The effect of treatment for sleep apnoea on determinants of blood pressure control

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Peripheral chemosensitivity justifies differences in nocturnal–diurnal blood pressure in patients with sleep apnoea http://ow.ly/ntYr30eFU0b

Cite this article as: Casitas R, Martínez-Cerón E, Galera R, *et al*. The effect of treatment for sleep apnoea on determinants of blood pressure control. *Eur Respir J* 2017; 50: 1701261 [https://doi.org/10.1183/13993003.01261-2017].

ABSTRACT Our aim was to assess the effect of continuous positive airway pressure (CPAP) on the nocturnal evolution of peripheral chemosensitivity, renin–angiotensin–aldosterone system activity, sympathetic tone and endothelial biomarkers in obstructive sleep apnoea (OSA) patients with isolated nocturnal hypertension (INH) or day–night sustained hypertension (D-NSH).

In a crossover randomised trial, 32 OSA patients newly diagnosed with hypertension and without antihypertensive treatment were randomly assigned to 12 weeks of CPAP or sham CPAP. Peripheral chemosensitivity was evaluated before and after sleep using the hypoxic withdrawal test (%ΔV_I).

At baseline, D-NSH patients showed higher %ΔV_I before sleep and higher levels of aldosterone and diurnal catecholamines. CPAP only reduced the nocturnal increase of %ΔV_I in INH patients (6.9%, 95% CI 1.0–12.8%; p=0.026). CPAP-induced change from baseline in %ΔV_I after sleep was 7.5% (95% CI 2.6–12.2%, p=0.005) in the INH group and 5.7% (95% CI 2.2–9.3%, p=0.004) in the D-NSH group. In contrast, %ΔV_I before sleep only decreased with CPAP in the D-NSH patients (3.0%, 95% CI 0.5–5.6%; p=0.023).

In conclusion, CPAP reduces the nocturnal increase of peripheral chemosensitivity experienced by INH patients and corrects the high daytime sensitivity of patients with D-NSH. Differences in response to CPAP between these patients can help better understand the mechanisms of perpetuation of hypertension in sleep apnoea.

This article has supplementary material available from erj.ersjournals.com

Received: Nov 30 2016 | Accepted after revision: Aug 12 2017

Clinical trial: This study is registered at clinicaltrials.gov with identifier number NCT02398032.

Support statement: This study is supported by a grant from the Sociedad Madrileña de Neumología y Cirugía Torácica, Spain (02/200). Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: None declared.

Introduction

Obstructive sleep apnoea (OSA) is associated with an increased risk of hypertension [1, 2]. Although the pathophysiological mechanisms responsible for the development and maintenance of hypertension in OSA patients have not been elucidated fully, several contributing factors have been proposed, including sympathetic activation, activated renin–angiotensin–aldosterone system (RAAS), increased levels of circulating vasoconstrictors and endothelial dysfunction [3–5]. Of these, sympathetic activation, in response to intermittent hypoxaemia caused by the periodic collapse of the upper airway during sleep seems to have a central role in the genesis of sustained hypertension [6]. In turn, there is strong evidence that repetitive episodes of apnoea increase sympathetic activity *via* chemoreflex activation [7–9]. Activation of chemoreflexes in response to intermittent hypoxia leads to an increase in sympathetic neural outflow by a process that is predominantly mediated by the peripheral chemoreceptors in the carotid bodies [10]. It has been reported that chemoreflex deactivation decreases muscle sympathetic nerve activity and mean arterial pressure in OSA patients, providing important evidence that intermittent hypoxia requires the presence of functional arterial chemoreceptors to increase blood pressure [11].

Interestingly, various categories of hypertension have been characterised. While a night-time drop in blood pressure (dipping) is normal, ambulatory blood pressure monitoring has been used to identify a group of subjects with abnormally elevated night-time blood pressure but normal daytime blood pressure. This form of high blood pressure has been described as isolated nocturnal hypertension (INH) [12]. Several studies have suggested that INH could be an intermediate form of hypertension that precedes the development of day–night sustained hypertension (D-NSH) and that these patients have a higher risk of all-cause mortality and cardiovascular events than normotensive subjects [12–14]. Although several previous studies [15, 16] have demonstrated that OSA is a major cause of non-dipping, the characteristics and determinants of INH in OSA patients has been very poorly evaluated. Furthermore, comparison of the pathophysiological mechanisms involved in the development of OSA/secondary hypertension between patients with INH and D-NSH might be an appropriate model to better understand the sequence of changes by which apnoea-related nocturnal hypertension evolves into sustained hypertension during wakefulness. In addition, various meta-analyses have shown that suppression of apnoeas using continuous positive airway pressure (CPAP) achieves reduction in blood pressure in OSA patients [17, 18], although there is no accurate information available about its specific effect on the pathogenic pathways in patients with INH or D-NSH.

In the present study, we tested the hypothesis that the CPAP effect on blood pressure could be mediated by different effects on the nocturnal evolution of peripheral chemosensitivity in OSA patients with INH or D-NSH. Secondary outcomes were to assess whether the magnitude of the CPAP effect on sympathetic activation, RAAS activity and levels of circulating vasoconstrictors is different in OSA patients with INH or D-NSH and to identify baseline differences between OSA patients with these two types of blood pressure dysregulation.

Methods

Study design and patients

A double-blind, placebo-controlled, randomised crossover study was conducted in patients newly diagnosed with hypertension and OSA (figure 1a).

Patients aged 18–75 years, with a recent diagnosis of OSA (apnoea–hypopnoea index (AHI) $\geqslant$10 events·h^{-1}) and a diagnosis by 24-h ambulatory blood pressure monitoring (ABPM) of INH (night-time blood pressure of $\geqslant$120 mmHg systolic or $\geqslant$70 mmHg diastolic and a daytime blood pressure <135/85 mmHg) or D-NSH (night-time blood pressure of $\geqslant$120 mmHg or $\geqslant$70 mmHg diastolic and a daytime blood pressure of $\geqslant$135 mmHg systolic) [19] were eligible for study enrolment. Exclusion criteria are described in the online supplementary material. The study protocol was approved by the ethics committee of the Hospital Universitario La Paz (Madrid, Spain; HULP PI-0252) and participants provided written informed consent.

