Original Article

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INFOGRAPHIC

Cardiovascular effects after five nights without continuous positive airway pressure for obstructive sleep apnea: a randomized controlled trial

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Objectives: Although continuous positive airway pressure (CPAP) effectively prevents sleep apnea and reduces blood pressure, many patients do not use CPAP every night. This trial investigates cardiovascular effects after sleeping five nights without CPAP.

Methods: We randomized 100 patients (67 men and 33 women with a mean age 64 ± 9 years) using CPAP treatment for moderate-to-severe sleep apnea to either withdraw treatment for five nights ($n = 50$) or to continue with CPAP ($n = 50$). The primary outcomes were arterial stiffness and 24 h blood pressure.

Results: The 24 h SBP increased by a mean of 2.8 mmHg [95% confidence interval (CI) 0.2–5.4 mmHg] ($P = 0.035$) and DBP increased by a mean of 1.7 mmHg (95% CI 0.1–3.3 mmHg) ($P = 0.032$) in the group without CPAP compared to the CPAP group. There was a significant effect on blood pressure in women but not in men. In women, SBP increased by 5.1 mmHg (95% CI 1.0–9.5 mmHg) ($P = 0.017$) and DBP by 2.9 mmHg (95% CI 0.4–5.6 mmHg) ($P = 0.029$). Arterial stiffness remained unaffected. Secondary outcomes that worsened in patients without CPAP included apnea–hypopnea index, oxygen desaturation index, hemoglobin levels, and daytime sleepiness.

Conclusion: Blood pressure is affected after five nights of CPAP interruption, along with a rapid return of sleep apneas, nocturnal hypoxic events, daytime sleepiness and increased hemoglobin levels, but arterial stiffness was not affected. Blood pressure was affected in women only, suggesting a sex-related CPAP effect on blood pressure.

Graphical abstract: http://links.lww.com/HJH/C691

Keywords: 24-h blood pressure, arterial stiffness, continuous positive airway pressure, obstructive sleep apnea

Abbreviation: CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure

INTRODUCTION

About 400 million people worldwide are estimated to suffer from moderate-to-severe obstructive sleep apnea, and they run an increased risk for cardiovascular disease and hypertension [1–10]. Continuous positive airway pressure (CPAP) treatment can effectively treat sleep apnea and reduce arterial stiffness and blood pressure [11–15]. However, adherence to CPAP treatment is essential, as obstructive sleep apneas return after only one night without CPAP treatment [16].

Few trials, however, have investigated the effects of CPAP withdrawal on cardiovascular outcomes, including 24 h blood pressure. A PubMed search for randomized controlled trials on CPAP withdrawal identified only one group of researchers studying cardiovascular outcomes after 14 days on CPAP vs. subtherapeutic CPAP [17–19]. This group reported significant increases in morning office blood pressure with subtherapeutic CPAP [17,18] along with impaired endothelial function assessed by flow-mediated dilation [17]. The PubMed search found no trial that had studied how a few nights without CPAP treatments affect cardiovascular outcomes even though many patients with sleep apnea occasionally skip their CPAP treatment.

Here, we investigated whether five nights without CPAP affects arterial stiffness and 24-h blood pressure. In addition, we investigated whether five nights without CPAP affects NT-pro brain natriuretic peptide, nocturnal urine norepinephrine, glucose metabolism, blood lipids, inflammatory markers, the apnea–hypopnea index, oxygen-desaturation index, daytime sleepiness and lung function, with separate analyses for men and women.

METHODS

Study design

This open-label, randomized, parallel-group controlled clinical trial was conducted at the Department of

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Medicine, Umeå University Hospital, Sweden. The study was approved by the Regional Ethical Review Board at Umeå University and adhered to the standards of the Declaration of Helsinki. Written informed consent was obtained from all the participants. The trial is registered on ClinicalTrials.gov (NCT02329470).

