The Role of Continuous Positive Airway Pressure in Blood Pressure Control for Patients With Obstructive Sleep Apnea and Hypertension: A Meta-Analysis of Randomized Controlled Trials

Xinyu Hu, MD;[1] Jinqi Fan, PhD;[1] Shaojie Chen, PhD;[2] Yuehui Yin, MD;[1] Bernhard Zrenner, MD[3]

From the Department of Cardiology, the Chongqing Cardiac Arrhythmias Service Center, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China;[1] Department of Medicine/Cardiology, Shanghai General Hospital, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China;[2] and Medizinische Klinik I, Krankenhaus Landshut/Achdorf, Landshut, Germany[3]

The aim of this study was to review the effect of continuous positive airway pressure (CPAP) on blood pressure (BP) in patients with obstructive sleep apnea (OSA) and hypertension. Biomedical databases were searched for randomized controlled trials (RCTs) comparing CPAP with control among these patients. Seven RCTs reporting 24-hour ambulatory BP were identified for meta-analysis. CPAP was associated with significant reductions in 24-hour ambulatory systolic blood pressure (SBP) (−2.32 mm Hg; 95% confidence interval [CI], −3.65 to −1.00) and diastolic blood pressure (DBP) (−1.98 mm Hg; 95% CI, −2.82 to −1.14). CPAP led to more significant improvement in nocturnal SBP than that in diurnal SBP. Subgroup analysis showed that patients with resistant hypertension or receiving antihypertensive drugs benefited most from CPAP. Meta-regression indicated that CPAP compliance, age, and baseline SBP were positively correlated with decrease in 24-hour DBP, but not reduction in 24-hour SBP. *J Clin Hypertens (Greenwich).* 2015;17:215–222. © 2015 Wiley Periodicals, Inc.

Obstructive sleep apnea (OSA) is a highly prevalent but often underdiagnosed clinical condition among hypertensive patients. The disease is characterized by recurrent obstruction of the upper airway, leading to repetitive episodes of apnea and intermittent hypoxia during sleep.[1] Contemporary epidemiologic research has estimated that 4% to 6% of the general middle-aged population is affected by OSA, and this number is believed to keep growing in the near future.[2] Research has shown cross-talks between OSA and hypertension, and this relationship is independent of concurrent demographic variables such as age and body mass index (BMI).[3] Early data show that hypertension was found in more than 50% of OSA patients, while around one third of hypertensive patients have concurrent OSA.[4] OSA has now been recognized as an important cause or risk factor predisposing to hypertension.[5]

Continuous positive airway pressure (CPAP) is currently an effective therapeutic strategy for patients with OSA.[6] For patients with hypertension secondary to or complicated with OSA, blood pressure (BP) control can be theoretically improved if the apnea were effectively treated by CPAP given the causal links between OSA and hypertension. Practically, clinical and basic studies have shown that CPAP can regulate the BP control by a series of mechanisms including attenuation of sympathetic nervous overactivity.[6,7]

Previous meta-analyses of randomized controlled trials (RCTs) have shown that CPAP reduces BP in patients with OSA.[8–12] However, the magnitude of BP reduction remains to be investigated because of a considerable proportion of normotensive patients enrolled in these studies. Moreover, in a review of published RCTs on this topic, including the ones most recently reported, the effect of CPAP on BP control among OSA remained a subject of debate.[13–20] Therefore, we performed the present systematic review and meta-analysis of relevant RCTs aiming to comprehensively evaluate the role of therapeutic CPAP in BP control for OSA patients with hypertension.

METHODS

Study Search Strategy

We searched the database of Medline, Embase, the Cochrane Central Register of Controlled Trials, and relevant Web sites (www.acc.org, www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org) for target studies before July 2014 by using the following keywords: "sleep apnea syndrome" or "obstructive sleep apnea" or "OSA," "hypertension" or "hypertensive," and "continuous positive airway pressure" or "CPAP."

