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Original Article

Randomized controlled trial of continuous positive airway pressure treatment of resistant hypertensive patients combined with obstructive sleep apnea/hypopnea syndrome

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Abstract: *Background:* The aim of this study was to determine whether continuous positive airway pressure (CPAP) could reduce blood pressure in resistant hypertensive patients with obstructive sleep apnea/hypopnea syndrome (OSAHS). *Methods:* A total of 90 patients with resistant hypertension and moderate to severe OSAHS were randomized to the control group (n = 47) or CPAP group (n = 43), with anti-hypertensive treatment or anti-hypertensive plus CPAP treatment for 3 months, respectively. Main outcomes were changes in 24-hour mean and systolic and diastolic blood pressure using an ambulatory blood pressure monitoring system. *Results:* Ninety patients completed the follow-up. Compared to the control group, the CPAP group achieved a greater decrease in 24-hour mean blood pressure (-2.2 ± 4.6 vs 1.7 ± 5.2 mm Hg; $P < 0.001$), 24-h SBP (-2.3 ± 10.6 vs 2.8 ± 7.5 mm Hg; $P = 0.010$), 24-h DBP (-2.1 ± 6.2 vs 1.1 ± 7.8 mm Hg; $P = 0.033$), nocturnal SBP (-3.9 ± 11.5 vs 4.4 ± 10.7 mm Hg; $P < 0.001$), and DBP (-3.1 ± 7.0 vs 1.6 ± 13.2 mm Hg; $P = 0.042$). There was a significant positive correlation between hours of CPAP use and decrease in 24-hour mean blood pressure (r = 0.653, $P < 0.001$), SBP (r = 0.619, $P < 0.001$), and DBP (r = 0.570, $P < 0.001$). *Conclusion:* Among patients with OSAHS and resistant hypertension, CPAP treatment for 3 months significantly reduced 24-hour mean and systolic and diastolic blood pressure. Therefore, the present study reinforces the therapeutic efficacy of CPAP in resistant hypertensive patients with OSAHS in a Chinese population.

Keywords: Obstructive sleep apnea syndrome, continuous positive airway pressure, hypertensive, resistant hypertension, ambulatory blood pressure monitoring

Introduction

Obstructive sleep apnea/hypopnea syndrome (OSAHS), the most common form of sleep-disordered breathing, is characterized by disruptive snoring, recurrent episodes of hypopneas and apneas, arousal, and nocturnal intermittent hypoxemia during sleep [1]. OSAHS has been increasingly recognized as an independent risk factor for development of hypertension [2-4]. In particular, moderate or severe OSAHS [apnea-hypopnea index (AHI) ≥ 15 events/hour] is present in 30% or more of patients with primary hypertension and in up to 80% of those with drug-resistant hypertension [5, 6], defined as blood pressure that is higher than normal values despite treatment with at least three classes of anti-hypertensive medications [7]. In addition, severity of OSAHS has been directly related to increased risks of incident hypertension. However, treatment of OSAHS has been associated with a lower risk of hypertension [8], suggesting that effectively controlling OSAHS has the potential to improve hypertensive symptoms in routine clinical practice.

Continuous positive airway pressure (CPAP) is the most widely accepted strategy of therapy for severe or symptomatic OSAHS [9]. It has been hypothesized that CPAP treatment may induce a significant reduction in blood pressure in resistant hypertension, thus improving OSAHS [10]. Several randomized controlled trials (RCT) [11-13] and meta-analyses [6, 7] have shown a significant improvement in blood pressure with CPAP treatment in moderate or

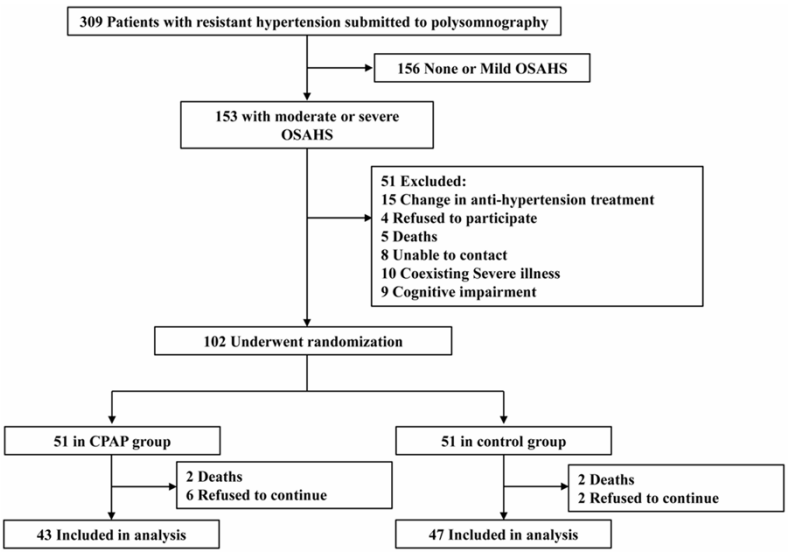

Figure 1. Flowchart of the study.

