American Journal of Hypertension Advance Access published August 14, 2014

CLINICAL TRIAL

Long-Term Effects of Continuous Positive Airway Pressure on Blood Pressure and Prognosis in Hypertensive Patients with Coronary Heart Disease and Obstructive Sleep Apnea: A Randomized Controlled Trial

Zhiwei Huang,[1] Zhihong Liu,[1] Qin Luo,[1] Qing Zhao,[1] Zhihui Zhao,[1] Xiuping Ma,[1] Weihua Liu,[1] and Dan Yang[1]

BACKGROUND
Obstructive sleep apnea (OSA) can result in hypertension and significantly increase cardiovascular morbidity and mortality. There are few reports on the long-term effects of continuous positive airway pressure (CPAP) on blood pressure in patients with uncontrolled hypertension with coronary heart disease (CHD) and OSA.

METHODS
We conducted a prospective, long-term follow-up study in 83 patients with uncontrolled hypertension, CHD, and OSA randomized to control or CPAP groups. Daytime systolic blood pressure (SBP), diastolic blood pressure (DBP), and severe cardiovascular and cerebrovascular events (SCCEs) were recorded at baseline and follow-up.

RESULTS
Seventy-three patients completed the study with a median follow-up of 36 (interquartile range = 24–54) months. The 2 groups had similar characteristics at baseline. CPAP was used for 4.5 ± 1.1 hour/night. SBP in the CPAP group was significantly reduced at follow-up (143 ± 7 mm Hg vs. 139 ± 7 mm Hg, $P = 0.04$), and SBP decreased by 8 mm Hg (95% confidence interval = 1.4–9.9; $P = 0.01$). Hypertension control was improved (CPAP, 69.4% for CPAP users vs. 43.2% for control subjects; $P = 0.02$); however, DBP did not reach statistical difference between the groups (81 ± 10 mm Hg vs. 79 ± 8 mm Hg; $P = 0.49$). In the CPAP group, the Epworth Sleepiness Scale was markedly reduced (7.0 ± 3.4 vs. 3.7 ± 2.3; $P < 0.001$). There was 1 SCCE in the CPAP group (heart failure), and 5 SCCEs in the control group (acute myocardial infarction: 2 (with 1 death); stroke: 3), but there was no significant difference identified.

CONCLUSIONS
Long-term CPAP application in uncontrolled hypertension with CHD and OSA significantly reduced daytime SBP, improved hypertension control and daytime sleepiness, and decreased the trend in SCCEs compared with control subjects.

CLINICAL TRIAL REGISTRATION NUMBER:
ClinicalTrials.gov NCT02059993.

Keywords: antihypertensive drugs; blood pressure; continuous positive airway pressure; coronary heart disease; hypertension; obstructive sleep apnea.

doi:10.1093/ajh/hpu147

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive partial (hypopnea) or complete (apnea) occlusion of the upper airway during sleep, which is caused by collapse of the pharyngeal airway and results in sleep fragmentation and oxyhemoglobin desaturation.[1] A study by Kiely and colleagues has shown that >20% of hypertensive patients exhibit OSA, whereas the prevalence of hypertension in the setting of OSA is >50%.[2] One study confirms that OSA is an important identifiable cause of hypertension.[3] OSA is considered as one of the most common risk factors of resistant hypertension.[4,5] The estimated prevalence of OSA among male patients with coronary artery disease (CAD) is 37%.[6] A previous study has suggested that OSA significantly increases cardiovascular morbidity and mortality, especially in patients with preexisting cardiovascular disease.[7] Several studies[8–13] have found that continuous positive airway pressure (CPAP) reduces systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with OSA. Additionally, some articles have reported that there is a protective effect of CPAP therapy against death from cardiovascular disease in patients with severe OSA.[14,15] Other studies have not demonstrated that CPAP has an antihypertensive effect.[16,17] However, relevant studies have a relative short study duration, with few extending longer than 1 year. In our opinion, they are not sufficient to detect the real effects of CPAP on blood pressure (BP). Based on our

Correspondence: Zhihong Liu (zhihongliufuwai@163.com).

Initially submitted April 28, 2014; date of first revision May 26, 2014; accepted for publication June 30, 2014.

