

Early Variations in Augmentation Index and Pulsed Wave Velocity in Patients with Obstructive Sleep Apnea and Arterial Hypertension Post CPAP Treatment

Abstract

Background: Obstructive sleep apnea (OSA) is a risk factor for hypertension and if left untreated, is associated with high cardiovascular morbidity and mortality. Continuous positive airway pressure (CPAP) is considered the therapy of choice for moderate and severe OSA. (CPAP) reduces peripheral blood pressure and arterial stiffness. Arterial stiffness is measurable and evaluated by pulse wave velocity (PWV) and augmentation index as early markers of atherosclerosis and cardiovascular (CV) risk. The aim of this study was to assess the early effects of (CPAP) on augmentation index and pulsed wave velocity of arterial stiffness in patients with (OSA) and arterial hypertension.

Patients and Methods: The study conducted at Zagazig Cardiology and Chest Departments. Sixty patients divided into two groups: each group was thirty patients, the first group: moderate OSA with hypertension, the second group: severe OSA with hypertension. Inclusion criteria: Patients referred to the Sleep Clinic of the Chest Department, because of snoring or sleepiness with confirmed moderate-to-severe OSA (apnea/hypopnea index >15/h and >30 /h) and known to have hypertension on continuous antihypertensive treatment with BP less than 140/90 mmHg. Exclusion criteria: Patients with severe chronic diseases, peripheral vascular disease, and diabetes. Sleep study was done to confirm the diagnosis of OSA. Ambulatory blood pressure monitoring was done to confirm the diagnosis of hypertension. Non-invasive assessment of central aortic pressure and measuring pulse wave velocity and augmentation index .Standard CPAP intervention was done. Follow-up was done after 12 weeks of standard CPAP intervention.

Results: The effective CPAP treatment after 12 weeks showed significant BP reduction, in central systolic BP (6.2 ± 1.6 mmHg, $P < 0.005$), diastolic BP (4.4 ± 0.7 mmHg, $P < 0.001$) and, brachial sys-tolic BP (5.4 ± 1.4 mmHg, $P < 0.03$) and diastolic BP (4.2 ± 0.8 mmHg, $P < 0.05$) and achieved PWV reduction by 1.7 ± 1.2 m/sec ($P < 0.005$) and a significant reduction in augmentation index (the augmentation index was $24.8\% \pm 11.9\%$) and the significant reduction in augmentation index up to 6.1% ($P < 0.05$).

Conclusion: The effective CPAP therapy reduces both central aortic and peripheral blood pressure and improvements in arterial stiffness parameters. The effective reduction of augmentation index and arterial stiffness will prevent cardiovascular morbidity and mortality.

Keywords: Hypertension; Obstructive Sleep Apnea; Continuous Positive Airway Pressure; Pulse Wave Velocity; Augmentation Index; Arterial Stiffness

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Introduction

Obstructive sleep apnea (OSA) is a chronic repeated upper-airway obstruction during sleep, characterized by repetitive apnea, hyperpnoea and oxygen desaturations leading to interrupted sleep, variations in blood pressure, and increased sympathetic nervous system activity [1]. The prevalence of OSA is 2-4 % in the general population [2-4]. The prevalence of cardiovascular disease (systemic hypertension, coronary artery disease and cerebrovascular disease) was high in OSA patients [5]. The number of OSA patients with hypertension is high

(35 %) to (70 %) [6,7] and nearly 30 % of patients presenting with hypertension also have OSA [8]. OSA has been proven to be a causal factor in the pathogenesis of vascular dysfunction and hypertension [9]. The Noninvasive assessment of arterial stiffness by the measurement of pulsed wave velocity (PWV) and augmentation index is a predictor of cardiovascular morbidity and mortality in hypertensive patients [10].The Continuous positive airway pressure (CPAP), is considered the first line treatment for OSA and can decrease the arterial stiffness in hypertensive patients with obstructive sleep apnea [11,12].

The aim of this study was to assess the early effects of (CPAP) on augmentation index and pulsed wave velocity of arterial stiffness in patients with (OSA) and arterial hypertension.

