

SCIENTIFIC INVESTIGATIONS

Effect of continuous positive airway pressure treatment on ambulatory blood pressures in high-risk sleep apnea patients: a randomized controlled trial

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Study Objectives: The long-term effect of continuous positive airway pressure (CPAP) on 24-hour blood pressure (BP) in patients at high risk with obstructive sleep apnea (OSA) is uncertain. We aimed to determine the effect of CPAP treatment on ambulatory BP in individuals with moderate or severe OSA and cardiovascular disease or multiple cardiovascular disease risk factors without severe sleepiness.

Methods: In this randomized, controlled, parallel group study, 169 participants were randomly assigned to CPAP treatment or the control group. The primary outcome was the change in mean 24-hour systolic BP between groups from baseline to the average of 6- and 12-month measurements using mixed-effect linear regression models.

Results: The 24-hour systolic BP did not significantly differ by group, although there was a trend of decrease in the CPAP group (treatment effect -2.7 mm Hg [95% confidence interval -5.9 to 0.6]; $P = .105$) compared with control. CPAP had the greatest effect on nighttime systolic BP (treatment effect -5.9 mm Hg [95% confidence interval -9.9 to -1.9]; $P = .004$). Similar improvements in other nocturnal BP indices were observed.

Conclusions: In patients at high risk with moderate-severe OSA without severe sleepiness, CPAP resulted in modest BP improvements over 6 to 12 months of follow-up, with possibly larger effects for nocturnal BP. Use of office blood pressure may underestimate the effect of CPAP on BP profile in patients with OSA.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Title: Sleep Apnea Intervention for Cardiovascular Disease Reduction; Identifier: NCT01261390; URL: <https://clinicaltrials.gov/ct2/show/NCT01261390>.

Keywords: sleep apnea, CPAP, ambulatory blood pressure, clinical trial

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The long-term effect of continuous positive airway pressure (CPAP) on 24-hour blood pressure in patients at high risk with obstructive sleep apnea is uncertain. The purpose of this study was to compare ambulatory blood pressures among participants at high risk of cardiovascular disease randomized to CPAP vs control.

Study Impact: CPAP therapy led to a modest improvement in blood pressure over 6 to 12 months, consistent with findings from prior trials of shorter duration. The greatest effect observed was on nocturnal blood pressure. The study contributes to the cumulative data suggesting long-term benefit of CPAP therapy on blood pressure in patients at high risk with sleep apnea.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death in the United States and is a significant cause of morbidity and health care expenditures.¹ Obstructive sleep apnea (OSA) affects approximately 26% of the general population, and its prevalence among individuals with CVD is even higher.^{2–4} Increasing evidence suggests that OSA is an important modifiable risk factor for CVD, including stroke, coronary artery disease, heart failure, and atrial fibrillation.^{5–8} OSA is also an independent predictor for the development of hypertension,⁹ a well-recognized risk factor for cardiovascular events. Additionally, a blunted or absent nocturnal

fall in blood pressure (BP), as may occur with OSA,^{10,11} has been associated with an increase in all-cause mortality.¹² Treatment of OSA with continuous positive airway pressure (CPAP) has been shown to lower BP in several short-term clinical trials.^{13–17} Although observational studies have shown that CPAP improves clinical outcomes in patients with OSA and CVD,^{18–24} evidence from randomized controlled trials in this population is limited. In a study of high-risk patients and moderate or severe OSA, CPAP therapy reduced the 24-hour mean arterial pressure (MAP) at 12 weeks by 2.4 mm Hg compared to the control group.²⁵ The long-term effect of CPAP treatment on BP is less clear, since most prior CPAP trials have a follow-up period of 3 months or

less.^{13–15,17,25–32} Furthermore, only 3 of the 7 CPAP intervention trials with study duration of 6 months or greater used ambulatory BP monitoring (ABPM).^{16,19,33–37} All 3 studies assessed the effect of CPAP on BP in patients with OSA and resistant hypertension.^{16,33,37} Thus, in patients with CVD without resistant hypertension, the long-term impact of CPAP treatment on ambulatory BP needs further study.

The Best Apnea Interventions for Cardiovascular Disease Reduction (BestAIR) trial was designed as a planning study to assess key feasibility and optimal study design features in the context of a cardiovascular intervention trial in OSA.^{38,39} The primary physiological outcome was the effect of CPAP therapy on the mean 24-hour systolic BP (SBP). Prespecified secondary outcomes were changes in other ambulatory BP indices and the day-night BP ratios. We hypothesized that CPAP treatment would significantly decrease 24-hour BP and improve nocturnal BP profiles.

