Original Investigation

Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension
The HIPARCO Randomized Clinical Trial

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IMPORTANCE More than 70% of patients with resistant hypertension have obstructive sleep apnea (OSA). However, there is little evidence about the effect of continuous positive airway pressure (CPAP) treatment on blood pressure in patients with resistant hypertension.

OBJECTIVE To assess the effect of CPAP treatment on blood pressure values and nocturnal blood pressure patterns in patients with resistant hypertension and OSA.

DESIGN, SETTING, AND PARTICIPANTS Open-label, randomized, multicenter clinical trial of parallel groups with blinded end point design conducted in 24 teaching hospitals in Spain involving 194 patients with resistant hypertension and an apnea-hypopnea index (AHI) of 15 or higher. Data were collected from June 2009 to October 2011.

INTERVENTIONS CPAP or no therapy while maintaining usual blood pressure control medication.

MAIN OUTCOMES AND MEASURES The primary end point was the change in 24-hour mean blood pressure after 12 weeks. Secondary end points included changes in other blood pressure values and changes in nocturnal blood pressure patterns. Both intention-to-treat (ITT) and per-protocol analyses were performed.

RESULTS A total of 194 patients were randomly assigned to receive CPAP (n = 98) or no CPAP (control; n = 96). The mean AHI was 40.4 (SD, 18.9) and an average of 3.8 antihypertensive drugs were taken per patient. Baseline 24-hour mean blood pressure was 103.4 mm Hg; systolic blood pressure (SBP), 144.2 mm Hg; and diastolic blood pressure (DBP), 83 mm Hg. At baseline, 25.8% of patients displayed a dipper pattern (a decrease of at least 10% in the average nighttime blood pressure compared with the average daytime blood pressure). The percentage of patients using CPAP for 4 or more hours per day was 72.4%. When the changes in blood pressure over the study period were compared between groups by ITT, the CPAP group achieved a greater decrease in 24-hour mean blood pressure (3.1 mm Hg [95% CI, 0.6 to 5.6]; $P = .02$) and 24-hour DBP (3.2 mm Hg [95% CI, 1.0 to 5.4]; $P = .005$), but not in 24-hour SBP (3.1 mm Hg [95% CI, −0.6 to 6.7]; $P = .10$) compared with the control group. Moreover, the percentage of patients displaying a nocturnal blood pressure dipper pattern at the 12-week follow-up was greater in the CPAP group than in the control group (35.9% vs 21.6%; adjusted odds ratio [OR], 2.4 [95% CI, 1.2 to 5.1]; $P = .02$). There was a significant positive correlation between hours of CPAP use and the decrease in 24-hour mean blood pressure ($r = 0.29$, $P = .006$), SBP ($r = 0.25$; $P = .02$), and DBP ($r = 0.30$, $P = .005$).

CONCLUSIONS AND RELEVANCE Among patients with OSA and resistant hypertension, CPAP treatment for 12 weeks compared with control resulted in a decrease in 24-hour mean and diastolic blood pressure and an improvement in the nocturnal blood pressure pattern. Further research is warranted to assess longer-term health outcomes.

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Systemic hypertension is one of the most treatable cardiovascular risk factors.[1] Between 12% and 27% of all hypertensive patients require at least 3 antihypertensive drugs for adequate blood pressure control and are considered patients with resistant hypertension.[2-4] Patients with resistant hypertension are almost 50% more likely to experience a cardiovascular event than hypertensive patients without resistant hypertension, and the incidence of resistant hypertension is expected to increase.[5]

Obstructive sleep apnea (OSA) affects 4% to 6% of the general middle-aged population[6,7] and increases with age.[8] It is characterized by the repeated collapse of the upper airway during the night, causing intermittent hypoxemia and sleep disruption, which in turn are associated with an increased risk for neurocognitive and cardiovascular morbidities.[9] Recent studies have shown that OSA may contribute to poor control of blood pressure[10] and that a very high percentage (>70%) of resistant hypertension patients have OSA.[11] Accordingly, international guidelines now recognize OSA as one of the most common risk factors of resistant hypertension.[4]

AHI *apnea-hypopnea index*

ABPM *ambulatory blood pressure monitor*

CPAP *continuous positive airway pressure*

DBP *diastolic blood pressure*

OSA *obstructive sleep apnea*

SBP *systolic blood pressure*

Continuous positive airway pressure (CPAP) is the treatment of choice for severe or symptomatic OSA.[12] A meta-analysis suggests that CPAP treatment reduces blood pressure levels to a clinically meaningful degree,[13] but whether this positive effect is more pronounced in patients with resistant hypertension is unclear because studies on this issue are scarce and based on single-center approaches.[14-16] The objective of our study was to conduct a randomized, multicenter clinical trial to assess the effect of CPAP treatment on blood pressure values and nocturnal blood pressure patterns of patients with resistant hypertension and OSA.

