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New perspective on exploring the predictive factors of blood pressure reduction during CPAP treatment in people with severe OSA and hypertension: a prospective observational study

Zili Meng,[1] Ying Chen,[1] Ting Yang,[1] Bo Sun,[1] Chao Luo,[1] Guihong Wei,[1] Xiaochen Xie,[1] Yang Gu,[1] Ning Ding,[2] Xilong Zhang,[2] Jing Xu[1]

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ZM and YC are joint first authors.

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[1]Department of Respiratory and Critical Care Medicine, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian, China
[2]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Correspondence to
Dr Jing Xu;
xj680390@126.com

ABSTRACT

Background The predictive factors of blood pressure (BP) response to continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA) are still being explored. We aimed to assess the antihypertensive effect of CPAP considering the obstructive respiratory event-triggered BP surge profiles in 130 subjects with severe OSA and untreated hypertension.

Methods Nocturnal BP was monitored continuously and synchronised with polysomnography. Event-triggered BP surge profiles were studied: BP surge as the value of event-related systolic BP (SBP) elevation; BP index as the number of BP surge events of ≥10 mm Hg per hour. Patients were then divided into two groups according to the median BP index (high and low BP surge groups) and assigned to 4 weeks of CPAP. Changes in BPs and plasma biomarkers were compared. After the initial evaluation, patients with a better BP response in the high BP surge group were then followed up for the second evaluation at 24 months.

Results Overall, a modest decrease was observed in both office and asleep BPs at the 4-week follow-up; however, BPs dropped more markedly in patients in the high BP surge group than those in the low BP surge group, in both office SBP (5.3 mm Hg vs 2.2 mm Hg, p=0.003) and diastolic BP (4.0 mm Hg vs 1.2 mm Hg, p<0.001), especially the asleep SBP (9.0 mm Hg vs 2.1 mm Hg, p<0.001). For 30 cases in the high BP surge group, optimal BP control was achieved in 60.0% of patients and BP<140/90 mm Hg reached up to 83.3% after 24 months of CPAP. Linear regression revealed that BP index was significantly associated with BP decrease during CPAP treatment.

Conclusions Our results suggested that high event-triggered BP surge was a sensitive predictor of BP response to CPAP in patients with severe OSA and untreated hypertension.

Trial registration number Clinical Trials.gov Identifier: NCT03246022; https://clinicaltrials.gov/ct2/show/NCT03246022?term=NCT+03246022&draw=2&rank=1.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The clinical or biological profiles that can predict the antihypertensive effect of continuous positive airway pressure (CPAP) are still under active investigation. How can we identify the subgroup of obstructive sleep apnoea (OSA) in whom blood pressure (BP) could be reduced to a greater extent by CPAP treatment?

WHAT THIS STUDY ADDS

⇒ In this study of 130 patients with severe OSA and untreated hypertension, we found that the impact of CPAP on BP control depended on the obstructive respiratory event-triggered BP surge profiles; only patients with high BP surge profiles could benefit from CPAP in terms of BP reduction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study stressed that a specific analysis of event-triggered BP surge profiles seems to be necessary to treat patients with severe OSA and hypertension efficiently.

INTRODUCTION

Obstructive sleep apnoea (OSA) may trigger multiple pathways involved in blood pressure (BP) elevation, such as activation of the renin–angiotensin–aldosterone system (RAAS), persistently elevated sympathetic tone, activated inflammation and oxidative stress, and endothelial dysfunction.[1 2] It has been widely demonstrated that OSA is closely linked to hypertension,[3] especially in patients with severe OSA.[4]

Continuous positive airway pressure (CPAP) therapy is the standard treatment for severe OSA, which could eliminate recurrent

hypoxia events to restore the BP regulation pathways.[5 6] Since OSA and hypertension are tightly linked, it may be expected that abolition of apnoeas acutely reduces BP levels. However, the effects of CPAP on BP reduction have been disappointing and inconsistent, with a meta-analysis showing reductions in BP of 2–3 mm Hg.[7] Even in resistant hypertension, CPAP reduced systolic and diastolic BP (SBP and DBP, respectively) by only ~3 mm Hg.[8] Factors such as the severity, hypersomnolence, high baseline BP values or good CPAP adherence may contribute to modulation of the BP response to CPAP.[7 9] However, these findings were challenged by a study of Pengo *et al*,[10] who found no significant differences in BP-lowering effect by CPAP when the subgroup analysis divided studies according to body mass index (BMI), CPAP adherence, daytime sleepiness and an apnoea–hypopnoea index (AHI)≥30 events/hour. Do some 'OSA phenotypes' with specific BP responses to CPAP exist? If so, successful identification of such phenotype could facilitate decision-making in precision medicine for BP control in clinical practice.

Studies using continuous BP monitoring devices reported that an apnoea episode induces a transient BP elevation (ie, BP surge) at the time of its termination,[11] resulting in high baseline BP levels.[12 13] This acute haemodynamic response is closely associated with the specific sleep stage, the oxygen desaturation rate, the magnitude of desaturation and episode duration.[12 14 15] It seems that individual postapnoeic BP surges are highly variable due to the variability of the episodes' conditions. According to this, OSA patients may present different night-time BP profiles. For high BP surge phenotype, frequent BP peaks result in elevated asleep BP, which is associated with nocturnal hypertension or the non-dipper BP status. In this phenotype, CPAP seems to reduce the average BP levels by abolishing these frequent BP surges. The intriguing hypothesis that the differences in BP responses to CPAP therapy may vary depending on the event-triggered BP surges category was proposed.

In the present study, we explored this hypothesis by assessing event-triggered BP surge profiles via continuous beat-to-beat BP monitoring in a group of subjects with severe OSA and untreated hypertension. Our primary outcomes were that patients with higher BP surges could achieve a remarkable reduction in BP with CPAP therapy, while patients with lower surges may exhibit a mild BP response. Second, as heightened sympathetic activity was demonstrated to be tightly associated with the development of hypertension, we further explored whether the differences in BP responses to CPAP therapy were associated with the extent of reduced sympathetic overactivity induced by CPAP.