[1]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

knowledge, there are few reports about long-term effects of CPAP, including whether CPAP application can improve the prognosis of OSA patients with preexisting CHD under conventional medications.[18,19] Therefore, we conducted a long-term, prospective, controlled study to investigate the effects of CPAP on BP, prognosis, clinical symptoms, and severe cardiovascular and cerebrovascular events (SCCEs) in hypertensive patients with CHD and OSA on conventional treatment.

METHODS

Study design and setting

We performed a prospective, randomized, single-center clinical trial of parallel groups in hypertensive patients with CHD and OSA. We used a computer program to produce the randomized treatment number. These were stored in sequentially numbered opaque envelopes. The project manager was responsible for the allocation and had no contact with any of the participants throughout the trial. Patients were randomly assigned to either CPAP or no therapy (control). This study was approved by the ethics committee of Fuwai Hospital (No. 2009215). Informed consent was obtained from each patient.

Patient selection

We recruited consecutive patients from outpatient and inpatient departments of Fuwai Hospital from January 2009 to June 2012. Patients who were diagnosed with moderate to severe OSA (moderate OSA was defined as an apnea–hypopnea index (AHI) of 15–29 episodes/hour, and severe OSA was defined as an AHI of at least 30 episodes/hour) documented by polysomnography,[20] hypertension (hypertension is defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg at rest or treatment with antihypertensive medication) and confirmation of CHD (selective coronary angiograms showed at least 1 major epicardial coronary artery luminal stenosis segment ≥70%, or left main coronary artery stenosis ≥50%, history of myocardial infarction, or coronary artery bypass grafting documented by medical record) were included in this study. The criteria for inclusion were as follows: (i) men and women aged 45–75 years; (ii) verified diagnosis of hypertension by medical history or treatment with antihypertensive medications; (iii) established diagnosis of CHD; (iv) at least 3-month optimal treatment for hypertension but BP still >140/90 mm Hg or >130/80 mm Hg in patients with diabetes; and (v) moderate to severe OSA. The subjects were excluded if they had secondary hypertension (including renal artery stenosis, chronic renal disease, and primary aldosteronism), central sleep apnea (defined as at least 50% of respiratory events having a pattern of apnea or hypopnea without thoracic and abdominal movement), an Epworth Sleepiness Scale (ESS) score ≥15, a history of significant hepatic failure or severe pulmonary disease, malignant cancer with a life expectancy of <2 years, severe psychiatric disease, sustained excessive alcohol use, or New York Heart Association class III–IV heart failure; regularly used medications that can affect BP (including corticosteroids or sedative drugs); currently used CPAP treatment for OSA or pharyngeal surgery for OSA; declined to participate; or were unable to give informed consent.

Study protocol

At baseline, resting BP was measured; demographic data, including age, sex, medical history, therapeutic regimen, lifestyle habits, height (cm), weight (kg), waist circumference (cm), hip circumference (cm), and neck circumference (cm), were recorded; and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Patients assessed their subjective daytime somnolence using the ESS,[21] a self-completed questionnaire specific to symptoms of daytime sleepiness in various daytime situations. Patients underwent regular clinical examination and laboratory tests to exclude secondary hypertension. After the initial evaluation, physician would give lifestyle advice (including smoking cessation and heavy drinking discontinuation). Participants were assigned antihypertensive and CHD drugs treatments based on current guidelines (defined as conventional medications) in a 3-month run-in period that allowed for modifications in therapeutic schedule. Patients enrolled in the study were advised not to change their therapeutic regimen without permission from their physicians. Drug change was defined as any adjustment of antihypertensive treatment. SCCEs included new-onset acute myocardial infarction (AMI), hospitalization for heart failure, need for repeated coronary revascularization, stroke, and death associated with cardiovascular and cerebrovascular disease.