Participants and setting

The study included adults with moderate and severe sleep apnea (apnea–hypopnea index >15) who had been undergoing effective CPAP treatment for 2–24 months with an average CPAP use of more than 4 h per night over the past month. Patients were excluded if they had an acute myocardial infarction within 3 months or had diagnosed atrial fibrillation, dementia or severe physical or mental disorders. In addition, patients were excluded if they were professional drivers or were shift workers.

Randomization and masking

Patients were randomized by a person not involved in the study to continue with CPAP or withdraw for five nights with an allocation ratio of 1 : 1. Study personnel phoned this person who had picked an envelope from a box with equal number of envelopes allocated to 'withdraw CPAP' and 'continue with CPAP'. The person who conducted the randomization noted the allocation, patient code number and informed the study personnel. Patients and investigators were aware of the treatment allocations, but the data were blinded before analysis.

Primary outcomes

The primary outcomes were the difference in change from baseline to follow up in arterial stiffness and in 24 h systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Arterial stiffness, a proxy for global arterial endothelial function, is measured noninvasively by calculating pulse wave velocity and augmentation index [20,21]. Pulse wave velocity (Vicorder, Skidmore Medical, Bristol, UK) was measured after 15 min of rest in the supine position. The pulse wave velocity (m/s) was recorded from the carotid artery to the proximal right femoral artery using cuffs around the neck and thigh and corrected for heart rate. The augmentation index was derived from pulse wave analysis obtained from radial artery applanation tonometry on the right arm (SphygmoCor, AtCor Medical, Sydney, Australia) and corrected for a fixed heart rate of 75 bpm. All values were obtained from a mean of three measurements with a difference of less than 5%.

Blood pressure monitoring (ABPM Medical 90217 ambulatory blood pressure monitor, Spacelab, Redmond, USA) was started at 8 a.m. and continued for 24 h. Daytime was defined as 6 a.m. to 10 p.m. and night-time as 10 p.m. to 6 a.m.

Secondary outcomes

The secondary outcomes were NT-pro brain natriuretic peptide (Human NT-proBNP DuoSet ELISA, R&D systems, UK), high-sensitivity C-reactive protein, glucose, insulin, HbA1C, triglycerides, cholesterol, hemoglobin and creatinine levels in peripheral blood as well as nocturnal urinary norepinephrine, lung function (JAEGER MastersScope, Germany), exhaled nitric oxide (NIOX, Circassia, Sweden), the apnea–hypopnea index, oxygen desaturation index and daytime sleepiness (Epworth Sleepiness Scale [22] and the Karolinska Sleepiness Scale [23]). Another secondary outcome was sex differences.

Overnight ambulatory sleep apnea recordings included airflow, thoracic and abdominal respiratory effort, finger pulse oximetry and body position (Embletta, X 10 system, Embla Systems, Canada). Apneas and hypopneas were scored manually by a certified sleep technician (C.S.) according to the American Academy of Sleep Medicine guidelines [24]. Lights out and final wake up in the morning were recorded by the patients, and sleep time was estimated from the recordings.

Procedures

On day 1, patients arrived at the hospital in the morning for baseline investigations. They answered a questionnaire, and height and weight were measured manually. Office blood pressure was taken in the left arm in the supine position after a 15 min rest. The 24 h blood pressure monitoring started between 8 and 9 a.m., recording blood pressure every 30 min for 24 h. The participants were also given the ambulatory nocturnal sleep apnea recording device. In addition, the participants were given a container to collect urinary samples during the night. These samples were used to determine urine norepinephrine levels.

On day 2, the participants returned the 24 h blood pressure recording, the sleep apnea recording and the urine sample. Blood samples were obtained while fasting. Arterial stiffness measurements started at 8 : 30 a.m. in a room with a temperature of 24 °C (75 °F). After these measurements were obtained, lung function tests, exhaled nitric oxide tests and electrocardiograms were conducted. Breakfast was given at about 10 a.m. CPAP use was obtained from the devices, and the patients were randomized to continue with CPAP or to withdraw for the next five nights at home.