Study Selection

Clinical trials based on the following predefined inclusion criteria were retrieved: (1) those enrolling adult participants with OSA and hypertension; (2) those comparing therapeutic CPAP treatment and control (no CPAP, sham-CPAP, oral placebo tablet, or mere standard conservative care); (3) those reporting

Drs Hu, Fan, and Chen contributed equally to this paper.

Address for correspondence: Yuehui Yin, MD, Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University. 76 Linjiang Rd, Yuzhong district, Chongqing 400010, China
E-mail: yinyh63@163.com

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adequate data of 24-hour ambulatory blood pressure monitoring; (4) those following up at least 1 month; and (5) those using a prospective randomized method. If multiple publications of the same trial were identified, only the most recent publication was included. Two investigators (Hu XY, Fan JQ) independently performed study selection and data extraction. Disagreements were resolved through discussion with the participation of a third investigator (Yin YH).

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Outcome Measures Meta-Analyses' (PRISMA) guidelines.

Data Collection and Assessment of Quality

We extracted prespecified data elements from each trial, including study design, inclusion/exclusion criteria, intervention methods, patient characteristics, concomitant antihypertensive medication, CPAP compliance, and outcomes of 24-hour ambulatory BP. The Jadad scale was used to evaluate the quality of the RCTs. A study with scores three or higher on the Jadad scale was considered high-quality.

Quantitative Data Analysis

The absolute efficacy of CPAP was quantified by calculating the mean difference of outcomes (systolic and diastolic BP change). For parallel trials, it was calculated as the mean difference (CPAP minus control treatment) of the change (follow-up minus baseline). For crossover trials, it was calculated as the mean difference between the end of the CPAP treatment and control periods. The computational method of Follmann and colleagues[21] assumed a correlation coefficient of 0.5 between baseline and endpoint BP. Effect sizes and the corresponding 95% confidence intervals (CIs) were analyzed by pooling available data using the Comprehensive Meta-Analysis V2 software (Biostat, Englewood, NJ). An α value of 0.05 was considered statistically significant. Heterogeneity was examined by I^2 index and the tau-square test. I^2 statistic with values over 50% or between-studies heterogeneity $P<.10$ indicated high heterogeneity, where random-effects model would be performed instead of fixed-effects model to compute the data.

RESULTS

Literature Search and Quality Assessment

Figure 1 shows the detailed flow chart of the selection process of the studies. By using our predefined searching strategy, seven RCTs were consequently selected for data extraction and meta-analysis.[13,14,16–20] Table I summarizes the outcomes of quality assessment and Jadad scores of included studies ($\kappa=0.91\pm0.06$).

Characteristics of the Studies and Patients Included

The main characteristics of included trials are presented in Table II. Seven studies of 794 patients were analyzed.

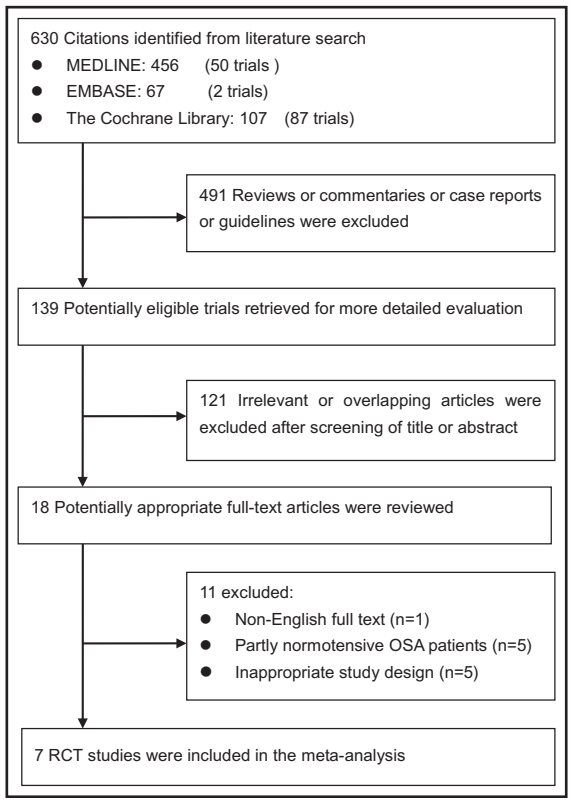

FIGURE 1. Flowchart of selected and identified studies. OSA indicates obstructive sleep apnea; RCT indicates randomized controlled trial.