Patients visited the sleep research laboratory at 1 and 3 months after randomization and every 6 months thereafter. Follow-up ended on 31 December 2013, and was carried out in all cases by the same investigator. Every medical appointment involved protocol-based assessments of the following: morning office BP and heart rate after the patient rested for 10 minutes, adherence to CPAP, medical treatment, lifestyle habits, height, weight, waist circumference, hip circumference, neck circumference, and ESS. Any SCCEs were recorded, and patients or their relatives were asked to provide relevant medical documents. The physicians that handled the medical treatment as well as the clinical assessment and measured BP during the follow-up were blinded to the CPAP status of the patients. Patients were asked to bring the empty blister packs of their pills to ensure compliance with the treatment. Hypertension control was defined as resting BP <140/90 mm Hg or <130/80 mm Hg in patients with diabetes.[22]

BP measurement

To avoid the white-coat effect, BP measurements at the time of follow-up were recorded in a home-like environment. The physician in charge of BP measurements received training of BP measurements for 2 weeks before the trial. The morning BP was measured with a mercury sphygmomanometer by an experienced physician unaware of the patient's group assignment. Patients were seated for at least 10 minutes in a quiet environment with feet on the floor

and their arm supported at heart level. An appropriate sized cuff was placed on the arm with the lower edge of the cuff 2 cm above the antecubital fossa. The first and last Korotkoff sounds were used to determine SBP and DBP, respectively. The average of 3 consecutive BP measurements with 2-minute intervals on the same arm of the patient was recorded for the study.

Sleep evaluation

An overnight polysomnography was performed on all of the included patients in the Sleep Center of Fuwai Hospital by using the Embletta (Medcare Flaga, Reykjavik, Iceland) to record nasal airflow, finger pulse oximetry, thoracic and abdominal movement, body position, and snoring. The sleep was monitored automatically for 7 hours, starting from 30 minutes after the subjects went to bed. Polygraphy data were scored manually by trained personnel. Polysomnography was repeated in both groups at the end of follow-up. Apnea was defined as airflow reduction to ≤10% of the baseline value for 10 seconds or more. Hypopnea was defined as a 30%–90% reduction in oronasal airflow for >10 seconds, associated with an oxygen desaturation of ≥4%.[23] The severity of OSA was quantified numerically as the number of the AHI. AHI was defined as the total number of apneas and hypopneas occurring per hour of sleep. Subjective daytime somnolence was assessed with the ESS questionnaire. A total score >10 was considered indicative of excessive daytime sleepiness.

CPAP application

The CPAP group received fixed-level CPAP titration using an automated pressure setting device for 1 night. The optimal CPAP pressure for each patient in the CPAP group was set at the minimum pressure required to abolish snoring, obstructive respiratory events, and airflow limitation for 95% of the night, according to a previous validation by our study.[24] The fixed pressure was then maintained throughout the study in patients who used a CPAP machine. CPAP compliance and AHI were objectively measured by the built-in compliance software of CPAP devices from the regular examination at the time of follow-up. Patients are generally considered adequately adherent to their CPAP treatment if the mean CPAP use was at least 4 hours/night. Each patient received standardized instructions by 1 investigator specialized in OSA and by a home healthcare provider at the start of the CPAP treatment. A specialist OSA team assisted patients with telephone or outpatient advice for any difficulties with CPAP during the study, and masks were adjusted as necessary.

Statistical analysis

Continuous variables with normal distribution are expressed as mean ± SD, and continuous variables without normal distribution were expressed as median (interquartile range), whereas categorical variables are reported as absolute numbers and percentages. The sample size was calculated to assess a minimum reduction of 5 ± 5 mm Hg in systolic BP after CPAP treatment, assuming an alpha error of 5% and a statistical power of 80%. For baseline comparison between the control and CPAP groups, a 2-tailed test was used for normally distributed variables, and a Mann–Whitney test for non-normally distributed variables. The intragroup changes from baseline to the end of follow-up were assessed with a paired *t* test and Wilcoxon signed rank test. The χ^2 test was used to compare categorical variables. Fisher's exact test was used when ≥1 cells contained values ≤5. SPSS version 18 software (SPSS, Chicago, IL) was used for statistical analysis. $P < 0.05$ was considered statistically significant.