On day 6, we conducted a follow-up for the fifth night according to randomization. The 24-h blood pressure monitoring was started between 8 and 9 a.m., recording blood pressure every 30 min for 24 h. Participants were also given the ambulatory nocturnal sleep apnea recorder and a container to collect a urine sample during the night. This sample was used to determine urine norepinephrine level.

On day 7, the participants returned the 24 h blood pressure recording, the sleep apnea recording and the urine sample. Blood samples were obtained while fasting. Arterial stiffness measurements started at 8 : 30 a.m. in a room with a temperature of 24 °C (75 °F). This was followed by lung function tests, exhaled nitric oxide tests and electrocardiograms. The CPAP use was obtained from the device.

Adverse events

All patients were questioned about adverse effects at follow-up.

Statistical methods

It was estimated that 90 patients, 45 in each group, would be needed to detect a mean (SD) blood pressure difference of 3 (5) mmHg, and 17 patients in each group would be

needed to detect a mean difference of 1 (1) m/s in pulse wave velocity, with a power of 80% and a significance level of 5%.

Outcomes were analyzed using a repeated measurement design, with measurements taken at baseline and follow-up, with the factors sex (women/men) and randomization. Confidence intervals for the difference in response to CPAP treatment were based on estimated marginal means. Model assumptions were evaluated using residual analysis. Variables for high-sensitivity C-reactive protein and insulin, which exhibited heavy-tailed distributions, were log-transformed to meet model assumptions. In the supplementary materials, http://links.lww.com/HJH/C663, the effect of CPAP treatment was adjusted for blood pressure medication and hypertension. Due to the minimal number of missing values, a complete case analysis was conducted. All analyses were performed using SPSS version 25.

RESULTS

A total of 179 patients were assessed for eligibility; of these, 27 did not meet the inclusion criteria. Of the 152 invited patients, 52 declined to participate mainly because of work or living too far from the hospital. Therefore, 100 patients were randomized to either withdrawing CPAP for 5 days (31 men and 19 women) or continuing CPAP treatment for 5 days (36 men and 14 women). All the patients used auto-CPAP (AutoSet ResMed, Sydney, Australia), and they had been treated with CPAP for a mean (SD) of 10.6 (6.3) months before the starting of the study. All the women were postmenopausal. One man in the control group declined further participation after baseline measurement, so 99 patients were analyzed at follow-up, 5 days after baseline investigations. All the patients were analyzed according to intention-to-treat analysis. Recruitment was performed between 31 December 2014 and 31 August 2016. A flow diagram is shown in Fig. 1 and baseline characteristics are given in Table 1. During the investigations, 61 participants had hypertension, and 66 participants were treated with antihypertensive medications, that is, angiotensin-converting enzyme inhibitors, A2-blockers, beta-blockers, calcium antagonists or diuretics.

Arterial stiffness

Arterial stiffness did not differ in terms of change among patients who discontinued CPAP vs. the controls (patients who continued CPAP). The mean difference in the change in pulse wave velocity was 0.3 m/s (95% CI −0.01 to 0.5 m/s) ($P = 0.09$) (Fig. 2 and Table 2). In the augmentation index 75, the mean was −0.2% (95% CI −1.7 to 1.3%) ($P = 0.81$) (Table 2).

24-hour blood pressure

One patient in the CPAP group failed to measure blood pressure. The other patients on average had 40 (6) successful blood pressure readings during 24 h at baseline, and each patient had 41 (6) readings at follow-up.

