Effect of Continuous Positive Airway Pressure on Ambulatory BP in Patients With Sleep Apnea and Hypertension: A Placebo-Controlled Trial

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Effect of Continuous Positive Airway Pressure on Ambulatory BP in Patients With Sleep Apnea and Hypertension*

A Placebo-Controlled Trial

Francisco Campos-Rodriguez, MD; Antonio Grilo-Reina, MD; Jose Perez-Ronchel, MD; Mercedes Merino-Sanchez, MD; Maria A. Gonzalez-Benitez, MD; Manuel Beltran-Robles, MD; and Carmen Almeida-Gonzalez, MD

**Background:** Obstructive sleep apnea syndrome (OSAS) is an independent risk factor for arterial hypertension. Several controlled trials have investigated the effect of continuous positive airway pressure (CPAP) on BP in patients with OSAS, but its effect on hypertensive patients has not been analyzed specifically.

**Objective:** To analyze the effect of CPAP on ambulatory BP in patients with OSAS and hypertension who were undergoing antihypertensive treatment.

**Design and patients:** We conducted a parallel, randomized, placebo-controlled trial in 68 patients with OSAS and hypertension, who were receiving treatment with antihypertensive medication. Patients were randomly allocated to either therapeutic or subtherapeutic CPAP for 4 weeks. Ambulatory BP was registered at baseline and after treatment. Antihypertensive treatment was not changed during the study. Changes in BP were assessed on an intention-to-treat basis.

**Results:** There were no baseline differences in the apnea-hypopnea index, comorbidities, or ambulatory BP between groups. Objective compliance with CPAP was similar in both the therapeutic and subtherapeutic groups (5.0 ± 1.4 h/d vs 4.4 ± 1.9 h/d, respectively; \( p = 0.13 \) [mean ± SD]). There was a small and statistically nonsignificant decrease (−0.3 ± 6.3 mm Hg vs −1.1 ± 7.9 mm Hg; difference, −0.8 mm Hg [95% confidence interval, −2.7 to 4.3]; \( p = 0.65 \)) in 24-h mean BP (24hMBP) in both subtherapeutic and therapeutic groups after 4 weeks of treatment. No significant changes in systolic, diastolic, daytime, or nighttime BP were observed. The normal circadian dipper pattern was restored in a higher proportion of patients in the therapeutic group compared to the subtherapeutic CPAP group, although differences were not significant (11 of 32 patients vs 3 of 25 patients; odds ratio, 3.84; 95% confidence interval, 0.82 to 20.30; \( p = 0.10 \)). There was no correlation between the magnitude of change in 24hMBP and CPAP compliance, OSAS severity, or number of antihypertensive drugs used.

**Conclusion:** Four weeks of CPAP did not reduce BP in patients with OSAS and hypertension who were treated with antihypertensive medication, compared to placebo group.

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**Key words:** ambulatory BP monitoring; continuous positive airway pressure; hypertension; sleep apnea syndrome

**Abbreviations:** ABPM = ambulatory BP monitoring; ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; ESS = Epworth sleepiness scale; OSAS = obstructive sleep apnea syndrome; \( \text{Sa}_\text{o}_2 \) = arterial oxygen saturation; 24hMBP = 24-h mean arterial BP

The obstructive sleep apnea syndrome (OSAS), a disorder affecting 2 to 4% of the adult population, is characterized by repetitive episodes of upper airway obstruction during sleep that provoke frequent arousals, sleep fragmentation, oxygen desaturation, and excessive daytime sleepiness. Several studies have reported a high prevalence (50 to 70%) of arterial hypertension in patients with OSAS.
Some population studies have identified OSAS as an independent risk factor for hypertension. Hypothetically, treatment of OSAS should improve BP control. Several clinical trials have shown that continuous positive airway pressure (CPAP), the most effective treatment for OSAS, reduces sympathetic activity by avoiding the repetitive burst of sympathetic nerve traffic that follows an episode of apnea. CPAP also reduces the production of free-oxygen radicals and circulating levels of some markers of inflammation (C-reactive protein, inflammatory cytokines) and reverses the endothelial dysfunction caused by OSAS. However, most studies evaluating the effects of CPAP on BP were either not controlled or enrolled a relatively small number of participants. In recent years, conflicting results from some well-designed, controlled studies have shown either a clear improvement or only minor but insignificant reductions in BP measurements. There is no agreement whether OSAS patients with hypertension would experience a greater decrease in BP with CPAP treatment or behave similar to normotensive patients.