Methods

Study Design

This study was approved by the ethics committee of each participating center. All the participants provided informed signed consent to participate in the study. Our study was an open-label, randomized, multicenter clinical trial of parallel groups with a blinded end point design conducted in 24 teaching hospitals in Spain in patients diagnosed with resistant hypertension and OSA. Patients were randomly assigned to either CPAP or no therapy (control) and maintained their usual, unmodified blood pressure control medication.

Selection of Patients

Patients were consecutively recruited from the Hypertension Clinical Units of the participating centers. Patients were initially eligible for participation in the study if they had primary resistant hypertension, were aged 18 to 75 years, and signed the informed consent to participate. All the major causes of resistant hypertension were ruled out in each Hypertension Clinical Unit including primary aldosteronism, renal artery stenosis, and renal insufficiency. Initial exclusion criteria also included pregnancy, disabling hypersomnia requiring urgent treatment (defined as an Epworth Sleepiness Scale [ESS] ≥18), current use of CPAP treatment, poor adherence with antihypertensive treatment, long-term treatment with oral corticosteroids or nonsteroidal anti-inflammatory drugs, renal insufficiency (creatinine concentration higher than 1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4] in peripheral blood sample), a cardiovascular event in the month prior to the inclusion in the study, and the regular use of sedative drugs such as benzodiazepines, major opiates, and antipsychotics, which could significantly modify the results of sleep studies and alcohol intake (more than 100 grams of alcohol per day).

Procedures

Initial Visit

At the initial visit, all the patients completed a standardized protocol that included general and anthropometric data, history of cardiovascular diseases, current medications, and clinical history related to OSA. The ESS was used to quantify daytime somnolence. Good adherence to the antihypertensive treatment was verified by means of the Haynes-Sackett test.[17] This test is a method for assessing self-reported adherence. Patients were also asked to bring the empty blister packs of their antihypertensive pills to check the number of tablets missed per month. Good adherence was considered to occur when the percentage of doses taken was between 80% and 120% of the prescribed dose (some patients took more than the prescribed dose).

Sleep Studies

All the included patients underwent attended respiratory polygraphy[18] in the sleep laboratory of each center. Respiratory polygraphy included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and oxygen saturation (Sa_{O_2}). Polygraphy data were scored manually by trained personnel. Apnea was defined as an interruption of oronasal airflow for more than 10 seconds. Hypopnea was defined as a 30% to 90% reduction in oronasal airflow for more than 10 seconds, associated with an oxygen desaturation of 4% or higher. Apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of recording, and $TSat_{90}$ was defined as the percentage of recording time with Sa_{O_2} less than 90%. Those tests in which the patients claimed to sleep less than 4 hours or in which there were less than 5 hours of nocturnal recording were repeated. Central sleep apnea was defined as at least 50% of respiratory events having a pattern of apnea or hypopnea without respiratory effort.

24-Hour Ambulatory Blood Pressure Monitoring

All patients with an AHI of 15 or higher underwent an initial 24-hour ABPM measurement to ascertain the presence of resistant hypertension and its control in accordance with standard recommendations.[19,20]

The summary values in the ABPM report of each patient in the data analysis were used. Data related to the average daytime and nighttime systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (defined as [⅔ DBP value] + [⅓ SBP value])[21]; types of nocturnal blood pressure patterns (according to the increase [riser], decrease [dipper], or absence of a difference [nondipper] of at least 10% in the value of the average nighttime blood pressure levels compared to the average daytime levels);[20] variability of blood pressure (defined as the standard deviation of the 24-hour mean blood pressure); heart rate; and both SBP and DBP 24-hour peak and valley values (defined as the maximum [peak] and minimum [valley] 24-hour blood pressure values) were recorded. Blood pressure levels were measured every 20 minutes in both the daytime and nighttime periods.