Patients and Methods

The study was conducted at Zagazig Cardiology and Chest Departments from December 2015 to December 2016.

- A. Inclusion criteria:** Patients referred to the Sleep Clinic at the Chest Department, because of snoring or sleepiness with confirmed moderate-to-severe OSA (apnea/hypopnea index $>15/h$ and $>30/h$) and known to have hypertension on continuous antihypertensive treatment with BP less than 140/90 mmHg.
- B. Exclusion criteria:** Patients with severe chronic diseases, eg liver cirrhosis, cardiomyopathy, renal failure and peripheral vascular diseases. Sixty patients were enrolled in this study and divided into two groups; each group was 30 patients, the first group: moderate OSA with hypertension, the second group: severe OSA with hypertension.

Study protocol

Polysomnography & CPAP treatment: Polysomnography was done to confirm the diagnosis of OSA. All patients underwent overnight polysomnography using a standard technique. Polysomnography was done (SOMNOscreen plus 4447, Germany). The system consists of 4 channels of electroencephalography, 2 channels of electrooculography, submental electromyography, oronasal airflow, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position detector, electrocardiogram and tracheal sound. Sleep stages were scored [13]. Apnea was defined as complete stopping of airflow lasting more than 10 seconds. Hypopnea was defined as 30% or more reduction in respiratory airflow lasting ≥ 10 seconds which is accompanied by a decrease of $\geq 4\%$ in oxygen saturation or arousal in EEG. Apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour. OSAS was defined as apneas or hypopneas ≥ 5 AHI events per hour in the presence of clinical symptoms suggesting OSAS [14,15]. According to the severity, included patients were classified as mild OSA (AHI between 5 and 15), moderate OSA (AHI between 15 and 30) and severe OSA (AHI ≥ 30) [16,17]. The patients with OSA underwent auto CPAP titration (Weinmann, prisma 20A auto CPAP, Germany) and the target CPAP pressure was P95 recorded by the device. Effective OSA therapy was defined as $>25\%$ drop in AHI of CPAP treatment and mean reduction in Epworth Sleepiness Score of 3 points [18,19].

Blood pressure measurement: Ambulatory blood pressure monitoring was done to confirm the diagnosis of hypertension. Arterial hypertension was diagnosed according to current guidelines published by the European Society of Hypertension [20]. BP measurements were determined using a conventional mercury sphygmomanometer [21]. Non-invasive assessment of central aortic pressure and measuring pulse wave velocity and augmentation index. The brachial pulse wave velocity (PWV), central BP, and systolic wave augmentation index were measured

using a mobil-o-graph 24h PWA monitor (IEM, Stolberg, Germany) using single oscillometric measurement of the brachial BP by simultaneously obtaining the pulse wave contour [22,23]. The new oscillometric device mobil-o-graph 24h PWA monitor (IEM, Stolberg, Germany) with appropriately sized arm cuffs. After obtaining brachial BP, the cuff was again inflated, maintaining the diastolic pressure level for 10 s for assessment of the pulse waveform [6]. Each measurement cycle with the mobil-o-graph [24]. By inflating the cuff after conventional BP measurement to the diastolic BP level, the brachial arterial pressure waveform can be determined with a high-fidelity pressure sensor. Using generalized transfer functions, the aortic pressure waveform can be generated from the obtained brachial artery pulse waveform. The measurement was in the supine position after 15 minutes rest by PWA of the brachial artery waveform using mobil-o-graph 24h PWA monitor (IEM, Stolberg, Germany). Augmentation index were both corrected for a heart rate of 75 beats per minute (AIx_{75}) using an automatic calculation determined by the PWA software. The augmentation index is the ratio of the augmentation pressure (due to the reflected component of the pulse pressure wave) to pulse pressure, expressed as a percentage. A decrease in AIx_{75} and an increase in time to reflection indicate improvements in arterial stiffness [25]. Central blood pressure and arterial stiffness were measured at baseline before CPAP therapy and follow-up was done after 12 weeks of standard CPAP intervention.