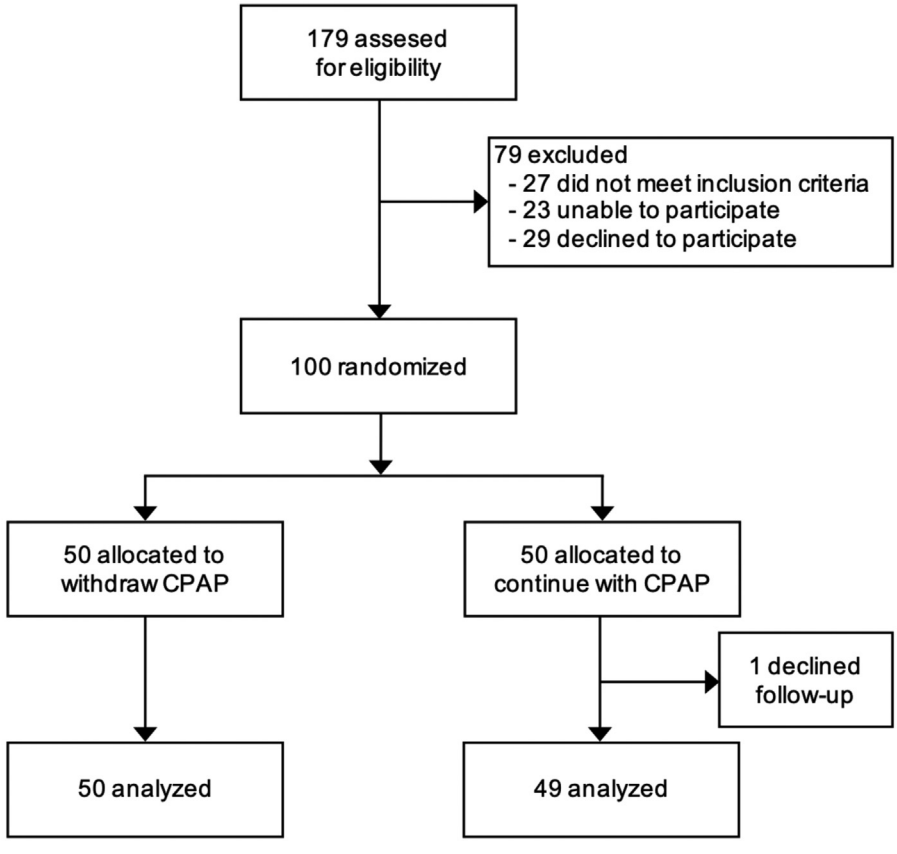

FIGURE 1 Trial profile. CPAP, continuous positive airway pressure.

TABLE 1. Baseline characteristics

	Control group (CPAP use) ($n=50$)			CPAP withdrawal group ($n=50$)		
	Women and men combined	Women ($n=14$)	Men ($n=36$)	Women and men combined	Women ($n=19$)	Men ($n=31$)
Age (years) [mean (SD)]	65 (9)	68 (6)	63 (10)	63 (9)	66 (6)	61 (10)
BMI (kg/m^2) [mean (SD)]	32 (5)	35 (6)	31 (4)	32 (5)	32 (6)	32 (4)
CPAP use last month (h/night) [mean (SD)]	6.5 (1.3)	6.8 (1.6)	6.4 (1.2)	6.2 (1.3)	6.6 (1.2)	6.0 (1.2)
CPAP use night before study start (h/night) [mean (SD)]	6.6 (1.5)	6.7 (1.0)	6.6 (1.6)	6.6 (1.5)	6.8 (1.7)	6.5 (1.3)
Hypertension (*n*/total)	33/50	10/14	23/36	28/50	11/19	17/31
Diabetes mellitus (*n*/total)	6/50	2/14	4/36	8/50	4/19	4/31
Ischemic heart disease (*n*/total)	6/50	2/14	4/36	9/50	1/19	8/31
Current smokers (*n*/total)	1/50	0/14	1/36	4/50	1/19	3/31
Ex-smokers (*n*/total)	27/50	8/14	19/36	22/50	9/19	13/31

CPAP, continuous positive airway pressure.

Compared to the CPAP group, the non-CPAC group's 24-h SBP increased by a mean of 2.8 mmHg (95% CI 0.2–5.4 mmHg) ($P=0.035$) and the DBP increased by a mean of 1.7 mmHg (95% CI 0.1–3.3 mmHg) ($P=0.032$) (Fig. 3 and Table 2). There was no association between blood pressure and months on CPAP treatment before study start.

