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Original Article

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Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Does Not Reduce Arterial Stiffness in Patients With Type 2 Diabetes After One Year of Follow-Up

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Abstract

Background: The aim of this study is to evaluate the effects of 12-month continuous positive airway pressure (CPAP) treatment on arterial stiffness in patients with type 2 diabetes.

Methods: Obstructive sleep apnea (OSA) and type 2 diabetes frequently co-exists. Both diseases increase arterial stiffness, a marker of cardiovascular risk. Treating OSA with CPAP may lower arterial stiffness. In a recent randomized trial, we found that CPAP treatment for 12 weeks did not reduce arterial stiffness in type 2 diabetes patients with OSA. Participants from the randomized trial were invited to a follow-up study 12 months after inclusion. We evaluated arterial stiffness by measuring carotid-femoral pulse wave velocity (cfPWV) using SphygmoCor.

Results: Forty-six patients (63.9% of the original 72 patients, age 63.8 ± 6.5 years, diabetes duration 16.1 ± 9.7 years, body mass index (BMI) 34.7 ± 3.9 kg/m^2) partook in the study. Mean duration of CPAP treatment was 10.5 ± 1.5 months. Baseline cfPWV was 10.7 m/s. At follow-up cfPWV was 10.6 m/s, change in cfPWV: -0.12 m/s, 95% confidence interval (CI): -0.6, 0.4, P = 0.6. Baseline systolic blood pressure (BP) was 136.2 mm Hg. At follow-up BP was 137.9 mm Hg, change in BP: 1.6 mm Hg, 95% CI: -2.3, 5.5.

Conclusions: We found no effect of 9 - 12-month CPAP treatment on arterial stiffness or BP in patients with long duration of type 2 diabetes and OSA.

Keywords: Arterial stiffness; Pulse wave velocity; Diabetes; Obstructive sleep apnea

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Introduction

Obstructive sleep apnea (OSA) is characterized by repeated episodes of partial or complete occlusion of the upper airways resulting in fragmented sleep and intermittent hypoxemia. OSA is highly prevalent in patients with type 2 diabetes [1]. Both OSA and type 2 diabetes are associated with an increase in cardiovascular disease (CVD) and mortality [2-5].

Arterial stiffness is an early marker of cardiovascular (CV) risk and has been shown to predict CV events independently of traditional risk factors [6, 7]. In addition, reduction in arterial stiffness may be associated with improved CV outcome [8, 9]. The gold standard for assessing arterial stiffness is carotid-femoral pulse wave velocity (cfPWV) [10]. Both type 2 diabetes and OSA are associated with increased arterial stiffness [11-14].

In our recent randomized study [15] the use of continuous positive airway pressure (CPAP) for 3 months did not reduce PWV in patients with type 2 and OSA. After the study period ended, all patients received treatment with CPAP. The aim of this study is to evaluate the effects of CPAP on arterial stiffness at follow-up of 1 year after the original study.

Materials and Methods

The study design and inclusion criteria have been reported

in details previously [15]. Briefly, the patients were recruited from outpatient clinics at three Danish hospitals. The patients were screened for OSA using ApneaLink (ResMed Corp., CA, USA).

Subjects

Subjects with type 2 diabetes were eligible for participating in the study if they had treatment naive OSA with apnea-hypopnea index (AHI) of 15 or more and were 18 years or older. Exclusion criteria included history of stroke or myocardial infarction within 3 month prior to study start; employment in transport industry; uncontrolled hypertension > 160/95 mm Hg, heart failure (New York Heart Association (NYHA) class III or IV); history of alcohol or drug abuse; pregnant or nursing women.

Study design

The study is a follow-up of a randomized controlled multicentre study with an intervention of 3 months of CPAP treatment versus no treatment. The study was approved by the local research ethics committee and registered at Clinicaltrials.gov under the identifier NCT02482584. The study was conducted according to the Declaration of Helsinki (ethical principles for medical research involving human subjects). After 3 months the patients in the control group were invited to receive CPAP treatment and the patients in the active treatment arm to continue CPAP. All the participants were invited for a follow-up evaluation 12 months after inclusion in the original study and thus had duration of CPAP treatment between 9 and 12 months. As all patients received treatment at follow-up the patients were treated as a single group.

Study parameters

At baseline and at the follow-up visit blood pressure (BP) was measured using a fully automated oscillometric device (Microlife WatchBP Office, Microlife AG, Widnau, Switzerland). Measurements were performed after a resting period of 10 min with the patient in a sitting position.