A controlled trial specifically addressing the effect of CPAP in a population of treated hypertensive patients with OSAS has not been previously reported. Therefore, the aim of this study was to analyze the effect of CPAP on ambulatory BP monitoring (ABPM) in patients with OSAS and hypertension who were receiving antihypertensive treatment.

**Materials and Methods**

**Design and Setting**

This is a parallel, randomized, double-blind, placebo-controlled trial of patients in the Respiratory Department, Valme University Hospital, Seville, Spain. All patients were initially seen as outpatients at the Sleep Disorders Unit, where they had been referred with a suspected diagnosis of OSAS by primary care or hospital-based physicians.

Patients were considered for inclusion in the trial if they were between 30 and 70 years of age with an apnea-hypopnea index (AHI) ≥ 10 events/h in conventional polysomnography, and a previous diagnosis of systemic arterial hypertension following the Joint National Committee criteria, with treatment of hypertension with at least one drug for at least 3 months previous to the inclusion in the study. Patients were excluded if they had > 30% of central apnea, respiratory failure, heart failure (New York Heart Association class III-IV), ischemic heart disease, cardiac arrhythmia, neoplastic or systemic diseases, or if they were professional drivers. Patients with secondary hypertension were also excluded. The local ethics committee approved the trial and patients gave written informed consent.

**Procedures**

Hypertension was defined as a systolic BP > 140 mm Hg and/or diastolic BP > 90 mm Hg in three independent measurements using a conventional sphygmomanometer. When necessary, antihypertensive treatment was temporarily withdrawn to confirm the diagnosis of hypertension. Treatment was not withdrawn during the study period for ethical reasons.

The diagnosis of OSAS was based on standard polysomnography (Ultrason; Nicollot Biomedical; Madison, WI) during a full night in the sleep laboratory. Polysomnographic studies included recording of EEG, electro-oculogram, electromyogram, oronasal flow, thoracoabdominal movements, ECG, and arterial oxygen saturation (SaO2), and were analyzed manually by skilled staff, according to standard criteria. Airflow was registered with a thermistor, respiratory efforts with strain strips, and transcutaneous SaO2 was monitored continuously using a pulse oximeter (Nellcor Pulse Oxymeter N-200; Nellcor Puritan Bennett; Pleasanton, CA). Apnea was defined as complete cessation of airflow for > 10 s and was classified either as obstructive or central based on the presence or absence of respiratory efforts. Hypopnea was defined as a reduction of ≥ 50% in oronasal flow for > 10 s followed by a ≥ 4% decrease in SaO2 or an arousal. AHI, minimum SaO2, percentage of time spent with SaO2 < 90%, and desaturation index (number of dips of > 4% per hour of sleep in SaO2) were recorded for each patient.

ABPM was measured using a noninvasive portable validated recorder (Spacelab 90207; Space Labs Medical; Redmond, WA). A BP cuff was fitted on the nondominant arm of the patient for 24 h by a trained nurse. Patients were then sent home and asked to perform usual daily activities. The monitor was programmed to record BP every 30 min and data were considered valid if, at least, the monitor recorded 21 adequate readings over the 24 h. BP data were processed automatically with the software of the device. A dipping pattern was defined as a reduction in the average systolic and diastolic BP at night > 10% compared to daytime values. Based on ABPM, hypertension was considered noncontrolled at the beginning of the study in those patients with daytime BP values > 135/85 mm Hg or nighttime BP values > 120/75 mm Hg.