severe OSAHS patients with resistant hypertension. However, the effectiveness of CPAP on blood pressure in patients with mild OSAHS has been inconsistent, compared to moderate or severe OSAHS patients [14, 15]. Notably, most studies have recruited a relatively small number of participants and have not implemented a prolonged assessment of CPAP therapy on blood pressure in patients with OSAHS in a Caucasian population [6, 7]. Moreover, there are few reports demonstrating the significance of CPAP in a Chinese population with resistant hypertension and OSAHS.

The present study aimed to identify the effects of CPAP treatment on blood pressure of patients with resistant hypertension and OSAHS in a Chinese population.

Patients and methods

Patients

Three hundred and nine patients with resistant hypertension were recruited from the Jiangxi Province Chest Hospital, between January 2013 and June 2017. Patients were aged 18 to 80 years and provided informed consent. The 24-hour ambulatory blood pressure monitoring (ABPM) criteria were used to define resistant hypertension, with blood pressure remaining above the goal (i.e., average SBP ≥ 130 mm Hg, average DBP ≥ 80 mm Hg, or both) despite concurrent use of at least 3 anti-hypertensive medications, as described previously [13]. Subsequently, patients were invited to undergo overnight polysomnography (Alice6, Philips, Netherlands). Those with moderate to severe OSAHS (AHI ≥ 15 events/h) were selected. Initial exclusion criteria included pregnancy, upper airway malformations, disabling hypersomnia requiring urgent treatment (defined as an Epworth Sleepiness Scale [ESS] ≥ 18), current use of CPAP treatment, poor adherence with anti-hypertensive treatment, long-term treatment with oral corticosteroids or nonsteroidal anti-inflammatory drugs, and renal insufficiency (creatinine concentrations higher than 1.5 mg/dL in peripheral blood samples). The local Ethics Committee approved the protocol (approval No. 2013/A093). No patients were included in the protocol before study registration.

24-hour ambulatory blood pressure monitoring (ABPM)

24-hour ABPM (SpaceLabs 90217; SpaceLabs, Medical Inc, Redmond, Washington, USA) was performed, as described previously [16, 17]. Summary values in the ABPM report of each patient were used for data analysis. Data related to average diurnal and nocturnal systolic blood pressure (SBP), diastolic blood pressure (DBP), and 24-hour mean blood pressure [defined as (2/3DBP value) + (1/3SBP value)] were analyzed [18].

Continuous positive airway pressure (CPAP) treatment

Patients randomized to the CPAP treatment group were titrated in the sleep laboratory on a second night by an auto CPAP device (REMstar ProMSeries with C-Flex, Philips Respironics), within a period of less than 15 days after the diagnostic study, to obtain fixed CPAP pressure values, according to previous descriptions [13].

Statistical analysis

Continuous data are described as mean (standard deviation, SD). A two-tailed unpaired Stu-

Table 1. Baseline characteristics of all patients randomized to the control group and CPAP group

Characteristics	Control group (n = 47)	CPAP group (n = 43)	All patients (n = 90)
M/F	31/16	26/17	57/33
Age, y	58.7 (10.2)	61.2 (9.3)	59.9 (9.8)
BMI, kg/m^2	31.9 (4.3)	31.7 (4.1)	31.8 (4.2)
Obesity (BMI > 30 kg/m^2), %	59.6	62.8	61.1
Epworth Sleepiness Scale	9.8 (2.7)	10.0 (3.0)	9.9 (2.9)
AHI	40.10 (16.60)	46.53 (15.83)	43.18 (16.47)
AHI ≥ 30, n, %	35 (74.5)	37 (86.0)	72 (80.0)
Diabetes mellitus, n, %	14 (29.8)	12 (27.9)	26 (28.9)
Dyslipidemia, n, %	23 (48.9)	20 (46.5)	43 (47.8)
Neck circumference, cm	41.87 (3.01)	41.30 (2.64)	41.08 (2.84)
History of resistant hypertension, y	10.94 (3.69)	9.77 (3.70)	10.38 (3.72)
Mean O_2 saturation (%)	91.26 (3.50)	90.93 (3.98)	91.10 (3.72)
Heart rate, beats/min	76.34 (7.74)	76.40 (7.96)	76.38 (7.80)
Variability, mm Hg	10.4 (2.7)	10.6 (3.1)	10.5 (2.9)
24 h mean blood pressure, mm Hg	105.9 (6.0)	106.2 (5.3)	106.1 (5.6)
24 h SBP	145.2 (9.2)	148.9 (11.0)	147.0 (10.2)
Diurnal	149.5 (10.0)	153.2 (11.9)	151.2 (11.0)
Nocturnal	141.0 (8.7)	144.6 (10.4)	142.7 (9.7)
24 h DBP	86.3 (6.5)	84.9 (5.6)	85.6 (6.1)
Diurnal	89.8 (6.5)	88.5 (5.8)	89.2 (6.2)
Nocturnal	82.8 (6.8)	81.3 (5.5)	82.0 (6.1)