METHODS

Detailed methods are reported in the **supplemental material**.

Study design

BestAir was a randomized, parallel-group clinical trial with blinded assessment of outcomes designed to evaluate the effect of CPAP on ambulatory BP among patients with moderate or severe OSA without severe sleepiness at high risk for CVD events. The rationale and protocol for the trial was previously reported.³⁸ Participants were recruited from outpatient clinics from 3 medical centers in Boston, MA. Participants were asked to use a nasal CPAP mask open to atmosphere without a CPAP device and complete a diary during a 2 week run-in period. Those who reported wearing the mask for at least 11 of the 14 nights were eligible for randomization.

Participants were randomized to 1 of 2 active CPAP arms or 1 of 2 control arms in a 1:1:1:1 fashion with a block-size of 4, based on 3 stratification factors: diagnostic type (full-night or split-night with titration), site, and CVD status (established or risk factors) (see supplemental material). The 4 arms were designed to test features for optimizing the delivery of the active and control interventions. The 2 active CPAP arms were CPAP alone and CPAP with motivational enhancement, and the 2 control arms were sham CPAP and no CPAP therapy.⁴¹ All participants received CMT consisting of education on sleep hygiene, sleep positional therapy, healthy lifestyle, and use of nasal dilator strips during sleep. Motivational enhancement consisted of a behavioral intervention to improve CPAP adherence.⁴⁰ The original primary outcome was the change in mean 24-hour SBP from baseline to 12 months between the CPAP and control arms. Due to a longer-than-expected time to complete enrollment, patients randomized after January 2013 were followed for only 6 months.^{38,39} Revised power calculation using methods accounting for repeated measurements were made to reflect this design change and was approved by the Data Safety Monitoring Board (see supplemental material). The revised primary outcome was the change in mean 24-hour SBP

from baseline to the average of month 6 and 12 measurements between control and CPAP arms. The study was approved by the Institutional Review Board at each participating center. All participants provided written informed consent.

Eligibility criteria were used to identify those at high risk for CVD events, as may be recruited in future large scale trials. Eligible participants had an apnea-hypopnea index $3\% \geq 15$ events/h (or ≥ 10 events/h if only the apnea-hypopnea index 4% was available; $n = 2$) and were either aged 45 to 75 years with established CVD or cardiometabolic disease (coronary artery disease, ischemic stroke, or diabetes) or aged 55 to 75 years with 3 or more CVD risk factors (male, body mass index ≥ 30 kg/m², hypertension, dyslipidemia, or ≥ 10 pack-years of smoking). Major exclusion criteria were cardiovascular event < 4 months prior to enrollment, prior CPAP use, and excessive sleepiness (Epworth Sleepiness Scale score > 14 or report falling asleep while driving within the past 2 years). Sleep studies to determine eligibility were completed either as part of routine care (in-laboratory polysomnography) or administered by the study investigators (Embletta Gold or X100, Embla, ON, Canada). Participants who had not undergone an in-lab CPAP titration used an auto-adjusting device for a minimum of 5 days to identify the pressure for ongoing fixed CPAP pressure.

All study investigators other than the lead biostatistician were blinded to the study arm to which the participant was randomized. Other blinded personnel were data processors, research nurses, and technicians who obtained questionnaires and physiologic measurements. The study coordinator (and her designated research assistant) who needed to ensure appropriate visits were scheduled and perform follow-up calls to ascertain events, the respiratory therapist, the psychologist, and data entry personnel, were not blinded. Unblinded personnel did not administer tests that could be influenced by interview or administration technique.

Outcomes

Outcomes were measured at baseline, 6 and 12 months. Ambulatory BP was measured with the 90207 Ambulatory BP Monitor (Spacelabs Healthcare, Snoqualmie, WA). Devices were mounted on the nondominant arm and programmed to measure BP at 20-minute intervals between 7 AM and 11 PM and at 30-minute intervals between 11 PM and 7 AM. At least 10 valid daytime and 4 valid nighttime readings were required. Mean 24-hour BP was calculated as a weighted average of the mean BP during wakefulness and sleep, with weights determined by the percentage of reported time spent in each state, as recorded in the sleep diary. The day-night BP ratios were defined as the difference between the daytime and nighttime BP divided by the daytime BP*100% and were calculated from the weighted average BP values. The MAP was calculated as one-third of SBP plus two-thirds of diastolic blood pressure (DBP). Resistant hypertension was defined as a mean resting office SBP > 140 mm Hg and/or a mean resting office DBP > 90 mm Hg despite the use of ≥ 3 antihypertensive medications.