Patients were evaluated at the Hypertension Unit, Internal Medicine Department, to exclude the presence of secondary hypertension. Each patient underwent a physical examination, and his or her detailed clinical history was recorded. Weight, height, body mass index (BMI), BP, fasting total cholesterol, triglycerides, and glucose levels were measured. Daytime sleepiness was assessed using the Epworth sleepiness scale (ESS). Information about antihypertensive medication was recorded.
once the diagnosis of OSAS was established and baseline ABPM measured, for a second night CPAP was titrated. Patients were then randomly assigned to either therapeutic or subtherapeutic CPAP groups using a series of presealed envelopes. Patients were informed that they would receive one of two levels of CPAP (one higher and other lower) during the study period and its effect on BP was being evaluated. Patients were also told that at the end of the study, they would be prescribed a level of CPAP that best controlled their OSAS. Patients were informed that they could leave the study at any time if they wish.

Patients assigned to therapeutic CPAP underwent a full-night polysomnographic titration at the sleep laboratory (Arial; Respirationics; Murrysville, PA). The level of CPAP was increased until respiratory events, snores, and oxygen desaturation were eliminated during all sleep stages in the supine position, so that residual AHI was always <10/h. Patients randomized to subtherapeutic CPAP also underwent a mock titration night. In these cases, a constant pressure of <2 cm H2O was applied by setting the CPAP device to the lowest pressure, inserting a flow-restricting connector at the machine outlet, and making an extra 1-cm hole in the nasal mask. In each case, a manometer was used to confirm that pressure delivered was always < 2 cm H2O.

After the titration night, patients were prescribed CPAP (effective or subtherapeutic) for ambulatory use. During the study, all participants could contact researchers by telephone for advice if required. After 4 weeks of treatment, patients returned for a new ABPM; during this visit, ESS and objective compliance with CPAP (reading the internal time counter of the device) was assessed, and BMI was registered. Particular attention was paid to check that patients had not changed their antihypertensive treatments since baseline evaluation. If any changes in either type of medication or dose had occurred, the patient was excluded from the study. In patients assigned to subtherapeutic CPAP, a new full-night titration was performed in order to establish the effective CPAP pressure.

The study was blinded since the patients were naïve to CPAP and did not know if they were prescribed an effective or subtherapeutic pressure. The research faculty who assigned patients to treatment groups did not take part in the outcome assessments, and the nurse who fitted the monitors did not know the treatment group of the patients. Investigators that assessed the study outcome were unaware of the randomization status, making the study double blind.

Data Analysis

The main outcome variable was 24-h mean arterial BP (24hMBP), and change in this pressure was measured after 4 weeks of treatment in the therapeutic and subtherapeutic CPAP groups. Secondary outcome variables included changes in systolic and diastolic BP, changes in mean daytime and nighttime BP, heart rate, and pulse pressure in both groups, as well as changes in the dipping pattern. In addition, whether the degree of changes in 24hMBP correlated with the severity of baseline OSAS (measured by AHI and desaturation index), CPAP compliance, or number of antihypertensive drugs was also a secondary outcome variable.

Statistical software (version 13.0; SPSS; Chicago, IL) was used for data processing and statistical analysis. Continuous variables are expressed as mean ± SD, and qualitative variables are expressed as a percentage. A two-tailed t test for independent samples or a χ² test was used to compare baseline variables in the two groups. Changes in BP were assessed using the unpaired t test on an intention-to-treat basis. The relationships between AHI, desaturation index, CPAP compliance, number of antihypertensive drugs, and the magnitude of change in 24hMBP with CPAP were assessed with the Pearson correlation; p < 0.05 was considered significant.

The sample size for the study was calculated to detect a change of 5 mm Hg in 24hMBP after the treatment between subtherapeutic and therapeutic CPAP groups. Accordingly, we calculated that 34 patients in each group should complete the study if an α error of 0.05, a power of 0.8, and a SD of 7.2 (obtained from a pilot study of this sample) were used.