METHODS

Participants

This single-centre, prospective, observational study registered at ClinicalTrials.gov (NCT 03246022). We conformed to the principles outlined in the Declaration of Helsinki. All participants provided written informed consent before study participation. Between April 2018 and July 2020, patients were eligible if they were aged between 18 and 75 years, office BP was consistently higher than 140/90 mm Hg in the past week, without any treatment, and with an AHI≥30 events/hour. Exclusion criteria included: other sleep disorders, chronic severe disease, refusal to participate, secondary hypertension, severe hypertension (clinical SBP≥180 mm Hg or DBP≥110 mm Hg), previous or current use of CPAP or other treatments for OSA. Besides, patients treated with antihypertensive, antidepressant or psychotropic drugs and those being unable to provide informed consent were also excluded.

Patient and public involvement statement

Patients were not involved in the development of study design or recruitment of participants.

Sleep study and CPAP treatment

A detailed questionnaire was made to assess the daily BPs, comorbidities, current medication, smoking and alcohol use, clinical history and anthropometric data. Daytime sleepiness was assessed using the Epworth Sleepiness Scale. All recruited participants underwent a full overnight polysomnography (PSG) study in sleep centre (PSG, SOMNOscreen plus PSG+). Recordings were manually scored by a qualified technologist. Apnoea was defined as an interruption of oronasal airflow for more than 10 s. Hypopnoea was defined as a 30%–90% decrease in oronasal airflow with an associated ≥3% oxygen desaturation. AHI was calculated on the basis of the total number of episodes of apnoea and hypopnoea per hour of sleep. OSA was defined as AHI≥5 events/hour, whereas AHI≥30 events/hour indicated severe OSA. During the second night, a trained specialist administered a night of CPAP titration to ensure that the optimum therapeutic pressure was sufficient to hold open the pharynx.

Definition of BP parameters and grouping

In addition to provide a BP diary, all subjects had their BP assessed when they were referred to the sleep laboratory, where office BP was obtained at 5 min intervals by conventional mercury sphygmomanometry and the average of three BP measurements was calculated. We defined hypertension as an office BP measurement of more than 140/90 mm Hg according to the international guidelines.[16] Beat-to-beat BP was continuously monitored by a pulse transit time (PTT)-based method, which was synchronised with the PSG (SOMNO screen plus PSG+). PTT is the time the pulse wave needs for travelling between two points in the arterial system, here from the heart to the fingertip. This time can be calculated from the R-peak in the ECG signal and the arrival time of the corresponding pulse wave at the finger (determined from

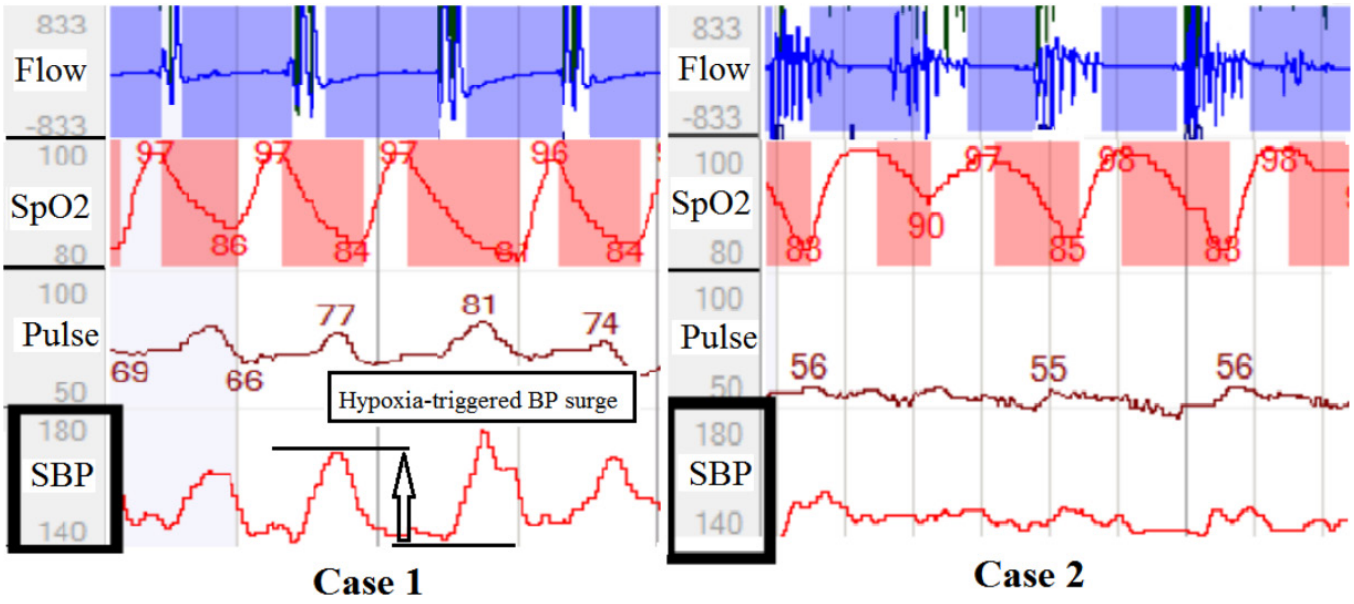

Figure 1 The obstructive respiratory event-triggered blood pressure (BP) surge profiles of two cases. Note: all parameters were based on polysomnography recording. BP values were measured by a pulse transit time-based method, which was synchronised with the polysomnography. Event-triggered BP surge was defined as the gap between the peak value of postapnoeic systolic BP (SBP) and the lowest SBP during an obstructive respiratory event. Case 1 shown a commonly detected phenomenon that an episode causes an acute transient BP surge, while in case 2, the phenomena of remarkable BP fluctuations was not detected during the frequent apnoea/hypopnoea episodes.