Ethical consideration: This study was approved by Ethics Committee of Faculty of Medicine, Zagazig University, Egypt. A written consent from every patient to participate in the study was obtained. Consistence with ethical standards. Conflict of interest: The authors announce that they have no conflict of interest.

Statistic analyses: The data analysis was performed using the SPSS Statistics 21.0 (IBM, New York, NY, USA) software. The mean \pm standard deviation was used for analysis of quantitative data. A paired T test was used for comparison between the parameters before and after CPAP that showed changes during treatment. P value <0.05 was considered to be statistically significant.

Results (Table 1)

As regards the demographic data: there were no statically significant differences between two groups as regards age, gender, body mass index (BMI) and Epworth sleepiness scale (ESS) denoting matching of the studied patients.

Table 2

In group I: The effective CPAP treatment after 12 weeks showed a statistical significant differences between brachial systolic BP before CPAP (141.6 ± 2.1) after (140.6 ± 1.5) ($P < 0.000$) and diastolic BP before CPAP (85.3 ± 8.2) after (80.9 ± 7.5) ($P < 0.000$).

In group II: The effective CPAP treatment after 12 weeks showed a statistical significant differences between brachial systolic BP before CPAP (166.4 ± 3.2) after (135.4 ± 0.5) ($P < 0.000$) and diastolic BP before CPAP (96.7 ± 4.5) after (86.8 ± 2.3) ($P < 0.000$).

Table 3

In group I: The effective CPAP treatment after 12 weeks showed a statistical significant differences between central sys-

tolic BP before CPAP (129.6±1.8) after (124.2±0.4) ($P < 0.000$) and diastolic BP before CPAP (86.8±2.3) after (82.6±1.5) ($P < 0.000$).

In group II: The effective CPAP treatment after 12 weeks showed a statistical significant differences between central systolic BP before CPAP (155.7±3.7) after (126.4±1.2) ($P < 0.000$) and diastolic BP before CPAP (97.3±2.8) after (85.6±1.9) ($P < 0.000$).

Table 4

In group I: The effective CPAP treatment after 12 weeks showed a statistical significant differences between pulsed wave velocity before CPAP (12.6±2.5) after (10.9±1.3) ($P < 0.001$) and augmentation index before CPAP (21.6 ± 11.0) after (18.7 ± 9.3) ($P < 0.05$).

Table 1: Demographic data of the study groups.

	All Patients at Baseline (n=60) Mean ± SD	All Patients at 12 Weeks Follow Up (n=60) Mean ± SD	Group I AHI (15-30) (n=30)	Group II AHI (>30) (n=30)	P-value
Age (years)	63.3±11.5	63.3±11.5	61.8±13.1	62.4±11.7	NS
Gender					
-male	42 (70%)	42 (70%)	22(73.33%)	20 (66.6%)	NS
-Female	18 (30%)	18 (30%)	8 (26.66%)	10 (33.4%)	
BMI (Kg/m ²)	30.7±5.5	30.6±6.5	30.4±5.5	32.9±6.5	NS
ESS	10.2±5.5	7.2±5.4	9.2±4.5	13.9±4.6	<0.05

BMI: Body Mass Index; ESS: Epworth Sleepiness Scale

Table 2: Brachial blood pressure measurements before and 3 months after CPAP treatment.

	Group I (N=30) Mean ± SD		Group II (N=30) Mean ± SD	
	Before CPAP	After CPAP	Before CPAP	After CPAP
SBP (mmHg)	141.6±2.1	135.4±0.5	166.4±3.2	140.6±1.5
P value	<0.000		<0.000	
DBP (mmHg)	85.3±8.2	80.9±7.5	96.7±4.5	86.8±2.3
P value	<0.000		<0.000	

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Table 3: Central blood pressure measurements before and 3 months after CPAP treatment.