Three studies recruited patients with OSA and hypertension,[13,14,16] and the other four trials selectively enrolled patients with OSA and resistant hypertension.[17–20] Untreated hypertensive patients at baseline were enrolled in one study.[16] Of the seven RCTs, six studies were parallel[14,16–20] and one study was a crossover design.[13] Four RCTs examined CPAP vs no CPAP[17–20] and three compared CPAP with sham-CPAP.[13,14,16] The treatment duration ranged from 1 to 6 months. All studies reported the changes in 24-hour ambulatory BP, and the outcomes of diurnal and nocturnal ambulatory BP were available in five studies.[16–20]

The diagnoses of OSA in the included trials were all made by polysomnography monitoring. The majority of enrolled patients were documented as moderate to severe OSA (apnea hypopnea index $\geq$15). The mean age of participants in individual trials varied from 53.2 to 59.2 years. All included trials predominantly recruited males patients (mean percentage 74%). The mean BMIs were all beyond 30 kg/m^2. The mean Epworth Sleepiness Scale ranged from 5 to 15 (total score 24), while the mean CPAP adherence ranged from 4.5 hours to 6.0 hours per night. There were no significant differences in the patients' main baseline characteristics between CPAP and control group.

TABLE I. Main Characteristic of the Trials Included in the Meta-Analysis

No.	Trial	Journal, Year of Publication	Study Duration, mo	Age Range, y	AHI, Events per h	Trial Type	Intervention/ Control	Jadad Scale	Site
1	Lloberes et al[20]	J Hypertens, 2014	3	>18	≥15	Parallel RCT	CPAP+drugs/drugs	3	Barcelona, Spain
2	Martinez-Garcia et al[19]	JAMA, 2013	3	18–75	≥15	Parallel RCT	CPAP+drugs/drugs	3	Valencia, Spain
3	Pedrosa et al[18]	CHEST, 2013	6	30–65	≥15	Parallel RCT	CPAP+drugs/drugs	3	Sao Paulo, Brazil
4	Lozano et al[17]	J Hypertens, 2010	3	18–80	≥15	Parallel RCT	CPAP+drugs/drugs	2	Barcelona, Spain
5	Duran-Cantolla et al[16]	BMJ, 2010	3	18–75	≥15	Parallel RCT	CPAP/sham	5	Vitoria, Spain
6	Campos-Rodriguez et al[14]	CHEST, 2006	1	30–70	≥10	Parallel RCT	CPAP/sham	4	Sevilla, Spain
7	Robinson et al[13]	Eur Respir J, 2006	1	>18	>5	Crossover RCT	CPAP/sham	4	Oxford, UK

Abbreviations: AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; RCT, randomized controlled trial.

Pooled Analysis

Pooled outcome was displayed as forest plot. As illustrated in the forest plot in Figure 2, the net change in 24-hour ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) was significantly decreased in patients receiving CPAP therapy compared with those in the control group (change in SBP, −2.32 mm Hg, 95% confidence interval [CI], −3.65 to −1.00, *P*=.001; change in DBP, −1.98 mm Hg, 95% CI, −2.82 to −1.14, *P*<.001, respectively), without significant heterogeneity (I^2=0% for SBP, I^2=21% for DBP, respectively).

Five studies with 691 patients were pooled for the subset analysis of diurnal and nocturnal BP change. Nocturnal BP was significantly decreased by CPAP treatment compared with control (pooled SBP change −2.74 mm Hg, 95% CI, −4.26 to −1.23, *P*<.001; pooled DBP change −1.75 mm Hg, 95% CI, −2.79 to −0.71, *P*=.001, respectively) (Table III) without significant heterogeneity across trials (I^2=0%, I^2=0%, respectively).