The sleeping and awaking periods were determined by instructing the patients to record the approximate times when they fell asleep and woke up. The 24-hour ABPM criteria used to define resistant hypertension were blood pressure that remained above goal (ie, average SBP ≥130 mm Hg, average DBP ≥80 mm Hg, or both) in spite of concurrent use of at least 3 antihypertensive medication agents prescribed at doses that provide optimal benefit—1 of them being, ideally, a diuretic, if no contraindication exists.[4] Patients not fulfilling resistant hypertension criteria were excluded from the study.

Main Outcome Measures

The primary end point was the change in the 24-hour ambulatory mean blood pressure from baseline to 12 weeks of CPAP or control. Secondary end points included changes in other blood pressure values, especially diurnal and noctunal SBP and DBP, and changes in nocturnal blood pressure patterns.

Random Allocation

Patients with an AHI of 15 or higher in whom resistant hypertension was confirmed were eligible for randomization. The clinician responsible used a specific software designed for this study (Random function of JavaScript math package) to determine the group allocation for patients. Random allocation stratified by site was used without any other restriction. The software only revealed the allocation group when an investigator provided the data of a fully eligible patient, which guaranteed the concealment of the randomization sequence.

CPAP Pressure Titration

For those patients randomized to CPAP treatment, optimal CPAP pressure was titrated in the sleep laboratory on a second night by an auto CPAP device (REMstar Pro M Series with C-Flex, Philips Respironics) within a period of less than 15 days after the diagnostic study to obtain a fixed CPAP pressure value, according to a previous validation by the Spanish Sleep Network.[22] The optimal pressure was determined by 2 blinded expert researchers, based on the visual evaluation of the raw data recording from the night study, with no significant leaks (less than 0.40 L/s). This fixed pressure was then maintained throughout the study in those patients assigned to the CPAP group.

Follow-up

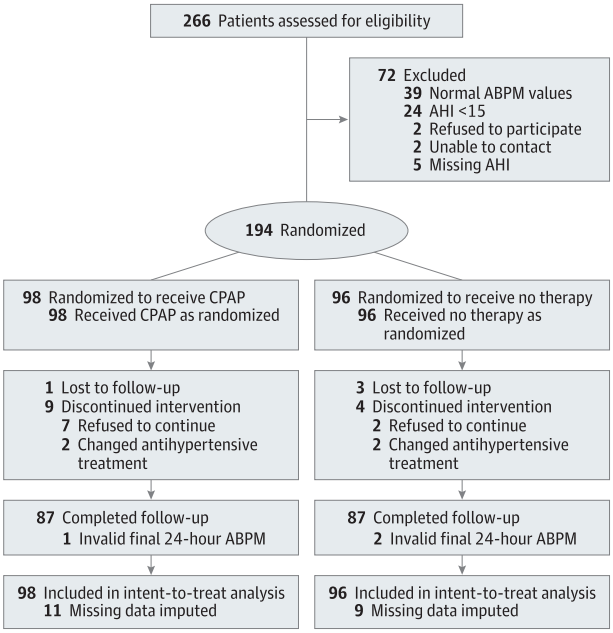
Treatment with CPAP was continued for 3 months, during which the patient had direct contact with the research team at all times for clinical problem-solving issues. Medical appointments were scheduled for all patients (with or without CPAP) 2 weeks after randomization and, subsequently, at 4, 8, and 12 weeks. We considered adherence as adequate if the mean CPAP use was at least 4 hours per night. Every medical appointment involved protocol-based assessments of the following: adherence to CPAP and antihypertensive treatment, appearance of any noteworthy new medical circumstances (especially changes in treatments, clinical or anthropometric variables, or new vascular events), and reevaluation of the exclusion criteria. At the last medical appointment, after 12 weeks of treatment, a repeat 24-hour ABPM test was conducted in all patients. The CPAP device used was able to store all the data from the 3 months of use and record the residual AHI, leaks, and other information for each night for analysis using specific software (Encore Pro, Philips Respironics). Data were collected from June 2009 to October 2011.

Statistical Analysis

Continuous variables were expressed as mean (SD), while categorical variables were reported as absolute numbers and percentages. The normality of the distribution of variables was tested using the Kolmogorov-Smirnov test. Calculation of the sample size aimed to detect a reduction of 4 mm Hg or more in 24-hour mean blood pressure, assuming a pooled standard deviation of 8.7,[23] an α error of 5%, and a statistical power of 80%, with a total of 70 patients needed per randomized treatment group, including both an intention-to-treat (ITT) analysis (analyzed data from all randomized patients) and a per-protocol analysis (analyzed data only from patients with adequate adherence to CPAP who finished the study).