RESULTS

Eighty patients fulfilled the inclusion criteria, but 8 of them declined to take part in the trial for several reasons: the extra time needed to participate (n = 3); lived too far away (n = 3); and refused treatment with CPAP (n = 2). The remaining 72 patients began the study, but 4 of them withdrew before the end point: 2 patients in the subtherapeutic CPAP group (1 patient did not tolerate placebo CPAP, and 1 patient changed treatment), and 2 patients in the therapeutic CPAP group (1 patient changed treatment, and 1 patient did not come to the second ABPM). Finally, 34 patients in each group completed the study. Baseline characteristics and BP measurements were similar in both the therapeutic and subtherapeutic CPAP groups (Tables 1, 2). The average percentage of ABPM valid recordings was 89% (only two patients had < 80% of valid recordings: one patient had 77% and another patient had 78%). Fifty-seven patients (83.8%) had a nondipping pattern; in 12 patients (17.6%), hypertension was noncontrolled at entry despite pharmacologic treat-

<table>
<thead>
<tr>
<th>Table 1—Baseline Characteristics of the Sample*</th>
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<tbody>
<tr>
<td>Variables</td>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Male sex</td>
</tr>
<tr>
<td>BMI kg/m²</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>ESS score</td>
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<tr>
<td>Sleep efficiency, %</td>
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<tr>
<td>Slow-wave sleep, %</td>
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<tr>
<td>Rapid eye movement</td>
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<td>AHI, events/h</td>
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<td>Time with SaO₂</td>
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<td>&lt;90%, %</td>
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<td>Desaturation index &gt;4%/h</td>
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<tr>
<td>Antihypertensives drugs</td>
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<td>ACE inhibitors</td>
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*Data are presented as mean ± SD or No. (%).
Therapeutic CPAP (n = 34) | Subtherapeutic CPAP (n = 34) | p Value
--- | --- | ---
24hMBP, mm Hg | 97.7 ± 10.7 | 96.2 ± 10.1 | 0.57
24-h systolic BP, mm Hg | 131.9 ± 13.5 | 130.4 ± 15.9 | 0.49
24-h diastolic BP, mm Hg | 78.4 ± 10.3 | 77.6 ± 8.7 | 0.73
Daytime BP, mm Hg | 100.8 ± 10.7 | 98.9 ± 10.0 | 0.46
Nighttime BP, mm Hg | 94.6 ± 11.1 | 93.5 ± 11.4 | 0.69
Pulse pressure, mm Hg | 54.0 ± 9.8 | 53.7 ± 13.7 | 0.91
Heart rate, beats/min | 75.5 ± 9.8 | 72.4 ± 10.5 | 0.22
Nondipper pattern | 32 (94) | 25 (74) | 0.04
Noncontrolled hypertension | 5 (14.7) | 7 (20.5) | 0.75

*Data are presented as mean ± SD or No. (%).

The mean level of CPAP applied in the therapeutic CPAP group was 9.5 ± 1.9 cm H₂O (range, 7 to 14 cm H₂O).

Patients were taking an average of 2.1 ± 0.9 antihypertensive drugs, which included diuretics (58.8%), angiotensin-converting enzyme (ACE) inhibitors (41.1%), angiotensin receptor antagonist (42.6%), calcium-channel blockers (36.7%), β-blockers (19.1%), and others (8.8%) when CPAP was prescribed. Among all patients, 47% were treated with two drugs, while 23.5%, 20.5%, and 8.8% were treated with one, three, or four drugs, respectively. The most common combination of the two drugs was diuretics plus ACE inhibitors (26.4%). There were no significant differences in the average number or classes of antihypertensive drugs used by the patients in therapeutic or subtherapeutic CPAP groups (Table 1).

Comorbidities were similar in patients of both therapeutic and subtherapeutic CPAP groups (Table 1). Obesity was present in 75% (51 patients; mean BMI, 35.9 kg/m²), hypercholesterolemia in 63.2% (43 patients), and type II diabetes mellitus in 42.6% (29 patients). Only 11 patients were habitual smokers (average of 15 cigarettes per day).

After 4 weeks of treatment with CPAP, no changes in BMI were found compared to baseline (34.7 ± 6.0 kg/m² vs 33.9 ± 6.2 kg/m², p = 0.82). Daytime sleepiness significantly decreased in the therapeutic CPAP group (ESS, 15.0 ± 3.9 vs 11.2 ± 3.0; p < 0.001) but not in the subtherapeutic CPAP group (ESS, 13.6 ± 3.6 vs 12.2 ± 3.2; p = 0.12). Patients used CPAP at an average of 4.7 ± 1.7 h/d (range, 1.0 to 9.6 h/d), and adherence to treatment was similar in both therapeutic and subtherapeutic CPAP groups (5.0 ± 1.4 h/d vs 4.4 ± 1.9 h/d; p = 0.13).