Statistical analysis

Analyses compare data from the combined control arms with the combined CPAP arms as specified a priori. As this was a

planning study with a relatively small sample size, this approach provides greater power to detect any CPAP effect than pairwise comparisons among individual arms. The primary study outcome was the change in mean 24-hour SBP from baseline to the average of 6-month and 12-month measurements between CPAP and control arms. Based on an estimated mean improvement in SBP of 5.3 mm Hg (standard error 1.33) as previously reported,¹⁴ we estimated that 76 individuals were required in each combined comparison arm for a statistical power of 0.80 and a 2-sided α of 0.05.

Between-group comparisons of baseline values were made using Fisher's exact tests for categorical data and 2-sample *t* tests or Wilcoxon rank sum tests for continuous data. The primary analysis was based on an intent-to-treat approach. For endpoints with repeated measurements at baseline, 6-months, and 12-months, such as 24-hour BP, mixed-effects linear regression models were used to compare the longitudinal profiles between the CPAP and control groups, with time (0, 6, and 12 months) as a categorical variable and with the assumption of equal means at baseline to reflect the randomized design. This approach allowed use of all available data, including those randomized after January 2013. Participants with at least 1 measurement at any of the 3 visits (baseline, 6-months, and 12-months) were included. Stratification factors were included as covariates. Secondary analyses were conducted for the BP outcomes, adjusting for baseline BP as covariates without assuming equal baseline means. A per-protocol analysis for the BP outcomes was also performed after excluding participants in the control group who crossed over to the CPAP arm and those in the CPAP arm who did not initiate CPAP. A sensitivity analysis was performed after excluding participants with poor CPAP adherence (average use < 4 h/night over 6 months). Additional secondary analyses were conducted to evaluate potential treatment effect modification by the randomization stratification factors for the primary outcome.

Two-sided *P* values < .05 were considered statistically significant. Mixed-effects linear regression analyses were performed using R version 3 or higher. All other analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). The trial was registered at clinicaltrials.org, NCT01261390.

RESULTS

Study population

Screening began in February 2011, and randomization took place from April 2011 to August 2013, with the final follow-up visit completed in March 2014.³⁸ A total of 475 patients completed screening sleep studies (in-laboratory polysomnography *n* = 36, home sleep apnea test *n* = 439), with 227 patients identified with moderate or severe OSA and completing the run-in phase (Figure 1). Of these, 169 participants were randomized. Of the randomized participants, 108 were recruited before January 2013 and were followed for 12 months, and the remainder were followed for 6 months.

Baseline characteristics of the study participants are presented in Table 1. Mean (standard deviation) age was 63.8 (7.3) years and 65.1% were men. The mean body mass index and apnea-hypopnea index were 31.7 (5.9) kg/m² and 29.2 (16.6)

events/h, respectively. The majority of participants had a diagnosis of hypertension (85.2%) and reported using antihypertensive agents (median number of medications: 2). Overall, the sample had relatively well-controlled baseline office BP. Only 5.5% of the study participants had resistant hypertension. Baseline demographic factors and resting BP levels were comparable for the CPAP and control groups, although the control group had a slightly higher AHI and was more likely to report use of β -adrenergic blockers. A small number of participants in both groups reported changes in the number of antihypertensive medications (see Table S3 in the supplemental material).