Abbreviations: CPAP, continuous positive airway pressure; M, male; F, female; y, year; BMI, body mass index; AHI, apnea-hypopnea index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

dent's *t*-test for independent samples or χ^2 test was used to compare baseline variables in the two groups. Differences between quantitative variables were analyzed using Student's *t*-test for unpaired data. Spearman's rank analysis was used to identify the correlation of number of hours of CPAP use and decrease in 24-hour mean blood pressure, SBP, and DBP in patients with resistant hypertension and OSAHS. Version 17 of SPSS (SPSS, Inc., Chicago, IL, USA) for Windows statistical program was used. GraphPad Prism Version 7.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used to draw the histogram. $P < 0.05$ indicates statistically significant differences.

Results

Study population

This study initially recruited 309 patients with clinical suspicion of resistant hypertension and OSAHS was screened using complete polysomnography. A total of 153 patients had moderate/severe OSAHS (AHI ≥ 15), while 156 patients were excluded with none or mild OSAHS. In addition, 51 patients were excluded while 102 patients were randomized, including 51 to the control group (2 died before the beginning and 2 refused to continue) and 51 to the CPAP group (2 died before the beginning and 6 refused to continue). Finally, there were a total of 47 patients in the control group and 43 patients in the CPAP group, eligible for clinical parameter analyses (**Figure 1**).

Baseline characteristics of all 90 participants of the CPAP and control groups are summarized in **Table 1**. The gender ratio among participants was 57/33 (M/F). The mean (SD) for age was 59.9 (9.8) years, while body mass index (BMI) was 31.8 (4.2), AHI was 43.18 (16.47) events per hour, and obesity ratio was 61.1%. The mean Epworth Sleepiness Scale (ESS) was 9.9. Data were similar in the two groups of patients. Incidence of diabetes mellitus and dyslipidemia, neck circumference, history of resistant hypertension, mean O_2 saturation, heart rates, and variability were displayed, showing no significant differences between the two groups. Furthermore, baseline values of 24-hour mean blood pressure, 24-hour SBP and DBP, diurnal SBP and DBP, and nocturnal SBP and DBP were measured using an ambulatory blood pressure monitoring system. Comparing baseline values, there were no significant differences between the control group and CPAP group (**Table 1**).

Mean use of anti-hypertensive drugs was 4.4 in all patients. Approximately thirty-six percent of patients were treated with three anti-hyperten-

Table 2. Description of anti-hypertensive medications in randomized patients

	Control group (n = 47)	CPAP group (n = 43)	All patients (n = 90)
No. of anti-hypertensive drugs	4.5 (1.5)	4.2 (1.2)	4.4 (1.4)
Diuretic, n, %	40 (85.1)	37 (86.0)	77 (85.6)
Calcium channel blockers, n, %	31 (66.0)	29 (67.4)	60 (66.7)
β-Blockers, n, %	29 (61.7)	25 (58.1)	54 (60.0)
α_1-Blockers, n, %	15 (31.9)	16 (37.2)	31 (34.4)
Angiotensin II receptor blockers, n, %	34 (72.3)	30 (69.8)	64 (71.1)
Angiotensin-converting enzyme inhibitors, n, %	21 (44.7)	18 (41.9)	39 (43.3)
Renin blockers, n, %	7 (14.9)	5 (11.6)	12 (13.3)
Others, n, %	4 (8.5)	5 (11.6)	9 (10.0)

sive medications, 22% with four drugs, and 42% with more than five drugs. Use of anti-hypertensive medications is detailed in **Table 2**.

