ORIGINAL ARTICLE
SLEEP

Blood pressure response to CPAP treatment in subjects with obstructive sleep apnoea: the predictive value of 24-h ambulatory blood pressure monitoring

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ABSTRACT The reduction in blood pressure (BP) with continuous positive airway pressure (CPAP) is modest and highly variable. In this study, we identified the variables that predict BP response to CPAP.

24-h ambulatory BP monitoring (ABPM), C-reactive protein (CRP), leptin, adiponectin and 24-h urinary catecholamine were measured before and after 6 months of CPAP in obstructive sleep apnoea (OSA) patients.

Overall, 88 middle-aged, obese male patients with severe OSA (median apnoea–hypopnoea index 42 events·h^{-1}) were included; 28.4% had hypertension. 62 patients finished the study, and 60 were analysed. The daytime diastolic BP (−2 mmHg) and norepinephrine (−109.5 nmol·day^{-1}) were reduced after CPAP, but no changes in the 24-h BP, night-time BP, dopamine, epinephrine, CRP, leptin or adiponectin were detected. The nocturnal normotension was associated with an increased night-time-BP (+4 mmHg) after CPAP, whereas nocturnal hypertension was associated with a reduction of 24-h BP (−3 mmHg). A multivariate linear regression model showed differential night-time BP changes after CPAP. Specifically, low night-time heart rate (<68 bpm) and BP dipper profile were associated with increased night-time BP and new diagnosis of nocturnal hypertension.

Our results suggest that nocturnal hypertension, circadian BP pattern and night-time heart rate could be clinical predictors of BP response to CPAP and support the usefulness of 24-h ABPM for OSA patients before treatment initiation. These results need to be confirmed in further studies.

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Introduction

Obstructive sleep apnoea (OSA) has been linked to a number of cardiovascular diseases, including hypertension, acute coronary syndrome, arrhythmia, coronary heart disease, stroke and increased mortality [1, 2]. The pathogenesis of this association is probably multifactorial, involving sympathetic nervous system overactivation, oxidative stress, inflammation, metabolic and hormonal deregulation and the impairment of endothelial and cardiac function [3]. As a consequence of heightened sympathetic activity, OSA patients at all levels of severity experience a marked increase in blood pressure (BP) during sleep and wakefulness [4, 5]. The night-time BP increase results in the lack of a circadian BP pattern and a higher incidence of nocturnal hypertension [6, 7], which are associated with target organ damage and worsened cardiovascular outcomes [7–9].

According to several meta-analyses, continuous positive airway pressure (CPAP) treatment reduces BP in normotensive and hypertensive patients with OSA [10–13]. However, the impact of CPAP treatment on BP is not regular. In minimally symptomatic patients, CPAP has a neutral effect on BP [14], whereas in subjects with resistant hypertension, CPAP can decrease the systolic BP by 5–7 mmHg [15]. Additionally, although the effect of CPAP treatment on BP is related to treatment compliance, there is individual variability that could be related to epigenetic factors, at least in part [16].

According to these data, beyond the variable effect of CPAP on BP in OSA patients, the identification of the clinical and biological profiles that best predict the BP response to this treatment is necessary. Interest should be focused on night-time BP effects, based on evidence that night-time BP is considered to be a better predictor of cardiovascular morbi-mortality [17]. To address this issue, we designed a pre–post study to identify clinical characteristics at baseline, including 24-h ambulatory blood pressure monitoring (ABPM), a sleep study and cardiovascular biomarkers, which could allow us to discriminate patients who would benefit from CPAP treatment from those who would not, with regard to BP.

Methods

Study design and patients

The present study was an observational, multicentre, pre–post study that aimed to assess changes in BP after 6 months of CPAP treatment in patients who were newly diagnosed with severe OSA. Patients were consecutively recruited from the sleep units of University Hospital Arnau de Vilanova and Santa Maria (Lleida, Spain) and Araba Hospital (Vitoria, Spain). Eligible patients were males and females aged 30–80 years, with or without a prior history of hypertension (defined as taking antihypertensive medication or a blood pressure >140/90 mmHg) and with an apnoea–hypopnea index (AHI) ⩾15. We excluded subjects with CPAP treatment, psychological or physical incapacities, drug or alcohol addiction or chronic intake of hypnotics, or who refused to participate in the study. The study was approved by the ethics committee (ID number 710), and the patients provided signed informed consent.