After BP measurement the patients rested for 5 min in the supine position after which measurements of arterial stiffness were performed. Arterial stiffness was measured as cfPWV using the SphygmoCor device (version 9, AtCor Medical, Sydney, Australia). Using a tonometer (Millar, STP-304, Houston, Texas, USA), sequential electrocardiogram-referenced recordings of the pulse waves at the carotid and femoral arteries were performed. The transit time was determined using the intersecting tangent method [16]. The travel distance of the pulse wave was determined as the distance from the measuring point at the carotid artery to the measurement point in the femoral artery multiplied by 0.8 as recommended [10]. The distance was measured using a caliper. We performed three consecutive measurements. As recommended by the manufacturer, only cfPWV measurements with a standard deviation of less than 20% were accepted.

Study endpoints

The primary endpoint of our study was the change in cfPWV from baseline to 12-month follow-up. Secondary endpoint was change in BP from baseline to 12-month follow-up.

Statistical analysis

Data distribution was assessed by histograms and QQ-plots. Summary data are presented as frequencies, as mean ± standard deviation (SD) for normally distributed data or as median and interquartile range for skewed data. Primary outcome analyses were performed using a linear mixed effect model. Statistical analysis was performed using STATA software package version 14.2 (StataCorp, Texas, USA). A two-sided P value of less than 0.05 was considered to be statistically significant.

Results

Forty-six (63.9% of the original 72 patients included in the study) accepted our invitation to participate in the follow-up measurements. Twenty-two patients from the treatment group and 24 patients from the control group accepted participation (Table 1).

No differences were observed between the group accepting follow-up at 12 months and the group who refrained other than a higher number of patients using sodium-glucose cotransporter 2 (SGLT2) inhibitors in the group who refrained from participation in the follow-up (Supplementary Material 1, www.jofem.org).

In a multivariate analysis we found that higher age, higher levels of hemoglobin A1c (HbA1c), current smoking and longer diabetes duration was associated with higher baseline cfPWV. Higher levels of creatinine were associated with a lower cfPWV, whereas baseline body mass index (BMI) or AHI had no effect on cfPWV (Table 2).

Use of CPAP

The mean duration of CPAP use at follow-up was 10.5 ± 1.5 months. CPAP compliance was recorded after 3 months, but not at 12-month follow-up.

Effect of CPAP treatment on arterial stiffness

No significant change from baseline was observed in cfPWV after CPAP treatment for an average of 10.5 months, delta cfPWV (follow-up - baseline): -0.1 m/s, 95% CI -0.6, 0.4, P = 0.6, for the group as a whole (Table3).

We observed no significant difference in the change in cf-

Table 1. Baseline Characteristics

N	46
Age (years)	63.8 ± 6.5
Male, n	37 (80.4%)
Diabetes duration (years)	16.1 ± 9.7
Apnea-hypopnea index (events/h)	34 (15 - 73)
Oxygen desaturation index (events/h)	36.4 ± 15.7
BMI (kg/m^2)	34.7 ± 3.9
Systolic blood pressure (mm Hg)	136.4 ± 12.9
Diastolic blood pressure (mm Hg)	80.4 ± 6.9
HbA1c (mmol/mol)	64.7 (53 - 87)
Fasting blood glucose (mmol/L)	9.5 ± 2.3
Creatinine (µmol/L)	83.3 (43 - 203)
Total cholesterol (mmol/L)	4.0 ± 0.9
HDL cholesterol (mmol/L)	1.2 ± 0.3
LDL cholesterol (mmol/L)	2.1 ± 0.8
Triglyceride (mmol/L)	1.9 (0.6 - 3.9)
Smoking	
Currently, n (%)	6 (13.0%)
Former, n (%)	18 (39.1%)
Never, n (%)	22 (47.8%)
Statin use, n (%)	36 (78.3%)
Aspirin use, n (%)	25 (54.4%)
Antidiabetic medication	
No medication, n (%)	3 (6.5%)
Metformin, n (%)	36 (78.3%)
Insulin, n (%)	29 (66.0%)
GLP-1 analog, n (%)	27 (58.7%)
DPP-4 inhibitor, n (%)	3 (6.5%)
SGLT2 inhibitor, n (%)	5 (10.9%)
Sulphonylurea, n (%)	1 (2.2%)
Blood pressure medication	
No medication, n (%)	4 (8.7%)
Beta blockers, n (%)	18 (39.1%)
Thiazide, n (%)	19 (41.3%)
ACE-inhibitor, n (%)	24 (52.2%)
AT2 antagonist, n (%)	14 (30.4%)
Calcium blockers, n (%)	18 (39.1%)
Loop diuretics, n (%)	8 (17.4%)
Other, n (%)	7 (15.2%)
cfPWV (m/s)	10.7 ± 2.0