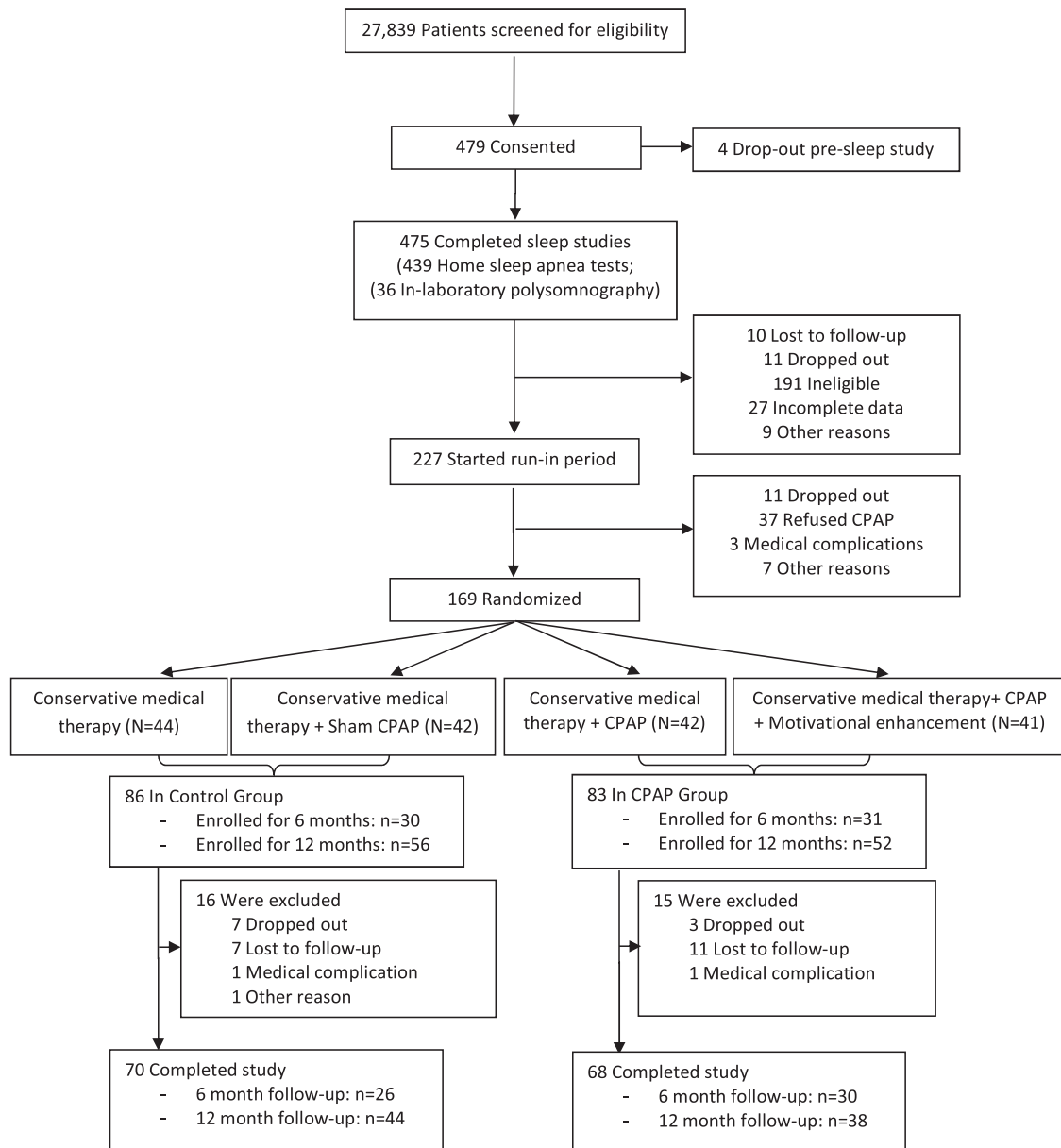
Outcomes

The mean (standard deviation) baseline 24-hour SBP/DBP was 126.8 (14.4)/72.9 (8.3) mm Hg and 121.4 (11.1)/71.9 (7.2) mm Hg in the control and CPAP groups, respectively. By chance, the mean baseline daytime, nighttime, and 24-hour SBP were significantly higher in the control group than in the CPAP group (Table 2). The changes in mean 24-hour BP between the CPAP and control groups from baseline to the average of the 6-month and 12-month measurements (mean treatment effects), unadjusted for baseline BP, are presented in Table 2 and shown graphically in Figure 2. At study completion, CPAP was associated with a nonsignificant decrease in mean 24-hour SBP of -2.7 mm Hg [95% confidence interval (CI) -5.9 to 0.56 ; *P* = .105]. In contrast, CPAP therapy resulted in significantly lower nighttime SBP (mean treatment effect [95% CI] -5.9 [-9.9 , -1.9] mm Hg; *P* = .004), DBP (-2.2 [-4.4 to -0.0] mm Hg; *P* = .050), and MAP (-3.4 mm Hg [95% CI -6.0 , -0.7]; *P* = .012). CPAP also resulted in an improved day-night SBP ratio (mean treatment effect 2.7 [95% CI 0.2 to 5.3]; *P* = .037). In secondary analyses, after adjusting for baseline BP values, the effect of CPAP on nighttime BP was attenuated and no longer statistically significant (mean treatment effect [95% CI]: SBP -2.9 mm Hg [-7.4 to 1.7]; *P* = .212; DBP -1.7 mm Hg [-4.1 to 0.7]; *P* = .170; MAP -2.1 mm Hg [-5.0 to 0.9]; *P* = .165) (see Table S1). No significant effect modifications by the stratification factors were found for the primary outcome.