Procedures

Potential participants were screened for OSA using an overnight attended polysomnography (Sleep Screen; Viasys Healthcare, Hoechberg, Germany), analysed using standard criteria [20, 21]. Lung function tests were performed for each patient at inclusion [22, 23].

A more detailed description of procedures and outcomes assessment is provided in the online supplementary material.

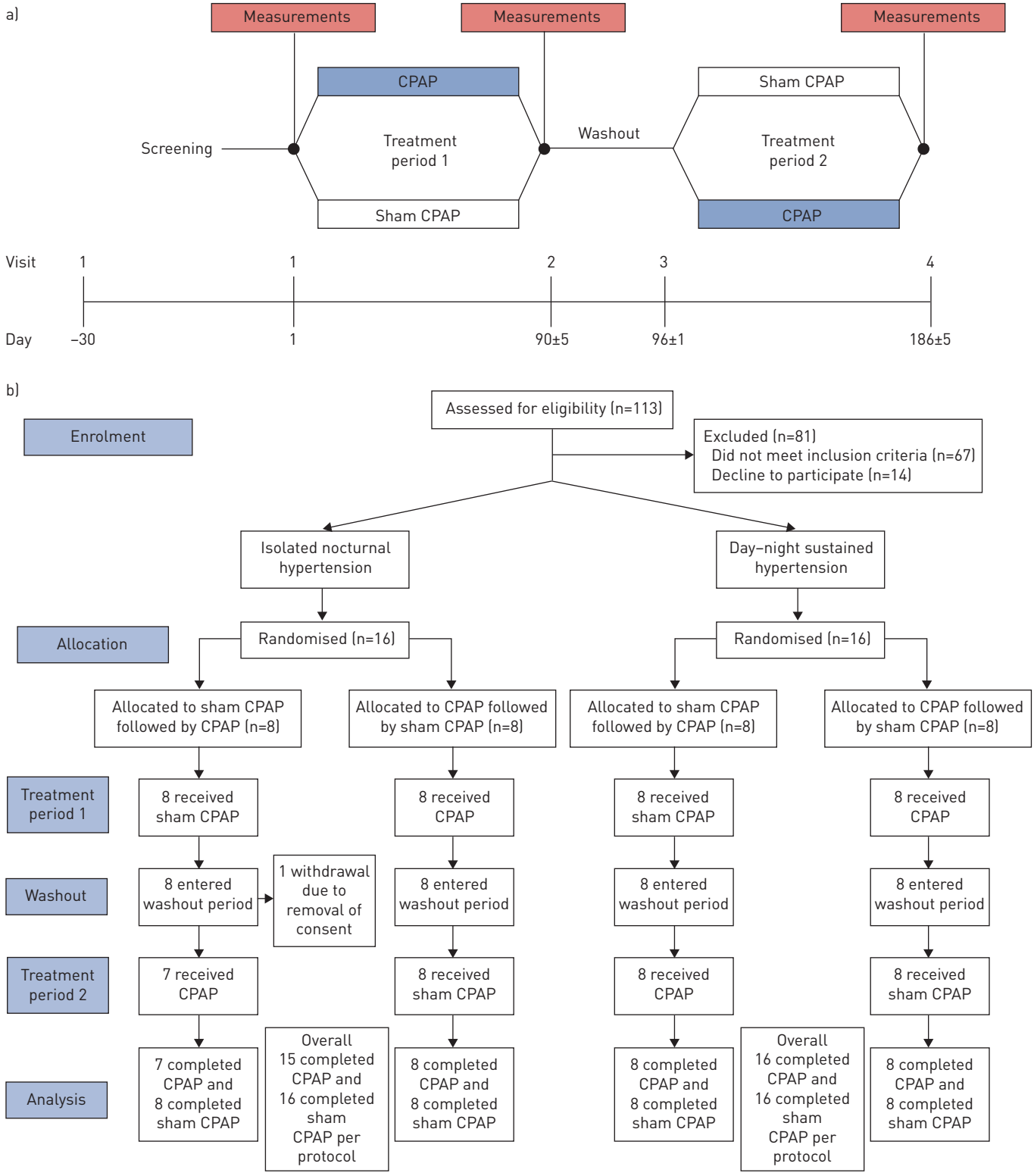

FIGURE 1 Study design, enrolment and outcomes. a) Study design: each patient, in two separate treatment periods, received 12 weeks of continuous positive airway pressure (CPAP) treatment and sham CPAP separated by 5–7 days of washout; b) flow chart of the study.

Intervention

Patients with an AHI $\geqslant$10 events·h^{-1} were randomly assigned using stratification (INH/D-NSH) to receive effective CPAP or sham CPAP for two 12-week periods. Immediately afterwards, the other treatment was applied with a washout period of 5–7 days. Optimal CPAP pressure was titrated using an auto-CPAP device

[24]. The CPAP device used (S9; ResMed, Sydney, Australia) recorded all the data from the 6 months of use. Adherence was considered adequate if CPAP use was $\geqslant$4 h·night^{-1} and >5 days·week^{-1} [25]. Patients remained blinded as to whether they were receiving effective CPAP or sham treatment, and systemic hypertension was not treated with drugs during the study period. Moreover, the researchers who performed the study determinations were unaware of both the subject group and the patient's treatment assignment at each visit.

Outcome assessment and follow-up

The primary study outcome was the change in the nocturnal increase of peripheral chemosensitivity. Secondary outcomes included change in peripheral chemosensitivity and blood gases before and after sleep, as well as in RAAS activity, urinary catecholamines, biomarkers of endothelial dysfunction and blood pressures.

Patients were evaluated at baseline and 3 and 6 months afterwards. At each visit, anthropometric characteristics, Epworth sleepiness scale score and adherence to CPAP or sham were recorded. Simultaneously, a 24-h ABPM and urine collection for determination of catecholamines were performed. Before going to bed and immediately after waking, peripheral chemosensitivity and blood gases were measured. The next morning, immediately after waking, the same measurements were repeated with a venous blood extraction to analyse RAAS and endothelial biomarkers.