BMI: body mass index; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; GLP-1: glucagon-like peptide; DPP-4: dipeptidyl peptidase 4; SGLT2: sodium-glucose cotransporter 2; ACE: angiotensin-converting enzyme; AT2: angiotensin-2; cfPWV: carotid-femoral pulse wave velocity.

Table 2. Multivariate Analysis With Baseline cfPWV as Dependent Variable

Independent variables	Coefficient	P	95% CI
Sex (male)	-0.26	0.45	-0.96, 0.43
AHI (5 events/h)	0.04	0.41	-0.05, 0.13
HbA1c (5 mmol/mol)	0.29	0.001	0.12, 0.47
Age (5 years)	0.47	< 0.001	0.25, 0.68
BMI (5 kg/m^2)	0.1	0.67	-0.35, 0.55
Diabetes duration (5 years)	0.19	0.01	0.04, 0.33
Systolic BP (5 mm Hg)	0.09	0.12	-0.02, 0.19
Creatinine (5 µmol/L)	-0.08	0.01	-0.14, -0.02
Smoking	1.1	0.01	0.26, 1.93

cfPWV: carotid-femoral pulse wave velocity; AHI: apnea-hypopnea index; BMI: body mass index; HbA1c: hemoglobin A1c; BP: blood pressure; CI: confidence interval.

PWV, between the patients who had been treated for 9 months and patients who had received 12 months of treatment with CPAP, delta cfPWV 12 months - delta cfPWV 9 months: -0.25 m/s; 95% CI -1.3, 0.8, P = 0.6.

Adjusting for mean arterial pressure (MAP), heart rate (HR), number of antihypertensive drugs and BMI did not alter the above findings (results not shown).

Effect of CPAP treatment on BP

No significant change from baseline was observed in systolic BP at follow-up (follow-up - baseline): 1.6 mm Hg, 95% CI: -2.27, 5.46, P = 0.42 for the group as a whole (Table 3).

We observed no significant difference in the change in systolic BP between the patients who had been treated for 9 months and patients who had received 12 months of treatment with CPAP, delta BP 12 months - delta BP 9 months: -6.8 mm Hg, 95% CI: -14.2, 0.5, P = 0.1.

After adjusting for number of antihypertensive drugs and BMI the results remained unchanged (results not shown).

Discussion

In the current study, we observed no effect of prolonging CPAP treatment from 3 months to a median of 10.5 months on cfPWV or BP.

Both type 2 diabetes and OSA are associated with in-

Table 3. Change in Arterial Stiffness and Blood Pressure at Follow-Up

	Baseline	At follow-up	Change	P
cfPWV (m/s)	10.7	10.6	-0.12	0.64
Systolic BP (mm Hg)	136.4	138.1	1.60	0.42
Diastolic BP (mm Hg)	80.4	79.8	-0.58	0.57

cfPWV: carotid-femoral pulse wave velocity; BP: blood pressure.

creased BP, arterial stiffness and excess mortality [4, 5, 11, 13]. Several studies have previously shown that CPAP treatment of OSA can reduce arterial stiffness and BP in various patient populations [17-19]. However, none of these studies have been conducted in a population of patients all of whom had type 2 diabetes. Furthermore, most of the studies have been of short duration. In our original randomized study [15] we observed no effect of CPAP treatment on arterial stiffness or BP after 3-month treatment with CPAP. We speculated that the lack of effect could be attributed to the short duration of treatment. However, the results of our current study show that extending the duration of treatment does not reduce arterial stiffness or BP in our population of patients with OSA and type 2 diabetes. It is noteworthy that despite a wide range of baseline AHI, the severity of OSA had no independent influence on baseline cfPWV, indicating that intervention with CPAP *a priori* is unlikely to change cfPWV in patients with OSA and type 2 diabetes.

The lack of change in arterial stiffness observed in our study, is in agreement with recent findings by Galerneau et al [20], who found no reduction in arterial stiffness after treatment with CPAP for a median of 7.5 years in obese patients with OSA, of whom 20% had diabetes. These results were found in spite of high adherence to CPAP treatment. Likewise, no effect on BP was observed.