Although the pooled mean difference of diurnal DBP was found significantly to be −2.85 mm Hg (95% CI, −5.58 to −0.12, *P*=.041), the pooled diurnal SBP change was −3.58 mm Hg (95% CI, −8.04 to 0.89, *P*=.117) without statistical significance. A significant heterogeneity for diurnal SBP and DBP was found to be 89% and 88%, respectively.

Additionally, subgroup analysis for 24-hour BP was performed to identify the magnitude of the effect of CPAP in different subgroups. The pooled results from trials of resistant hypertension[17–20] showed that OSA patients with resistant hypertension had a significantly greater reduction in 24-hour SBP change (−3.88 mm Hg; 95% CI, −6.55 to −1.22, *P*=.004), as well as 24-hour DBP change (−3.65 mm Hg; 95% CI, −5.19 to −2.10, *P*<.001) after CPAP intervention, as compared with controls.

In addition, in the seven RCTs, the patients who received antihypertensive medication at baseline had significantly more reduction in 24-hour ambulatory SBP (−2.73 mm Hg; 95% CI, −4.96 to −0.51, *P*=.016) and 24-hour ambulatory DBP (−3.19 mm Hg; 95% CI, −4.59 to −1.79, *P*<.001) than those in the control group.

By using further sensitivity analyses for the above pooled comparisons, there was no significant alteration of the statistical significance of these primary results by using a one-study removing method.

Meta-Regression

Meta-regression demonstrated that effective CPAP pressure (*P*<.001), CPAP compliance (*P*<.001), patient age (*P*<.05), OSA severity (*P*<.001), treatment duration (*P*<.001), and baseline SBP (*P*<.001) were positively correlated with improvement in diurnal BP by CPAP treatment. The analysis also showed that CPAP compliance (*P*=.016), age (*P*=.024), and baseline SBP (*P*=.036) were positively associated with reduction in 24-hour ambulatory DBP by CPAP (detailed in Table IV).

Assessment of Publication Bias

To assess for the risk of publication bias, funnel plots of standard error and difference in means were constructed, with no significant asymmetry detectable, as shown in Figure 3.

DISCUSSION

Mechanism Related to BP-Lowering Effect With CPAP

As a result of pharyngeal collapse, OSA induces intermittent hypoxemia and CO_2 retention, with oxygen saturation dropping to as much as <60% in severe cases This leads to disordered autonomic and hemodynamic responses during sleep, particularly featured by

TABLE II. Baseline Clinical Characteristic of the Study Populations

Trial	Stduy Duration, mo	Sample Size, No.	CPAP Patients, No.	Antihypertensive Drugs at Baseline	Antihypertensive drugs (Mean±SD), No.	CPAP Pressure (Mean±SD), cm/H_2O	CPAP Compliance (Mean±SD), h/Night	Mean Age, y	Male, %	BMI (Mean±SD), kg/m^2	AHI (Mean±SD), No./night	ESS (Mean±SD), No.
Lloberes et al[20]	3	58	29	Yes	NR	9.6±1.5	5.7±1.5	58.7±9.5	72.4	32.0±4.9	50.0±20.3	7.3±4
Martinez-Garcia et al[19]	3	194	98	Yes	3.7±0.9	8.5±2.1	5±1.9	56.0±9.5	68.6	34.1±5.4	40.4 ±18.9	9.1±3.7
Pedrosa et al[18]	6	35	19	Yes	4 (4–5)[a]	11.5±0.5	6.02±0.33	56±1	77.0	32 (28–39)[b]	29 (24–48)[c]	10±1
Duran-Cantolla et al[16]	3	340	169	No	0	8.8±1.6	4.5±1.7	53.2±10.2	79.0	31.9±5.7	44.5±24.6	10.3±4.2
Lozano et al[17]	3	64	29	Yes	3.41±0.57	9.62±1.54	5.6±1.52	59.2±9.9	75.9	30.8±5	52.67±21.5	6.14±3.30
Campos-Rodriguez et al[14]	1	68	34	Yes	2.0±0.9	9.5±1.9	5.0±1.4	55.3±9.6	55.8	35.7±5.6	58.3±24.6	15.0±3.9
Robinson et al[13]	1	35	18	Yes	NR	10.4±1.5	5.2±2.1	54±8	88.6	33.2±5.3	28.1 (18.0–38.0)	5.3 (3.0–7.0)[d]