Peripheral chemosensitivity was evaluated using the withdrawal test, as described previously [26]. Briefly, the difference between the ventilation before and 5–20 s after performing two breaths of 100% oxygen in a mildly hypercapnic hypoxic state was defined as the withdrawal response (ΔV_I), and $\%\Delta V_I$ ($\Delta V_I/V_I$, 0×100) was used as an index of the peripheral chemoreceptor activity [26, 27].

Statistical analysis

A sample size calculation was performed assuming a peripheral chemosensitivity of 24.0±3.6% in OSA patients [26]. Based on a two-tailed test with α=0.05, β=0.20 and an expected dropout rate of 15%, 16 subjects were necessary in each group to recognise as statistically significant a difference $\geqslant$4 units with the intervention in the active *versus* the control group.

Data are summarised as mean±SD, median (interquartile range) or frequencies. Outcomes analysis used intention-to-treat principles and included all participants as randomised. No imputation of the missing data was performed for the main or secondary outcome measurements. A sensitivity analysis using different approaches including no imputation, baseline observation carried forward, last observation carried forward and multiple imputation showed similar results for the primary outcome and the treatment effect. Between-group baseline comparisons were based on two-sample t-tests, Mann–Whitney or Chi-squared tests. The intragroup differences from the beginning to the end of the study were evaluated using a paired t-test. Comparisons of effects of the treatment over time were made with repeated-measures ANOVA, with treatment as a within-subject factor and order as a between-subject factor. When ANOVA results showed significant differences between treatment conditions, *post hoc* multiple comparisons were performed using the Bonferroni test. In addition, a per-protocol analysis based on data from patients with adequate adherence to CPAP was performed. Relationships between variables were determined by Pearson's correlation and stepwise multiple linear regression analysis. A two-sided p-value <0.05 was considered significant.

Results

Figure 1b is a flow chart of the study participants. Out of 113 patients assessed for eligibility, 46 met inclusion/exclusion criteria. 14 patients declined to participate and ultimately 32 patients were randomised, 16 with INH and 16 with D-NSH. One participant with INH was lost to follow-up after having concluded the sham CPAP period due to withdrawal of consent because of change of residence. Finally, 15 patients with INH and 16 patients with D-NSH concluded the two treatment periods with sham CPAP or CPAP.

Baseline differences between OSA patients with INH and D-NSH

Demographic and baseline characteristics are provided in tables 1 and 2. The two study groups were similar in anthropometric characteristics, sleep parameters and lung function. However, some differences in chemosensitivity, sympathetic tone and aldosterone levels were detected between the two hypertensive OSA groups. In comparison with patients with INH, the patients with D-NSH showed higher levels of aldosterone and diurnal catecholamines, with no differences in nocturnal catecholamines, plasma renin activity, aldosterone/renin ratio or levels of circulating vasoconstrictors (table 1). Moreover, OSA patients with D-NSH had a higher peripheral chemosensitivity before sleep, with a prominent nocturnal increase in both groups that reached a similar level of chemosensitivity after sleep (table 2).

TABLE 1 Baseline characteristics of the study groups

	Isolated nocturnal hypertension	Day–night sustained hypertension	p-value
Subjects n	16	16	
Male	13 (81)	13 (81)	NS
Age years	58±13	54±9	NS
BMI kg·m^{-2}	30.0±5.2	28.3±6.0	NS
Current smokers	1 (6)	5 (31)	NS
Epworth sleepiness score	8.2±2.5	9.1±2.2	NS
Total sleep time min	354±82	323±100	NS
Sleep efficiency %	76.5±19.8	71.8±19.6	NS
Sleep onset latency min	23±47	16±20	NS
WASO min	96±94	122±89	NS
REM latency min	95±91	85±54	NS
NREM1 %	24.2±9.2	21.9±11.5	NS
NREM2 %	53.2±9.9	47.8±20.1	NS
SWS %	5.4±4.3	5.5±4.0	NS
REM %	14.9±12.6	18.4±13.6	NS
AHI events·h^{-1}	44.0±16.9	37.9±19.9	NS
Mean S_{pO_2} %	94±2	92±2	NS
Minimum S_{pO_2} %	74±8	77±8	NS
FVC % pred	103±19	109±15	NS
FEV_1 % pred	109±19	112±18	NS
FEV_1/FVC	0.85±0.05	0.81±0.05	NS
TLC % pred	97±15	96±11	NS
FRC % pred	99±26	95±11	NS
RV % pred	107±26	110±18	NS
P_{Imax} kPa	9.0±1.8	9.0±2.2	NS
Daytime systolic BP mmHg	129±5	141±14	0.003
Daytime diastolic BP mmHg	76±7	88±5	<0.001
Daytime mean BP mmHg	94±5	106±8	<0.001
Night-time systolic BP mmHg	126±9	130±16	NS
Night-time diastolic BP mmHg	74±5	77±9	NS
Night-time mean BP mmHg	91±5	94±11	NS
Nocturnal deep mean BP mmHg	2.7±7.5	11.1±5.3	0.001
Dipper profile %			0.007
Normal dipping	12.5	66.7	
Attenuated dipping	56.3	26.7	
Rising	31.3	6.7	
Diurnal noradrenaline µg·g^{-1}	48.9±18.3	71.1±24.9	0.007
Diurnal adrenaline µg·g^{-1}	5.5±5.1	7.8±2.7	0.006
Nocturnal noradrenaline µg·g^{-1}	39.9±13.2	48.5±12.2	NS
Nocturnal adrenaline µg·g^{-1}	3.3 (4.5–7.9)	6.1 (5.4–6.8)	NS
Creatinine mg·dL^{-1}	1.01±0.10	0.97±0.15	NS
Plasma renin activity ng·mL^{-1}·h^{-1}	1.53±0.81	2.03±0.80	NS
Aldosterone ng·dL^{-1}	14.23±7.78	21.00±8.12	0.022
Aldosterone/renin ratio	11.4±6.8	11.8±6.7	NS
L-endothelin pg·mL^{-1}	0.91±0.30	1.13±0.40	NS
sVCAM-1 ng·mL^{-1}	1083±792	1017±807	NS
sICAM-1 ng·mL^{-1}	352±164	341±202	NS

Data are presented as mean±SD, mean (interquartile range) or n (%), unless otherwise stated. NS: nonsignificant; BMI: body mass index; WASO: wake after sleep onset; REM: rapid eye movement; NREM: non-REM; SWS: slow-wave sleep; AHI: apnoea–hypopnoea index; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; P_{Imax}: maximal inspiratory pressure; BP: blood pressure; sVCAM: soluble vascular cell adhesion molecule; sICAM: soluble intercellular adhesion molecule.