The lack of effect observed in our study can probably in part be contributed to our study population. It has previously been shown that the increased arterial stiffness in patients with OSA is primarily caused by conventional risk factors for CV disease such as age, BP and diabetes whereas the severity of OSA is only a minor contributor [21].

We included a population of patients with type 2 diabetes. At baseline, our patients had a high prevalence of hypertension, high BMI and long duration of diabetes. We showed that age, diabetes duration and poor glycemic regulation all are associated with increased arterial stiffness. The fact that diabetes is a major contributor to arterial stiffness has been shown by other study of Laugesen et al [22], and by the findings of Galerneau et al [20], who showed a 13.75% increase in PWV in patients with diabetes compared to patients without diabetes. Similar, a 12.63% increase was found in patients with hypertension compared to normotensive individuals. The presence of diabetes and hypertension may cause vascular changes, which cannot be reversed with CPAP treatment.

Diagnosing OSA and treatment with CPAP in patients with diabetes should still be prioritized as CPAP has been shown to reduce daytime sleepiness and improve quality of life [23]. However, our study shows that the indication for CPAP treatment should not be to reduce arterial stiffness, at least not in patients with long duration of diabetes. Further studies should focus on treating OSA in patients with newly diagnosed diabetes to see if early intervention can reduce progression of arterial stiffness in these patients.

Our study has several strengths; we used the gold standard for evaluating arterial stiffness. We had a longer follow-up time than most studies allowing us to evaluate the effects of CPAP treatment over a longer period of time. We examined the effects of CPAP in a homogeneous population of patients with diabetes, which is important because of the high degree of co-existence of OSA, and diabetes.

Our study also has several limitations. The major limitation of our study is the lack of a control group after the initial 3 months. We observed no change in arterial stiffness in our CPAP treated patients, but cannot exclude the possibility that the intervention may have prevented a potential increase in arterial stiffness in untreated patients. However, the findings by Galerneau et al [20] showed that compliance to CPAP had no effect on progression of arterial stiffness, therefore it is probably unlikely that we would have observed a difference between treated and untreated individuals. Another limitation is the lack of control over the participant's medication. After the initial 3 months of the study, changes in antidiabetic and antihypertensive treatment were allowed if the patients usual care provider found it necessary. Changes in medication may therefore have influenced the results. However any change in medication is likely to improve BP or diabetes control. Therefore, changes in medication would have been expected to increase any positive effects of CPAP treatment. Thus, changes in medication are unlikely to have altered our results.

We do not have data on CPAP compliance after 12 months. This lack of data prevents us from detecting any effects in patients compliant to CPAP treatment. However, in the study by Galerneau et al [20], CPAP compliance had no significant impact on arterial stiffness. Likewise, in our original randomized study, we saw no difference in arterial stiffness between the compliant and non-compliant patients. Therefore, the addition of compliance data is probably unlikely to alter our findings.

Another limitation is the number of patients accepting participation in the follow-up. Only 64% of the participants from our original study accepted participation, which potentially could influence our findings. However, we observed no baseline differences between the patients who accepted and those who rejected participation. It is probably unlikely that patients rejecting participation would be highly compliant and have a large effect of CPAP. On the contrary, we would expect that the patients with the greatest subjective effect of the treatment would be most compliant to treatment and most likely to participate at follow-up [24]. These patients could therefore be expected to have the greatest effect of CPAP treatment. Therefore, it is less likely that the results of our study would have shown an effect of CPAP treatment even if all patients had participated in the follow-up.

In our study we found no effect of 9 - 12 months of CPAP treatment on arterial stiffness or BP in overweight patients with long duration of type 2 diabetes and OSA.

Supplementary Material

Suppl 1. Difference in baseline characteristics of patients accepting participation in the follow-up study and those rejecting participation.

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Conflict of Interest

None of the authors have declared any conflict of interest. I.E.M. and Maribo Medico have not had any influence on the design or conducting of the study, nor have they influenced the analysis of data or the manuscript.

Informed Consent

Written consents from all participants were obtained prior to participation.

Author Contributions

CK performed measurements, collected data, performed statistical analysis and wrote the manuscript. AMB performed measurements, collected data and reviewed/edited the manuscript. PLP, MGK, BT and LT contributed to the discussion and reviewed/edited the manuscript. KWH and EL contributed to the discussion, reviewed/edited the manuscript, and are the guarantors of the study.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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