the Pleth analysis of the pulse oximeter at the finger). The stiffness and tension in the arterial walls are the major factors determining the speed of transmission of the pulse wave, and this in turn depends on a large extent BP. An acute rise in BP increases arterial wall tension and stiffness, thus shortening PTT, and in that respect, PTT may better reflect dynamic BP changes. The non-invasive device has been shown to be consistent with cuff-based manometry device and had a high reproducibility.[17–19] PTT calibration was implemented when measured by cuff realised three consecutive stable results, and the continuous BP monitoring was begun.[20] The following BP parameters were calculated: asleep BP, the average BP values while being asleep as detected by PSG; event-triggered BP surge profiles: BP surge was calculated as the gap between the peak value of postapnoeic SBP and the lowest SBP during an obstructive respiratory event; BP index was the frequency of BP surges, which was defined as the number of BP surge events of ≥10 mm Hg per hour.[12 15] Figure 1 displays the details of event-triggered BP surge profiles in two cases: case 1 shows a commonly detected phenomenon, that from the beginning to the end of an obstructive respiratory event, where BP was gradually elevated with a progressively declining SpO_2, while these remarkable BP fluctuations were not present in case 2. Initially, patients were divided into three equal groups based on BP index/AHI of the whole cohort. At the period of calculating the sample size of this protocol, a pilot study was performed. We found no significant differences in BP-lowering effect in response to CPAP between groups 1 and 2 according to the pilot study's data. Based on a study conducted by Sánchez-de-la-Torre *et al*,[21] we regrouped the patients into two groups based on the median BP index and, found a greater BP reduction in the high BP surge group than in patients with low BP surges after CPAP treatment. Thus, after the initial assessment of BP surge profiles in all enrolled subjects, the entire cohort was divided into two groups based on the median BP index (high BP surge group: BP index≥36.2, N=65; low BP surge group: BP index<36.2, N=65) and assigned to optimal CPAP treatment.

Blood sampling for biomarker assays

Blood samples were collected on the next morning after fasting for 8 hours before and after 4 weeks of CPAP treatment. ELISA kits were used for quantitative in vitro determination of serum concentrations of circulating biomarkers to reflect sympathetic tone (norepinephrine (NE)), RAAS activity (angiotensin II (AngII)), inflammation and oxidative stress (interleukin 6 (IL-6), superoxide dismutase (SOD), 8-iso-prostaglandin F2α (8-iso-PGF2α)), as well as the endothelium system (endothelin-1 (ET-1)), respectively.

Follow-up

After the titration night, patients were sent home with their therapeutic machine for 4 weeks, and CPAP compliance was checked daily. At the study entry, the participants could contact researchers directly at all times for clinical problem-solving issues and were instructed to perform home BP measurements to check their BP daily. During follow-up, patients whose BP was consistently≥180/110 mm Hg or who complained of clinical

symptoms were excluded from the study and immediately given clinical intervention. After 4 weeks of therapy, patients reattended for a repeated PSG and BP recording. Finally, patients with a better BP response in the high BP surge group (considered as asleep SBP reduction above the 50th percentile value) were then followed up at 24 months for the second evaluation, and the same procedure was performed. Attention was paid to check that patients had not received any antihypertensive treatment since the initial evaluation; otherwise, they were excluded.

Statistical analyses

Continuous variables were summarised as mean (SD) or median (IQR), the categorical data were described as the absolute value and its proportions. The differences between the baseline characteristics of two subgroups were assessed by means of the Student's t-test, Mann-Whitney U test or χ^2 test. The sample size was calculated to detect a difference of at least 3.04 mm Hg in nighttime SBP reduction between groups based on considering the non-dipper status.[22] Accordingly, a total of 62 patients were needed per treatment group if an error of 0.05 (2-tailed test), a statistical power of 0.9 and a pooled SD of 5.2 (obtained from a pilot study of this sample) were used.

The multiple imputation method was used to estimate values for the missing data, and an intention-to-treat analysis was undertaken. For the 4-week evaluation, the intragroup comparisons from beginning to the end of the study were evaluated using a paired t-test. Intergroup differences of the change in BP were established by means of a general linear model adjusted for age, hypersomnolence, sex, smoking and drinking status, the baseline values of BP, BMI, CPAP use and AHI, with the OSA subgroup (low and high BP surge) as a fixed factor. For the 24-month evaluation, comparisons of variables (baseline, 4 weeks and 24 months) were made by generalised estimated equation.

Multiple linear regression models were established to explore the factors affecting BP decrease during CPAP treatment. Age, sex, BMI, baseline BP values, hypersomnolence and CPAP compliance were always entered in the models. The relevant sleep parameters ($p \leq 0.1$) and other relevant demographics ($p \leq 0.1$) were entered in the models as independent variable using a stepwise method. Because the reference ranges for the levels of plasma biomarkers were variably reported between studies, the percentage changes of biomarkers in post-CPAP treatment levels relative to pre-CPAP treatment levels were performed in correlation analysis to examine the underlying mechanisms associated with the BP response to CPAP. All statistical analyses were performed with the SPSS statistical software package (V.20.0), all tests were two-sided, and a p value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 130 untreated hypertensive patients with severe OSA who received CPAP treatment were included in the analysis. Of these, 119 patients (91.5%) were men. The mean (SD) for age was 44.3 (9.9) years, the mean BMI was 29.8 (3.3) kg/m^2 and the mean AHI was 66.0 (17.6) events per hour. The mean (SD) for baseline office SBP was 151.3 (7.4) mm Hg and DBP was 95.9 (6.8) mm Hg. The average CPAP duration was 6.2 (1.2) hour per night, the mean CPAP pressure used was 10.2 (1.3) mm Hg and the residual AHI was 3.2 (2.3) events/hour. In comparison with the low BP surge group, the high BP surge group included patients who were younger, had higher BMIs and waist circumferences; this group also exhibited more severe sleep respiratory disorder parameters, higher levels of asleep BPs and mean BP surge. No differences were observed in sex distribution, drinking, tobacco use, comorbidities, baseline office SBP values, CPAP uses, mean CPAP pressure and plasma biomarkers between groups (table 1).