Effect of CPAP treatment on peripheral chemosensitivity

In the OSA patients with INH, the average use of CPAP treatment was similar to sham CPAP (5.3±0.8 *versus* 5.2±1.0 h·night^{-1}; p=0.568), and the mean CPAP pressure used was 8.6±1.2 cmH_2O. The group with

TABLE 2 Baseline blood gases and peripheral chemosensitivity before and after sleep in the two populations of hypertensive obstructive sleep apnoea patients

	INH			D-NSH			INH *versus* D-NSH	
	Before	After	p-value	Before	After	p-value	Before	After
pH	7.45±−0.02	7.44±0.02	0.044	7.43±0.04	7.42±0.03	NS	NS	NS
P_{aO_2} mmHg	81.5±8.0	81.2±7.7	NS	84.6±6.8	83.9±6.3	NS	NS	NS
P_{aCO_2} mmHg	39.0±3.2	39.8±3.0	NS	39.5±2.0	40.1±2.6	NS	NS	NS
V'_{I_N} L·min^{-1}	10.1±4.3	10.3±5.4	NS	9.6±3.2	9.8±3.0	NS	NS	NS
V'_{I_N}/BSA, L·min^{-1}·m^{-2}	5.2±2.2	5.3±2.9	NS	5.1±1.6	5.2±1.5	NS	NS	NS
V'_{I_0} L·min^{-1}	17.9±4.7	18.9±8.3	NS	18.4±5.3	18.6±5.1	NS	NS	NS
V'_{I_0}/BSA, L·min^{-1}·m^{-2}	9.2±2.5	7.8±4.5	NS	9.8±2.6	9.9±2.8	NS	NS	NS
$V'_{I_{5-20}}$ L·min^{-1}	13.4±3.2	12.8±6.1	NS	13.1±3.7	12.5±3.3	NS	NS	NS
ΔV_I L·min^{-1}	4.5±1.9	6.1±2.7	0.026	5.3±1.7	6.1±1.9	0.016	NS	NS
ΔV_I/BSA L·min^{-1}·m^{-2}	2.3±0.9	3.1±1.5	0.026	2.8±0.9	3.3±1.0	0.015	NS	NS
ΔV_I %	24.3±5.8	32.6±6.0	0.010	28.7±3.3	32.6±3.2	0.002	0.005	NS

Data are presented as mean±SD, unless otherwise stated. INH: isolated nocturnal hypertension; D-NSH: day–night sustained hypertension; NS: not significant; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: carbon dioxide arterial tension; V'_{I_N}: inspiratory minute ventilation during room air breathing; BSA: body surface area; V'_{I_0}: inspiratory minute ventilation during mildly hypercapnic hypoxic state; $V'_{I_{5-20}}$: inspiratory minute ventilation 5–20 s after changing the inspiratory gas to 100% oxygen; ΔV_I: withdrawal response or index of the peripheral chemoreceptor activity.

D-NSH reached similar levels of CPAP or sham CPAP use (5.2±0.8 *versus* 5.3±0.7 h·night^{-1}; p=0.327), with a mean CPAP pressure of 9.3±1.8 cmH_2O.

Figure 2 and online supplementary table S1 and figure S1 summarise the effect of CPAP intervention on peripheral chemosensitivity. The order in which patients received treatment and placebo had no impact on this primary efficacy outcome. After 3 months of CPAP, nocturnal increase in peripheral chemosensitivity (%ΔV_I after sleep−%ΔV_I before sleep) was reduced in OSA patients with INH (6.9%, 95% CI 1.0–12.8; p=0.026), but not in the OSA patients with D-NSH (2.7%, 95% CI −1.1–6.5; p=0.153). This difference seems to be due to a different CPAP effect on peripheral chemosensitivity before and after sleep in both groups of patients. Thus, while CPAP induced a decrease in %ΔV_I after sleep in both INH (7.5%, 95% CI, 2.6–12.2%; p=0.005) and D-NSH OSA patients (5.7%, 95% CI 2.2–9.3%; p=0.004), %ΔV_I before sleep only decreased significantly with CPAP treatment in patients with D-NSH (3.0% 95% CI 0.5–5.6%; p=0.023), who have a higher baseline value. No change was found after sham CPAP. Moreover, variations in blood gases were not detected in either treatment group.

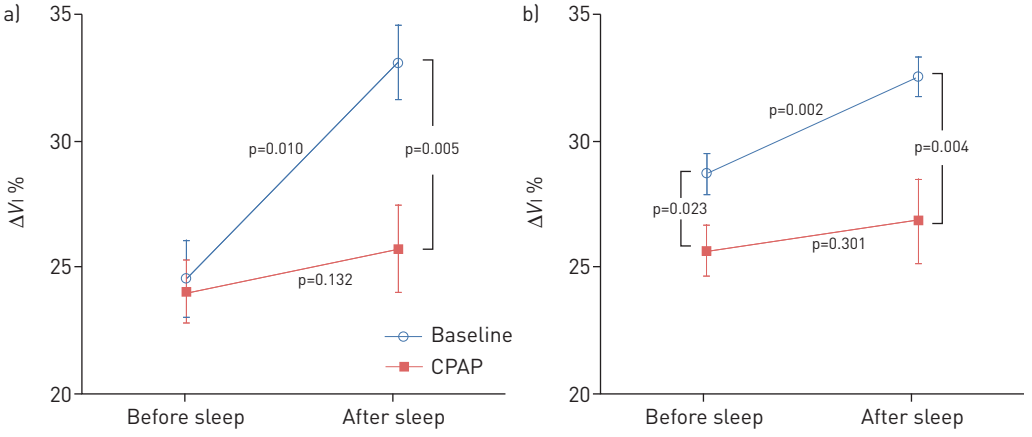

FIGURE 2 Comparison of the nocturnal evolution of peripheral chemosensitivity at baseline and after 3 months of continuous positive airway pressure (CPAP) treatment in patients with a) isolated nocturnal hypertension and b) day–night sustained hypertension. Data are presented as mean±SEM. ΔV_I: withdrawal response or index of the peripheral chemoreceptor activity.