Table 2—Baseline Characteristics of 24-h ABPM*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Therapeutic CPAP (n = 34)</th>
<th>Subtherapeutic CPAP (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After CPAP</td>
<td>Baseline</td>
</tr>
<tr>
<td>24hMBP, mm Hg</td>
<td>96.2 ± 10.1</td>
<td>95.9 ± 10.8</td>
<td>97.7 ± 10.7</td>
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<tr>
<td>24-h systolic BP, mm Hg</td>
<td>132.9 ± 13.5</td>
<td>131.3 ± 13.5</td>
<td>100.8 ± 10.7</td>
</tr>
<tr>
<td>24-h diastolic BP, mm Hg</td>
<td>78.4 ± 10.3</td>
<td>76.8 ± 9.0</td>
<td>94.6 ± 11.1</td>
</tr>
<tr>
<td>Daytime BP</td>
<td>98.9 ± 10.0</td>
<td>98.8 ± 11.2</td>
<td>54.0 ± 9.8</td>
</tr>
<tr>
<td>Nighttime BP</td>
<td>93.5 ± 11.4</td>
<td>93.1 ± 11.0</td>
<td>72.4 ± 10.5</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>53.7 ± 13.7</td>
<td>53.0 ± 12.7</td>
<td>75.5 ± 9.8</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. (%).
p = 0.78), systolic BP (–3.0 ± 9.6 mm Hg vs –2.0 ± 8.7 mm Hg; p = 0.54), and diastolic BP (–2.5 ± 7.4 mm Hg vs –1.4 ± 3.3 mm Hg; p = 0.73) in the therapeutic CPAP group compared to the subtherapeutic CPAP group.

Fifty-seven patients had a nondipping pattern at baseline evaluation. After 4 weeks of treatment with CPAP, only 3 of 25 patients (12%) in the subtherapeutic CPAP group became dippers, compared to 11 of 32 patients (34.3%) in the therapeutic CPAP group, although the differences did not reach statistical significance (odds ratio, 3.84; 95% confidence interval, 0.82 to 20.30; p = 0.10). However, two patients who were initially classified as dippers in the therapeutic CPAP group remained to dippers after treatment, while five of nine patients in the subtherapeutic CPAP group changed to a nondipper pattern after treatment with placebo CPAP.

**DISCUSSION**

The results of this study show that 4 weeks of therapeutic CPAP did not significantly improve ABPMs compared to subtherapeutic CPAP in patients with OSAS and systemic arterial hypertension undergoing antihypertensive treatment. Changes in 24hMBP between groups did not correlate with CPAP compliance, OSAS severity, or the number of antihypertensive drugs used. A trend was shown toward restoring the normal circadian dipper pattern in the therapeutic CPAP group compared to the subtherapeutic CPAP group, although differences were not significant.

The present study is a prospective, randomized, double-blind, placebo-controlled trial. Subtherapeutic CPAP treatment was used as placebo. Several trials using subtherapeutic CPAP as placebo suggested it to be a true placebo, since they observed that pressures < 2 cm H₂O do not significantly improve sleep structure or AHI. However, a diagnosis of OSAS and CPAP titration were always based on a full-night, conventional polysomnography at the sleep laboratory. Therefore, we believe that our results could not be attributed to errors in the diagnosis of OSAS, CPAP titration, or type of placebo used.