Outcomes

In the CPAP group, mean (SD) use of CPAP treatment was 4.7 (1.4) hours/night, with 67.4% of patients with more than 4 hours/night. Mean use of CPAP pressure was 8.8 (2.4) mm Hg. As shown in **Table 3**, differences between the control group and CPAP group regarding blood pressure changes during follow-ups are presented. The 24-hour mean blood pressure at study entry and termination was 105.9 (6.0) mm Hg and 107.6 (5.8) mm Hg vs 106.2 (5.3) mm Hg and 104.0 (4.5) mm Hg in the control group and CPAP group, respectively. The 24-hour SBP, diurnal, or nocturnal SBP at study entry and termination was 145.2 (9.2) mm Hg and 148.0 (9.2) mm Hg, 149.5 (10.0) mm Hg and 150.6 (10.3) mm Hg or 141.0 (8.7) mm Hg and 145.4 (12.2) mm Hg vs 148.9 (11.0) mm Hg and 146.6 (7.7) mm Hg, 153.2 (11.9) mm Hg and 152.5 (9.7) mm Hg or 144.6 (10.4) mm Hg and 140.7 (9.5) mm Hg in the control group and CPAP group, respectively. The 24-h DBP, diurnal, or nocturnal DBP at study entry and termination was 86.3 (6.5) mm Hg and 87.4 (7.3) mm Hg, 89.8 (6.5) mm Hg and 90.4 (5.9) mm Hg or 82.8 (6.8) mm Hg and 84.4 (13.4) mm Hg vs 84.9 (5.6) mm Hg and 82.8 (6.3) mm Hg, 88.5 (5.8) mm Hg and 87.3 (6.8) mm Hg or 81.3 (5.5) mm Hg and 78.2 (8.0) mm Hg in the control group and CPAP group, respectively. Compared to the control group, the CPAP group achieved a greater decrease in 24-hour mean blood pressure (**Figure 2**), SBP (**Figure 3**), and DBP (**Figure 4**). There were significant reductions in nocturnal SBP (**Figure 3**) and DBP (**Figure 4**) in the CPAP treatment group, whereas no significant changes in diurnal SBP and DBP were observed with CPAP treatment. **Figure 5** shows a positive linear correlation between number of hours of CPAP use and decrease in 24-hour mean blood pressure ($r = 0.653$, $P < 0.001$; **Figure 5A**), SBP ($r = 0.619$, $P < 0.001$; **Figure 5B**), and DBP ($r = 0.570$, $P < 0.001$; **Figure 5C**).

Discussion

Resistant hypertension has been closely associated with OSAHS, contributing to poor control of blood pressure [19]. International guidelines have affirmed that minimal reduction in SBP (even 2-3 mm Hg) could dramatically reduce subsequent cardiovascular mortality in routine clinical practice [13]. Therefore, effective blood pressure control may effectively reduce adverse outcomes by OSAHS in patients with resistant hypertension. Emerging evidence has suggested that CPAP can effectively reduce AHI, cardiovascular morbidity, and cardiovascular mortality, one of the most effective therapies for OSAHS [7, 20]. However, there remains conflicting conclusions about whether CPAP can effectively control blood pressure in resistant hypertensive patients with OSAHS. Currently, at least four meta-analyses [6, 7, 21, 22] and six randomized controlled trials [10, 13, 23-26] have suggested that CPAP therapy is accompanied by a reduction in blood pressure in patients with resistant hypertension and OSAHS. However, Muxfeldt et al. found that CPAP treatment only had a beneficial effect on nighttime systolic blood pressure, with no significant effects on clinic and ambulatory blood pressure in patients with resistant hypertension and OSAHS [25].

The present study showed that 3 months of CPAP treatment achieved a mean reduction of 2.3 mm Hg and 2.1 mm Hg in 24-hour SBP and

Table 3. Effects of 3 months of continuous positive airway pressure treatment on blood pressure levels