Abbreviations: CPAP, continuous positive airway pressure; NR, not reported; SD, standard deviation. [a]Representing the mean number of antihypertensive drugs and 95% confidence interval. [b]Representing the mean baseline body mass index (BMI) and 95% confidence interval. [c]Representing the mean baseline apnea hypopnea index (AHI) and 95% confidence interval. [d]Representing the mean baseline Epworth Sleepiness Scale (ESS) and 95% confidence interval.

chemoreflex-mediated sympathetic activity and peripheral blood vessel constriction effect, consequently resulting in a high level of blood pressure through the night.[22,23] In addition, induced by recurrent hypoxemia, vasoactive substance such as endothelin and angiotensin, or other pathological effects such as oxidative stress, systemic inflammation and insulin resistance may all contribute to the upregulation of blood pressure.[24–27] To treat the obstructive apneas, CPAP can hold the collapsed airway open, improve the patients' ventilation situation by which CPAP can attenuate subsequent overactivity of sympathetic nervous axis and relevant disorders, and thus decrease BP during sleep.[28]

Previous Studies and Findings of the Present Meta-Analysis

Which patient group benefits the most by BP improvement from CPAP therapy remains a subject of interest. Existing evidence suggested that there were viable effects of CPAP on BP in patients with OSA. Previous meta-analyses[10–12] enrolling a considerable number of normotensive patients showed a near 2-mm Hg BP reduction after CPAP treatment. By including OSA patients complicated with hypertension, the pooled results of the present meta-analysis demonstrated a weighted mean reduction in 24-hour ambulatory SBP of 2.32 mm Hg and DBP of 1.98 mm Hg, suggesting a greater magnitude in BP reduction among hypertensive and OSA patients.

Furthermore, subgroup analysis including trials of resistant hypertension[17–20] showed that OSA patients with resistant hypertension had a more substantial reduction in 24-hour SBP and 24-hour DBP change after CPAP intervention as compared with overall patients. This result was also echoed by early studies.[29] It was extrapolated that CPAP may be a first-choice adjunctive treatment strategy for OSA patients with refractory hypertension.

Effective CPAP therapy and antihypertensive pharmacotherapy are both considered to be of importance in the improvement of BP control.[30] In the systematic review of included trials, six studies[13,14,17–20] in which the patients received antihypertensive medication appeared to achieve a greater BP reduction than those without antihypertensive drugs enrolled in one study.[16] This synergic efficacy was also shown by our subgroup meta-analysis, indicating that the combination therapy of CPAP and antihypertensive drug therapy should be recommended as a standard treatment for OSA and hypertension.

The present meta-analysis revealed that CPAP had significant BP-lowering effects mainly on nocturnal SBP; however, its impact on diurnal SBP seemed modest. Mechanism research has showed that CPAP continuously supports the collapsed airway and prevents hypoxia events, thus balancing autonomic nervous activity and regulating BP during the night.[7,31] Immediate nocturnal BP improvement can be achieved by the direct effect of CPAP in minutes,[29] whereas the regulation of daytime BP