Four-week follow-up evaluation

As shown in figure 2, 11 patients did not come for the second PSG: 2 were lost to follow-up, 1 had severe hypertension, 1 had taken antihypertensive medicine, 3 refused to continue and 4 had poor CPAP adherence. Eventually, a total of 119 subjects completed the 4-week follow-up. For the entire sample, a modest but significant decrease in BP was observed after 4 weeks of CPAP therapy compared with baseline (office SBP: 3.8 mm Hg (95% CI 3.1 to 4.4); DBP: 2.6 mm Hg (95% CI 2.1 to 3.2); and asleep SBP: 5.5 mm Hg (95% CI 4.3 to 6.7); DBP: 3.0 mm Hg (95% CI 2.4 to 3.6), all $p<0.05$). However, BP values dropped more markedly in patients with high BP surge than in those with low surge, including both office SBP (5.3 mm Hg vs 2.2 mm Hg, difference: 2.6 mm Hg (95% CI 0.9 to 4.4), $p=0.003$) and DBP (4.0 mm Hg vs 1.2 mm Hg, difference: 2.6 mm Hg (95% CI 1.2 to 4.0), $p<0.001$), especially the asleep SBP (9.0 mm Hg vs 2.1 mm Hg, difference: 6.3 mm Hg (95% CI 3.2 to 9.3), $p<0.001$), while no significant difference was observed in asleep DBP (4.1 mm Hg vs 1.9 mm Hg, difference: 1.6 mm Hg (95% CI 0 to 3.2), $p=0.055$). In terms of plasma biomarkers, CPAP resulted in a significant reduction in ET-1, IL-6, SOD from baseline in both the high and low BP surge groups, while NE and AngII were only reduced in the high BP surge group but not in the low BP surge group (table 2).

Predictive factors for BP response to CPAP

Table 3 shows a linear regression model to explore the factors that could predict post-CPAP changes in BPs. For entire study samples, BP changes were directly correlated with the BP index (office SBP: $\beta=0.485$, $p<0.001$; DBP: $\beta=0.427$, $p<0.001$; mean arterial pressure (MAP): $\beta=0.426$, $p<0.001$ and asleep SBP: $\beta=0.293$, $p=0.005$; DBP: $\beta=0.337$, $p<0.001$; MAP=0.405, $p<0.001$) after adjusting

Table 1 Baseline characteristics of study groups

Characteristics	High BP surge group (N=65)	Low BP surge group (N=65)	P value
Demographics and medical history			
Age (years)	42.2±9.8	46.4±9.6	0.013
Men	60 (92.3)	59 (90.8)	0.753
BMI (kg/m^2)	31.0±2.7	28.6±3.4	<0.001
ESS (0–24)	12.6±4.8	12.1±4.7	0.547
Neck circumferences (cm)	43.4±2.7	42.2±3.8	0.064
Waist circumferences (cm)	110.3±6.4	106.9±8.0	0.009
Alcohol drinking	48 (73.8)	43 (66.2)	0.339
Active smokers	35 (53.8)	30 (46.2)	0.380
Diabetes mellitus	9 (13.8)	8 (12.3)	0.795
Ischaemic heart disease	5 (7.7)	6 (9.2)	0.753
Polysomnographic variables			
AHI (events/hours)	77.5±12.2	54.6±14.4	<0.001
REI (events/hours)	63.8±17.7	45.5±18.7	<0.001
T90 (%)	48.4±19.1	23.5±15.6	<0.001
$MSpO_2$ (%)	89.0 (87.0–91.0)	92.0 (90.5–93.0)	<0.001
$LSpO_2$ (%)	62.7±9.4	70.3±9.8	<0.001
TST (hours)	6.6±1.3	6.8±1.1	0.366
ODI (events/hours)	75.3±13.1	50.7±14.6	<0.001
Residual AHI (events/hours)	3.6±2.7	2.7±1.6	0.019
Post-$MSpO_2$ (%)	96.0 (95.0–96.1)	95.0 (94.1–96.0)	0.588
BP parameters (mm Hg)			
Office SBP	151.9±7.4	150.7±7.3	0.364
Office DBP	97.6±6.3	94.3±7.0	0.006
Office MAP	114.9±6.6	112.6±6.5	0.042
Asleep SBP	151.3±10.1	146.3±8.3	0.002
Asleep DBP	97.4±6.3	94.3±7.0	0.002
Asleep MAP	115.4±7.8	110.6±6.9	<0.001
Mean BP surge	19.6±5.8	11.3±4.1	<0.001
BP index (events/hours)	52.4±12.1	20.1±9.6	<0.001
CPAP use (hours/night)	6.3±1.2	6.0±1.3	0.193
CPAP treatment pressure	10.2±1.3	10.1±1.2	0.730
Laboratory tests*			
Norepinephrine (pg/mL)	555.78±321.87	463.67±223.47	0.060
Angiotensin II (pg/mL)	1.71±0.89	1.48±0.73	0.144
Endothelin-1 (pg/mL)	1.53±0.39	1.49±0.37	0.563
8-iso-Prostaglandin F2α (pg/mL)	98.04±34.38	92.08±21.34	0.237
Interleukin 6 (pg/mL)	2.04±0.69	1.95±0.79	0.506
Superoxide dismutase (ng/mL)	81.97±31.97	78.03±24.23	0.430

BP surge, the gap between the peak value of post-apnoeic SBP and the lowest SBP during an obstructive respiratory event; mean BP surge was calculated as the average value of all obstructive respiratory events-related BP elevation. BP index, the events of BP surge≥10 mm Hg per hour, which used to reflect the frequency of BP surge. Laboratory tests were used to reflected sympathetic tone (norepinephrine), renin–angiotensin–aldosterone system activity (angiotensin II), inflammation and oxidative stress (interleukin 6, 8-iso-Prostaglandin F2α, superoxide dismutase) and endothelium system (endothelin-1).
AHI, apnoea–hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; $LSpO_2$, the lowest oxygen saturation during sleep; MAP, mean arterial pressure; $MSpO_2$, mean oxygen saturation during sleep; ODI, mean arterial oxygen desaturation per hour of sleep; REI, respiratory event index; SBP, systolic blood pressure; T90, percentage of sleep time with oxygen saturation<90%; TST, total sleep time.

for the relevant variables. In contrast, we did not find any association between BP reductions and AHI, CPAP use, hypersomnolence or baseline BP values. Figure 3 shows a positive linear correlation between the CPAP-induced relative changes of NE and the decrease in office BPs (SBP: r=0.357, DBP: r=0.371, MAP: r=0.536; all p<0.001) and asleep BPs (SBP: r=0.549, DBP: r=0.470, MAP: r=0.509; all p<0.001). In contrast, AngII was only associated with asleep BPs (SBP: r=0.549, p=0.001; DBP: r=0.274, p=0.001; MAP: r=0.305, p<0.001) but not with office BPs. The remaining plasma biomarkers changes (SOD, IL-6, ET-1, 8-iso-PGF2alpha) showed no associations with the BP response to CPAP therapy.