RESULTS

The study flow chart is depicted in Figure 1. A total of 243 patients were screened between January 2009 and June 2012. Out of 97 (39.9%) patients diagnosed with OSA, 5 subjects declined to participate in the study, and 9 subjects were excluded because of the following: AHI <15 (n = 8 patients) and severe heart failure (n = 1 patient). A total of 83 patients fulfilled the inclusion criteria. Of these, 42 patients were allocated to the CPAP treatment, and 41 subjects served as controls. In addition, 4 participants (all had no SCCEs) withdrew before the end of study, 2 patients in the CPAP group withdrew before the 1-month visit (because of intolerance of CPAP treatment), and 2 patients in the control group withdrew before the 6-month visit (owing to live far from Beijing, complained of inconvenience). Two subjects were lost to follow-up in the control group, and 4 patients (all had no SCCEs) with very poor CPAP compliance were also excluded. One participant in the control group died from AMI before the 36-month visit and was included in the study analysis. Thirty-six patients in the CPAP group and 37 subjects in the control group completed the study. The median duration of follow-up was 36 (interquartile range = 24–54) months.

Demographic and clinical data at baseline

Baseline characteristics and BP measurements were similar between the groups (Table 1). The mean age was 62.4 ± 6.7 years. Most subjects (82.2%) in this study were male and overweight (79.4% had BMI >25). Of all the included patients, 36.8% had severe OSA, and 28 participants (38.4%) had daytime somnolence. Comorbidities were similar between the CPAP treatment and the control groups. There were no significant differences with respect to drug number and category used by the patients between the 2 groups. The SBPs in the CPAP treatment and control groups were 148 ± 11 mm Hg and 146 ± 8 mm Hg, respectively ($P = 0.41$), and the DBPs in the 2 groups were 83 ± 8 mm Hg and 83 ± 7 mm Hg, respectively ($P = 0.85$).

Changes of clinical characteristics at follow-up

The data from the follow-up are summarized in Table 2. The duration of follow-up did not differ significantly between the CPAP and control groups. Thirty-nine patients (57.4%) were followed for >36 months, and the shortest duration

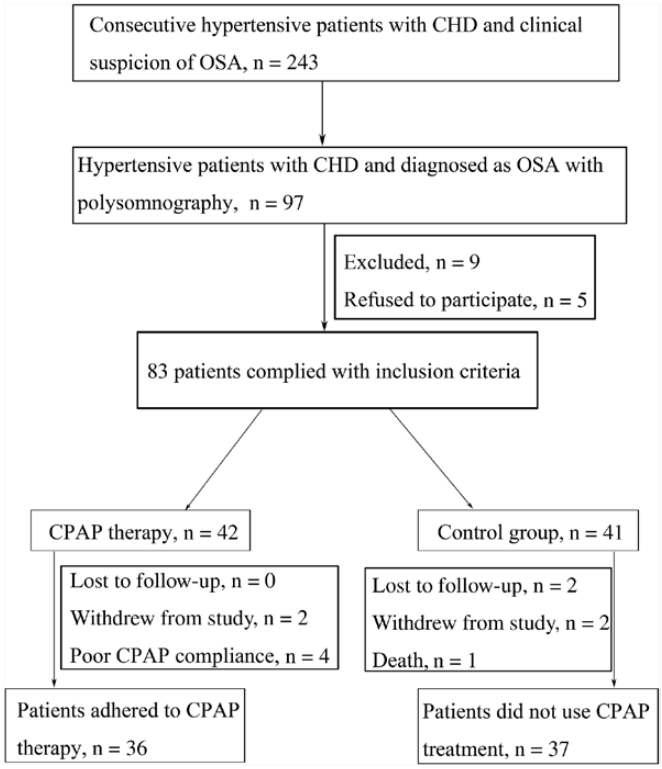

Figure 1. Flow diagram of the study. Abbreviations: CHD, coronary heart disease; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