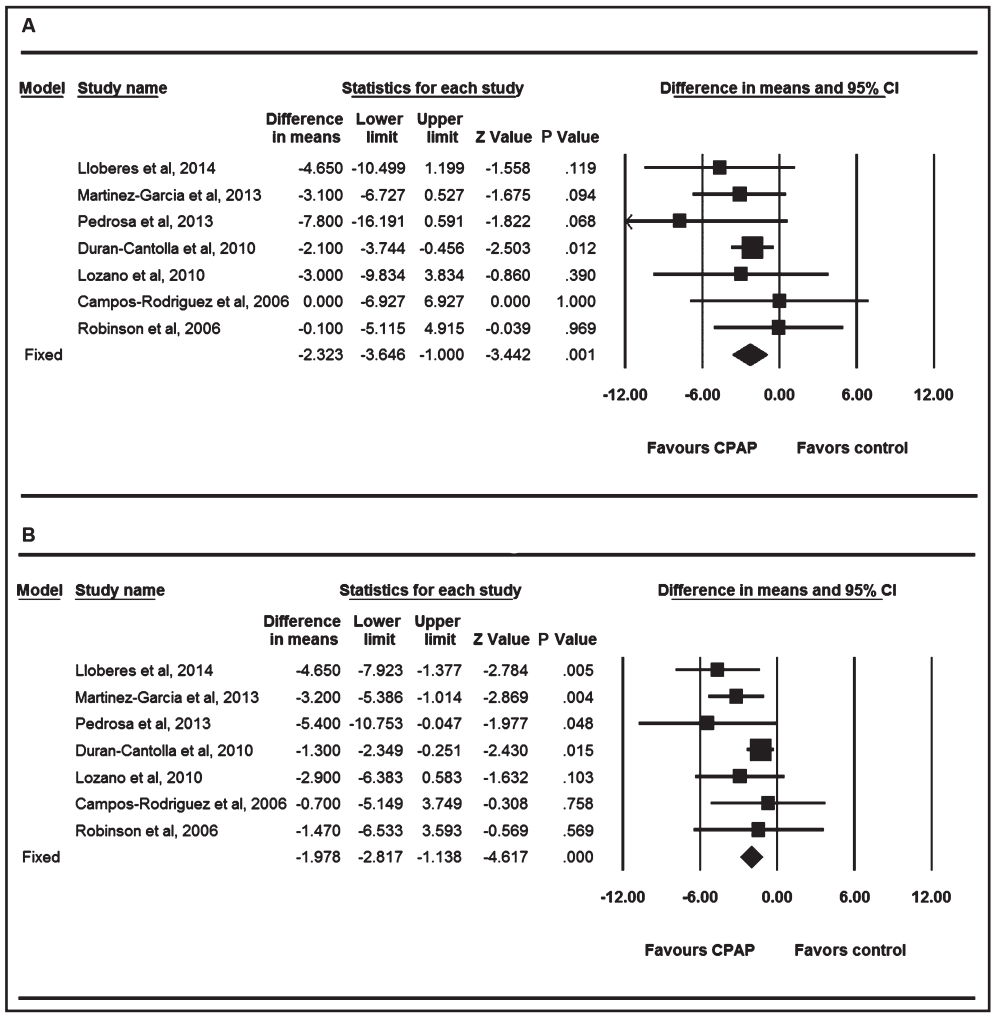

FIGURE 2. Forest plot for 24-hour ambulatory systolic blood pressure (A) and diastolic blood pressure (B). CI indicates confidence interval; CPAP, continuous positive airway pressure.

TABLE III. Results of Subgroup Analysis of 24-h Ambulatory Blood Pressure Change

Pooled Effects	Trials, No.	Mode	Difference in Means	Standard Error	(Lower limit, Upper Limit)	*P* Value
Diurnal SBP change	5	Random	−3.58	2.28	(−8.04, 0.89)	.117
Diurnal DBP change	5	Random	−2.85	1.39	(−5.58, −0.12)	.041
Nocturnal SBP change	5	Fixed	−2.74	0.77	(−4.26, −1.23)	<.001
Nocturnal DBP change	5	Fixed	−1.75	0.53	(−2.79, −0.71)	.001
24-h SBP baseline drugs=0	1	Fixed	−2.10	0.84	(−3.74, −0.46)	.012
24-h SBP baseline drugs>0	6	Fixed	−2.73	1.14	(−9.83, 3.83)	.016
24-h SBP hypertension	3	Fixed	−1.81	0.78	(−3.34, −0.29)	.020
24-h SBP resistant hypertension	4	Fixed	−3.88	1.36	(−6.55, −1.22)	.004
24-h DBP baseline drugs=0	1	Fixed	−1.30	0.54	(−2.35, −0.25)	.015
24-h DBP baseline drugs>0	6	Fixed	−3.19	0.72	(−4.59, −1.79)	<.001
24-h DBP hypertension	3	Fixed	−1.28	0.51	(−2.28, −0.27)	.013
24-h DBP resistant hypertension	4	Fixed	−3.65	0.79	(−5.19, −2.10)	<.001