Follow-up

The patients answered a detailed questionnaire that included comorbidities, toxic habits, current medications, anthropometric data and OSA clinical history at baseline. Follow-up visits were performed at 1, 3 and 6 months. Daytime sleepiness was assessed at each visit using the Spanish version of the Epworth Sleepiness Scale (ESS) [18].

Procedures

Sleep study and CPAP treatment

The OSA diagnosis was obtained *via* a conventional polysomnographic (EMBLA S7000; Embla Systems, Broomfield, CO, USA) or cardiorespiratory sleep study (Embletta; ResMed, Sydney, Australia), according to international recommendations [19] as previously described [18] and as specified in the online supplementary material.

CPAP titration was performed using an autoCPAP device (Auto-set-T; ResMed), following a validated protocol according to Spanish guidelines. The optimal pressure was determined from the raw data, and the patients were provided a CPAP machine for home use. At each visit, CPAP compliance was objectively measured as the hours of CPAP use per day according to the internal clock on the CPAP device, and patient compliance was defined as ⩾4 h of use.

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Conflict of interest: None declared.

Biochemical measurements

Blood and 24-h urine samples were collected at baseline and after 6 months of treatment. Haematological parameters and leptin, adiponectin and high-sensitivity C-reactive protein (hsCRP) levels were measured from blood samples. The levels of dopamine, epinephrine and norepinephrine were quantified in the 24-h urine samples (methodology is detailed in the online supplementary material).

24-h ABPM

The patients were subjected to 24-h ABPM at baseline and after 6 months of CPAP treatment (Spacelabs monitor 90207; OSI Systems, Hawthorne, CA, USA), and BP levels and heart rate (HR) levels were measured every 20 and 30 min during the daytime and night-time periods, respectively. The 24-h ABPM procedure, diagnoses of hypertension and nocturnal hypertension and assessment of circadian pattern were performed according to international recommendations [20] (online supplementary material).

Statistical analyses

Quantitative variables with a normal distribution are presented as mean±SD and the remaining variables are presented as median (interquartile intervals). Qualitative variables are presented as the absolute and relative frequencies. Post-CPAP changes in quantitative variables were assessed as differences from baseline and described as median (interquartile intervals). The Chi-squared or Fisher's exact test were used to compare qualitative variables. The bivariate analysis of the associations between changes in the night-time mean BP and baseline was based on correlations (Pearson and Spearman) for quantitative variables and mean differences for qualitative variables. We applied a multivariate linear regression model to assess changes in the night-time mean BP, and all significant covariates were included. We recoded quantitative variables that, according to their median or cut-off value, improved the coefficient of determination.

We performed a *post hoc* analysis of the statistical power to assess whether a group of four variables could significantly predict the post-CPAP changes in the night-time mean BP by fitting a linear multiple regression model. We defined the null hypothesis in terms of the determination coefficient of the model and assessed the statistical significance of its deviation from the zero value. Thus, having fixed a type I error of 0.05 and after recruiting 88 patients and losing 32% of patients to follow-up, we maintained 80% power to detect a significant coefficient of determination >0.18 (that is, an effect size of 0.22).

Results

The 88 included patients were middle-aged, obese males with severe OSA and an ESS of 10.7±5.02 (table 1). Of the entire sample, 28.4% had previously reported hypertension, 34.1% exhibited a nondipper circadian pattern and 50% had nocturnal hypertension.

62 patients completed the follow-up, and 60 were included in the post-CPAP analysis and in the multivariate model (figure 1). Table 1 shows the baseline characteristics of this subgroup of patients. After 6 months of CPAP treatment, there was a reduction in ESS, red blood cells and haemoglobin and norepinephrine urine levels (−109.5 nmol·day^{-1}; p<0.001), suggesting a decline in sympathetic activity (online supplementary table S2). No other significant changes were observed in the other tested biomarkers (dopamine, epinephrine, hsCRP, adiponectin and leptin). Despite the marked reduction in the norepinephrine level, no significant changes were found for the 24-h BP (mean, systolic (SBP) and diastolic (DBP)) or night-time BP. Only the daytime DBP was significantly reduced by −2 mmHg (p=0.018) after treatment. We observed an additional benefit in compliant patients who experienced a significant reduction (−2 mmHg) in daytime SBP (p=0.047), daytime DBP (p=0.0014) and 24-h DBP (p=0.026) (online supplementary table S3).