Blood pressure, mm Hg	Control group (n = 47)			CPAP group (n = 43)			*P* value
	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	
24 h mean blood pressure	105.9 (6.0)	107.6 (5.8)	1.7 (5.2)	106.2 (5.3)	104.0 (4.5)	-2.2 (4.6)	< 0.001
24 h SBP	145.2 (9.2)	148.0 (9.2)	2.8 (7.5)	148.9 (11.0)	146.6 (7.7)	-2.3 (10.6)	0.010
Diurnal	149.5 (10.0)	150.6 (10.3)	1.1 (8.8)	153.2 (11.9)	152.5 (9.7)	-0.7 (12.8)	0.446
Nocturnal	141.0 (8.7)	145.4 (12.2)	4.4 (10.7)	144.6 (10.4)	140.7 (9.5)	-3.9 (11.5)	< 0.001
24 h DBP	86.3 (6.5)	87.4 (7.3)	1.1 (7.8)	84.9 (5.6)	82.8 (6.3)	-2.1 (6.2)	0.033
Diurnal	89.8 (6.5)	90.4 (5.9)	0.6 (7.4)	88.5 (5.8)	87.3 (6.8)	-1.2 (7.7)	0.268
Nocturnal	82.8 (6.8)	84.4 (13.4)	1.6 (13.2)	81.3 (5.5)	78.2 (8.0)	-3.1 (7.0)	0.042

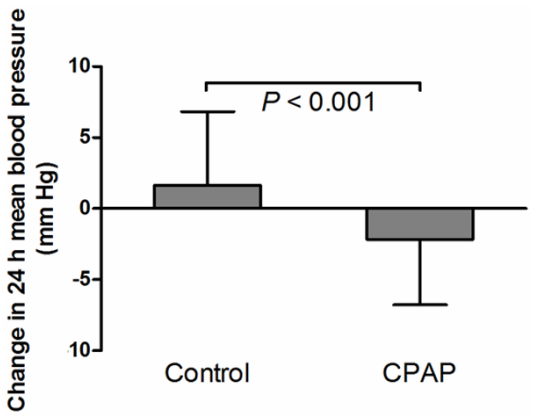

Figure 2. Effects of CPAP treatment on 24-hour mean blood pressure in patients with resistant hypertension and OSAHS.

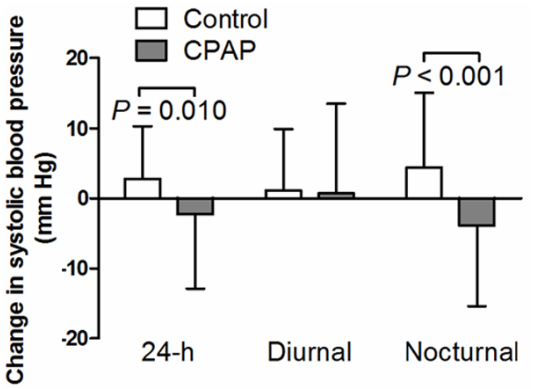

Figure 3. Effects of CPAP treatment on systolic blood pressure in patients with resistant hypertension and OSAHS.

DBP, respectively. Moreover, a reduction of nocturnal SBP (3.9 mm Hg) and DBP (3.1 mm Hg) also occurred in patients with resistant hypertension and OSAHS. Muxfeldt et al. showed a significant reduction in night-time SBP (4.7 mm Hg) with 6-months of CPAP treatment in 46 patients with ABPM-confirmed resistant hypertension [25]. Pedrosa et al. found that treatment of OSAHS with CPAP significantly reduced daytime SBP (6.5 mm Hg) and DBP (4.5 mm Hg) in patients with resistant hypertension [26]. Martínez-García et al. found a significant decrease in 24-hour mean blood pressure (3.1 mm Hg) and 24-hour DBP (3.2 mm Hg), but not in 24-hour SBP after 3 months of CPAP treatment on 98 patients with resistant hypertension, compared with 96 controls [13]. Lozano and his colleagues showed a decrease in 24-hour DBP (4.9 mm Hg), 24-hour DBP (6.98 mm Hg), and 24-hour SBP (9.71 mm Hg) in resistant hypertensive patients with OSAHS via CPAP treatment [10]. These studies provided evidence of the effects of CPAP in reducing blood pressure in patients with resistant hypertension and OSAHS.

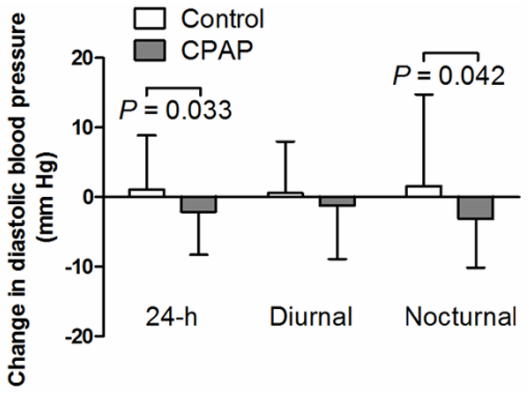

Figure 4. Effects of CPAP treatment on diastolic blood pressure in patients with resistant hypertension and OSAHS.