Similar results were seen in the per-protocol analysis (excluding 4 participants who crossed over from the control arm to the CPAP arm and 10 participants from the CPAP arm who did not start CPAP treatment) (see Table S2). Specifically, CPAP did not result in a statistically significant improved mean 24-hour SBP (mean treatment effect -2.9 mm Hg [95% CI -6.2 to 0.4]; *P* = .087) but did significantly lower the nighttime SBP and MAP (-5.6 mm Hg [-9.7 to -1.5]; *P* = .007 and -3.0 mm Hg [-5.7 to -0.3]; *P* = .030, respectively).

At 6 months and 12 months, the mean (standard deviation) CPAP use was 3.82 (2.86) and 3.44 (2.99) h/night, respectively. Changes in 24-h SBP from baseline to the last visit were not associated with hours of CPAP use within the CPAP users (Spearman correlation 0.05, *P* = .7). When restricting the CPAP sample to individuals with an average of 4 or more hours per night of CPAP use over 6 months (*n* = 42), similar results were observed as in the primary analysis (SBP mean treatment effect -1.7 mm Hg [95% CI -5.6 to 2.1]; *P* = .385; nighttime SBP effect -5.9 [-10.6 , -1.1]; *P* = .017).

Figure 1—Study flowchart.



CPAP = continuous positive airway pressure.

DISCUSSION

In this randomized controlled trial of patients with moderate to severe OSA with CVD or multiple CVD risk factors and without severe sleepiness, CPAP use was associated with a modest, nonsignificant improvement in 24-h mean SBP over 6 months and 12 months. CPAP had the greatest effect on nocturnal systolic and diastolic BP and the day-night SBP ratio. Notably, these changes occurred in a group of patients who used an average of 2 BP lowering medications and were largely followed by cardiologists or other specialists where BP and other cardiovascular risk factors were managed.

The observed average 24-hour SBP reduction of 2.7 mm Hg in data from this 12-month trial, although not statistically significant, is consistent with the 1–3 mm Hg mean SBP reduction reported in the literature.^{25,26,31,42} Similar BP reduction by CPAP was observed in a meta-analysis of randomized controlled trials that included studies of generally short duration (≤ 12 weeks).⁴² As our study had been designed to detect a larger effect reported in an early study using ABPM, it was under-powered to detect the more modest changes in SBP reported more recently. In interpreting these findings, it is important to recognize that modest reductions in BP likely have important public health implications. A meta-analysis of

Table 1—Baseline characteristics of the study population.