was 18 months. There was no significant difference in BMI between the groups. In the CPAP group, AHI decreased from 28.3 ± 13.0 events/hour (baseline) to 2.8 ± 1.4 events/hour (as estimated by the CPAP machine's software). The AHI in the control group did not change significantly. Compared with the control group, ESS score was markedly reduced in the therapeutic CPAP group (7.0 ± 3.4 vs. 3.7 ± 2.3; $P < 0.001$). Smoking, diabetes mellitus, heart rate, neck circumference, and number of drug treatment were not significantly different in the CPAP and control groups. The mean time of CPAP treatment used by patients was 4.5 ± 1.1 hour/night. DBP at follow-up was lower but did not reach statistical difference between the groups (81 ± 10 mm Hg for controls vs. 79 ± 8 mm Hg for CPAP users, $P = 0.49$; Δ: 3 ± 11 mm Hg vs. 4 ± 11 mm Hg, $P = 0.75$) (Figure 2). However, SBP was significantly different at the follow-up visit between the groups (143 ± 7 mm Hg for controls vs. 139 ± 7 mm Hg for CPAP users, $P = 0.043$; Δ: 3 ± 6 mm Hg vs. 8 ± 11 mm Hg, $P = 0.01$) (Figure 2). The proportion of controlled hypertension in the CPAP group was better than in the control group at the end of the study ($P = 0.024$). The number of antihypertensive drugs was not significantly different at the time of follow-up between the 2 groups. Three patients in the CPAP group reported that nocturia significantly decreased. The CPAP group had an SCCE rate of 2.8% (n = 1/36; hospitalization for heart failure = 1), and the control group had an SCCE rate of 13.5% (n = 5/37; AMI = 2 (1 died from AMI before the 36-month visit), stroke = 3). Although there was no difference identified, there was a trend toward a lower percentage of SCCEs in the CPAP group.

DISCUSSION

To the best of our knowledge, this is the longest randomized controlled trial specifically designed to investigate the effects of CPAP treatment on BP and prognosis in hypertensive patients with CHD and OSA. Our study demonstrated that long-term CPAP therapy significantly reduced daytime SBP and improved hypertension control but did not further decrease daytime DBP in hypertensive patients with CHD and OSA on conventional antihypertensive treatment. There was a decreased trend in SCCEs in the CPAP group. Symptoms of daytime somnolence associated with OSA in the CPAP group were significantly improved compared with controls.

Previous studies have addressed the effects of CPAP on daytime BP in OSA patients. However, many of these trials did not specifically investigate the effects of CPAP on hypertensive patients, but instead were mainly targeted at normotensive subjects.[25–27] Our study is different from these studies in that the enrolled subjects were all hypertensive patients with CHD and OSA. Both groups received conventional antihypertensive treatment during the course of study. Furthermore, a median long-term follow-up period of 36 (interquartile range = 24–54) months is sufficient to detect changes in BP.

Several studies have analyzed the long-term effects of CPAP on BP but have resulted in variable and conflicting outcomes. Campos-Rodriguez *et al.*[28] showed that CPAP treatment did not reduce BP in 68 OSA patients with hypertension over a period of 4 weeks. The results are different from our study. The reasons for this are unclear but may

Table 1. Baseline characteristics of patients in the continuous positive airway pressure and control groups

Variable	Control (n = 37)	CPAP (n = 36)	*P* value
Age, y	62.7 ± 6.7	62.0 ± 6.8	0.68
Male sex	32 (86.5)	28 (77.8)	0.33
BMI, kg/m^2	27.5 ± 2.6	27.9 ± 3.6	0.58
Smokers	23 (62.2)	19 (52.8)	0.42
Diabetes mellitus	14 (37.8)	12 (33.3)	0.69
Myocardial infarction	14 (37.8)	11 (30.6)	0.51
Neck circumference, cm	40.9 ± 2.0	41.2 ± 4.0	0.65
Heart rate, bpm	64.0 ± 5.7	67.1 ± 9.7	0.10
AHI, events/h	28.7 ± 12.4	28.3 ± 13.0	0.89
ESS, points	8.3 ± 3.4	9.3 ± 3.1	0.20
Minimum SaO_2, %	79.0 ± 4.7	78.9 ± 4.1	0.93
SBP, mm Hg	146 ± 8	148 ± 11	0.41
DBP, mm Hg	83 ± 7	83 ± 8	0.85
Beta-blocker	29 (78.4)	27 (75.0)	0.73
CCB	19 (51.4)	17 (47.2)	0.72
ACEI	15 (40.5)	13 (36.1)	0.70
ARB	13 (35.1)	11 (30.6)	0.68
Diuretics	19 (51.4)	21 (58.3)	0.55
Antihypertensive drugs	3.2 ± 0.4	3.3 ± 0.6	0.82

Values are mean ± SD or No. (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure.