There were significant interactions between CPAP treatment and sex for SBP ($P<0.001$) and DBP ($P<0.001$). Compared to women continuing CPAP, the women who discontinued CPAP had a significant increase in SBP and DBP (Fig. 3 and Table 2), a difference that was not seen in men. The mean difference in SBP and in DBP for the women continuing CPAP and the women who skipped CPAP was 5.1 mmHg (95% CI 1.0–9.5 mmHg) ($P=0.017$) and 2.9 mmHg (95% CI 0.3–5.4 mmHg) ($P=0.029$), respectively. Hypertension and use of antihypertensive medications during the trial did not alter the blood pressure response to CPAP or the sex-related differences in blood pressure response to CPAP (Table S1, http://links.lww.com/HJH/C663).

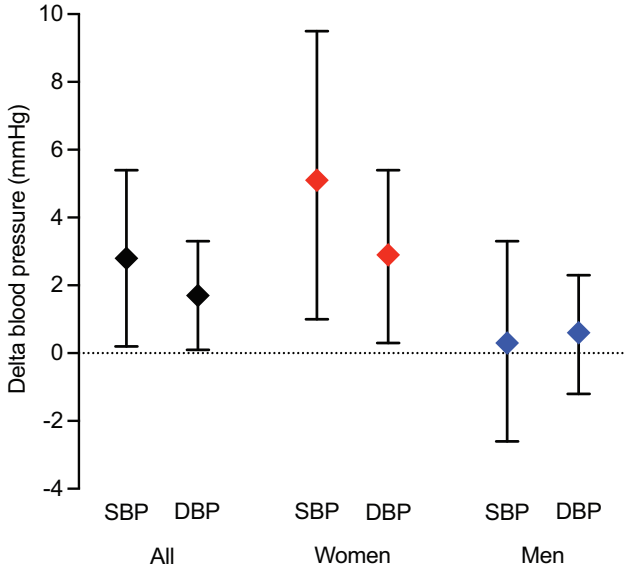

FIGURE 2 Difference in change in SBP and DBP between patients randomized to discontiue CPAP and to continue CPAP (mean and 95% confidence interval).

Secondary outcomes

The mean apnea–hypopnea index increased in participants who discontinued CPAP vs. controls by 30 events/h (95% CI 24–35 events/h) ($P<0.001$), and the oxygen desaturation index increased by 30 events/h (95% CI 24–35 events/h) ($P<0.001$). Serum hemoglobin levels increased by 2.3 g/l (95% CI 0.7–3.9 g/l) ($P=0.006$). The Epworth Sleepiness Scale score increased by 3.4 units (95% CI 2.0–4.9 units) ($P<0.001$), and the Karolinska Sleepiness Scale increased significantly at 8 a.m. by 1.9 units ($P<0.001$), at 3 p.m. by 0.8 units ($P=0.007$), and at 8 p.m. by 0.8 units ($P=0.044$) (Tables S2 and S3, http://links.lww.com/HJH/C663).

Discontinued CPAP did not affect office blood pressure, peripheral blood levels of NT-pro brain natriuretic peptide, high-sensitivity C-reactive protein, serum glucose, insulin, HbA1c, triglycerides, cholesterol and creatinine (Tables S2 and S4, http://links.lww.com/HJH/C663). In addition, discontinued CPAP did not affect exhaled nitric oxide and lung function (i.e. vital capacity and forced expiratory volume in 1 s) (Tables S4 and S5, http://links.lww.com/HJH/C663). Nocturnal urine norepinephrine levels were also unaffected by discontinued CPAP, although 34 urine norepinephrine samples were lost due to a malfunctioning freezer.

No serious adverse events were recorded in any patient during the trial. Without CPAP, 17 patients reported daytime sleepiness, four reported headaches, two experienced irritabilities one had to leave a shared bedroom because of heavy snoring, one had heart palpitations and one experienced periodic leg movements during sleep. Of the patients who continued with CPAP, one reported periodic leg movements during sleep, one reported daytime sleepiness and one reported neck and shoulder pain.