	All Patients (n = 169)	Control Group (n = 86)	CPAP Group (n = 83)
Age, years	63.8 (7.3)	63.7 (6.9)	63.8 (7.8)
Male sex, n (%)	110 (65.1)	55 (64.0)	55 (66.3)
Race/ethnicity, n (%) ^a			
White	151 (89.3)	77 (89.5)	74 (89.2)
Black	11 (6.5)	6 (7.0)	5 (6.0)
Hispanic	6 (3.6)	2 (2.3)	4 (4.8)
Other	7 (4.1)	3 (3.5)	4 (4.8)
Education, n (%) ^a			
< High school	2 (1.2)	1 (1.2)	1 (1.2)
High school graduate	57 (33.7)	24 (27.9)	33 (39.8)
Bachelors or higher	110 (65.1)	61 (70.9)	49 (59.0)
Body mass index (kg/m ²) ^b	31.7 (5.9)	32.3 (6.5)	31.1 (5.2)
Neck circumference (cm)	41.5 (3.9)	41.9 (3.9)	41.1 (4.0)
Smoking history, n (%)			
Current	13 (7.7)	5 (5.8)	8 (9.6)
Former	85 (50.3)	40 (46.5)	45 (54.2)
Never	71 (42.0)	41 (47.7)	30 (36.2)
Hypertension	144 (85.2)	73 (84.9)	71 (85.5)
Epworth Sleepiness Scale score	8.3 (4.5)	8.5 (4.5)	8.0 (4.5)
History of CVD or diabetes, n (%)			
Coronary artery disease	58 (34.3)	28 (32.6)	30 (36.1)
Diabetes	63 (37.3)	35 (40.7)	28 (33.7)
Stroke	4 (2.4)	2 (2.3)	2 (2.4)
Medication use, n (%)			
ACE inhibitor or ARB	68 (40.2)	33 (38.4)	35 (42.2)
β-Adrenergic blockers ^c	104 (61.5)	60 (69.8)	44 (53.0)
Diuretic	57 (33.7)	27 (31.4)	30 (36.1)
Calcium channel blockers	45 (26.6)	25 (29.1)	20 (24.1)
α ₁ -Adrenergic blockers	1 (0.6)	0 (0.0)	1 (1.2)
Others	1 (0.6)	1 (1.1)	0 (0.0)
Lipid lowering medication	140 (82.8)	71 (82.6)	69 (83.1)
Diabetic medication	52 (30.8)	29 (33.7)	23 (27.7)
Number of antihypertensive drugs, median (IQR)	2 (1,3)	2 (1,3)	2 (1,3)
Mean resting office SBP (mm Hg) ^d	125.2 (17.2)	124.4 (16.7)	126.1 (17.9)
Mean resting office DBP (mm Hg) ^d	70.3 (9.2)	69.4 (8.6)	71.3 (9.7)
Resistant hypertension, n (%)	9 (5.5)	5 (6.2)	4 (4.9)
Diurnal BP profile (%) ^e			
SBP ratio	10.5 (9.6)	9.7 (10.5)	11.2 (8.6)
DBP ratio	13.7 (9.6)	13.0 (10.2)	14.3 (8.9)
MAP ratio	12.2 (9.4)	11.5 (10.1)	12.9 (8.6)
Apnea-hypopnea index (events/h) ^f			
Mean	29.2 (16.6)	32.0 (19.1)	26.2 (12.9)
Median (IQR)	23.9 (17.4, 33.4)	26.1 (18.2, 37.4)	22.7 (16.6, 31.4)
Sleep time with SpO ₂ < 90%, %			
Mean	9.2 (14.3)	9.9 (15.2)	8.5 (13.3)
Median (IQR)	3.5 (0.9,11.0)	3.7 (1.2,12.0)	3.2 (0.6,10.8)

Data presented as mean (SD) unless otherwise specified. ^aEducation, race and ethnic group were self-reported. ^bThe body-mass index is the weight in kilograms divided by the square of the height in meters. ^cBetween group difference $P = .028$. ^dResting office BP was the average of the last two readings out of three separate readings taken one minute apart in the office after participant has been sitting quietly for at least 5 minutes using an automated BP sphygmomanometer. ^eBP ratio is defined as the difference between the daytime and nighttime BP divided by the daytime BP*100%. ^fAHI was based on the 3% desaturation criterion except for 2 individuals where only AHI4% desaturation was available. In these 2 individuals, the AHI was multiplied by 1.25 to approximate the AHI3% distribution. ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blockers, CPAP = continuous positive airway pressure, CVD = cardiovascular disease, DBP = diastolic blood pressure, IQR = interquartile range, MAP = mean arterial pressure, SBP = systolic blood pressure, SD = standard deviation, SpO₂ = oxygen saturation measured by pulse oximetry.

Table 2—Primary and secondary 24-hour blood pressure outcomes.