Nevertheless, our study has some potential deficiencies. The study size was calculated to detect a variation of 5 mm Hg in 24hMBP after CPAP treatment between groups. Therefore, it is possible that patient population was not large enough to detect changes < 5 mm Hg. However, the small decrease in 24hMBP detected with CPAP (< 1 mm Hg) suggests that even with a larger sample size, differences between groups may not be shown. The difficulty in enrolling patients with hypertension and OSAS, but without other diseases, willing not to modify their medication throughout the study has prevented us from including more patients. Another possible drawback is the 4-week duration of the
study, since it may be not long enough to show significant changes in BP. However, we believe that to maintain an ineffective treatment for longer periods in hypertensive patients with OSAS, some of them with severe or poorly controlled disease, would be unethical. Another limitation refers to BP recording methods. Although the ABPM device is a non-invasive portable validated recorder widely used in previous studies, patients wore it for 24 h, and BP values were recorded every 30 min, it cannot be ruled out that differences in the recording methods or BP device could have some influence on the results. Some authors believe that a 48-h recording is preferably to avoid the “ABPM pressor effect,” which implies that patients evaluated for the first time show a significant reduction during the second day of BP monitoring as compared with the first in the diurnal mean of systolic and diastolic BP. This effect was not observed when patients were evaluated for the second or successive times. In our trial, this pressor effect would have occurred in the first (baseline) but not in the second (after treatment) BP monitoring, and therefore a beneficial effect of CPAP on BP would have been shown. However, we did not find a significant reduction in BP after treatment, so the “pressor effect” cannot explain our results. However, hypertensive patients with untreated severe OSAS are known to experience an increased variability in BP measurements. Beat-by-beat BP monitoring devices would be more reliable to detect changes in these cases with marked BP variability. Unfortunately, the device used in our trial, although validated, can only record BP values intermittently, and some information is missed. Therefore, lack of recorded changes does not necessarily mean that CPAP treatment has no effect on BP. However, it must be taken into account that most studies addressing the effect of CPAP on BP have used devices that record BP values intermittently (usually every 20 to 30 min); despite this drawback, some of them have been able to show improvements in BP with CPAP.

Several controlled trials investigating the effect of CPAP on 24-h BP have shown either significant improvement or only minor reductions in some BP measurements.Dimsdale et al compared therapeutic and subtherapeutic CPAP in 39 patients during 7 days and found that the decrease in daytime

Figure 2. Individual values for BP at baseline and after CPAP treatment for therapeutic CPAP (top) and subtherapeutic CPAP (bottom) groups.
BP was similar in both groups. In addition, BP decrease in 10 hypertensive patients (25%) who had their medication withdrawn during the study was similar to nonhypertensive patients. Barbe et al.\textsuperscript{25} in a placebo-controlled trial involving 55 normotensive asymptomatic patients with severe OSAS, found that 6 weeks of therapeutic CPAP did not modify BP compared to sham CPAP. Several noncontrolled studies did not find significant changes in BP with CPAP. Hedner et al.\textsuperscript{6} reported that BP and cardiac structure remained unchanged in 12 patients treated with CPAP for 20 months, despite a marked reduction of catecholamine excretion. Sanner et al.\textsuperscript{14} treated 69 OSAS patients with CPAP for 9 months and found a significant decrease in mean BP, while in a subgroup of patients BP did not improve. Additionally, there was no association between the degree of BP decrease and the degree of OSAS improvement. Finally, Hermida et al.\textsuperscript{26} compared 83 OSAS patients treated with CPAP and 39 without CPAP during 4 months and found a small but nonsignificant decrease in ABPM values in treated patients compared to nontreated patients.

Faccenda et al.\textsuperscript{17} compared therapeutic CPAP with an oral placebo in 68 patients without hypertension, for 1 month in a cross-over study, and showed a significant reduction of 1.5 mm Hg in diastolic BP with a surprisingly low compliance (3.3 h/d). Pepperell et al.\textsuperscript{18} analyzed 118 patients and found a significant reduction (2.5 mm Hg) in 24hMBP after 1 month of therapeutic CPAP compared to placebo. A subgroup of 22 patients (18%) undergoing antihypertensive treatment achieved a greater decrease in 24hMBP. Becker et al.\textsuperscript{19} studied 32 patients (21 were hypertensive and 15 were receiving treatment) for 9 weeks, and observed a 9.9 mm Hg decrease in 24hMBP in the therapeutic CPAP group compared to a placebo group. However, in this study, BP monitoring conditions were different than other studies, since the device was not ambulatory, restricting patient’s movement and requiring them to stay in the hospital for 24-h BP monitoring.