Twenty-four-month follow-up evaluation

After the 4-week follow-up analysis, a total of 30 patients with a better BP response in the high BP surge group were then followed up at 24 months. Five patients did not complete the follow-up: two had poor CPAP adherence, two received oral antihypertensive medicine and one refused to participate. In the second evaluation, no changes in BMI were found compared with baseline. We observed an office SBP of 151.4 (8.2) mm Hg and a DBP of 98.0 (7.1) mm Hg at baseline and an office SBP of 129.7 (8.8) mm Hg and a DBP of 85.3 (5.7) mm Hg after 24 months of CPAP treatment. Regarding BP changes, 24 months of CPAP treatment achieved a greater decrease in both office SBP/DBP/MAP (SBP: 21.7 mm Hg (95% CI 20.0 to 23.4); DBP: 12.6 mm Hg (95% CI 10.5 to 14.8);

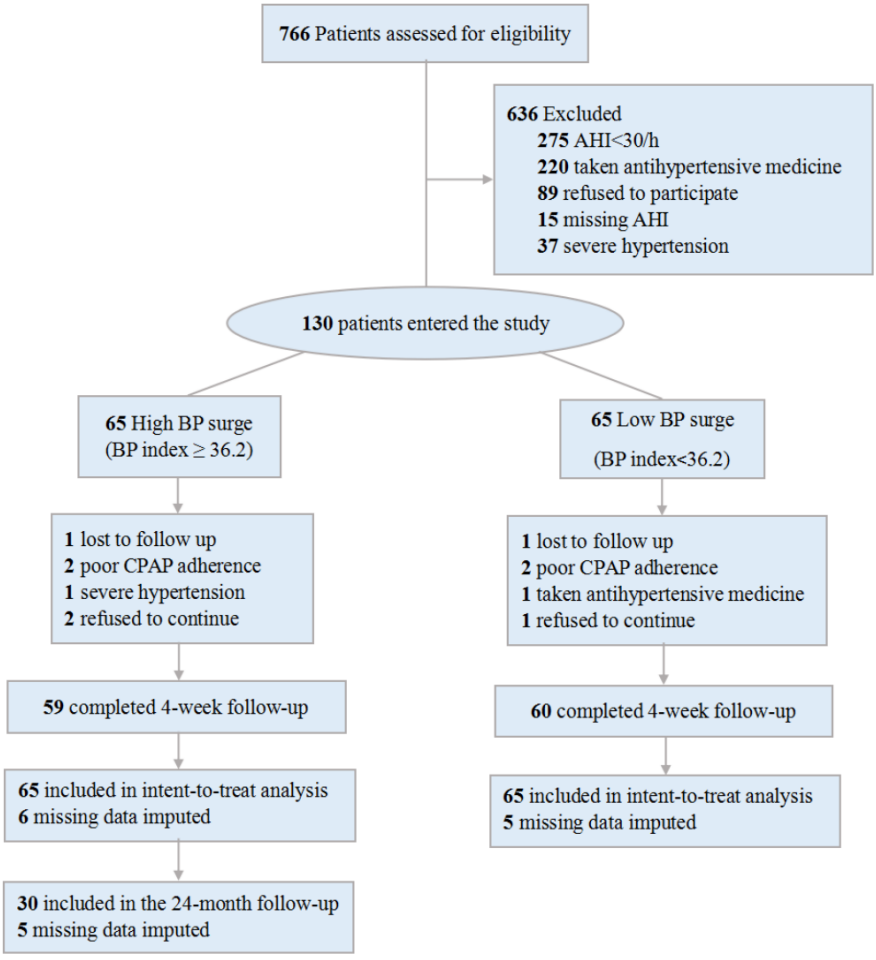

Figure 2 Flowchart of patients recruitment, run-in and follow-up. AHI, apnoea–hypopnoea index; BP, blood pressure; CPAP, continuous positive airway pressure.

MAP: 15.6 mm Hg (95% CI 14.0 to 17.2), all p<0.001) and asleep SBP/DBP/MAP (SBP: 31.4 mm Hg (95% CI 28.4 to 34.4); DBP: 15.7 mm Hg (95% CI 13.4 to 17.9); MAP: 21.1 mm Hg (95% CI 19.0 to 23.2), all p<0.001) (figure 4). Notably, optimal BP control (office SBP<130 mm Hg) was achieved in 60.0% of patients and BP<140/90 mm Hg reached up to 83.3% after 24 months of CPAP treatment.

DISCUSSION

At the study entry, CPAP compliance, BP values and clinical symptoms were checked daily. At the 2-week follow-up, mild but significant differences were observed between the two groups and no patients had clinical symptoms. For this reason, the follow-up was extended to 4 weeks. At the 4-week follow-up, one patient had severe hypertension and one patient received oral antihypertensive drugs due to high BP levels. For this reason, the timing of the 4-week follow-up was chosen for exploring BP responses to CPAP. As anticipated, the impact of CPAP on BP control depends on the event-triggered BP surges. Our study, therefore, stressed that BP surge profile could be considered when selecting the optimal antihypertensive therapeutic approach for patients with severe OSA and hypertension.