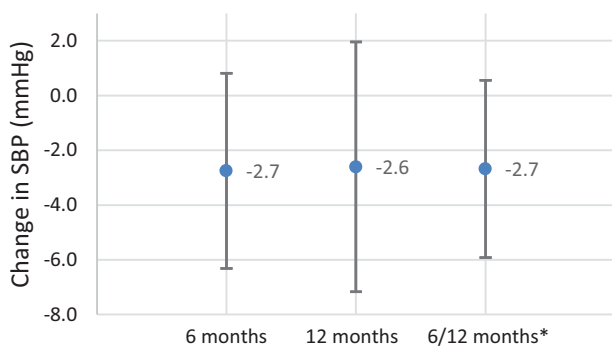
	Control Group (n = 81)			CPAP Group (n = 82)			Mean Treatment Effect (95% CI)	P
	Baseline	6-mo FU	12-mo FU	Baseline	6-mo FU	12-mo FU		
Primary Outcome								
24-hour SBP	126.8 (14.4)	127.5 (14.4)	127.9 (14.4)	121.4 (11.1)	122.6 (10.3)	121.4 (10.7)	−2.7 (−5.9, 0.6)	.105
Secondary Outcomes								
Daytime SBP	130.5 (14.4)	131.8 (14.8)	130.9 (15.3)	125.6 (11.5)	127.8 (11.9)	126.0 (13.2)	−1.7 (−5.2, 1.7)	.325
Nighttime SBP	117.7 (18.2)	119.0 (16.1)	120.1 (14.4)	111.5 (13.0)	111.7 (10.9)	111.3 (10.5)	−5.9 (−9.9, −1.9)	.004
24-hour DBP	72.9 (8.3)	73.3 (9.9)	72.6 (7.6)	71.9 (7.2)	71.5 (7.9)	70.0 (6.3)	−1.6 (−3.3, 0.0)	.055
Daytime DBP	75.8 (8.5)	76.4 (10.1)	75.2 (8.0)	75.2 (7.4)	74.9 (8.5)	73.2 (7.3)	−1.4 (−3.3, 0.4)	.124
Nighttime DBP	65.9 (10.1)	66.6 (10.6)	66.1 (8.3)	64.3 (8.6)	64.5 (8.3)	63.0 (6.2)	−2.2 (−4.4, −0.0)	.050
24-hour MAP	90.8 (9.5)	91.4 (10.6)	91.1 (8.8)	88.4 (7.6)	88.5 (7.8)	87.1 (6.7)	−1.9 (−4.0, 0.1)	.066
Daytime MAP	94.0 (9.6)	94.9 (10.7)	93.8 (9.4)	92.0 (7.9)	92.5 (8.7)	90.9 (8.3)	−1.5 (−3.7, 0.8)	.193
Nighttime MAP	83.2 (12.1)	84.1 (11.7)	84.1 (9.0)	80.1 (9.5)	80.2 (8.3)	79.1 (6.8)	−3.4 (−6.0, −0.7)	.012

Data presented as mean (SD) and all outcomes are measured in mm Hg. Significant between group differences in baseline 24-hour SBP, daytime SBP, and nighttime SBP ($P = .009, 0.024,$ and $0.008,$ respectively). Sample based on $n = 163$ with valid baseline, 6-month or 12-month blood pressure readings. CI = confidence interval, DBP = diastolic blood pressure, FU = follow-up, MAP = mean arterial pressure, SBP = systolic blood pressure.

61 observational studies showed that a 2-mm Hg reduction in SBP is expected to reduce mortality from stroke by about 10% and mortality from ischemic heart disease or other vascular causes by about 7%.⁴³ A second meta-analysis of 147 randomized trials assessing the effect of BP lowering on stroke and coronary heart disease found effects of similar magnitude in patients with and without CVD and in patients with BP as low as 110/70 mm Hg prior to treatment.⁴⁴ The SPRINT trial reported that among patients at high risk for cardiovascular events but without diabetes, targeting a SBP < 120 mm Hg resulted in lower rates of fatal and nonfatal major cardiovascular events and death compared to a target of < 140 mm Hg.⁴⁵ CPAP may therefore be an important modality for achieving intensive BP targets in this population.

There is growing recognition of the adverse impact of nocturnal elevations in BP and the nondipping pattern on the cardiovascular system. A blunted decline in the physiological fall in nocturnal BP has been associated with increased left ventricular hypertrophy, microalbuminuria, decreased arterial compliance, and with an increased risk of future cardiovascular events and mortality, even after adjusting for 24-h BP.^{46,47} Sleep apnea is thought to be an important contributor to nocturnal elevations in BP and to the absence of nocturnal BP fall. It is postulated that the recurrent episodes of upper airway obstruction, intermittent hypoxia and hypercapnia, and repetitive cortical arousal result in increased sympathetic nervous activity, leading to peripheral vasoconstriction, augmented catecholamine release, increased arterial stiffness, and impaired endothelial function. These changes result in acute fluctuations in nocturnal BP and ultimately to daytime hypertension. CPAP stents open the upper airway, thereby abolishing or reducing apneas and apnea-associated arousals and oxygen desaturation, thus preventing OSA-associated BP fluctuations and improving the diurnal BP profile. Recent meta-analyses of clinical trials have shown that CPAP therapy has the greatest effect on nocturnal BP.^{31,32,42} In the HeartBEAT study, a clinical trial of CPAP therapy in patients with sleep apnea and CVD or multiple CVD risk factors, CPAP resulted in a greater reduction in nighttime BP than in daytime BP compared to the control group (mean reduction in nighttime SBP, DBP, and MAP: −3.3, −3.7, and −3.5 mm Hg, respectively).²⁵ Many of these studies, however, were limited to follow-up of 3 months. Consistent with the literature, we found that CPAP had the greatest effect on nocturnal BP, and such effects were evident after 6 months and 12 months of intervention. Furthermore, we observed an improvement in the day-night SBP ratio with CPAP treatment, a strong predictor of mortality.⁴⁶ Our findings of nocturnal BP improvements in nonsleepy patients with relatively well-controlled daytime BP levels who are at high risk for cardiovascular events provide additional evidence that CPAP

Figure 2—Difference in mean (95% confidence interval) 24-hour systolic blood pressure (SBP) change from baseline between the CPAP and control arms.