DISCUSSION

To the best of our knowledge, this is the first randomized controlled trial investigating the effect of CPAP interruption on cardiovascular outcomes using arterial stiffness and 24-h blood pressure. The interruption had no effect on arterial stiffness, and the effect on 24-h blood pressure was modest after five nights without CPAP. The effect on blood pressure after few nights without CPAP was explained by changes in blood pressure in women, where SBP increased by a mean of 5 mmHg and DBP by 3 mmHg. Several secondary outcomes increased in patients without CPAP: apnea–hypopnea

TABLE 2. Arterial stiffness and 24-h blood pressure

	Control group (CPAP use)		CPAP withdrawal group		Between-group differences in change from baseline to follow-up (95% CI)
	Baseline	Follow-up	Baseline	Follow-up	
Women and men combined					
Pulse wave velocity (m/s)	7.7 ± 1.3	7.5 ± 1.2	7.8 ± 1.4	7.9 ± 1.3	0.3 (−0.01 to 0.5) $P = 0.090$
Augmentation index 75 (%)	21.5 ± 7.6	21.7 ± 7.9	22.5 ± 8.8	22.7 ± 8.0	−0.2 (−1.7 to 1.3) $P = 0.81$
24-h SBP (mmHg)	132.0 ± 13.7	128.5 ± 13.0	134.5 ± 11.3	133.8 ± 10.8	2.8 (0.2–5.4) $P = 0.035$
24-h DBP (mmHg)	79.0 ± 7.6	77.2 ± 7.3	79.7 ± 7.6	79.6 ± 7.3	1.7 (0.1–3.3) $P = 0.032$
Women					
Pulse wave velocity (m/s)	7.8 ± 1.3	7.4 ± 0.9	7.9 ± 1.4	7.7 ± 1.1	0.2 (−0.3 to 0.7) $P = 0.40$
Augmentation index 75 (%)	26.2 ± 5.8	27.0 ± 6.4	27.4 ± 7.2	27.1 ± 8.1	−1.1 (−3.6 to 1.4) $P = 0.38$
24-h SBP (mmHg)	133.2 ± 17.2	126.4 ± 16.4	134.6 ± 12.5	132.9 ± 11.9	5.1 (1.0–9.5) $P = 0.017$
24-h DBP (mmHg)	78.8 ± 7.2	75.4 ± 6.8	78.2 ± 6.1	77.7 ± 5.7	2.9 (0.3–5.4) $P = 0.029$
Men					
Pulse wave velocity (m/s)	7.6 ± 1.4	7.6 ± 1.3	7.8 ± 1.3	8.0 ± 1.4	0.3 (−0.0 to 0.6) $P = 0.08$
Augmentation index 75 (%)	16.8 ± 7.6	16.4 ± 7.9	17.6 ± 8.8	18.2 ± 8.0	1.1 (−0.6 to 2.9) $P = 0.20$
24-h SBP (mmHg)	130.8 ± 12.3	130.6 ± 11.5	134.5 ± 10.8	134.7 ± 10.3	0.3 (−2.6 to 3.3) $P = 0.82$
24-h DBP (mmHg)	79.2 ± 7.4	79.0 ± 7.4	81.2 ± 8.2	81.5 ± 7.8	0.6 (−1.2 to 2.3) $P = 0.54$

The data are presented as the mean (SD) unless otherwise stated. CPAP, continuous positive airway pressure.

index, oxygen desaturation index, hemoglobin levels and daytime sleepiness. This study has clinical and research implications. First, the findings support using CPAP every night to avoid increases in blood pressure. Second, the findings suggest a need to include more women in future studies on blood pressure related to sleep apnea and to present the results separately for women and men.