The analysis of the changes after CPAP treatment in patients with or without hypertension did not reveal any differences (data not shown). Notably, the assessment of these changes in patients with or without nocturnal hypertension showed a marked differential BP response (figure 2). After CPAP treatment (online supplementary table S2), nocturnal normotensive patients showed increases in the night-time mean BP (median increase of +4 mmHg; p=0.008), night-time SBP (median increase of +5 mmHg; p=0.014) and night-time DBP (median increase of +3 mmHg; p=0.008). In contrast, patients with nocturnal hypertension showed a decrease in the 24-h mean BP (median decrease of −3 mmHg; p=0.011), 24-h SBP (median decrease of −4 mmHg; p=0.015) and 24-h DBP (median decrease of −2 mmHg; p=0.017) after CPAP treatment (figure 2).

Differential night-time BP response to CPAP treatment predicted by haemodynamic biomarkers

A linear multiple regression model was used to identify the clinical and biological variables at baseline that could predict post-CPAP changes in night-time mean BP. The adjusted model explained 33.4% of the variability in the changes in the night-time mean BP after CPAP treatment (table 2) and included a

TABLE 1 Subject characteristics at baseline

	Analysed	Incomplete follow-up	p-value	All patients
Patients	60	28		88
Demographic and clinical characteristics				
Age years	52.3±9.56	49.0±11.7	0.205	51.2±10.3
Sex male	48 (80.0)	23 (82.1)	1.000	71 (80.7)
Hypertension	20 (33.3)	5 (17.9)	0.213	25 (28.4)
Diabetes mellitus	8 (13.3)	0 (0.00)	0.051	8 (9.1)
Dyslipidaemia	6 (10.0)	2 (7.14)	1.000	8 (9.1)
Ischaemic heart disease	4 (6.67)	0 (0.00)	0.302	4 (4.6)
Arrhythmia	3 (5.00)	0 (0.00)	0.548	3 (3.4)
Tobacco use	21 (35.0)	11 (39.3)	0.880	32 (36.4)
Alcohol	11 (18.3)	4 (14.3)	0.766	15 (17)
Anthropometric characteristics				
BMI $kg \cdot m^{-2}$	30.6 (28.0–33.5)	29.4 (27.4–33.3)	0.610	30.2 (27.9–33.4)
Neck circumference cm	41.7±3.35	41.2±3.06	0.517	41.6±3.26
OSA characteristics				
ESS score range (0–24)	10.8±4.74	10.4±5.67	0.743	10.7±5.02
AHI $events \cdot h^{-1}$	46.0 (32.5–60.8)	33.7 (26.7–57.0)	0.120	42.5 (29.9–58.9)
Min oxygen saturation %	81.0 (77.0–85.0)	80.5 (70.2–84.5)	0.564	81 (76–85)
Mean oxygen saturation %	93.3 (92.0–95.0)	92.5 (92.0–95.2)	0.793	93 (92–95)
t_{Sat90} %	4.03 (1.19–10.4)	4.32 (0.85–13.6)	0.690	4.1 (1.04–12.5)
Central apnoeas $events \cdot h^{-1}$	1.00 (0.00–12.0)	0.00 (0.00–7.50)	0.351	1 (0–9.8)
Blood cells				
Lymphocytes n 10^9 L	2.30 (1.95–2.72)	2.40 (2.09–2.84)	0.540	2.3 (2–2.7)
RBCs 1012 L	4.97 (4.67–5.25)	5.21 (4.84–5.46)	0.094	5 (4.7–5.3)
Haemoglobin $g \cdot dL^{-1}$	15.4 (14.2–16.4)	15.8 (15.1–16.2)	0.317	15.6 (14.6–16.4)
Platelets 109 L	214 (186–252)	213 (198–229)	0.470	213 (188–248)
Catecholamines and cardiovascular risk biomarkers				
Dopamine $nmol \cdot day^{-1}$	1358 (1071–1920)	1306 (952–2034)	0.743	1358 (986–1946)
Epinephrine $nmol \cdot day^{-1}$	30.0 (16.4–42.4)	21.8 (16.0–27.3)	0.044	22.0 (16.4–38.2)
Norepinephrine $nmol \cdot day^{-1}$	361 (225–479)	361 (277–468)	0.597	361 (236–479)
hsCRP $mg \cdot L^{-1}$	1.64 (1.12–4.08)	2.93 (1.79–6.48)	0.225	2.2 (1.2–5.3)
Leptin $ng \cdot mL^{-1}$	8.28 (4.85–10.7)	5.92 (3.29–11.5)	0.420	8 (4.5–10.9)
Adiponectin $\mu g \cdot mL^{-1}$	5.37 (3.08–7.63)	5.14 (4.18–7.10)	0.908	5.3 (3.6–7.5)
24-h ABPM				
24-h mean BP mmHg	92.5±8.41	92.5±8.08	0.991	92.5±8.3
24-h SBP mmHg	123 (116–129)	124 (117–129)	0.510	123 (116–129)
24-h DBP mmHg	77.2±7.66	76.4±8.73	0.690	77±8
24-h HR bpm	73.5±10.9	76.0±10.1	0.314	74.3±10.7
Daytime mean BP mmHg	96.4±8.71	95.6±8.65	0.694	96.1±8.7
Daytime SBP mmHg	127 (119–133)	126 (118–135)	0.803	127 (119–134)
Daytime DBP mmHg	81.3±8.24	79.4±9.40	0.391	80.7±8.6
Daytime HR bpm	76.7±11.6	77.9±10.5	0.631	77±11.2
Night-time median BP mmHg	83.0 (78.8–89.0)	83.0 (80.0–91.0)	0.533	83 (80–89)
Night-time SBP mmHg	112 (106–119)	117 (110–124)	0.125	114 (107–120)
Night-time DBP mmHg	68.5 (64.0–73.0)	67.0 (65.0–73.0)	0.981	68 (64–73)
Night-time HR bpm	66.0 (61.0–70.2)	71.5 (63.2–78.8)	0.049	67 (61.2–73)
Nondipper pattern DR $\geqslant$0.9	19 (31.7)	10 (40.0)	0.626	29 (34.1)
Medication				
β-Blockers	5 (8.33)	1 (3.57)	0.660	6 (6.82)
ACE inhibitors	7 (11.7)	3 (10.7)	1.000	10 (11.4)
Angiotensin receptor blocker	6 (10.0)	0 (0.00)	0.171	6 (6.82)
Calcium channel blocker	6 (10.0)	0 (0.00)	0.171	6 (6.82)
Diuretic	7 (11.7)	4 (14.3)	0.738	11 (12.5)
α-Adrenergic blockers	5 (8.33)	2 (7.14)	1.000	7 (7.95)
Antiplatelet	2 (3.33)	0 (0.00)	1.000	2 (2.27)
Anticoagulants	0 (0.00)	4 (14.3)	0.009	4 (4.55)
Hypolipidaemics	12 (20.0)	2 (7.14)	0.210	14 (15.9)
Antacids	13 (21.7)	2 (7.14)	0.130	15 (17.0)
Antiarrhythmics	1 (1.67)	1 (3.57)	0.538	2 (2.27)

