of interest.

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