The intragroup differences from the beginning to the end of the study were evaluated with a paired *t* test. Intergroup comparisons of the change in blood pressure were assessed by analysis of covariance (ANCOVA) to adjust for baseline blood pressure values. The hospital of inclusion and all the clinically relevant cardiovascular risk factors that differed significantly at baseline were also included as covariates. The validity of the models was assessed by the coefficient of determination R^2. Also, graphical examination was performed in order to confirm the assumptions of linearity and normality of the residuals. The χ^2 test was used to compare dichotomous variables. Multiple imputation techniques were used to estimate values for those patients without valid measurements of blood pressure after the 12-week follow-up. The multiple imputation method is implemented under the assumption that the missing data are missing at random. For the 20 patients with missing follow-up blood pressure measurements, imputed values of these measurements were generated on the basis of baseline blood pressure values, sex, age, AHI, ESS, and number of initial antihypertensive drugs. This was generated using multiple imputation by chained equations, the ice command in Stata (StataCorp), version 11.

Figure 1. Flowchart of the Study



ABPM indicates ambulatory blood pressure monitor; AHI, apnea-hypopnea index; and CPAP, continuous positive airway pressure.

Logistic regression analysis was used to estimate the odds ratio (OR) of having a dipper or riser pattern in the CPAP group compared with the control group. Baseline status was included as a covariate. Appropriate 95% CIs were also calculated. A 2-sided *P* value less than .05 was considered significant. Data management and statistical analyses were performed using Stata, version 11, and SPSS predictive analytics software (IBM), version 21.

Results

Of the initial 266 recruited patients, 194 were randomized, 98 to the CPAP group and 96 to the control group (ITT population), and 174 (87 CPAP, 87 control) of these completed the study and had valid 24-hour ABPM measurements (**Figure 1**). Of the 194 randomized patients, 133 patients (68.6%) were men. The mean (SD) for age was 56.0 (9.5) years; body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), 34.1 (5.4); AHI, 40.4 (18.9) events per hour (96.1% of events were obstructive); and antihypertensive drugs taken per patient, 3.8 (0.9). Patients showing an AHI of 30 or higher were 63.9%; an ESS of 10 or higher, 43.2%. The mean ESS was 9.1 (SD, 3.7; range, 1-18). No patient had central sleep apnea. The mean (SD) for baseline 24-hour mean blood pressure was 103.4 (9.6) mm Hg; SBP, 144.2 (12.5) mm Hg; and DBP, 83.0 (10.5) mm Hg. Patients with a nondipper blood pressure nocturnal pattern were 42.8%; riser, 31.4% (**Table 1**). Ten patients were not taking a diuretic as antihypertensive treatment because of adverse effects. The use of antihypertensive medication is detailed in **Table 2**. Patients who did not complete the follow-up were similar to those who completed it, except that they took slightly more antihypertensive medication at baseline (4.3 incomplete study vs 3.7 completed study; *P* = .02).

The average use of CPAP treatment was 5 (1.9) hours per night, with 71 patients (72.4%) using it at least 4 hours per night. The mean CPAP pressure used was 8.5 (2.1) mm Hg. The residual AHI following the application of CPAP during the titration study was 4.1 (3.8) mm Hg.

Intention-to-Treat Analysis

For the ITT analysis, imputed values for blood pressure measurements were calculated for the 20 patients with missing follow-up blood pressure measurements due to failure to complete the protocol or an invalid 24-hour ABPM study. When the changes in blood pressure during the study period were compared between study groups by ITT (98 patients in the CPAP group; control group, 96 patients), the CPAP group achieved a greater decrease in 24-hour mean blood pressure (3.1 mm Hg [95% CI, 0.6 to 5.6]; *P* = .02) and 24-hour DBP (3.2 mm Hg [95% CI, 1.0 to 5.4]; *P* = .005), but not 24-hour SBP (3.1 mm Hg [95% CI, −0.6 to 6.7]; *P* = .10) compared to the control group (**Table 3**). The differences appeared greater for nocturnal blood pressure than for daytime blood pressure, although the 95% CIs for changes in nocturnal and daytime blood pressure overlapped. The model did not change when it was adjusted for potential confounders (baseline blood pressure, AHI, ESS, nocturnal blood pressure pattern, and previous cardiovascular events) except for the statistically significant reduction observed in SBP values not seen in the unadjusted model (Table 3). Regarding nocturnal patterns, the percentage of patients displaying a nocturnal blood pressure dipper pattern at the 12-week follow-up was greater in the CPAP group than in the control group (35.9% CPAP vs 21.6% control; adjusted OR, 2.4 [95% CI, 1.2 to 5.1]; *P* = .02). (**Table 4**). Also, fewer patients in the CPAP group displayed a nocturnal riser pattern at the end of the study compared to the control group (adjusted OR, 0.45 [95% CI, 0.23 to 0.91]; *P* = .03) (Table 4).

