Continuous Positive Airway Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Meta-Analysis of Randomized Controlled Trials

Liping Liu, MD;[1,2] Qunan Cao, MD;[1] Zhenzhen Guo, MD;[1] Qiuyan Dai, MD, PHD[1]

From the Department of Cardiology, Shanghai General Hospital of Nanjing Medical University, Shanghai, China;[1] and Department of Cardiology, Yancheng First People Hospital, the Fourth Affiliated Hospital of Nantong Medical University, Jiangsu, China[2]

This study aimed to analyze the effect of continuous positive airway pressure (CPAP) on blood pressure (BP) in patients with obstructive sleep apnea (OSA) and resistant hypertension. Randomized controlled trials (RCTs) that evaluated the effect of CPAP on BP in patients with OSA and resistant hypertension, indexed in MEDLINE, Embase, and the Cochrane Library from inception until March 20, 2015, were included in the meta-analysis. A total of five RCTs were identified to meet the inclusion criteria. The pooled changes after CPAP treatment for 24-hour ambulatory systolic BP and diastolic BP (DBP) were −4.78 mm Hg (95% confidence interval [CI], −7.95 to −1.61) and −2.95 mm Hg (95% CI, −5.37 to −0.53) in favor of the CPAP group. CPAP was also associated with reduction in nocturnal DBP (mean difference, −1.53 mm Hg, 95% CI, −3.07 to 0). The results indicated a favorable reduction in BP with CPAP treatment in patients with OSA and resistant hypertension. *J Clin Hypertens (Greenwich).* 2016;18:153–158. © 2015 Wiley Periodicals, Inc.

Resistant hypertension is defined as blood pressure (BP) that remains over normal levels in spite of concurrent use of three antihypertensive medications of different classes, ideally including a diuretic, at optimal tolerated doses, or requiring four or more medications to achieve goal BP.[1] According to National Health and Nutrition Examination Survey (NHANES) 2003–2008, 8.9% of all US adults with hypertension and 12.8% of antihypertensive drug–treated adults had resistant hypertension.[2] The prevalence of resistant hypertension in treated patients had risen from 15.9% in 1998–2004 to 28% in 2005–2008.[3] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), after approximately 5 years of follow-up, 34% of participants remained uncontrolled on an average of two agents, and 23% of participants with controlled BP were taking three or more agents.[4] Only 49% of participants were controlled on one or two agents showing that approximately 50% of participants would have needed three or more BP agents. Importantly, cardiovascular risks associated with target organ damage and cardiovascular complications in patients with resistant hypertension are significantly higher than those with nonresistant hypertension,[5,6] thus highlighting the need for more efforts to improve the prognosis of patients with resistant hypertension.

Obstructive sleep apnea (OSA) is characterized by recurrent partial or complete collapse of the upper airway during sleep, causing intermittent hypoxemia and sleep disruption.[7] The apnea-hypopnea index (AHI) is a measure of the number of apnea and hypopnea episodes per hour of monitored sleep. According to the American Academy of Sleep Medicine, an OSA diagnosis is defined by ≥15 events per hour (with or without OSA symptoms) or five or more events per hour with OSA symptoms.[8] OSA is related to multiple cardiovascular diseases, such as coronary heart diseases, hypertension, hypertrophic cardiomyopathy, heart failure, stroke, and atrial fibrillation.[6,7,9–11] In addition, OSA is reported to be the most common secondary cause of resistant hypertension.[12] The severity of OSA is directly associated with the degree of BP elevation, which may suggest that treatment of OSA has the potential to improve BP control.[13–15]

Continuous positive airway pressure (CPAP) as initial therapy for OSA recommended by the American College of Physicians delivers compressed air into the airway to keep it open. However, the beneficial effect of CPAP on BP in patients with OSA and resistant hypertension is inconsistent.[16–20] Therefore, we conducted a meta-analysis to evaluate the efficacy of CPAP in patients with OSA and resistant hypertension.