Continued

TABLE 1 Continued

	Analysed	Incomplete follow-up	p-value	All patients
Oral antidiabetics	6 (10.0)	0 (0.00)	0.171	6 (6.82)

Data are presented as n, mean±SD, n (%) or median (intequartile interval). BMI: body mass index; OSA: obstructive sleep apnoea; ESS: Epworth Sleepiness Scale; AHI: apnoea–hypopnea index; t_{Sat90}: time spent at night with an oxygen saturation <90%; RBCs: red blood cells; hsCRP: high-sensitivity C-reactive protein; ABPM: ambulatory blood pressure monitoring; BP: blood pressure; DBP: diastolic blood pressure; HR: heart rate; SBP: systolic blood pressure; DR: dipping ratio; ACE: angiotensin-converting enzyme.

significant interaction between dipping status and mean night-time HR (<68 bpm *versus* ⩾68 bpm). The contribution of CPAP compliance to the model approached significance. Therefore, the relevance of CPAP compliance on the impact of CPAP treatment on BP was included. The interaction between dipping status and night-time mean HR levels defined four OSA phenotypes. The baseline characteristics are presented in online supplementary table S4, and the post-CPAP changes are presented in table 3 and figure 3.

First, dipper patients with low night-time HR, particularly noncompliant patients (noncompliers +9.7 mmHg, p=0.0013; compliers +5.4 mmHg, p=0.0007), exhibited a marked increase in the night-time mean BP after CPAP treatment (table 2). Consequently, 33.3% of these patients were newly diagnosed with nocturnal hypertension, and 41.67% showed a change from a dipper pattern at baseline to a nondipper pattern after 6 months of CPAP treatment. In addition, the night-time HR significantly increased after treatment.

A neutral change in BP after CPAP treatment was observed in dipper and nondipper patients with a high night-time HR (⩾68 bpm). Finally, nondipper patients with a low night-time HR showed an important beneficial change after CPAP treatment in decreasing the night-time BP (median decrease of −6.2 mmHg, p<0.01) (table 3). After considering the association with CPAP adherence, compliant patients exhibited the greatest night-time BP decrease of −7.1 mmHg (p=0.0014) (table 3).