There were no differences in the percentage of patients reaching a normotensive range in the ABPM (<130/80 mm Hg) between the CPAP group and control group at the end of the study (18.4% CPAP vs 13.8% control; *P* = .41).

Analysis According to CPAP Tolerance (Per-Protocol Analysis)

In a per-protocol analysis (71 patients in the CPAP group; control group, 87 patients), patients in the CPAP group showed a statistically significant decrease in 24-hour mean blood pressure of 4.4 mm Hg (95% CI, 1.8-7), *P* = .001; SBP, 4.9 mm Hg (95% CI, 1.2-8.6), *P* = .01; and DBP, 4.1 mm Hg (95% CI, 1.9-6.4), *P* < .001. This difference was more evident during the night, with a decrease of 7.1 mm Hg (*P* = .003) in nocturnal SBP and 4.1 mm Hg (*P* = .003) in nocturnal DBP. Moreover, the proportion of patients who had a dipper pattern at the end of follow-up was greater in the CPAP group

Table 1. Baseline Characteristics of All Randomized Patients

	Mean (SD)		
	All Patients	Control Group	CPAP Group
Patients, No.	194	96	98
Age, y	56.0 (9.5)	58.2 (9.6)	57.8 (9.5)
Men, No. (%)	133 (68.6)	62 (64.6)	71 (72.4)
BMI	34.1 (5.4)	33.6 (6.9)	34.3 (5.7)
≥30, No. (%)	113 (79.6)	52 (76.4)	61 (82.4)
Neck circumference, cm	42.2 (4.9)	41.5 (4.7)	42.9 (5.1)
Epworth Sleepiness Scale	9.1 (3.7)	9.3 (4.0)	8.9 (4.0)
≥10, No. (%)	76 (43.2)	43 (47.3)	33 (38.9)
Years since diagnosis of resistant hypertension	12.8 (8.6)	13.1 (8.0)	12.5 (9.2)
No. of systemic hypertension drugs	3.8 (0.9)	3.9 (0.9)	3.7 (0.9)
Past cardiovascular events, No. (%)	42 (21.4)	24 (25)	18 (18)
Apnea-hypopnea index, event/h	40.4 (18.9)	39.5 (19.2)	41.3 (18.7)
≥30, No. (%)	124 (63.9)	56 (58.3)	68 (69.4)
$TSat_{90}$, median (IQR)	9 (2-20)	8 (2-19)	9.5 (4-22)
Mean O_2 saturation, %	92.0 (3.8)	92.0 (4.8)	91.9 (2.5)
24-h mean blood pressure, mm Hg	103.4 (9.6)	102.9 (9.6)	103.9 (9.6)
24-h SBP, mm Hg	144.2 (12.5)	143.5 (13.2)	144.9 (11.7)
Diurnal	146.1 (12.7)	145.1 (13.3)	147.2 (12.1)
Nocturnal	140.8 (16.3)	140.4 (16.8)	141.2 (15.8)
24-h DBP, mm Hg	83.0 (10.5)	82.6 (10.0)	83.4 (11.1)
Diurnal	85.2 (11.0)	84.6 (10.4)	85.7 (11.6)
Nocturnal	78.6 (11.7)	78.6 (11.1)	78.5 (12.4)
Nocturnal blood pressure pattern, No. (%)			
Dipper	50 (25.8)	25 (26.0)	25 (25.5)
Nondipper	83 (42.8)	37 (38.5)	46 (46.9)
Riser	61 (31.4)	34 (35.4)	27 (27.6)
Variability, mm Hg	11.7 (3.1)	11.6 (3.5)	11.7 (3.6)
Heart rate, beats/min	71.8 (11.3)	73.3 (11.1)	70.3 (11.7)
Valley blood pressure, mm Hg			
24-h SBP	111.5 (14.7)	111.0 (14.3)	111.9 (15.4)
24-h DBP	64.2 (12.2)	60.3 (11)	59.6 (11.6)
Peak blood pressure, mm Hg			
24-h SBP	160.9 (17.7)	160.2 (17.3)	161.8 (18)
24-h DBP	93.5 (13.1)	92.8 (12.4)	93.9 (13.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; $TSat_{90}$, nighttime spent with an oxygen saturation below 90%.