Effect of CPAP treatment on secondary outcomes

Changes in anthropometric characteristics and blood pressures are shown table 3. Weight remained stable during follow-up, with no significant differences between groups. While sham CPAP did not induce any changes in blood pressure values, 3 months of treatment with CPAP were associated with a decrease in night-time BP, which was particularly prominent in patients with INH. In this group, CPAP significantly reduced night-time systolic, diastolic and mean blood pressure by 4.5 (95% CI 1.9–7.9) mmHg, 2.9 (95% CI 0.8–5.0) mmHg and 3.3 (95% CI 1.3–5.4) mmHg, respectively (table 3). The CPAP effect on daytime blood pressure only reached statistical significance in patients with D-NSH, resulting in a mean blood pressure reduction of 3.2 (95% CI 0.1–6.3) mmHg. As stated in the protocol, patients did not receive any other antihypertensive treatment during their participation in the study, and none of the patients withdrew due to severe hypertension.

Changes in urinary catecholamines, RAAS activity and levels of circulating vasoconstrictors are summarised in table 4. After CPAP treatment, there was a decrease from baseline in the diurnal and nocturnal urinary excretion of noradrenaline in both INH and D-NSH patients. In contrast, only aldosterone levels reduced significantly after CPAP in OSA patients with D-NSH, who in turn had higher baseline values.

The per-protocol analysis (14 patients in each study group) produced similar results (online supplementary tables S2–S4).

Interestingly, in the OSA patients with INH alone, the CPAP-induced change from baseline in the nocturnal increase of peripheral chemosensitivity directly correlated with the change from baseline in the

TABLE 3 Weight and blood pressure changes from baseline in the study groups

	Sham CPAP	p-value	CPAP	p-value
Weight kg				
INH	0.7 (−1.0–2.3)	NS	0.3 (−0.5–1.2)	NS
D-NSH	0.5 (−0.6–1.6)	NS	0.7 (−0.9–2.2)	NS
Overall	0.6 (−0.4–1.5)	NS	0.5 (−0.3–1.4)	NS
Diurnal systolic BP mmHg				
INH	−1.1 (−3.6–1.5)	NS	−0.3 (−3.3–2.6)	NS
D-NSH	0.8 (−3.2–4.7)	NS	−3.6 (−7.3–0.2)	NS
Overall	−0.1 (−2.4–2.1)	NS	−2.0 (−4.3–0.3)	NS
Diurnal diastolic BP mmHg				
INH	1.0 (−1.3–3.3)	NS	0.1 (−2.8–2.9)	NS
D-NSH	−0.1 (−1.8–1.7)	NS	−3.1 (−6.2–0.1)	NS
Overall	0.5 (−0.9–1.8)	NS	−1.5 (−3.6–0.5)	NS
Diurnal mean BP mmHg				
INH	0.5 (−1.5–2.6)	NS	−0.1 (−2.8–2.6)	NS
D-NSH	0.0 (−2.5–2.5)	NS	−3.2 (−6.3–−0.1)	0.043
Overall	0.3 (−1.3–1.8)	NS	−1.7 (−3.7–0.3)	NS
Nocturnal systolic BP mmHg				
INH	−1.0 (−3.5–1.5)	NS	−4.5 (−7.0–−1.9)	0.002
D-NSH	0.5 (−4.2–5.2)	NS	−4.9 (−8.7–−1.0)	0.017
Overall	−0.2 (−2.8–2.3)	NS	−4.7 (−6.9–−2.5)	<0.001
Nocturnal diastolic BP mmHg				
INH	−0.3 (−2.0–1.3)	NS	−2.9 (−5.0–−0.8)	0.011
D-NSH	0.9 (−0.8–2.7)	NS	−2.6 (−5.9–0.6)	NS
Overall	0.3 (−0.8–1.5)	NS	−2.7 (−4.6–−0.9)	0.005
Nocturnal mean BP mmHg				
INH	−0.2 (−1.6–1.2)	NS	−3.3 (−5.4–−1.3)	0.004
D-NSH	0.8 (−1.6–3.2)	NS	−3.1 (−6.1–−0.1)	0.042
Overall	0.3 (−1.0–1.7)	NS	−3.2 (−5.0–−1.5)	0.001
Nocturnal dipping mean BP %				
INH	0.8 (−0.9–2.5)	NS	3.7 (1.1–6.2)	0.009
D-NSH	−0.9 (−2.6–0.8)	NS	0.0 (−2.1–2.1)	NS
Overall	−0.1 (−1.2–1.1)	NS	1.8 (0.1–3.5)	0.040

Data are presented as mean difference (95% CI), unless otherwise stated. Values have been adjusted for treatment order. CPAP: continuous positive airway pressure; INH: isolated nocturnal hypertension; NS: nonsignificant; D-NSH: day–night sustained hypertension; BP: blood pressure.

TABLE 4 Changes from baseline in urinary cathecholamines, activity of the renin–angiotensin–aldosterone system and systemic biomarkers in the study groups