	Group I (N=30) Mean ± SD		Group II (N=30) Mean ± SD	
	Before CPAP	After 3 months	Before CPAP	After 3 months
c SBP (mmHg)	129.6±1.8	124.2±0.4	155.7±3.7	126.4±1.2
P value	0		0	
cDBP (mmHg)	86.8±2.3	82.6±1.5	97.3±2.8	85.6±1.9
P value	0		0	

cSBP: Central Systolic Blood Pressure; cDBP: Central Diastolic Blood Pressure.

Table 4: Arterial stiffness measurements before and 3 months after CPAP treatments.

	Group I (N=30) Mean ± SD		Group II (N=30) Mean ± SD	
	Before CPAP	After 3 months	Before CPAP	After 3 months
PWV (m/sec)	12.6±2.5	10.9±1.3	13.9±2.8	12.1±1.6
P value	0.001		0.003	
AIx75	21.6 ± 11.0	18.7 ± 9.3	24.8 ± 11.9	21.7 ± 10.1
P value	<0.05		<0.05	

PWV: Pulsed Wave Velocity; AIx75: AIx values were normalized to a Standard Heart Rate of 75 per minutes.

In group II: The effective CPAP treatment after 12 weeks showed a statistical significant differences between pulsed wave velocity before CPAP (13.9 ± 2.8) after (12.1 ± 1.6) ($P < 0.003$) and augmentation index before CPAP (24.8 ± 11.9) after (21.7 ± 10.1) ($P < 0.05$). The effective CPAP treatment after 12 weeks showed significant BP reduction, in central systolic BP (6.2 ± 1.6 mmHg, $P < 0.005$), diastolic BP (4.4 ± 0.7 mmHg, $P < 0.001$) and, brachial systolic BP (5.4 ± 1.4 mmHg, $P < 0.03$) and diastolic BP (4.2 ± 0.8 mmHg, $P < 0.05$). and achieved PWV reduction by 1.7 ± 1.2 m/sec ($P < 0.005$) and a significant reduction in augmentation index (the augmentation index was $24.8\% \pm 11.9\%$) and the significant reduction in augmentation index up to 6.1% ($P < 0.05$).

Discussion

Arterial stiffening is the early signs of arterial remodeling, leading to high central aortic pressures [26-28]. The association between OSA and arterial stiffness has been suggested by several studies [27,29,30]. Controlled cross-sectional study has shown that in patients with minimally symptomatic OSA, arterial stiffness is increased, when compared with well matched control subjects without OSA [30]. Continuous positive airway pressure, as the primary way to treat OSA, is the most efficient therapy for maintaining upper-airway patency during sleep. Studies have shown that CPAP can improve endothelial function, sympathetic and vagal balance, and then further improve arterial stiffness [31-33]. Therefore, it is expected that CPAP therapy could decrease arterial stiffness in OSA patients. *Tsioufi et al.* [34] suggested that OSAS has a significant incremental effect on aortic stiffening in the setting of middle-aged essential hypertensive subjects. Thus, OSAS in a hypertensive patient may accelerate vascular damage, increasing cardiovascular risk. In the longitudinal community-based cohort study *Kaess et al.* [35] shows that higher aortic stiffness, forward wave amplitude (FWA), and augmentation index were associated with higher risk of incident hypertension. So, vascular stiffness may be a precursor rather than the result of hypertension. In our study we show that CPAP can improve arterial stiffness in patients with OSA and hypertension, and we speculated that it might be beneficial to delay or prevent the occurrence of cardiovascular disease in patients with OSA and hypertension [36]. As in the study of *Kartali* [28], the PWV is reduced at first night and further decreased after 3 months of treatment compared to baseline which implies that not only a functional, but also a structural change is taking place in the arteries.. It seems that the effect of CPAP on PWV reaches a very high point very early in its use and continuous use maintains the positive outcome, having reached a plateau. In the present study, addition of effective CPAP decreased arterial stiffness to a greater extent. 37 our study population showed high PWV values, which is in agreement with the data reported in the literature [37-39]. In our study The effective CPAP treatment after 12 weeks showed significant BP reduction, in central systolic BP (6.2 ± 1.6 mmHg, $P < 0.005$), diastolic BP (4.4 ± 0.7 mmHg, $P < 0.001$) and, brachial systolic BP (5.4 ± 1.4 mmHg, $P < 0.03$) and diastolic BP (4.2 ± 0.8 mmHg, $P < 0.05$) and achieved PWV reduction by 1.7 ± 1.2 m/sec ($P < 0.005$) and a significant reduction in augmentation index (the augmentation index was $24.8\% \pm 11.9\%$) and the significant reduction in augmentation index up to 6.1% ($P < 0.05$). It should