METHODS

Data Sources and Search Strategy

We searched MEDLINE, Embase, and Cochrane Library databases from inception until March 20, 2015, using the search terms "obstructive sleep apnea," "resistant hypertension," and "continuous positive airway pressure" or "positive airway pressure." Two authors (LLP, CQA) independently screened and retrieved titles and abstracts for eligibility, and relevant citations were checked by the third author (DQY). References, conference theses, and

Address for correspondence: Qiuyan Dai, MD, PhD, NO.100, Haining road, hongkou district, Shanghai 200080, China
E-mail: daiqiuyan@medmail.com.cn

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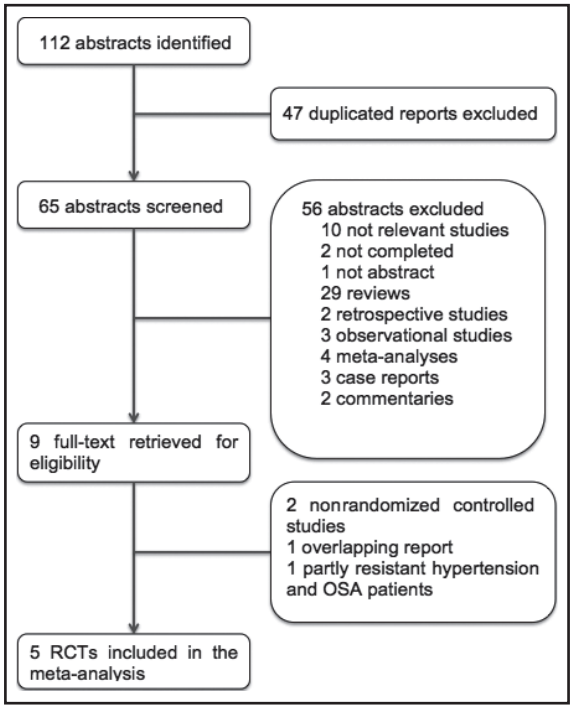

FIGURE 1. Flow diagram for inclusion of studies in the meta-analysis. OSA indicates obstructive sleep apnea; RCTs, randomized controlled trails.

reviewers were manually retrieved to identify additional studies.

Study Eligibility

Inclusion criteria were studies that enrolled patients aged 18 years and older with resistant hypertension and moderate/severe OSA. Exclusion criteria were pregnancy, poor antihypertensive treatment adherence, other secondary causes of hypertension (including primary aldosteronism, pheochromocytoma, Cushing syndrome, renal artery stenosis, renal failure, and occurrence of major cardiovascular events in the past 6 months), severe hypersomnia requiring treatment defined by an Epworth Sleepiness Scale (ESS) score >18, and current or previous CPAP use. The present meta-analysis was limited to published randomized clinical trials (RCTs). Case reports, reviews, and observational studies were excluded. All discrepancies were resolved through consensus by discussion with the third authors (DQY).

Endpoint Definitions

The primary endpoints were the effects of CPAP on 24-hour ambulatory BP (ABP) and daytime and nighttime BP, as compared with controls without CPAP treatment.

Data Extraction

Two authors (LLP, CQA) independently retrieved full-text articles of included studies and extracted patient characteristics, design, and outcomes. The extracted data were reviewed by the third author (DQY).

Quality Assessment

The quality of RCTs included in the meta-analysis was graded according to Jadad Score based on randomization, blinding and withdrawals, and dropouts of participants. A score from 0 to 2 means a low grade of quality and from 3 to 5 a high grade.

Data Synthesis and Statistical Analysis

The outcomes were analyzed by RevMan version 5.3 (Nordic Cochrane Centre, London, England). Mean and standard deviation were employed to describe continuous variables. Mean difference (MD) between CPAP and control groups in systolic BP (SBP) and diastolic BP (DBP) change and corresponding 95% confidence interval (CI) were calculated as the effect size. Forest plots were used to present findings. A random-effect model was utilized for all analyses. Statistical heterogeneity was evaluated using the I^2 test. I^2 >50% presented significant heterogeneity, where subgroup analyses were stratified by duration of follow-up, baseline BP, body mass index (BMI), AHI, ESS, and CPAP compliance. Sensitivity analyses were performed to evaluate the effect of each selected study on the overall result of the meta-analysis. Publication bias was evaluated by Begg test and Egger test. P values were two-tailed, with statistical significance specified at $\leq .05$.

RESULTS

The literature search yielded a total of 112 abstracts (Figure 1). Only nine full-text articles were retrieved and assessed for eligibility. Overall, we identified five RCTs that met the inclusion criteria. A total of 446 patients enrolled in the RCTs were included. Charac-

TABLE I. Characteristics of Included Studies in the Meta-Analysis

Study	Year	Country	Design	Follow-Up	Jadad Score
Lozano et al[20]	2010	Spain	RCT	3 months	3
Pedrosa et al[18]	2013	Brazil	RCT	6 months	3
Martinez-Garcia et al[19]	2013	Spain	RCT	3 months	3
Ana et al[17]	2014	Brazil	RCT	8 weeks	4
Elizabeth et al[16]	2015	NR	RCT	6 months	3

Abbreviations: NR, not reported; RCT, randomized controlled trial.