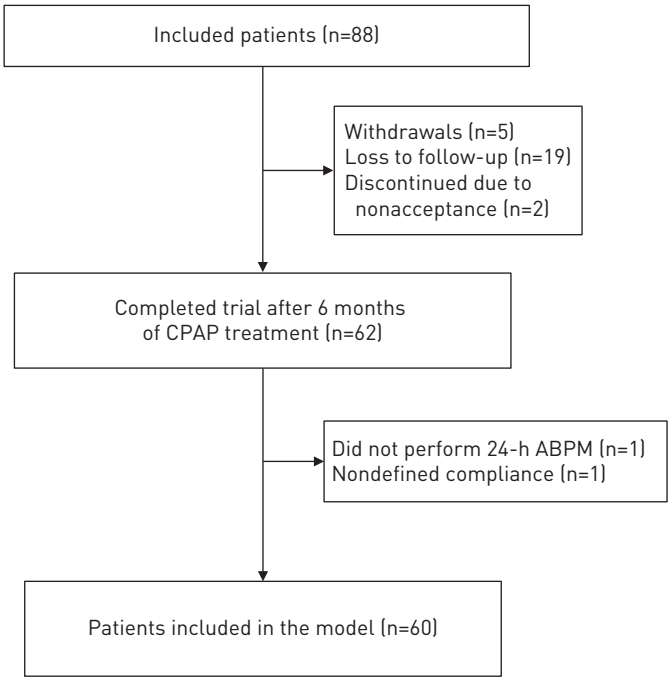

FIGURE 1 Study flowchart. 88 patients (34 from Lleida hospital and 54 from Vitoria hospital) were included. 26 did not finish the study: withdrawals n=5 (n=3 from Lleida, n=2 from Vitoria); lost to follow-up n=19 (n=7 from Lleida, n=12 from Vitoria); discontinued due to nonacceptance n=2 (from Lleida). 62 patients completed the 6-month follow-up (n=22 from Lleida and n=40 from Vitoria), and 61 performed the 24-h ambulatory blood pressure monitoring (ABPM) (n=22 from Lleida, n=39 from Vitoria). CPAP: continuous positive airway pressure.