In the past several years, data from meta-analyses and systematic reviews have shown the highly variable results of BP response to CPAP treatment.[7–10] Specific OSA phenotypes, such as patients with high adherence, more severe OSA or resistant hypertension, were reported clearly benefit from CPAP in terms of BP reduction.[8 9 23] However, both Barbé *et al*[24] and Martínez-Garcia *et al*[8] found that nearly 30% of patients who used CPAP for ≥4 hours per day showed no changes in BP values, and data from previous randomised controlled trials showed no association between baseline OSA severity and BP decrease.[25] Some data suggested that significant reductions in diurnal SBP and DBP were evident only in studies whose patients reported a greater degree of daytime hypersomnolence,[9] but results from a study of Durán-Cantolla *et al* did not support this conclusion.[26] For resistant hypertension, although CPAP was associated with clinically significant changes in BP, the evidence is not sufficient to support the benefits of CPAP in all OSA population.[27] Therefore, owing to the high heterogeneity of results observed, more high precision factors

Table 2 Changes from baseline in BPs and plasma biomarkers adjusted by confounding factors

Variables	High BP surge group		Low BP surge group		Follow-up at 4 weeks	
	Intragroup difference mean (95% CI)	P value	Intragroup difference mean (95% CI)	P value	Intergroup adjusted mean (95% CI)	P value
Office SBP (mm Hg)	5.3 (4.3 to 6.4)	<0.001	2.2 (1.5 to 2.8)	<0.001	2.6 (0.9 to 4.4)	0.003
Office DBP (mm Hg)	4.0 (3.3 to 4.7)	<0.001	1.2 (0.6 to 1.9)	0.001	2.6 (1.2 to 4.0)	<0.001
Office MAP (mm Hg)	3.3 (2.6 to 4.1)	<0.001	1.2 (0.8 to 1.6)	<0.001	1.7 (0.5 to 3.0)	0.006
Asleep SBP (mm Hg)	9.0 (7.3 to 10.8)	<0.001	2.1 (0.9 to 3.2)	0.001	6.3 (3.2 to 9.3)	<0.001
Asleep DBP (mm Hg)	4.1 (3.2 to 4.9)	<0.001	1.9 (1.2 to 2.7)	<0.001	1.6 (–0.0 to 3.2)	0.055
Asleep MAP (mm Hg)	5.7 (2.6 to 4.1)	<0.001	1.6 (0.7 to 2.4)	0.001	3.6 (1.8 to 5.4)	<0.001
Norepinephrine (pg/mL)	156.22 (106.92 to 205.52)	<0.001	13.77 (–16.38 to 43.94)	0.365	106.93 (26.33 to 187.54)	0.010
Angiotensin II (pg/mL)	0.19 (0.05 to 0.34)	0.009	0.09 (–0.05 to 0.23)	0.210	–0.03 (–0.30 to 0.24)	0.833
Endothelin-1 (pg/mL)	0.25 (0.14 to 0.35)	<0.001	0.20 (0.09 to 0.30)	<0.001	0.03 (–0.16 to 0.23)	0.729
8-iso-Prostaglandin F2α (pg/mL)	–26.32 (–38.98 to –13.64)	<0.001	–6.41 (–13.24 to 0.42)	0.065	–18.09 (–38.67 to 2.50)	0.083
Interleukin 6 (pg/mL)	0.25 (0.18 to 0.32)	<0.001	0.21 (0.10 to 0.32)	<0.001	–0.07 (–0.23 to 0.09)	0.385
Superoxide dismutase (ng/ml)	14.09 (6.17 to 22.02)	0.001	14.31 (8.07 to 20.55)	<0.001	–1.49 (–16.11 to 13.14)	0.840

Intragroup differences from beginning to the end of 4-week follow-up were evaluated using a paired t-test.
Intergroup comparisons were assessed by a general linear model adjusted for the age, hypersomnolence, sex, smoking and drinking status, the baseline values of BP, body mass index, continuous positive airway pressure use and apnoea–hypopnoea index, with the obstructive sleep apnoea subgroup (low and high BP surge) as a fixed factor.
BP, blood pressure; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 3 Independent of determinants of BPs response to CPAP in severe OSA

	Standardised regression coefficients (β)	95% CI for β	R^2	P value
Office SBP reduction				
BP index	0.485	(0.064 to 0.124)	0.229	<0.001
Office DBP reduction				
BP index	0.427	(0.043 to 0.094)	0.182	<0.001
Office MAP reduction				
BP index	0.426	(0.036 to 0.080)	0.181	<0.001
Asleep SBP reduction				
BP index	0.293	(0.033 to 0.175)	0.283	0.005
Baseline asleep SBP	0.224	(0.054 to 0.271)	0.338	0.004
BP surge	0.241	(0.039 to 0.472)	0.360	0.021
Asleep DBP reduction				
BP index	0.337	(0.031 to 0.089)	0.114	<0.001
Asleep MAP reduction				
BP index	0.405	(0.050 to 0.126)	0.273	<0.001
$MSpO_2$	–0.216	(–0.412 to –0.044)	0.306	0.015

Age, sex, body mass index, baseline BP values, hypersomnolence and CPAP compliance were always entered in the models as independents. The relevant sleep parameters (p≤0.1) and other relevant demograohic (p≤0.1) were entered in the models as independent variables using a stepwise method.
BP, blood pressure; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; $MSpO_2$, mean oxygen saturation during sleep; OSA, obstructive sleep apnoea; SBP, systolic blood pressure.

for predicting the antihypertensive effect of CPAP are needed.

Recently, a meta-analysis conducted by Pengo *et al* showed patients with higher baseline BP levels, aged less than 60 years and with severe hypoxia burden are more likely to experience greater BP-lowering effects in response to CPAP treatment.[10] We cannot exclude the possibility that OSA patients with severe hypoxaemia or high baseline BP levels may be more likely to derive antihypertensive benefits from CPAP therapy than patients without. Conversely, in our linear regression model, $MSpO_2$ was negatively correlated with asleep MAP reduction caused by CPAP, and a greater asleep SBP reduction was associated with baseline nocturnal SBP. In contrast, we did not find any association between BP reductions and AHI, CPAP use or hypersomnolence. When exploring the more sensitive predictors of BP decrease during CPAP treatment, $MSpO_2$, T90 and $LSpO_2$ were always entered in the models as dependents; we found that the BP index was more strongly correlated with BP reduction than hypoxia parameters (see table 3). By contrast, age was not a potential predictor to identify subgroups of patients who respond best to CPAP in our study. There are some explanations for this discrepancy. First, the population included in our study is relatively young, with an average age of 44.3 (9.9) years. We flailed to explore the effect of CPAP on BP reduction based on age 60 as a cut-off. Besides, not all studies have measured BP in the same way, and the different study populations were mixed with normotensive, controlled or uncontrolled hypertensive patients and different types of antihypertensive medications may also affect the BP response to CPAP treatment.