TABLE II. Baseline Characteristics of Patients Included in the Studies

Study	Lozano et al[20]	Pedrosa et al[18]	Martinez-Garcia et al[19]	Ana et al[17]	Elizabeth et al[16]
Participants (CPAP/control), No. (%)	64 (29/35)	35 (19/16)	194 (98/96)	47 (24/23)	117 (57/60)
Age, y	59.2±9.9	56±1	56.0±9.5	59.4±7.7	60.5±8.2
Men, No. (%)	44 (68.8)	27 (77)	133 (69)	27 (57)	47 (40)
Neck circumference, cm	NR	40±1	42.2±4.9	40±3.5	40±4
Waist circumference, cm	NR	107±2	NR	102.9±10.5	107±11
BMI, kg/m^2	30.8±5	32 (28–39)	34.1±5.4	29.8±4.4	33.4±5.3
AHI	52.67±21.5	29 (24–48)	40.4±18.9	20 (18–31)	41±21
ESS	6.14±3.3	10±1	9.1±3.7	10 (6–15)	11±6
24-h SBP, mm Hg	129.9±13.7	143.7±5.0	144.2±12.5	148±17	129±16
24-h DBP, mm Hg	76±10	86.1±5.3	83.0±10.5	88±13	75±12
CPAP compliance, h	5.6±1.5	6.0±0.2	5.0±1.9	≥4	4.8
Nondipper, No. (%)	29 (45.3)	NR	83 (42.8)	NR	73 (62.4)
Diuretics, No. (%)	NR	35 (100)	184 (94.8)	NR	117 (100)
CCBs, No. (%)	NR	27 (77)	142 (72.4)	NR	93 (79.7)
ACE inhibitors, No. (%)	NR	22 (63)	75 (38.3)	NR	75 (63.6)
ARBs, No. (%)	NR	11 (31)	132 (67.3)	NR	37 (31.4)
β-Blockers, No. (%)	NR	29 (83)	112 (57.1)	NR	93 (79.7)

Abbreviations: ACE, angiotensin-converting enzyme; AHI, apnea-hypopnea index; ARBs, angiotensin II receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; NR, not reported; SBP, systolic blood pressure.

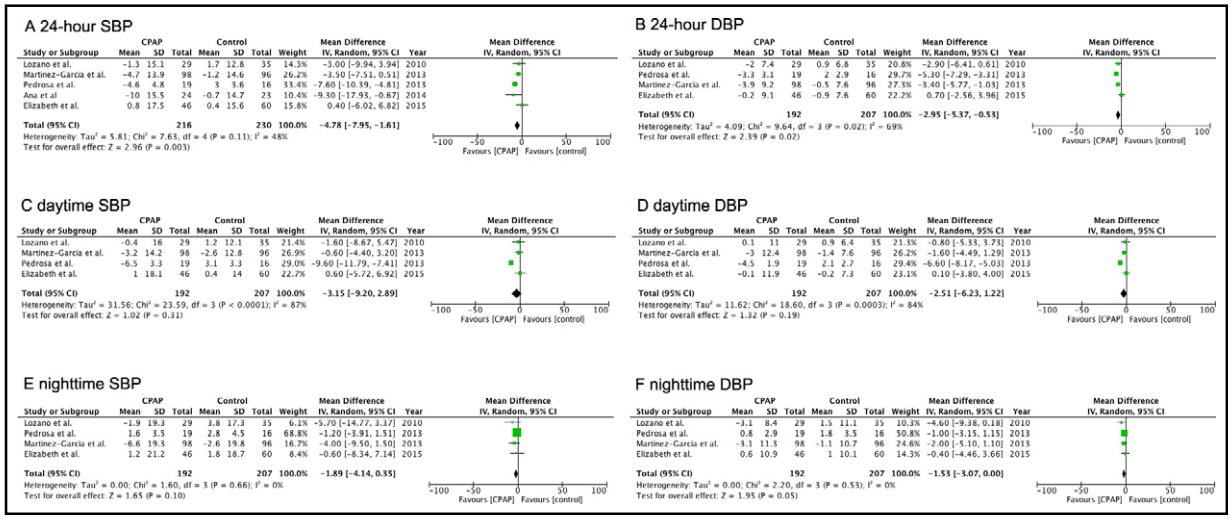

FIGURE 2. Comparison of change in the blood pressure between continuous positive airway pressure (CPAP) and control groups. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation; IV, inverse variance; CI, confidence interval.

teristics of included studies are shown in Table I. One of the five RCTs compared CPAP with sham CPAP and four examined CPAP vs no CPAP. Three RCTs followed up for ≤3 months and another two for 6 months. Baseline demographic characteristics of included studies are present in Table II. Participants in four RCTs were obese (BMI >30 kg/m^2).