(OR, 2.8 [95% CI, 1.3-6.3]; P = .01). Also, fewer patients in the CPAP group displayed a nocturnal riser pattern at the end of the study compared to the control group (OR, 0.43 [95% CI, 0.20-0.91]; P = .03).

Figure 2 shows a positive linear correlation between the number of hours of CPAP use and the decrease in 24-hour mean blood pressure (r = 0.29, P = .006); SBP, (r = 0.25; P = .02); and DBP, ; (r = 0.30, P = .005). Linear regression analysis shows an improvement of blood pressure figures of 1.3 mm Hg (95% CI, 0.4 to 2.2) for mean blood pressure; SBP, 1.9 mm Hg (95% CI, 0.6 to 3.3); and DBP, 1.0 mm Hg (95% CI, 0.1 to 1.8) for each additional hour of CPAP use.

Discussion

There is clinical evidence that OSA is a risk factor for the development and poor control of systemic hypertension.[10,24,25] Nevertheless, great variability has been observed with respect to the effect of treatment with CPAP on blood pressure, probably on account of the multifactorial nature of systemic hypertension.[5-22,24-29] This has led to an increasing interest in the analysis of subgroups of patients who could potentially benefit from the CPAP treatment. Obstructive sleep apnea is highly prevalent in patients with resistant hypertension, regardless of

Table 2. Use of Prescribed Antihypertensive Medication in Randomized Patients

	No. (%)		
		Treatment	
	All Patients	Control Group	CPAP Group
Patients, No.	194	96	98
Diuretic[a]	184 (94.8)	89 (93.7)	95 (96.9)
Calcium channel blockers	142 (72.4)	69 (71.9)	73 (73)
Angiotensin II receptor blockers	132 (67.3)	64 (66.7)	68 (68)
β-Blockers	112 (57.1)	54 (56.3)	58 (58)
Angiotensin-converting enzyme inhibitor	75 (38.3)	38 (39.6)	37 (37)
α_1-Blockers	65 (33.1)	32 (33.3)	33 (33)
Renin blockers	21 (10.7)	8 (8.3)	13 (13)
Others	8 (4.1)	4 (4.2)	4 (4)

Abbreviation: CPAP, continuous positive airway pressure.

[a] Ten patients were not taking diuretic treatment due to adverse effects.

Table 3. Effect of Continuous Positive Airway Pressure Treatment on Blood Pressure Levels in the Intention-to-Treat Population