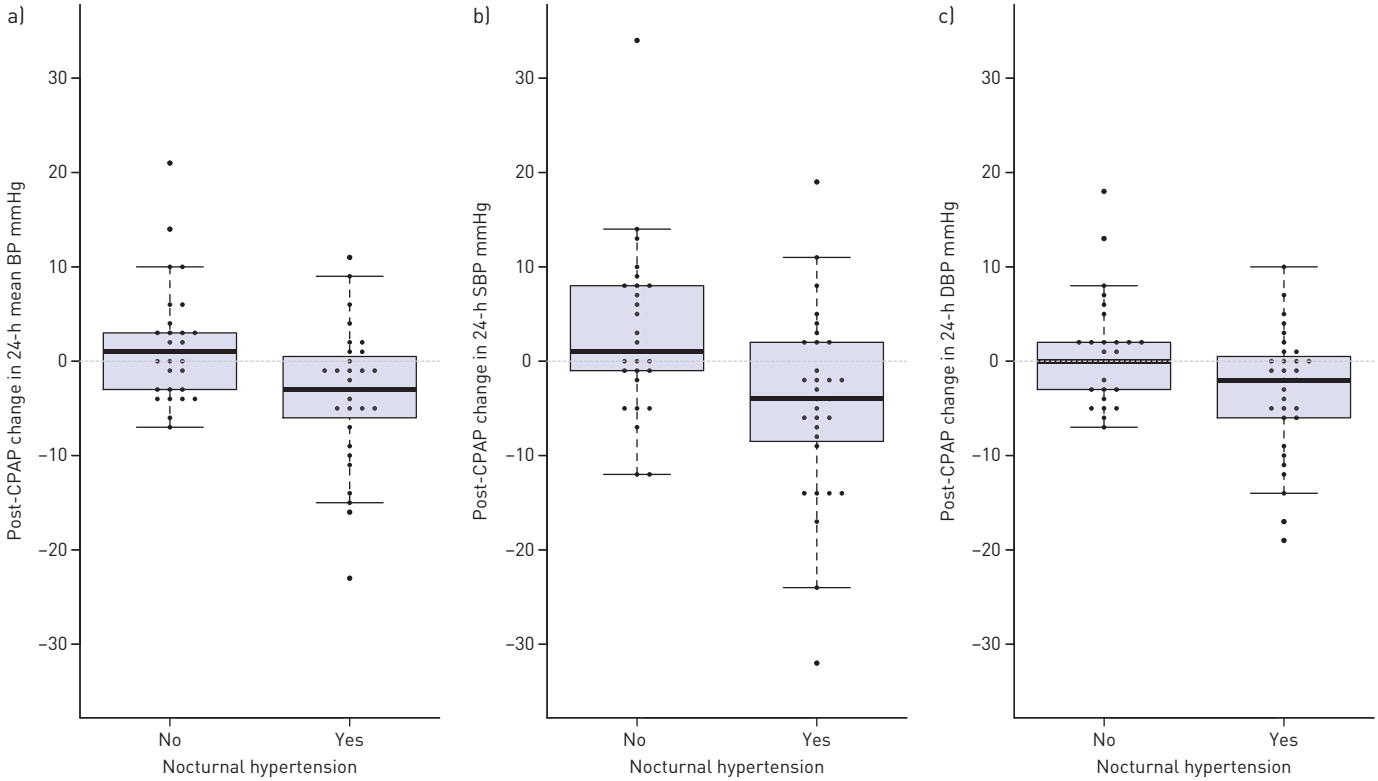

FIGURE 2 Change in blood pressure after continuous positive airway pressure (CPAP) treatment in patients with and without nocturnal hypertension. Blood pressure (BP) was assessed *via* 24-h ambulatory BP monitoring before and after 6 months of CPAP treatment in obstructive sleep apnoea patients with or without nocturnal hypertension. The bars represent the medians and interquartile intervals of the a) 24-h mean BP, b) 24-h systolic blood pressure (SBP) and c) 24-h diastolic blood pressure (DBP) changes assessed from baseline. The changes were different between groups; all p<0.01.

Discussion

The main contribution of this study is the possible identification, *via* 24-h ABPM, of OSA patients who will show a favourable decrease in BP after CPAP treatment. Reduced BP after CPAP treatment was observed in patients with nocturnal hypertension and in nondipper patients with ⩾4 h of CPAP use per

TABLE 2 Adjusted model and predicted post-continuous positive airway pressure (CPAP) mean change in night-time blood pressure

	Estimate	Pr (>|t|)	Noncompliers	Compliers
Multivariate linear regression model (A)				
(Intercept)	+9.7±2.85	0.001		
Nondipper	−12.6±2.55	<0.001		
Mean HR (68–105 bpm)	−6.6±2.39	0.008		
CPAP complier	−4.2±2.64	0.114		
Nondipper mean night-time HR (68–105 bpm)	+10.4±4.45	0.023		
Multiple R-squared 0.3335				
Estimated mean change according to A				
Dipper/low HR			+9.7**	+5.4***
Dipper/high HR			+3.1	−1.2
Nondipper/low HR			−2.9	−7.1**
Nondipper/high HR			+0.9	−3.3

Data are presented as mean±SD. CPAP compliance is defined as ⩾4 h·day^{-1}. HR: heart rate. **: p⩽0.01; ***: p⩽0.001.

TABLE 3 24-h ambulatory blood pressure monitoring (ABPM) changes after continuous positive airway pressure (CPAP) treatment. The groups were stratified by dipping status and night-time heart rate level at baseline

	Dipper/low HR	Dipper/high HR	Nondipper/low HR	Nondipper/high HR	p-value
Patients n	24	17	13	6	
24-h mean BP mmHg	2.5±6.3	−2.1±6.8	−4.2±9.1	−2.5±3.9	0.017
24-h SBP mmHg	4.2±8.6*	−2.3±8.3	−6.5±13.4**	−4±3.8	0.007
24-h DBP mmHg	1.7±5.5	−2.3±6.7	−3.5±8.2	−2±5.2	0.042
24-h HR bpm	1.5±4.78	−3.5±5.4	1±6.6	−6±6.5*	0.005
Daytime mean BP mmHg	0.9±6.4	−3.3±6.8	−3.9±10.1	−2±4.3	0.183
Daytime SBP mmHg	1.00 (−4.3–5.8)	−4 (−9.5–3.5)	−1 (−14.00–0.00)*	−0.5 (−6.5–1.8)	0.258
Daytime DBP mmHg	−0.1±5.8	−3.8±7.1*	−3.2±9.40	−2.2±5.4	0.357
Daytime HR bpm	0.1±5.4	−3.3±7.1	0.8±7.82	−6±7.8*	0.096
Night-time mean BP mmHg	6±6.97***	0.1±7.7	−6.2±8.32**	−3.3±6.3	<0.001
Night-time SBP mmHg	7.5±10.3***	−0.7±9.1	−8.3±12.0**	−5.2±5.9	<0.001
Night-time DBP mmHg	5.1±6.5***	−0.2±7.7	−4.8±6.65**	−2.7±7.6	0.001
Night-time HR bpm	3.9±5.7**	−2.7±4.8	0.3±3.84	−3.7±10.1	0.002