Iftikhar et al. [21] performed a meta-analysis of the effects of CPAP on blood pressure in patients with resistant hypertension and OSAHS, finding that CPAP treatment cannot sig-

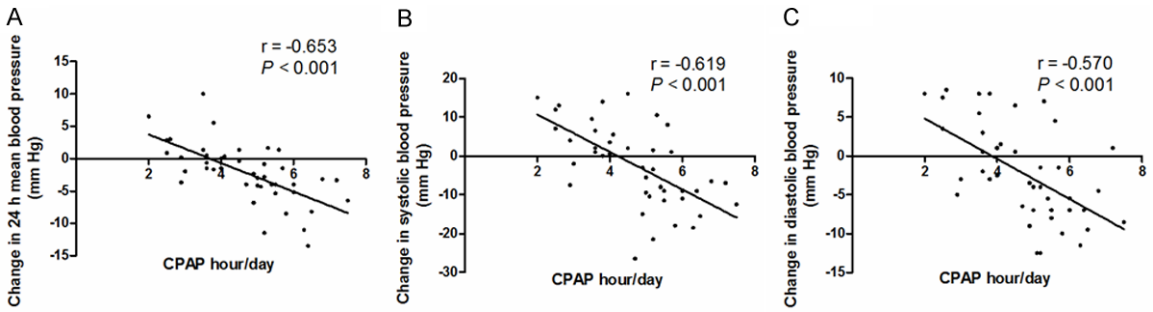

Figure 5. Correlation between continuous positive airway pressure (CPAP) use times and changes in 24-hour mean blood pressure (A), systolic blood pressure (B), and diastolic blood pressure (C) in the patients of the CPAP group that finished the follow-up.

nificantly improve nocturnal SBP/DBP but can significantly improve diurnal SBP/DBP. Similar results were reported by Pedrosa and his colleagues [26]. However, Hu et al. [27] summarized that CPAP led to more significant improvements in nocturnal SBP than in diurnal SBP in patients with resistant hypertension and OSAHS. Results obtained by Martínez-García et al. [13] were consistent with those obtained by Hu et al. [27]. The present study also found that nocturnal SBP/DBP, but not diurnal SBP/DBP, was decreased by 3.9 mm Hg and 3.1 mm Hg, respectively, in patients with OSAHS and resistant hypertension undergoing CPAP treatment. Therefore, patients with resistant hypertension and OSAHS should undergo combination therapy with antihypertensive medications and CPAP. Combination therapy is more significant than treatment with anti-hypertensive drugs alone.

Previous studies have indicated that the effects of CPAP on blood pressure levels are closely associated with the time of CPAP therapy [7, 10]. Lozano et al. found that CPAP treatment of more than 5.8 hours showed a greater reduction in night-time SBP and 24-hour DBP in patients with resistant hypertension and OSAHS than those with CPAP times less than 5.8 hours [10]. Martínez-García et al. showed a positive linear correlation between the time of CPAP therapy and decrease in 24-hour mean blood pressure, SBP, and DBP [13]. The present study corroborated these finding with a significant correlation between the hours of CPAP use and decrease in 24-hour mean blood pressure, SBP, and DBP in patients with OSAHS and resistant hypertension. Therefore, time of CPAP use was important in reducing blood pressure in patients with resistant hypertension and OSAHS. However, there is no uniform standard for time of CPAP use in clinical practice.

This study had several limitations. First, 3 months of follow-ups may have been insufficient to detect higher blood pressure reductions in patients with resistant hypertension and OSAHS. Some researchers, however, have suggested that 3 months of follow-ups resulted in significant changes in blood pressure with CPAP treatment [13, 28], while another study found significant changes in blood pressure only after 6 months [11]. Second, the number of RCTs included in this study was rather small, which may be biased toward meaningless results. Third, subgroups analysis of treatment times of CPAP was not performed in patients with resistant hypertension and OSAHS. Despite these limitations, the current study findings can be used to evaluate the magnitude of effects of CPAP on blood pressure with a larger number of participants and longer follow-up period.

In conclusion, CPAP treatment for 3 months resulted in the decrease of 24-hour mean, systolic, and diastolic blood pressure in patients with OSA and resistant hypertension. Moreover, correlation analysis indicated that decrease of 24-hour mean, systolic, or diastolic blood pressure is positively related to CPAP treatment times.

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Disclosure of conflict of interest

None.

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