*Difference between the CPAP and control arms in mean 24-hour SBP change from baseline to the average of 6-month and 12-month measurements. CPAP = continuous positive airway pressure.

treatment may be particularly useful for reducing cardiovascular morbidity and mortality in this patient population.

In keeping with the literature, adherence to CPAP treatment in our study was suboptimal despite rigorous efforts to support CPAP use, including use of a run-in period.^{48,49} Although suboptimal adherence to treatment will reduce statistical power in intention-to-treat analyses in any clinical trial, the observed CPAP adherence is consistent with what is observed clinically in individuals without significant OSA symptoms. Despite the modest adherence, we observed reductions in nighttime BP in our primary analyses. We did not observe a significant treatment effect on SBP with CPAP therapy when we restricted our analysis to participants with an average CPAP use of ≥ 4 h/night over 6 months, but these secondary analyses had limited power.

There are several strengths to our study. It is one of only 4 clinical trials evaluating the effect of CPAP treatment on ABPM with a follow-up duration of 6 months or longer, with the other 3 studies in patients with sleep apnea and resistant hypertension.^{16,33,37} The use of ABPM allowed for multiple BP measurements and may provide more reliable BP estimates than clinic measurements.⁵⁰ Furthermore, ABPM allowed for the assessment of nocturnal BP. These measurements are particularly reflective of OSA-related cardiovascular pathogenesis and are better predictors of future CVD and mortality than daytime BP.⁴⁶ Aside from the HeartBEAT study, this is the only other study of CPAP on ambulatory BP in patients with CVD or multiple risk factors.²⁵ However, participants in the HeartBEAT study were followed for only 12 weeks.

Our study has several limitations that warrant discussion. Several of the BP indices from 24-h measurements obtained at baseline differed by group despite successful randomization in achieving group balance for key demographic, health, and clinic BP. Consistent with our initial analysis plan, primary analyses did not adjust for baseline characteristics. Secondary analyses that adjusted for baseline 24-h BP values provided smaller and less significant estimates of a CPAP treatment effect. Given that no errors were identified in the randomization process, the between-group differences are most likely due to chance. Our findings of CPAP having a greater effect on nighttime than on daytime BP and the magnitude of BP reduction seen with CPAP use are also in keeping with previous literature.^{25,31,32,42} A second limitation is that we did not have 12-month follow-up data for all of our study participants. However, the use of mixed effects linear regression models allowed use of all data points at 6 months and 12 months, which provided an estimate of the average effect and is statistically valid. In addition, the participants who were followed to 12 months were those randomized before a certain date and not those who chose to remain in the study long term, thus we do not believe that the 12-month data are biased toward those more motivated to use therapy. We recruited from several recruitment sites (cardiology, sleep, and diabetes clinics), with individuals treated with 1 or 2 diagnostic pathways (home and in-lab studies), potentially introducing heterogeneity. However, we do not expect major differences in BP resulting from these differences. Furthermore, these design features may make our study findings more generalizable to clinical practice. The study was

powered to detect an effect on the primary outcome that was approximately twice as large as the observed change; although the observed change is consistent with recent literature, our study did not demonstrate significant differences in the primary 24-hour SBP outcome. While ABPM is routinely used to detect BP dipping patterns, it is possible that the arousals triggered by cuff inflation may have masked nocturnal drops in BP. Additionally, the study excluded patients with recent (< 4 month) cardiovascular events and those with poorly controlled hypertension (SBP > 170 mm Hg or DBP > 100 mm Hg), which may affect the generalizability of the study, particularly in regards to the impact of CPAP on individuals with resistant hypertension. Lastly, over the course of the trial, a small number of participants reported changes in antihypertensive medications, which may have attenuated measurable changes in blood pressure.

ABBREVIATIONS

ABPM, ambulatory blood pressure monitoring
 BP, blood pressure
 CI, confidence interval
 CMT, conservative medical therapy
 CPAP, continuous positive airway pressure
 CVD, cardiovascular disease
 DBP, diastolic blood pressure
 MAP, mean arterial pressure
 OSA, obstructive sleep apnea
 SBP, systolic blood pressure

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