The degree of arterial stiffness, a measure of the arterial endothelia's functioning, can be measured noninvasively by calculating the augmentation index and pulse wave velocity [20,21]. Sleep apnea is associated with increases in the augmentation index and pulse wave velocity, suggesting an increase in arterial stiffness [25,26]. In 2013, Phillips *et al.* [27] critically reviewed the experimental evidence for obstructive sleep apnea as causally related to arterial stiffness. In 2019, Theorell-Haglow *et al.* [28], pooling individual patient data from six studies on sleep apnea and arterial stiffness, reported that several measures of obstructive sleep apnea severity were associated with increased augmentation index, although the associations were weak. In 2021, a meta-analysis identified nine trials–three using both pulse wave velocity and augmentation index, three using only pulse wave velocity and tree using only augmentation index –which investigated arterial stiffness after onset of CPAP treatment during for between 3 weeks and 6 months compared with delayed CPAP onset [11]. The meta-analysis reported no effect on augmentation index and a small, yet significant, effect of on pulse wave velocity with a mean difference of 0.44 m/s. However, we found that CPAP interruption had no effect on either pulse wave velocity or augmentation index. The present study supports that CPAP interruption for a limited number of nights does not influence functional and structural changes in the arterial walls [27].

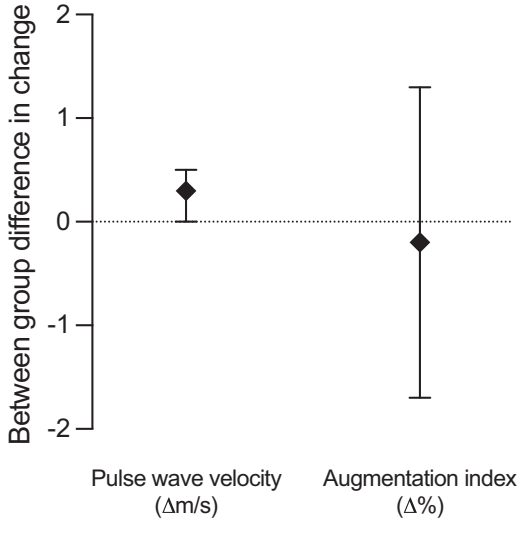

FIGURE 3 Difference in change in arterial stiffness between patients randomized to discontinue CPAP an to CPAP (mean and 95% confidence interval).

Previously Kohler *et al.* [17] and Schwarz *et al.* [18] investigated office blood pressure after 2 weeks on subtherapeutic compared with therapeutic CPAP. They reported mean increases in office SBP and DBP to be 8.5 and 6.9 mmHg, respectively, in 41 patients [17], and 10.8 and 7.8 mmHg, respectively, in 45 different patients [18]. Our results support an effect on blood pressure after CPAP interruption and that the effect is detected on 24-h blood pressure within 5 days of CPAP interruption.

In women, untreated obstructive sleep apnea is associated with stroke, and CPAP treatment reduces this risk [29]. The adjusted risk of stroke for each severity level of hypertension is reported to be 25% higher in women than men [30]. Women with sleep apnea are also reported to run a higher risk of heart failure and death than men with sleep apnea [29,31]. Cardiovascular disease in women is generally understudied and under-recognized [32]. Our findings highlight the need to include more women in future studies on blood pressure related to sleep apnea and to present the results separately for women and men.

Limitations of the study include that respiratory sleep apnea recordings and 24-h blood pressure monitoring could affect sleep quality, but this effect was the same in both study arms. Sleep apneas, nocturnal hypoxic events

and daytime sleepiness returned within five nights of CPAP interruption. We are, however, not aware of the minimal time of CPAP interruption required for these parameters to return, as we did not perform investigations for every night and day during the trial. Another limitation is the inability to explain why the observed sex differences in blood pressure occurred. The strengths include the randomized, controlled trial design, the outcomes in the form of 24-h blood pressure measurements and pulse wave velocity, and the reporting of all secondary outcomes.

In conclusion, blood pressure is affected after five nights of CPAP interruption, along with a rapid return of sleep apneas, nocturnal hypoxic events, daytime sleepiness and increased hemoglobin levels. However, the five nights without CPAP did not affect arterial stiffness. Blood pressure was affected in women only, suggesting a sex-related CPAP effect on blood pressure.

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Conflicts of interest

There are no conflicts of interest.

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