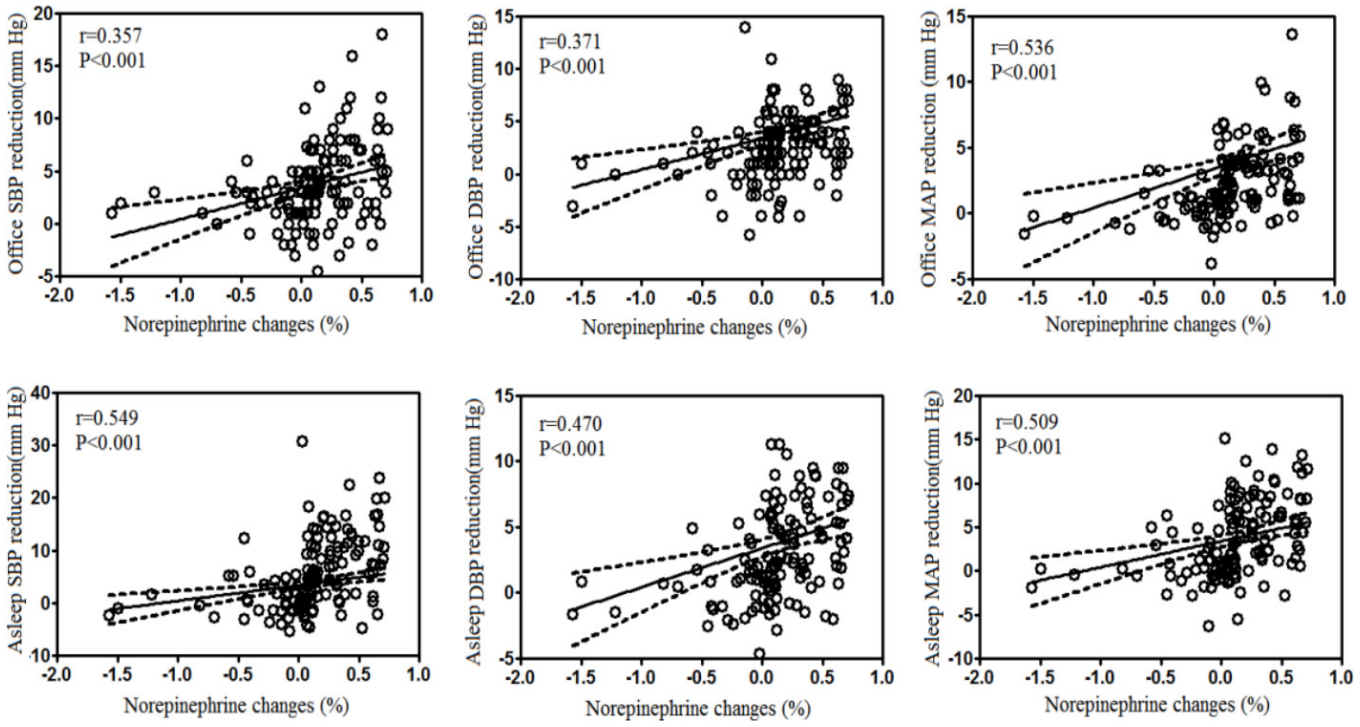

Figure 3 Correlation between the relative changes in norepinephrine and BP reduction during continuous positive airway pressure (CPAP) treatment. Note: norepinephrine changes were performed as the percentage changes of in post-CPAP treatment levels relative to pre-CPAP treatment levels. DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

OSA is a nocturnal breathing disorder, and the clinical variables related to BP effects during CPAP should consider the night-time conditions, such as hypoxaemic burden or night-time BP profiles. Recent studies focused on BP response to CPAP, taking into consideration the circadian BP pattern. Sapiña-Beltrán *et al* compared the effects of 12-week CPAP on BP between dipper and non-dipper hypertensive patients and found that only non-dipper patients benefit from CPAP treatment in terms of BP reduction.[22] Data from an observational, multicentre, pre–post study suggested that nocturnal hypertension and the circadian BP pattern could be clinical predictors of BP response to CPAP.[28] In our study, we explored this issue considering the more details of night-time BP properties and found that only patients with high BP surge would benefit the most from CPAP. It seems that the frequent exaggerated BP surges may elevate mean BP levels while being asleep and therefore result in the lack of dipping and the incidence of nocturnal hypertension. Similarly, Picard *et al* showed that the decrease in the frequency of BP surges leads to an improvement of BP: the maximum SBP decreased already after the first night