Comparison of Changes in BP Between CPAP and Control Groups

Figure 2 demonstrates the pooled change in 24-hour, daytime, and nighttime SBP and DBP. In comparison with the control group, CPAP reduced 24-hour SBP by 4.78 mm Hg (95% CI, −7.95 to −1.61; *P*=.003) and 24-hour DBP by 2.95 mm Hg (95% CI, −5.37 to −0.53; *P*=.02). There were no significant pooled changes in daytime SBP and DBP between two groups (MD, −3.15, 95% CI, −9.20 to 2.89; *P*=.31; MD, −2.51, 95% CI, −6.23 to 1.22; *P*=.19). Although the pooled MD of nighttime DBP was to be significant at −1.53 mm Hg (95%CI, −3.07 to 0; *P*=.05), the pooled nighttime SBP change was −1.89 mm Hg (95% CI, −4.14 to 0.35; *P*=.1) without statistical significance. There was no significant

TABLE III. Subgroup Analyses of 24-Hour DBP Data From the RCTs

Subgroup		24-Hour DBP				
		Studies, No.	MD	95% CI	*P* Value	I^2, %
Duration of follow-up, mo	≤3	2	−3.24	−5.21 to −1.28	.001	0
	>3	2	−2.44	−8.32 to 3.43	.41	89
Baseline SBP/DBP, mm Hg	<140/90	1	−2.9	−6.41 to 0.61	.11	0
	≥140/90	3	−2.89	−6.03 to 0.25	.07	79
BMI, kg/m^2	≤32	2	−4.55	−6.73 to −2.38	<.0001	26
	>32	2	−1.51	−5.51 to 2.5	.46	75
AHI	<30	1	−5.3	−7.29 to −3.31	<.0001	0
	>30	3	−1.99	−4.51 to −0.2	.12	52
ESS	<10	2	−3.24	−5.21 to −1.28	.001	0
	≥10	2	−2.44	−8.32 to 3.43	.41	89
CPAP compliance, h	≤5	2	−4.55	−6.73 to −2.38	<.0001	26
	>5	2	−1.51	−5.51 to 2.5	.46	75

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth sleepiness scale; MD, mean difference; RCTs, randomized controlled trials; SBP, systolic blood pressure.

heterogeneity in the analyses of 24-hour SBP and nighttime DBP.

Subgroup Analyses

Table III shows subgroup analyses of 24-hour DBP data from the RCTs. Heterogeneity in the 24-hour DBP subgroup analyses based on ESS <10, BMI <32 kg/m^2, and CPAP compliance ≤5 hours was not found.

Sensitivity Analysis

After further sensitivity analyses, there was no significant change in CPAP intervention on 24-hour SBP by using a one-study removing method.

Publication Bias

Egger's funnel plot revealed visual evidence of the publication bias (Figure 3). There was no evidence of publication bias among included studies (Begg test *P*=.086; Egger test *P*=.166).

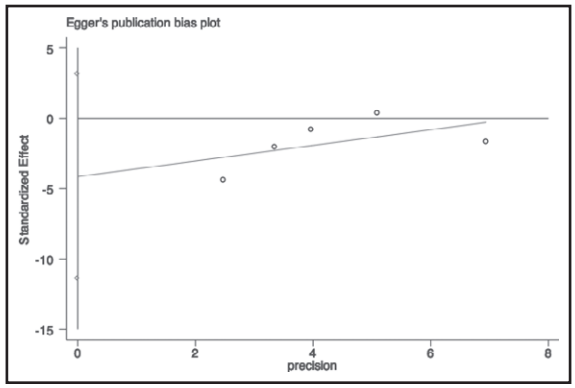

FIGURE 3. Egger's funnel plot for assessment of publication bias.