	Sham CPAP	p-value	CPAP	p-value
Diurnal noradrenaline μg·g^{-1}				
INH	−1.3 (−5.0–2.4)	NS	−9.1 (−16.3–−1.8)	0.018
D-NSH	0.0 (−7.3–7.2)	NS	−8.3 (−14.9–−1.8)	0.016
Overall	−0.7 (−4.6–3.2)	NS	−8.7 (−13.3–−4.1)	0.001
Diurnal adrenaline μg·g^{-1}				
INH	0.4 (0.1–0.7)	0.031	1.6 (−0.8–4.0)	NS
D-NSH	0 (−1.2–1.2)	NS	0.3 (−0.9–1.5)	NS
Overall	0.2 (−0.4–0.8)	NS	0.9 (−0.3–2.2)	NS
Nocturnal noradrenaline μg·g^{-1}				
INH	0.1 (−4.2–4.5)	NS	−8.1 (−14.5–−1.8)	0.016
D-NSH	0.9 (−1.8–3.7)	NS	−5.1 (−9.6–−0.7)	0.028
Overall	0.5 (−1.8–2.9)	NS	−6.6 (−10.3–−2.9)	0.001
Nocturnal adrenaline μg·g^{-1}				
INH	0.6 (−1.6–2.9)	NS	−0.9 (−2.0–0.2)	NS
D-NSH	0.3 (−0.4–1.0)	NS	0 (−1.7–1.6)	NS
Overall	0.4 (−0.6–1.5)	NS	−0.5 (−1.4–0.5)	NS
Creatinine mg·dL^{-1}				
INH	−0.02 (−0.12–0.08)	NS	0 (−0.09–0.09)	NS
D-NSH	0 (−0.4–0.3)	NS	−0.01 (−0.12–0.11)	NS
Overall	−0.01 (−0.06–0.04)	NS	0.00 (−0.07–0.07)	NS
Plasma renin activity ng·mL^{-1}·h^{-1}				
INH	0.06 (−0.03–0.14)	NS	0.21 (−0.05–0.47)	NS
D-NSH	0.07 (−0.16–0.30)	NS	0.03 (−0.23–0.28)	NS
Overall	0.07 (−0.05–0.18)	NS	0.11 (−0.06–0.29)	NS
Aldosterone ng·dL^{-1}				
INH	−0.39 (−1.34–0.57)	NS	0.35 (−1.56–2.26)	NS
D-NSH	−0.41 (−1.33–0.51)	NS	−2.05 (−3.90–−0.19)	0.033
Overall	−0.40 (−1.02–0.23)	NS	−0.89 (−2.21–0.44)	NS
Aldosterone/renin ratio				
INH	−0.88 (−1.84–0.08)	NS	−0.45 (−2.84–1.93)	NS
D-NSH	−0.88 (−1.84–0.08)	NS	−0.45 (−2.84–1.93)	NS
Overall	−0.69 (−1.87–0.50)	NS	−0.73 (−2.37–0.90)	NS
Endothelin 1 pg·mL^{-1}				
INH	−0.02 (−0.22–0.17)	NS	−0.18 (−0.0–−0.35)	0.049
D-NSH	−0.1 (−0.30–0.09)	NS	−0.05 (−0.20–0.10)	NS
Overall	−0.07 (−0.19–0.06)	NS	0.06 (−0.06–0.18)	NS
sVCAM-1 ng·mL^{-1}				
INH	−198 (−822–426)	NS	−558 (−1361–245)	NS
D-NSH	−381 (−835–73)	NS	260 (−415–915)	NS
Overall	−290 (−653–74)	NS	−154 (−666–358)	NS
sICAM-1 ng·mL^{-1}				
INH	59 (−52–170)	NS	0 (−0.02–0.01)	NS
D-NSH	−47 (−176–81)	NS	−15 (−48–179)	NS
Overall	−53 (−133–26)	NS	−8 (−23–8)	NS

Data are presented as mean difference (95% CI), unless otherwise stated. Values have been adjusted for treatment order. CPAP: continuous positive airway pressure; INH: isolated nocturnal hypertension; NS: nonsignificant; D-NSH: day–night sustained hypertension; sVCAM: soluble vascular cell adhesion molecule; sICAM: soluble intercellular adhesion molecule.

diurnal and nocturnal levels of noradrenaline (r=0.579, p=0.024 and r=0.621, p=0.013, respectively) (online supplementary figure S2).

Determinants of baseline night-time and daytime blood pressure

Online supplementary tables S5–S8 show the parameters related to baseline night-time and daytime blood pressure in patients with INH and D-NSH. The multivariate analysis showed that peripheral chemoreflex response after sleep is an independent determinant of night-time blood pressures in INH patients (table 5), as well as of the night-time systolic and diastolic blood pressure in patients with D-NSH (table 6). Interestingly, baseline blood pressure values showed a different pattern of relationships with other

TABLE 5 Independent determinants of night-time and daytime blood pressure in obstructive sleep apnoea patients with isolated nocturnal hypertension

	Unstandardised regression coefficients B±SE	95% CI for B	Standardised regression coefficients B	p-value	r^2	r^2 change
Night-time systolic blood pressure mmHg						
Constant	90.759±11.230	(67.824–113.694)		<0.001		
ΔV_I after sleep %	1.112±0.341	(0.415–1.808)	0.511	0.003	0.262	0.262
Night-time diastolic blood pressure mmHg						
Constant	52.951±7.055	(38.521–67.380)		<0.001		
ΔV_I after sleep %	0.678±0.214	(0.240–1.117)	0.506	0.004	0.256	0.256
Night-time mean blood pressure mmHg						
Constant	65.704±6.446	(52.520–78.888)		<0.001		
ΔV_I after sleep %	0.589±0.224	(0.131–1.047)	0.423	0.014	0.343	0.343
Nocturnal noradrenaline $\mu g \cdot g^{-1}$	0.167±0.081	(0.003–0.332)	0.334	0.047	0.428	0.085
Daytime systolic blood pressure mmHg						
Constant	120.072±3.116	(113.390–126.754)		<0.001		
Nocturnal noradrenaline $\mu g \cdot g^{-1}$	0.184±0.060	(0.055–0.312)	0.634	0.008	0.402	0.402
Daytime diastolic blood pressure mmHg						
Constant	91.773±5.694	(79.560–103.986)		<0.001		
Sleep efficiency %	−0.201±0.072	(−0.356–−0.046)	−0.597	0.015	0.357	0.357
Daytime mean blood pressure mmHg						
Constant	105.218±4.730	(95.073–115.363)		<0.001		
Sleep efficiency %	−0.148±0.060	(−0.276–−0.019)	−0.549	0.028	0.302	0.302

ΔV_I: peripheral chemosensitivity assessed by the withdrawal response.

potential determinants in the two groups of hypertensive OSA patients (tables 5 and 6). In patients with INH, night-time mean blood pressure and daytime systolic blood pressure were independently related to nocturnal noradrenaline excretion, whereas daytime diastolic and mean blood pressures were inversely related to sleep efficiency (table 5). In contrast, in patients with D-NSH, aldosterone levels were related to night-time systolic blood pressure as well as daytime systolic and mean blood pressure, whereas the aldosterone/renin ratio correlated with daytime diastolic blood pressure (table 6). Moreover, nocturnal and diurnal adrenaline secretions were related to night-time blood pressure, whereas diurnal and nocturnal noradrenaline excretions were related to daytime blood pressure (table 6).