	Mean (SD)							
	CPAP Group (n = 98)		Control Group (n = 96)		Intergroup Crude[a] Differences (95% CI)	*P* Value	Intergroup Adjusted[b] Differences (95% CI)	*P* Value
	Baseline	Follow-up	Baseline	Follow-up				
BP variables, mm Hg[c]								
24-h mean BP	103.9 (9.6)	99.8 (14.6)	102.9 (9.6)	102.1 (18.2)	3.1 (0.6 to 5.6)	.02	3.9 (1.3 to 6.6)	.004
24-h SBP	144.9 (11.7)	140.2 (13.1)	143.5 (13.2)	142.3 (17.1)	3.1 (−0.6 to 6.7)	.10	4.2 (0.4 to 8.0)	.03
Diurnal	147.2 (12.1)	144.0 (13.7)	145.1 (13.3)	142.5 (16.2)	−0.3 (−4.0 to 3.5)	.89	1.1 (−2.9 to 5.2)	.59
Nocturnal	141.2 (15.8)	134.6 (16.4)	140.4 (16.8)	137.8 (19.4)	3.7 (−0.8 to 8.2)	.11	5.8 (1.1 to 10.5)	.02
24-h DBP	83.4 (11.1)	79.5 (11.5)	82.6 (10.0)	82.1 (12.7)	3.2 (1.0 to 5.4)	.005	3.8 (1.4 to 6.1)	.002
Diurnal	85.7 (11.6)	82.7 (12.5)	84.6 (10.4)	83.2 (13.2)	1.5 (−0.8 to 3.9)	.20	2.3 (−0.1 to 4.8)	.07
Nocturnal	78.5 (12.4)	75.4 (11.7)	78.6 (11.1)	77.5 (13.5)	2.1 (−0.6 to 4.7)	.13	3.3 (0.5 to 6.1)	.02
Valley BP								
24-h SBP	111.9 (15.4)	106.2 (17.8)	111.0 (14.3)	103.3 (20.2)	−2.6 (−7.9 to 2.6)	.32	−0.4 (−6.0 to 5.3)	.90
24-h DBP	59.6 (11.6)	57.4 (11.1)	60.3 (11.0)	58.4 (13.1)	0.5 (−2.3 to 3.3)	.71	2.2 (−0.7 to 5.1)	.14
Peak BP								
24-h SBP	161.8 (18.0)	150.5 (25.1)	160.2 (17.3)	149.6 (28.9)	−0.3 (−8.0 to 7.4)	.93	0.5 (−7.5 to 8.6)	.89
24-h DBP	93.9 (13.7)	88.4 (14.2)	92.8 (12.4)	92.8 (14.0)	5.0 (1.8 to 8.3)	.003	5.7 (2.3 to 9.2)	.001
BMI	34.3 (5.7)	34.5 (5.2)	33.6 (6.9)	33.6 (6.0)	−0.4 (−1.8 to 1.0)	.54	0.1 (−0.4 to 0.7)	.64
ESS	8.9 (4.0)	5.5 (4.1)	9.3 (4.0)	9.0 (4.5)	3.3 (2.3 to 4.2)	<.001	3.4 (2.4 to 4.3)	<.001
Heart rate, beats/min	70.3 (11.7)	70.1 (14.8)	73.3 (11.1)	73.0 (11.7)	0.9 (−2.3 to 4.0)	.59	0.6 (−2.8 to 3.9)	.74
Variability	11.7 (3.6)	11.9 (4.4)	11.6 (3.5)	12.6 (4.3)	0.8 (−0.5 to 2.0)	.24	0.4 (−0.8 to 1.6)	.52

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure.

[a] Adjusted by baseline BP values.

[b] Adjusted by baseline BP, AHI, ESS, dipper or riser status, and previous cardiovascular events.

[c] Crude differences calculated as (change in CPAP group) − (change in control group).

other confounding variables such as the presence of obesity,[11,30,31] thus suggesting this subgroup of hypertensive patients is a potential worthwhile population for CPAP treatment.

International guidelines have pointed out that even minimal reductions in the blood pressure levels (to the order of 2-3 mm Hg of SBP) could have a clinically significant effect by greatly reducing subsequent cardiovascular mortality (between 6%-8% for stroke and 4%-5% for coronary heart disease).[32] Very few studies have assessed the role for CPAP treatment in patients with resistant hypertension and OSA. The available studies have found clinically significant reductions in blood pressure levels, especially during the night and particularly in patients with good adherence to CPAP treatment. However, all of these studies had significant methodological limitations (eg, lack of randomization[14,15] and small cohorts)[14-16] leading their authors to emphasize the need for further studies with rigorous study designs. In line with the published evidence, our results confirm that there is a clinically and statistically significant reduction in both 24-hour mean and diastolic blood pressure levels, especially during the night and in those patients with acceptable CPAP adherence.

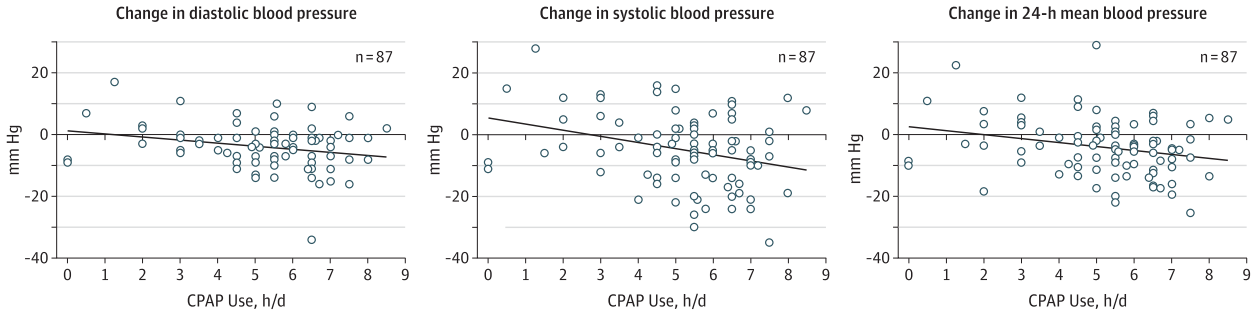
Table 4. Effect of Continuous Positive Airway Pressure Treatment on Prevalence of Blood Pressure Patterns