Table 2. Comparison of follow-up characteristics of patients between the control and continuous positive airway pressure groups

Variable	Control (n = 37)	CPAP (n = 36)	*P* value
Follow-up time, mo	36 (24–54)	36 (18–54)	0.85
SCCEs	5 (13.5)	1 (2.8)	0.20
BMI, kg/m^2	27.6 ± 2.6	28.0 ± 3.6	0.57
Smokers	12 (32.4)	8 (22.2)	0.33
Diabetes mellitus	18 (48.6)	15 (41.7)	0.55
Neck circumference, cm	40.5 ± 2.4	41.2 ± 4.3	0.41
Heart rate, bpm	65.0 ± 8.4	64.1 ± 7.0	0.64
ESS, points	7.0 ± 3.4	3.7 ± 2.3	<0.001
SBP, mm Hg	143 ± 7	139 ± 7 0.04	
DBP, mm Hg	81 ± 10	79 ± 8	0.49
SBP change, mm Hg	3 ± 6	8 ± 11	0.01
DBP change, mm Hg	3 ± 11	4 ± 11	0.75
Beta-blocker	28 (75.7)	26 (72.2)	0.74
CCB	16 (43.2)	17 (47.2)	0.73
ACEI	15 (40.5)	12 (33.3)	0.52
ARB	16 (43.2)	14 (38.9)	0.71
Diuretics	27 (73.0)	22 (61.1)	0.28
Drug change	19 (48.6)	15 (41.7)	0.55
Antihypertensive drugs	3.6 ± 0.5	3.3 ± 0.4	0.053
Hypertension control	16 (43.2)	25 (69.4)	0.02

Values are mean ± SD, median (interquartile range), or No. (%). Change is defined as baseline minus follow-up value.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure; SCCEs, severe cardiovascular and cerebrovascular events.

relate to the fact that the BMI in their study was significantly higher than in ours (75% of patients had obesity; mean BMI = 35.9 kg/m^2 vs. 27.7 kg/m^2). Obesity is an independent risk factor, may contribute to worsening of BP control, and is not affected by CPAP. Moreover, the study duration was only 4 weeks. Barbé *et al.*[9] conducted a multicenter, randomized controlled trial with the largest sample, which confirmed a small reduction in BP. The different results may have been caused by the fact that subjects were all nonsleepy hypertensive patients. In contrast, 38.4% participants in our study had daytime somnolence. Robinson *et al.*[29] reported that the fall in ESS score was an independent predictor of a fall in 24-hour ambulatory BP, but baseline severity of OSA, overnight hypoxia, caffeine intake, and being on antihypertensive drugs were not independent predictors of a fall in 24-hour ambulatory BP. We found that ESS score in the CPAP group was significantly reduced from 9.3 ± 3.1 at baseline to 3.7 ± 2.3 at the time of follow-up. The change in SBP in the 2 groups between baseline and post-treatment was remarkable (Δ:2.5 mm Hg for controls vs. 8.3 mm Hg for CPAP users; $P = 0.01$). One study from Kasiakogias *et al.*[30] suggested that long-term CPAP application is not associated with lower BP levels or a need for less antihypertensive drugs for BP control in nonsleepy, hypertensive, OSA patients on conventional antihypertensive treatment. The outcomes are different from ours. However, the study has some obvious limitations. The subjects in their study had a significant difference in severity of OSA at baseline ($P = 0.005$), and the rate of diuretics use in the study was only 36.3%. Furthermore, the study included patients who had no subjective complaints of sleepiness. The clinical significance of this is unknown.

Our outcomes suggest that CPAP was effective in lowering SBP in uncontrolled hypertensive patients with CHD and OSA and are consistent with the following trials. A few nonrandomized studies have consistently indicated that CPAP treatment in OSA patients with resistant hypertension mainly resulted in reductions in SBP (from 5.2 to 11 mm Hg).[31–33] International guidelines have pointed out that even minimal reductions in the SBP (2–3 mm Hg) in the older population could have a clinically significant effect by greatly reducing subsequent cardiovascular mortality (between 6%–8% for stroke and 4%–5% for coronary heart