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

appears to be more multifactorial, involving patients' physical activity, emotional stress, dietary habits, and smoke and alcohol consumption.[30]

To some extent, the effect of nocturnal BP regulation by CPAP treatment may also have an indirect impact on the increased daytime BP. Our meta-regression analysis

TABLE IV. Results of Meta-Regression of the 24-h Ambulatory and Diurnal BP Change

Explanatory Variable	Trials, No.	Patients, No.	24-h Ambulatory SBP (*P* Value)	24-h Ambulatory DBP (*P* Value)	Diurnal SBP (*P* Value)	Diurnal DBP (*P* Value)
Effective CPAP pressure, cm/H_2O	7	794	.730	.214	<.001	<.001
CPAP compliance, Hours per night	7	794	.328	.016	<.001	<.001
Mean age, y	7	794	.328	.024	.004	.003
Male (decimal)	7	794	.681	.324	.460	.792
Baseline BMI, kg/m^2	7	794	.673	.707	.082	.547
Baseline AHI, No.	7	794	.941	.649	<.001	<.001
Baseline ESS, No.	7	794	.840	.122	.621	.880
Study duration, mo	7	794	.097	.206	<.001	<.001
Antihypertensive drugs, No.	5	701	.405	.053	<.001	<.001
Baseline SBP, mm Hg	7	794	.201	.036	<.001	<.001
Crossover vs parallel trial	7	794	.368	.842	NA	NA

Abbreviations: AHI, apnea hypopnea index; BMI, body mass index; BP, blood pressure; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; NA, not available; SBP, systolic blood pressure.