Parameters related to the CPAP effect on blood pressure

The relationship between the absolute change in blood pressure after 3 months of CPAP therapy and the baseline characteristics of the subjects are shown in online supplementary figures S3 and S4. In patients with INH, changes from baseline in night-time blood pressure only directly correlated with baseline plasma renin activity, so that subjects with lower activity experienced a greater decline in blood pressure after treatment with CPAP (online supplementary figure S3). In contrast, the change from baseline in the daytime and night-time mean blood pressures of patients with D-NSH correlated inversely with baseline aldosterone levels and the aldosterone/renin ratio (online supplementary figure S4). This suggests that, in this group, CPAP might have a greater hypotensive effect in patients with higher RAAS activity.

Discussion

The main results from the present study are as follows. 1) Although nocturnal peripheral chemosensitivity increases in OSA patients with INH as well as those with D-NSH, the latter start at higher levels before sleep and present a greater concentration of baseline aldosterone; 2) while 3 months of CPAP treatment reduces peripheral chemosensitivity after sleep as well as catecholamine levels and arterial pressure in both patient groups, peripheral chemosensitivity before sleep and plasma aldosterone concentrations only decrease in patients with D-NSH; and 3) the baseline determinants for CPAP-induced reduction in blood pressure are different in the two groups of hypertensive OSA patients. In patients with INH, a greater decrease in blood pressure was achieved when plasma renin activity was lower, while in subjects with D-NSH the drop in blood pressure was greater when the baseline level of aldosterone and the aldosterone/renin ratio were higher. When considered as a whole, these findings reflect a dissimilar participation of

TABLE 6 Independent determinants of night-time and daytime blood pressure in obstructive sleep apnoea patients with day–night sustained hypertension

	Unstandardised regression coefficients B±SE	95% CI for B	Standardised regression coefficients B	p-value	r^2	r^2 change
Night-time systolic blood pressure mmHg						
Constant	48.184±23.145	−1.817–98.185		0.058		
Aldosterone ng·dL^{-1}	1.033±0.253	0.485–1.580	0.731	0.001	0.378	0.378
Δ*V*ı after sleep %	1.781±0.651	0.375–3.187	0.491	0.017	0.605	0.227
Night-time diastolic blood pressure mmHg						
Constant	22.049±11.305	−2.374–46.472		0.073		
Δ*V*ı after sleep %	1.419±0.354	0.655–2.183	0.593	0.001	0.491	0.491
Nocturnal adrenaline µg·g^{-1}	1.218±0.360	0.439–1.996	0.499	0.005	0.729	0.238
Night-time mean blood pressure mmHg						
Constant	97.976±5.195	86.752–109.200		<0.001		
Diurnal adrenaline µg·g^{-1}	−1.669±0.478	−2.702–−0.636	−0.561	0.004	0.439	0.439
Nocturnal adrenaline µg·g^{-1}	1.276±0.410	0.390–2.163	0.500	0.008	0.678	0.239
Daytime systolic blood pressure mmHg						
Constant	137.634±5.610	125.286–149.983		<0.001		
Diurnal noradrenaline µg·g^{-1}	0.230±0.044	0.134–0.326	0.649	<0.001	0.387	0.387
Sleep efficiency %	−0.252±0.052	−0.367–−0.138	−0.562	0.001	0.683	0.296
Aldosterone ng·dL^{-1}	0.481±0.128	0.199–0.762	0.443	0.003	0.788	0.105
Apnoea–hypopnoea index events·h^{-1}	−0.175±0.061	−0.310–−0.040	−0.396	0.015	0.879	0.090
Daytime diastolic blood pressure mmHg						
Constant	77.358±1.571	73.935–80.781		<0.001		
Diurnal noradrenaline µg·g^{-1}	0.056±0.019	0.015–0.097	0.431	0.012	0.645	0.645
Aldosterone/renin ratio	0.241±0.062	0.107–0.375	0.499	0.002	0.791	0.146
Nocturnal noradrenaline µg·g^{-1}	0.079±0.035	0.003–0.154	0.297	0.042	0.854	0.063
Daytime mean blood pressure mmHg						
Constant	86.524±2.005	82.155–90.893		<0.001		
Diurnal noradrenaline µg·g^{-1}	0.083±0.020	0.040–0.127	0.458	0.001	0.596	0.596
Aldosterone ng·dL^{-1}	0.289±0.053	0.173–0.405	0.519	<0.001	0.802	0.206
Nocturnal noradrenaline µg·g^{-1}	0.135±0.040	0.049–0.221	0.363	0.005	0.900	0.097

Δ*V*ı: peripheral chemosensitivity assessed by the withdrawal response.

pathogenic mechanisms involved in the development of hypertension in these two groups of OSA patients with blood pressure dysregulation.

The night-time increase in peripheral chemosensitivity, which is accompanied by overactivity of the sympathetic nervous system, is a common finding in our two study groups. This, together with the demonstration that the suppression of apnoea–hypopnoea decreases peripheral chemosensitivity, urinary catecholamine levels, and night-time and 24-h blood pressures, supports the fact that the increase of sympathetic activity during sleep and wakefulness *via* chemoreflex activation is one of the key mechanisms involved in the genesis of hypertension in OSA [28]. In this context, there is evidence suggesting potentiation of the peripheral chemoreflex in spontaneously hypertensive rats [29] and that the autonomic disturbance precedes the onset of hypertension [30]. Moreover, an exaggerated ventilatory response to hypoxaemia has been noted in borderline hypertensive human subjects [31]. As the potentiated chemoreflex-mediated sympathetic vasoconstriction is especially striking when apnoea is superimposed on hypoxaemia [32], the nocturnal enhance of peripheral chemosensitivity in OSA patients seems to be due to the succession of hypoxic episodes [33]. The oxygen-sensitive type I cells of the carotid bodies closely monitor oxygen tension in the arterial blood and, through release of various neurotransmitters, deliver afferent neural traffic information to the respiratory and cardiovascular networks in the brainstem, thereby triggering hyperventilation and increased sympathetic nerve activity [34].