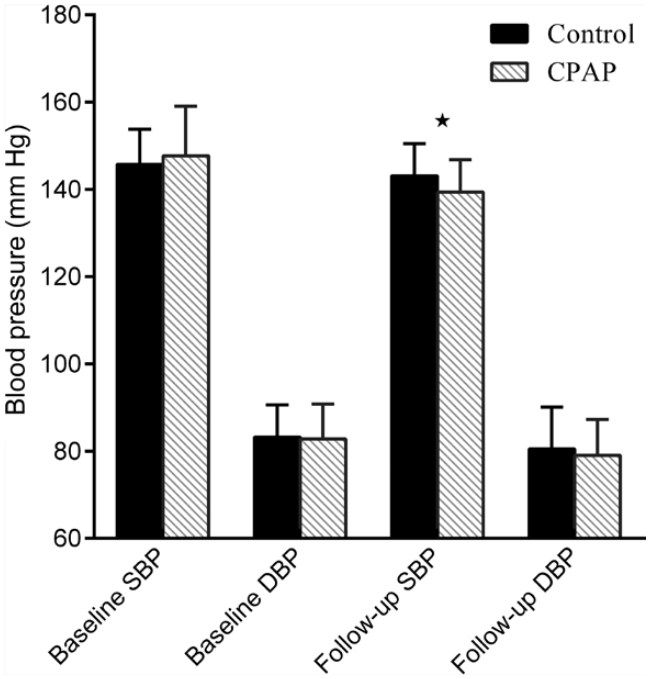

Figure 2. Comparison of blood pressure at baseline and follow-up between the continuous positive airway pressure (CPAP)–treated and control groups. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. ★ $P < 0.05$.

disease).[22] Untreated OSA is strongly associated with poor BP control, particularly severe OSA. A review study clearly demonstrates that untreated OSA is associated with greater difficulty in the control of hypertension.[34] This notion supports our finding that the rate of hypertension control in the control group is poorer than in the CPAP-treated group.

Additionally, compared with control subjects, only 1 patient presented with an SCCE in the CPAP group,but 5 subjects had SCCEs in the control group. Of the 5 subjects, 1 died from AMI. The data are encouraging, although there was no difference identified. We believe that a longer follow-up period and larger sample size may have resulted in a statistical difference. If the speculation is confirmed, it is very meaningful to the population with OSA and CHD. Boden-Albala and colleagues have shown that daytime sleepiness is an independent risk factor for stroke and other vascular events.[35] This may explain why the control group had a higher incidence of stroke than the CPAP group.

Nevertheless, our study has some limitations. First, the sample size was relatively small. However, we performed a long-term follow-up to determine the real effects of CPAP on BP in the specific population. Second, this was a non-double-blind study. However, the use of sham CPAP in the long-term study is impractical. Given this situation, the investigator responsible for BP measurements and clinical assessments was blind to the allocation of CPAP. It is useful to avoid observer bias. Third, we did not use 24-hour ambulatory BP to monitor changes in BP and could not evaluate the nighttime BP. However, 24-hour ambulatory BP may have a cuff pressure effect and cause arousal in sleeping subjects, thereby increasing the SBP and DBP. Also, most of our enrolled subjects were men. Further studies are required to extrapolate the results to the female population.

In conclusion, this study confirmed that long-term application of CPAP in uncontrolled hypertensive patients with CHD and OSA receiving standardized treatment significantly reduced daytime SBP, improved hypertension control and daytime sleepiness, and led to a decreased trend in SCCEs compared with control subjects. A practical clinical message from our study is that it would be wise and recommended to apply CPAP in uncontrolled hypertensive patients with moderate to severe OSA being treated with conventional BP medication. In the future, larger samples studies are necessary to clarify the impact of CPAP on prognosis in hypertensive patients with CHD and OSA.

ACKNOWLEDGMENTS

We thank Baoyu Feng for her contribution to the statistical analysis. This work was supported by the Research Fund of Capital Medical Development of Beijing Municipal Health Bureau (No. 2009–2012).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003; 290:1906–1914.