The present study differs from above mentioned studies, since we specifically analyzed a group of hypertensive patients undergoing antihypertensive treatment, which remained unchanged throughout the study. We did not find a significant decrease in ambulatory BP with therapeutic CPAP compared to subtherapeutic CPAP perhaps due to following reasons. Apart from previously discussed biases, it is possible that CPAP is ineffective for improving BP in a sample mainly composed of well-controlled hypertensive patients during the 4-week treatment; instead, it may require a longer treatment duration. In patients with these characteristics, it may take longer to achieve a significant reduction in BP measurements, and the advantages derived from CPAP on BP control may well occur in a time span beyond the duration of this trial. It is also possible that these patients had already achieved the maximum decrease in BP possible with pharmacologic treatment; as a result, CPAP could only add modest reductions in BP.

Another reason for our observed results could be that apart from OSAS, an independent hypertension risk factor, other variables may also contribute to worsening of hypertension and they are not affected by CPAP.\textsuperscript{2,30} Some studies\textsuperscript{31–33} have reported that BP control is more difficult in hypertensive patients with obesity or type II diabetes mellitus. Rauscher et al.\textsuperscript{34} studied 60 patients and attributed the reduction in BP to weight loss rather than to CPAP. Since a large number of our patient population were either obese (75%) or diabetic (42.6%), and BMI remained unchanged throughout the study, these could have contributed to only a slight decrease observed in BP with CPAP. Structural and functional hemodynamic changes in small arteries due to hypertension are also important. Although hemodynamic changes were not addressed in our study, others\textsuperscript{35,36} have reported that 6 to 24 months of antihypertensive drug treatment is needed to reverse the changes in small arteries structure and impaired endothelial function. Therefore, it is possible that our study period of only 4 weeks was insufficient to reverse vascular remodeling and improve BP that may be caused by CPAP. Finally, although compliance was only moderate in our study (average 4.7 h/d), it was in the range of other studies,\textsuperscript{18,19,25} and it did not correlate with changes in 24hMBP. Therefore, we think that our results could not be attributed to an insufficient use of the CPAP device.

Similar results were found in the small subgroup of 12 patients who were hypertensive at the beginning of the trial based on ABPM. Reductions in BP values were greater in the therapeutic CPAP group compared to the subtherapeutic CPAP group, but without statistical significance. However, this apparent lack of effect of CPAP must be analyzed cautiously, since this sample was very small to obtain firm conclusions. However, the normal circadian dipping status was restored in a higher proportion of patients in the therapeutic CPAP group compared to the subtherapeutic CPAP group (34.3% vs 12%; p = not significant). Although the difference did not reach statistical significance, there seemed to be a trend toward a beneficial effect of therapeutic CPAP, which may need a larger sample to show.

In our trial, the magnitude of change in 24hMBP did not correlate with OSAS severity, number of antihypertensive agents used, or CPAP compliance. These variables have not been analyzed in previous
studies, except for Pepperell et al., who showed that patients with severe OSAS had the largest lowering in BP with CPAP. This is in contrast with our study and could be explained since our patients had severe OSAS (60 of 68 patients had an AH1 > 30/h, with an average of 63.9/h), so differences among them would be more difficult to establish. However, a lack of correlation between these variables and changes in 24hMBP could be due to our small sample size, although a lack of effect of CPAP on BP cannot be excluded.

In conclusion, this study demonstrates that 4 weeks of therapeutic CPAP do not significantly improve ABPMs against placebo in OSAS patients with hypertension receiving antihypertensive treatment. Therefore, opposite to the findings in refractory hypertension receiving antihypertensive treatment, in patients with well-controlled hypertension a significant reduction in BP values should not be expected after CPAP treatment, at least in the short term. Despite these results, a long-term effect of CPAP on BP cannot be ruled out based on our findings. A new controlled study enrolling a larger sample size and a longer period of observation would be necessary to confirm our findings, since they may have implications for CPAP use recommendation.

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