be emphasized that, according to the literature, a decrease in PWV of 1.6 m/sec is equivalent to functional "rejuvenation" of vessels for 15 years [40,41]. The initial augmentation index has been reported to be an independent risk factor for cardiovascular disease, and the augmentation index has been reported to be higher in patients with OSA than in controls [42]. In our study, the effective CPAP treatment achieved a significant improvement in the augmentation index. Several recent studies have reported that aortic pressure is a more precise predictor of target organ damage than conventional brachial BP [43]. The central BP reduction observed in our study is in agreement with the results reported by Phillips et al after 2 months of CPAP (-4.2 mm Hg) [44]. It should be noted that this relatively minor central BP decrease may be significant in terms of prognosis, given the finding of the ASCOT-CAFÉ study that an intergroup difference of 3.6 mmHg in central BP decreased cardiovascular mortality by 24% and the risk of fatal and nonfatal stroke by 23% [42] which may explain the benefits in terms of cardiovascular morbidity and mortality. The basis of this "additional" reduction in central BP seems to be related to an impact on arterial stiffness and the reflected wave. In our study, the duration of CPAP treatment was 3 months, but seems to have been adequate to observe the "additional" effect on central BP. This "additional" decrease of central systolic BP was shown after effective CPAP was (6.2 ± 1.6 mmHg, $P < 0.005$). Therefore, our results suggest that the beneficial effect of CPAP in patients with OSA and arterial hypertension is related, at least in part, to an improvement in arterial stiffness and reflected wave parameters and augmentation index reduction. Recent guidelines by the UK National Institute for Health and Clinical Excellence (NICE) and US Preventive Services Task Force (USPSTF) suggest that the diagnosis of clinic hypertension be confirmed using ABPM in efforts to avoid misdiagnosis and overtreatment [45,46]. There are several validated devices available, which estimate cSBP using oscillometric upper-arm cuff-based methods: a Mobil-OGraph NG (IEM) uses ARCSolver algorithm to compute the cSBP, and the pressure waveform is obtained at the diastolic level. The Tel-O-GRAPH uses exactly the same mathematic algorithm for calculation of the cSBP (ARCSolver) as Mobil-O-GRAPH does. Until now, the measurements of cSBP with tonometry have been limited to clinical studies, because measurement performance required additional trained personnel, additional time, additional technical equipment and certain positions of the patients. The results of our study confirm the validity of the oscillometric measurement of cSBP using the inbuilt ARCSolver algorithm, as reported by several previous studies. These studies used a validated method with a new device [47-49].

Conclusion

The effective CPAP therapy in hypertensive patients with OSA reduces both central aortic and peripheral blood pressure and improvements in arterial stiffness parameters. The effective reduction of augmentation index and arterial stiffness will prevent cardiovascular morbidity and mortality.

Limitations

A single-center study and its relatively small sample size and short duration further studies in a larger number of patients are

needed. The main limitation of the study is that the validation was not performed against invasive measurement of cSBP, which was not done because of the obvious risk of invasive procedure. We are also aware that the brachial BP, which was used to compute the cSBP, can vary. Thus, the true brachial BP during the measurement with the Sphygmocor could have been changed compared with the used brachial BP value measured previously with the mobil-o-graph 24h PWA monitor, although the time delay between the measurements was as short as possible. Dependent on the subject's constitution, and thus contributing to a certain variation of the computed values, as well as certain population selection bias.

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