2. Kiely JL, McNicholas WT. Cardiovascular risk factors in patients with obstructive sleep apnoea syndrome. *Eur Respir J* 2000; 16:128–133.
3. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; 342: 1378–1384.
4. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117:e510–e526.
5. Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. *Am J Hypertens* 2014; e-pub ahead of print 14 April 2014.
6. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. *Chest* 1996; 109:659–663.
7. Peker Y, Hedner J, Kraiczi H, Löth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. *Am J Respir Crit Care Med* 2000; 162:81–86.
8. Campos-Rodriguez F, Perez-Ronchel J, Grilo-Reina A, Lima-Alvarez J, Benitez MA, Almeida-Gonzalez C. Long-term effect of continuous positive airway pressure on BP in patients with hypertension and sleep apnea. *Chest* 2007; 132:1847–1852.
9. Barbé F, Durán-Cantolla J, Capote F, de la Peña M, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, de Atauri JD, Terán J, Mayos M, Monasterio C, del Campo F, Gomez S, de la Torre MS, Martinez M, Montserrat JM. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010; 181:718–726.
10. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med* 2012; 8:587–596.
11. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation* 2003; 107:68–73.
12. Sanner BM, Tepel M, Markmann A, Zidek W. Effect of continuous positive airway pressure therapy on 24-hour blood pressure in patients with obstructive sleep apnea syndrome. *Am J Hypertens* 2002; 15:251–257.
13. Börgel J, Sanner BM, Keskin F, Bittlinsky A, Bartels NK, Büchner N, Huesing A, Rump LC, Mügge A. Obstructive sleep apnea and blood pressure. Interaction between the blood pressure-lowering effects of positive airway pressure therapy and antihypertensive drugs. *Am J Hypertens* 2004; 17:1081–1087.
14. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365:1046–1053.
15. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest* 2005; 127:2076–2084.
16. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. *Chest* 2006; 129:1459–1467.
17. Barbé F, Mayoralas LR, Duran J, Masa JF, Maimó A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agustí AG. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med* 2001; 134:1015–1023.
18. Cassar A, Morgenthaler TI, Lennon RJ, Rihal CS, Lerman A. Treatment of obstructive sleep apnea is associated with decreased cardiac death after percutaneous coronary intervention. *J Am Coll Cardiol* 2007; 50:1310–1314.
19. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. *Ann Intern Med* 2012; 156:115–122.
20. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22:667–689.
21. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991; 14:540–545.
22. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
23. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, Masa JF, González M, Sacristán L, Barbé F, Durán-Cantolla J, Aizpuru F, Mañas E, Barreiro B, Mosteiro M, Cebrián JJ, de la Peña M, García-Río F, Maimó A, Zapater J, Hernández C, Grau SanMarti N, Montserrat JM. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA* 2013; 310:2407–2415.
24. Zhao Q, Liu ZH, Luo Q, Zhao ZH, Zhang HL, Wang Y. Effects of continuous positive airway pressure on blood pressure and daytime sleepiness in obstructive sleep apnea patients with coronary heart diseases under optimal medications. *Sleep Breath* 2012; 16:341–347.
25. Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure: a placebo trial. *Hypertension* 2000; 35:144–147.
26. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 163:344–348.
27. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet* 2002; 359:204–210.
28. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. *Chest* 2006; 129:1459–1467.
29. Robinson GV, Langford BA, Smith DM, Stradling JR. Predictors of blood pressure fall with continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA).*Thorax* 2008;63:855–859.
30. Kasiakogias A, Tsioufis C, Thomopoulos C, Aragiannis D, Alchanatis M, Tousoulis D, Papademetriou V, Floras JS, Stefanadis C. Effects of continuous positive airway pressure on blood pressure in hypertensive patients with obstructive sleep apnea: a 3-year follow-up. *J Hypertens* 2013;31:352–360.
31. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, Bradley TD. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. *Eur Respir J* 2003; 21:241–247.
32. Martínez-García MA, Gómez-Aldaraví R, Soler-Cataluña JJ, Martínez TG, Bernácer-Alpera B, Román-Sánchez P. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. *Eur Respir J* 2007; 29:951–957.
33. Dernaika TA, Kinasewitz GT, Tawk MM. Effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea. *J Clin Sleep Med* 2009; 5:103–107.
34. Dudenbostel T, Calhoun DA. Resistant hypertension, obstructive sleep apnoea and aldosterone. *J Hum Hypertens* 2012; 26:281–287.
35. Boden-Albala B, Roberts ET, Bazil C, Moon Y, Elkind MS, Rundek T, Paik MC, Sacco RL. Daytime sleepiness and risk of stroke and vascular disease: findings from the Northern Manhattan Study (NOMAS). *Circ Cardiovasc Qual Outcomes* 2012; 5:500–507.