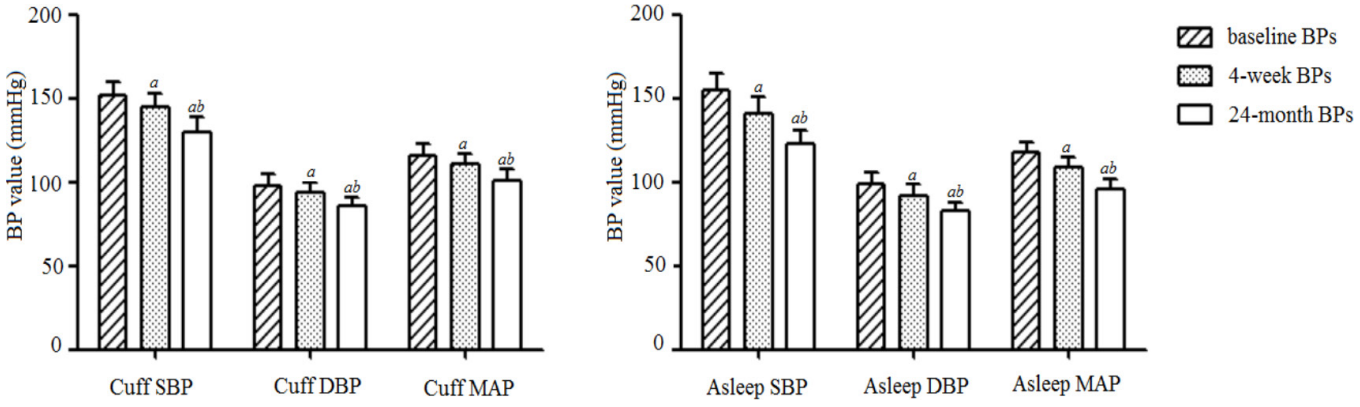

Figure 4 Comparison of the BP variables at baseline, 4-week and 24-month follow-up in 30 subjects. Note: a total of 25 patients completed the 24-month follow-up study. Comparisons of variables (baseline, 4 weeks and 24 months) were made by generalised estimated equation after five missing data was imputed. [a]P<0.05, significantly different from baseline value. [b]P<0.05, significantly different from variables at 4-week follow-up. BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

of CPAP therapy by 8 mm Hg and further after long-term treatment (−24 mm Hg).[29] Therefore, a specific analysis of event-triggered BP surges seems to be necessary to treat OSA patients with hypertension efficiently.

The mechanisms underlying the different BP responses to CPAP are unclear. Previously published data of muscle sympathetic nerve activity showed increased sympathetic activation during apnoeic episodes, which resulted in the pronounced postapnoeic BP rise.[30] Linz *et al* demonstrated that renal sympathetic denervation could suppress postapnoeic BP surges in a sleep apnoea model.[31] Together, it seems that suppressing apnoea can reduce sympathoexcitatory responsiveness and lead to a persistent reduction in BP. While this phenomenon was not a common feature in the entire OSA population. Our study suggested that a reduction of OSA-related stress by CPAP decreases plasma NE levels and consequently BP was only found in the high BP surge group but not in the low group. Similarly, Gilardini *et al* found that therapeutic CPAP normalises pathological urinary normetanephrine only in 38% of OSA patients.[32] Therefore, we speculated that a dissimilar participation of pathogenic mechanisms may be involved in the development of hypertension in these two groups of OSA with BP dysregulation. For patient with high BP surge, multifactorial restorable mechanisms may be involved, and these pathophysiology processes seem to be completely corrected by CPAP treatment, especially for sympathetic overactivity, which seems to be a physiological response triggered by apnoea, such as the oxygen-conserving reflex.[33] Unfortunately, this physiological phenomenon becomes pathological when the enhanced sympathoexcitation is sustained over years, as is the case in OSA patients with persistence of pathological sympathetic overactivity during CPAP intervention. Therefore, an intriguing hypothesis is that, patients with high postapnoeic BP surges present with a special OSA phenotype. It triggers some recoverable intermediary mechanism, for instance, physiological sympathetic overactivity induced by apnoea, which could be corrected, leading to stronger antihypertensive effects of CPAP.

The present study differs from previous reports. First, we only enrolled OSA patients with untreated hypertension to strictly control for potential confounding effects of concomitant medication. Specifically, a limitation regarding BP recording methods in previous studies should be mentioned. Although the 24-hour ambulatory BP monitoring device is a non-invasive portable validated recorder widely used in previous studies,[8 23] its discontinuous BP recording could not accurately trace night-time BP changes in OSA due to the exaggerated short-term BP variation. In our study, nocturnal BP was monitored continuously by PTT method and synchronised with PSG, which could be more reliably to describe for nocturnal BP profiles, such as event-triggered BP surges, spontaneous BP elevations or no fluctuation. On the other hand, considering there are still debating issues about BP measurement accuracy of cuffless devices, the definition of hypertension and daytime BP response were still measured by the traditional cuff devices.

Nevertheless, this prospective study had some potential deficiencies. First, clinical casual BP measurements were used for diagnosis of hypertension might mix with the white coat or masked hypertension in the study, which could cause selection bias of the study population. However, during the period of patient enrolment, all subjects were asked in detail about their daily BP data, and only subjects who knew that their office BPs were consistently above 140/90 mm Hg in the past week and without any treatment were included. By this procedure, the selection bias of the study population could be reduced as far as possible. Second, only severe OSA patients with untreated hypertension were included in this study, which means the results of the study not generalisable to the whole population of patients with OSA and hypertension. Third, although a greater BP reductions were observed in OSA patients with high BP surges during the 4-week follow-up, no patients were found to achieve optimal BP control, and it was hardly to confirm whether this OSA phenotype could obtain more antihypertensive benefits from long-term CPAP treatment. However, for poor BP control in some OSA patients, we believe that continuing an ineffective treatment for a longer observation period would be unethical. For these reasons, 24-month follow-up evaluation was only performed in a small subgroup of subjects without a control group. We know the evidence for the results may be insufficient; however, it provides some interesting clues for the clinical management of this OSA phenotype. That is, long-term CPAP therapy may lead to further BP reduction and even bring BP back into the normal range. Last, this is a single-centre, pre–post observation design without randomised controls; however, this preliminary exploratory study may provide new insight into predicting BP reduction under CPAP treatment. Further randomised controlled trials in large samples are needed to confirm our findings.

Conclusions

By analysing night-time BP profiles, we observed that not all respiratory events could induce a marked BP surge. For patients with severe OSA and untreated hypertension, CPAP treatment could only significantly reduce BP in those who exhibit high event-related BP surge profiles.

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Contributors JX was responsible for the overall content as the guarantor. She had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZM and YC contributed to the work equally and should be regarded as cofirst authors. JX, ZM, YC, CL and YG participated in the study conception and design. ZM, YC, TY, BS, XX participated in the study subjects' recruitment. JX, GW and CL participated in data acquisition, analysis and interpretation. ND and XZ participated in offering the important feedback and insightful comments on the manuscript. JX and ZM drafted the initial manuscript. All authors discussed the results and reviewed the manuscript.

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Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This observational study was approved by the Scientific Research and Technology Ethics Committee of Huaian No. 1 People's Hospital (IRB-KPJ 2017-008-01). The trial was conducted in accordance with the Declaration of Helsinki.

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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