In peripheral chemosensitivity, there is an initial differentiating element between OSA patients with INH and D-NSH, both at baseline as well as after CPAP therapy. Although there is a night-time increase in peripheral chemosensitivity in both groups, the patients with INH are able to reduce their level of peripheral chemosensitivity while awake, whereas in patients with D-NSH it remains elevated throughout the day. Thus, in patients with INH there is only evidence of a correction in nocturnal sympathetic tone after CPAP therapy; meanwhile, in patients with D-NSH, CPAP corrects sympathetic overactivity, during

both daytime as well as night-time. The information obtained from our study does not allow us to identify the mechanisms by which some OSA patients are able to control the night-time increase in peripheral chemosensitivity throughout the day, while other patients lose this capacity for adaptation and, therefore, retain an elevated sympathetic tone permanently.

Although our study has focused on alterations in peripheral chemosensitivity, we cannot exclude a potential role of central chemoreceptors in increasing the sympathetic tone through the stimulation of carbon dioxide-sensitive neurons of the retrotrapezoid body [35]. However, the patients evaluated in our study did not present hypercapnia and, except for a slight nocturnal increase in arterial carbon dioxide tension (P_{aCO_2}) in the INH group, did not show relevant changes in P_{aCO_2}.

Another important element distinguishing between the two groups of OSA patients are aldosterone levels, which are higher in D-NSH than in INH patients. Moreover, after 3 months of CPAP treatment, only in the former group did these levels diminish. This demonstrates that the increased secretion of aldosterone during repetitive apnoeic episodes could contribute to the maintenance of elevated blood pressure [36]. Nonetheless, it is interesting that the alterations identified in the plasma concentration of aldosterone of the patients with D-NSH are not parallel to the activity of plasma renin. To justify this finding, we should consider that obesity is also associated with increased levels of the circulating RAAS components [37, 38]. While the adipose tissue is an important source of the renin substrate (angiotensinogen), other mediators can stimulate aldosterone synthesis independently of angiotensin II [39, 40]. In this regard, animal studies suggest that acute hypercapnia or hypoxia separately increase plasmatic aldosterone concentration independent of increases in plasmatic renin activity [41, 42].

In any case, there is much evidence to suggest that elevated plasma concentrations of aldosterone could be more of a factor for the maintenance and perpetuation of hypertension than for its development [43]. This circumstance could justify the different behaviour of aldosterone in patients with INH and D-NSH, in addition to explaining why high aldosterone levels only predict a hypopressor response to CPAP in patients with D-NSH. In part, this finding concurs with a previous study in OSA patients with diurnal hypertension which showed that the suppression of apnoeas–hypopnoeas by means of automatic positive airway pressure treatment reduces aldosterone serum levels to levels similar to a type 1 angiotensin receptor blocker [44]. Along this line, there are data to suggest that excess aldosterone may be involved in the development of resistant hypertension in OSA [28]. In fact, a number of reports have suggested that primary aldosteronism may be a common cause of hypertension, with prevalence estimates ranging from 6% to 20%, whereas among patients with resistant hypertension, the prevalence ranges from 20% to 36% [45, 46]. Interestingly, recent studies also implicate aldosterone in the pathogenesis of metabolic syndrome [47]. Elevated aldosterone levels seem to lead not only to sodium retention and volume expansion, but also to increased inflammation and oxidative stress, which in turn promote insulin resistance, impaired pancreatic β-cell function, endothelial dysfunction and hypertension [48, 49].

In our opinion, the present study presents different strengths and weaknesses. Its strengths include the fact that, to our knowledge, it is the first to analyse the CPAP effect on OSA patients with isolated nocturnal hypertension while strictly controlling for the potential confounding effect of concomitant medication. Nonetheless, we also admit to its various limitations. The sample size is small, although sufficient according to our estimations, and able to detect a CPAP effect on blood pressure of a magnitude similar to that described in the literature. RAAS was evaluated solely by the description of its components at the end of sleep, without the use of sequential measurements or specific function tests, such as the angiotensin II challenge or renal vascular resistance measurement. The follow-up time is limited (3 months) to be able to guarantee adequate disguising of sham CPAP, although it could be insufficient to detect an additional response to CPAP. Lastly, the single-centre character of the study means that the results obtained should be extrapolated with caution.

In conclusion, the comparison of OSA patients with INH or D-NSH, both in baseline conditions and after CPAP treatment, is able to detect differences in the pathogenic mechanisms involved in the development of arterial hypertension in OSA. Specifically, it has been observed that, while awake, patients with D-NSH are not able to reduce the nocturnal increase in peripheral chemosensitivity experienced by all OSA patients, and they maintain higher daytime levels of plasma aldosterone. These alterations, which are partially reversible after 3 months of CPAP therapy, could explain why in some patients the transitory elevations in blood pressure related with apnoea–hypopnoea episodes perpetuate during wakefulness, establishing a continuum between INH and D-NSH. More information is required to assess whether these maintained alterations also contribute to the development of resistant hypertension in OSA patients, and whether these could be specific therapeutic targets.

Acknowledgements

Authors contributions are as follows. R. Casitas, E. Martínez-Cerón, R. Galera, I. Fernández-Navarro, B. Sánchez, A. García-Sánchez, E. Zamarrón and F. García-Río were responsible for developing the research question and securing funding; R. Casitas, E. Martínez-Cerón, R. Galera, C. Cubillos-Zapata, M.J. González-Villalba, I. Fernández-Navarro, B. Sánchez, A. García-Sánchez, E. Zamarrón and F. García-Río were responsible for the study design and collection of data; R. Casitas, E. Martínez-Cerón and F. García-Río were responsible for study management and coordination; R. Casitas, R. Galera, C. Cubillos-Zapata, M.J. González-Villalba, I. Fernández-Navarro, B. Sánchez and F. García-Río were responsible for the analysis; and F. García-Río drafted the paper. All authors have read and approved the final manuscript.

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