DISCUSSION

Compared with two previous meta-analyses of the CPAP effect on BP in patients with OSA and resistant hypertension, the present meta-analysis included two more recently published RCTs, including the unique randomized double-blind clinical trial. Based on ABP measurement, 24-hour, diurnal, and nocturnal BP were respectively analyzed. Among the five RCTs,[16–20] the magnitude of benefit effect of CPAP treatment on BP is discrepant. In the HIPARCO trial (the largest multicenter RCT), CPAP treatment achieved a significant decrease in 24-hour DBP (−3.2 mm Hg, 95% CI, −1.0 to −5.4) but not in 24-hour SBP compared with the control group in the intent-to-treat analysis.[19] The randomized double-blind clinical trial, which had a shorter follow-up, showed the greatest reduction in 24-hour SBP (9.3 mm Hg; 95% CI, −17.9 to −0.4), without significant effect on 24-hour DBP.[17] In the smallest RCT, CPAP treatment promoted significant reductions in daytime BP (−6.5 mm Hg for SBP and −4.5 mm Hg for DBP) but not in nighttime BP.[18] The other two RCTs provided no significant reduction in SBP and DBP in patients with OSA and resistant hypertension.[16,20] Our meta-analysis including the five RCTs showed that CPAP treatment resulted in a pooled reduction in 24-hour SBP of 4.78 mm Hg and DBP of 2.95 mm Hg in patients with OSA and resistant hypertension. The result indicated clinical significance because the prevalence of OSA in patients with resistant hypertension is significantly higher, ranging from 64%[12] to 85%,[21] and resistant hypertension increases the risk of cardiovascular events.[5,6] A 10-mm Hg reduction in SBP or a 5-mm Hg reduction in DBP contributes to a 22% decrease in the risk of coronary heart disease (CHD) events and a 14% decrease in the risk of stroke. A DBP reduction of 2 mm Hg decreases prevalence of hypertension by 17%, risk of CHD by 6%, and risk of stroke and transient ischemic attack by 15%.[22] It is necessary to undergo rational CPAP treatment for

patients with OSA and resistant hypertension in addition to antihypertensive drugs.

Data from a previous meta-analysis of CPAP on BP in patients with OSA and resistant hypertension showed a greater magnitude of BP reduction (−7.2 mm Hg for SBP and −4.99 mm Hg for DBP). A separate analysis of the RCTs showed a reduction in SBP and DBP by 6.74 mm Hg and 5.94 mm Hg, respectively.[23] However, the effect sizes were calculated on the basis of ambulatory or clinic BP. Clinic BP measurement has interobserver and intraobserver variation, and terminal digit preferences, all of which may bias the accuracy of measurement.[24,25] Moreover, clinic BP measurement cannot diagnose white-coat hypertension and pseudoresistant hypertension.[1] Ambulatory measurement of BP is also superior to clinical measurement in predicting cardiovascular mortality.[24]

In addition, our meta-analysis showed that CPAP treatment for patients with OSA and resistant hypertension reduced nighttime DBP by 1.53 mm Hg, but not daytime BP. The previous study showed that nocturnal BP levels are a better predictor of cardiovascular risk than daytime BP levels.[24] Therefore, it is important to control nocturnal BP for risk reduction of cardiovascular diseases.

The underlying mechanisms correlating OSA with resistant hypertension are not completely elucidated. OSA and hypertension are complex polygenic disorders, and identifying a genetic etiology is difficult when they are considered in isolation but even more difficult when considered together.[26] The elevated activation of sympathetic nervous system, endothelial dysfunction, oxidative stress, and inflammation have been considered to play important roles in the relationship between OSA and hypertension.[7,27–31] Substantial evidence has been provided to demonstrate the association of OSA with hyperaldosteronism in patients with resistant hypertension.[21,32] It is hypothesized that aldosterone excess promotes fluid accumulation in the neck and thus contributes to increased upper airway resistance, which may increase the severity of OSA and the related increase in BP levels.[33] Whether risk factors such as obesity, age, and sex play a role in the relationship between hypertension and OSA remains elusive.[34–37]

STUDY LIMITATIONS

There were some limitations to our study. First, several RCTs had a relative small sample size and short duration of follow-up, and the risk of potential bias could not be completely excluded. Second, the proportion of different antihypertensive drugs, such as spironolactone, was inconsistent among the RCTs, potentially affecting the results. Finally, the intervention employed in the control group involved no CPAP or sham CPAP treatment. However, sensitivity analysis showed that the result was unlikely to be altered by data from the RCT of sham CPAP.

CONCLUSIONS

CPAP treatment significantly reduced 24-hour SBP and DBP in patients with OSA and resistant hypertension, as well as nocturnal DBP. Further studies with a larger number of participants and longer follow-up period should be designed to evaluate the magnitude of the benefit effect of CPAP on BP and incidence of cardiovascular events, mortality, or other adverse events in patients with OSA and resistant hypertension.

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