	No. (%)					
	CPAP Group (n = 98)		Control Group (n = 96)			
	Baseline	Follow-up	Baseline	Follow-up	OR (95% CI)[a]	*P* Value
Prevalence dipper pattern	25 (25.5)	35 (35.9)	25 (26.0)	21 (21.6)	2.4 (1.2-5.1)	.02
Prevalence riser pattern	27 (27.6)	20 (20.5)	34 (35.4)	35 (36.8)	0.45 (0.23-0.91)	.03

Abbreviations: CPAP, continuous positive airway pressure; OR, odds ratio.

[a] Adjusted for baseline status. Control group data were reference values. Odds ratio (95% CI) of dipper or riser pattern 12 weeks after CPAP treatment relative to the control group.

Figure 2. Correlation Between Changes in 24-Hour Mean, Systolic, and Diastolic Blood Pressure and Number of Hours of Continuous Positive Airway Pressure Use



Correlation between continuous positive airway pressure (CPAP) use and change in blood pressure in the patients of the CPAP group who finished the follow-up.

The recovery of the dipper nocturnal pattern with antihypertensive treatment may be advantageous because the presence of nondipper or riser blood pressure nocturnal patterns has emerged as an independent cardiovascular risk factor. In our study, more than 70% of patients had a nondipper or riser pattern and CPAP treatment normalized the blood pressure nocturnal pattern in a significant percentage of these patients. Moreover, CPAP provided protection against having a riser pattern at the end of the study compared to the control group. This is an important point because patients with a riser blood pressure pattern exhibit the highest cardiovascular risk.[33,34]

Some authors have reported that the effect of CPAP treatment on blood pressure levels depends on the number of hours of CPAP use.[28] Our study corroborates this finding, with a significant correlation between the hours of CPAP use (especially in patients with at least 4 hours of use per night) and the decrease in blood pressure levels. Adherence to CPAP treatment was good in the present study, with more than 70% of patients using CPAP for 4 or more hours per night, an adherence rate similar to that reported in other large studies of patients with OSA.[35]

In our study we chose not to use sham CPAP as a placebo because studies have shown that excessive air leaking and low air pressure (necessary to deliver a very low, noneffective pressure of 2-3 cm H_2O), along with the persistence of symptoms such as snoring or breathing pauses, makes the patients realize that they are not receiving an effective treatment.[23,36] Several studies have reported lower CPAP compliance with sham CPAP compared to optimal CPAP, suggesting that this device fails to function as a true placebo.[37,38]

The major strength of our study is its randomized multicenter clinical trial design with a sample size sufficient to enable both an ITT and per-protocol analyses. In addition, resistant hypertension was established by means of 24-hour ABPM, as recently recommended to provide more accurate estimates of blood pressure in these patients.[19] Nevertheless, this study has several limitations. First, respiratory polygraphy does not permit any quantification of the duration of sleep. This is unlikely to affect our conclusions because patients in our study had an average AHI of more than 40 events per hour (severe OSA). Indeed, the correlation between the AHI calculated from respiratory polygraphy and the AHI derived from full polysomnography is very high in severe OSA.[39] Second, in this trial, we opted for titration of a fixed pressure by means of an auto CPAP device and then used this target pressure for the 3 months of the study. This approach was used because fixed CPAP pressure is the most common method applied to OSA patients in Spain. Moreover, a recent study failed to demonstrate any differences in blood pressure levels when using fixed CPAP pressure in comparison to auto CPAP devices.[40]

Conclusions

Among patients with OSA and resistant hypertension, CPAP treatment for 12 weeks, compared to control, resulted in a decrease in 24-hour mean and diastolic blood pressure and an improvement in the nocturnal blood pressure pattern. Further research is warranted to assess longer-term health outcomes.

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