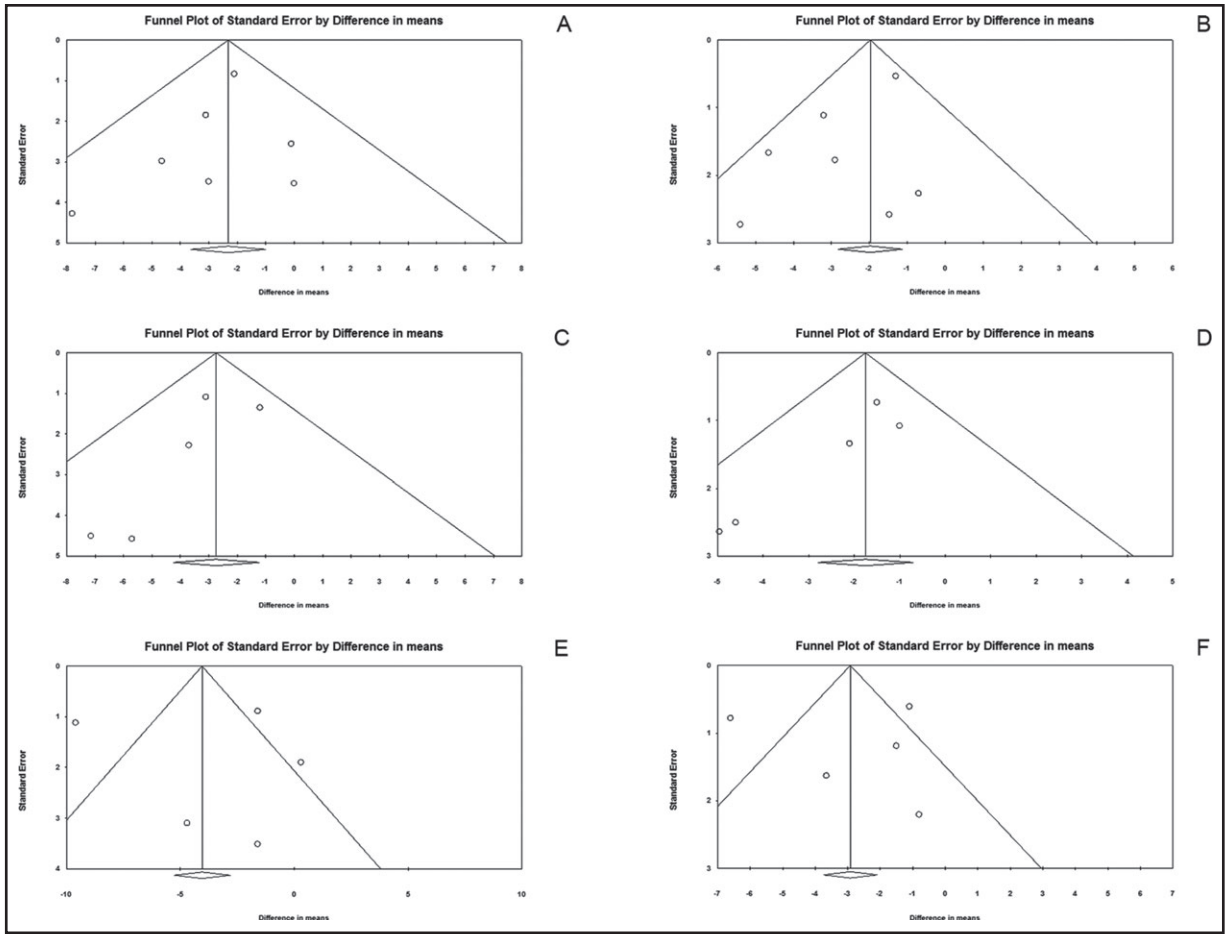

FIGURE 3. Funnel plot for 24-hour ambulatory systolic blood pressure (A), 24-hour ambulatory diastolic blood pressure (B), nocturnal systolic blood pressure (C), nocturnal diastolic blood pressure (D), diurnal systolic blood pressure (E), and diurnal diastolic blood pressure (F).

further demonstrated that effective CPAP pressure, better CPAP compliance, elder age, more sever OSA, longer treatment duration, and higher baseline SBP may be positive predictors of greater reduction of daytime BP by CPAP treatment. These findings were partly mirrored by previous results.[16,19] Our meta-regression also found

that CPAP compliance, age, and baseline SBP were positively correlated with the efficacy of CPAP treatment on control of 24-hour DBP, and no factors were associated with the improvement of 24-hour SBP.

Study Strengths and Limitations

There are several strengths in the current meta-analysis. By adopting predefined study selection criteria, all included trials were prospective randomized studies whose methodological quality was considered to be relatively high. Meta-analysis of randomized trials can provide confident evidence if the between-study bias is appropriately controlled. Moreover, the main baseline characteristics such as patient demographic profile were comparable between the treatment and control groups, and the time range of the included trials performed was within the recent decade. These features suggest a low risk of selection bias across trials and show an adequate power of our analysis.

Several limitations should be addressed when interpreting our results. First, most of the studies had a relative small sample size, and the risk of potential bias could not be completely excluded in view of intrinsic difference in study design. Second, the intervention applied in the control group was not univariate and included sham-CPAP or no CPAP treatment; however, data from several studies[17–19] showed that the adherence of sham-CPAP was relatively low during follow-up. Thus, a sham-CPAP intervention may be unlikely to alter our primary results as relative to no CPAP. Because of a limited follow-up period and a lack of individual data, hard endpoints such as incidence of cardiovascular events, mortality, or other adverse events were not analyzed in the current study.

CONCLUSIONS

For OSA and hypertensive patients, CPAP treatment results in a significant reduction in 24-hour ambulatory BP, which is characterized by nocturnal BP. Those with resistant hypertension or taking antihypertensive pharmacotherapy are shown to have more substantial BP reduction. CPAP adherence, age, and baseline SBP are positively correlated with the decrease of 24-hour DBP. In addition to aforementioned factors, effective CPAP pressure, OSA severity, and treatment duration may also predict improvement in diurnal BP control. None are associated with the reduction in 24-hour SBP.

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Conflicts of Interest: None.

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