Data are presented as mean±SD or median (interquartile intervals), unless otherwise stated. 24-h ABPM was performed in 60 patients before and after CPAP treatment. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate. $p \leqslant 0.1$; *: $p \leqslant 0.05$; **: $p \leqslant 0.01$; ***: $p \leqslant 0.001$.

night. However, increased BP was observed in nocturnal normotensive patients and in dipper patients with a low HR, even among CPAP compliers. The haemodynamic biomarkers at baseline, specifically the circadian BP pattern and night-time HR, facilitated the establishment of a predictive model of CPAP treatment responses. The identification of patients who could be adversely affected by CPAP treatment might prevent adverse increases in cardiovascular haemodynamic parameters and related negative long-term cardiovascular consequences, particularly in asymptomatic patients. According to our results, 24-h ABPM should be performed for the clinical management of OSA before initiating CPAP treatment.

Patients with OSA show increased BP and a higher incidence of hypertension [21–24]. Due to repetitive hypoxaemia and sympathetic excitation, OSA patients exhibit a rise in the nocturnal BP with a consequent absence of a decrease in the nocturnal BP (nondipper circadian pattern) and night-time hypertension

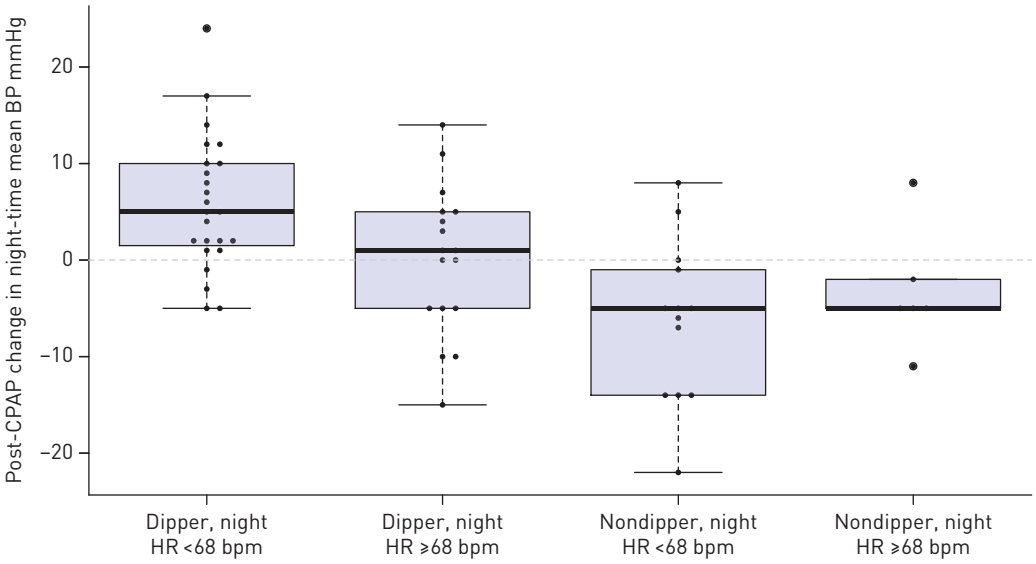

FIGURE 3 Change in night-time blood pressure (BP) after continuous positive airway pressure (CPAP) treatment in patients stratified by circadian BP pattern and night-time heart rate at baseline. The bars represent the medians and interquartile intervals for the night-time BP after 6 months of CPAP treatment (changes from baseline). The night-time BP was assessed *via* 24-h ambulatory BP monitoring. The groups were stratified by the circadian BP pattern (dipper pattern: dipping ratio (night-time/daytime BP) <0.9; nondipper pattern: dipping ratio ⩾0.9) and the mean night-time heart rate (HR) (low defined as <68 bpm and high as ⩾68 bpm). The changes were different between groups; p<0.001.

[6, 7]. Clinically, both elevated night-time BP and the nondipper pattern are considered important predictors of advanced target organ damage and future fatal and nonfatal cardiovascular events after adjustment for traditional risk factors in both hypertensive patients and the general population [25–28]. Accordingly, current therapeutic strategies for OSA patients are directed at decreasing the arterial BP and subsequently reducing the cardiovascular risk.

The beneficial effects of CPAP treatment have been documented in multiple studies and include reduced BP levels in patients with OSA (affected by patient adherence, age and hypertensive status) [13, 14, 29–33]. Specific OSA phenotypes, such as patients with symptomatic or resistant hypertension, clearly benefit from CPAP treatment [34]. In the current study, nocturnal hypertension was found to affect the outcome of CPAP treatment. We observed a favourable change in BP after CPAP treatment in nocturnal hypertensive patients, whereas nocturnal normotensive subjects experienced an unfavourable response (increased night-time BP levels).

Previous studies have suggested a possible detrimental effect of CPAP treatment, even when adherence to the use of CPAP is documented [18, 33, 34]. In the Barbé *et al.* [18] and Martinez-Garcia *et al.* [34] randomised controlled trials, 25–30% of patients who used CPAP for ⩾4 h per day showed no change or increased BP. Similarly, Bratton *et al.* [14] performed a meta-analysis in which CPAP treatment was associated with increased BP levels in minimally symptomatic patients (patients without excessive daytime sleepiness) and patients with low CPAP adherence. The inconsistency between these studies suggests the need to identify specific subsets of patients who are more likely to benefit from CPAP treatment and those who may be adversely affected. The characterisation of OSA phenotypes and the impact of CPAP treatment on the spectrum of OSA constitute the first step for the accurate application of precision medicine [35]. Moreover, diagnostic and personalised therapeutic decision-making tools are needed to manage sleep apnoea and to effectively predict responses to adherent CPAP use [16].

Several studies have reported that night-time BP is the BP measure with the best predictive value of cardiovascular risk [17, 25, 36]. A 10-mmHg increase in the mean night-time SBP is associated with a 21% increase in cardiovascular mortality [25]. Based on this consideration, we analysed the baseline characteristics to identify those variables with a predictive value for the night-time BP response to CPAP treatment. The circadian BP pattern and night-time HR can be used to distinguish two opposite phenotypes (with clinical implications) based on the night-time BP responses to CPAP treatment. Nondipper patients with a low HR (<68 bpm) experienced a night-time BP decrease after CPAP treatment. However, CPAP treatment was associated with increases in the night-time BP and HR in patients with "normal" haemodynamic characteristics at baseline (dipper pattern and low HR). This unfavourable change after CPAP treatment might worsen long-term cardiovascular outcomes. A possible explanation for these results is that these patients have adapted to OSA stress, counterbalancing the sympathetic hyperactivity, preserving the physiological circadian BP pattern and maintaining a lower HR at night.

Current international guidelines recognise the prognostic value of 24-h ABPM in some patients, specifically in patients with resistant hypertension, episodic hypertension and white-coat hypertension [20]. However, in the clinical management of OSA patients, 24-h ABPM is not recommended. Our findings reinforce the clinical value of 24-h ABPM for patients with OSA to effectively predict the response to CPAP treatment on cardiovascular haemodynamic outcomes.

The strengths of the present study include its multicentre design, the high adherence to CPAP treatment and the use of 24-h ABPM to detect changes in night-time and daytime BP, which is considered the gold standard for BP measurements [37]. Nevertheless, this study has several potential limitations. First, the small size of the study population indicates that the present study is an exploratory work that needs to be confirmed and validated in further studies. This issue was addressed by performing a *post hoc* analysis of the statistical power, as detailed in the methodology section. Second, although polysomnography and cardiorespiratory sleep studies were used to diagnose OSA, the agreement level of diagnostic efficacy between the two techniques is close to 90% [38]. Third, the study design does not make it possible to assess the changes that could occur in the absence of CPAP treatment for ethical reasons, and in consequence, the natural evolution of BP cannot be accounted. Nonetheless, such changes are unlikely to be observed in the absence of treatment during the relatively short follow-up time. Fourth, the study population includes a wide range of ages. Although this represents a possible limitation, the present study aims to apply the proposed model to the whole spectrum of OSA patients.

Conclusions

Ours results suggest that nocturnal hypertension, the circadian BP pattern and the night-time HR at baseline could be important clinical predictors of the BP response to CPAP treatment in patients with severe OSA. Our findings further support the usefulness of 24-h ABPM for OSA patients prior to

initiation of CPAP treatment for the prediction of treatment response and the avoidance of an unnecessary increase in cardiovascular risk. The results of the present study need to be confirmed and validated in further studies.

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