Effects of Continuous Positive Airway Pressure Treatment on Clinic and Ambulatory Blood Pressures in Patients With Obstructive Sleep Apnea and Resistant Hypertension
A Randomized Controlled Trial


Abstract—The effect of continuous positive airway pressure (CPAP) on blood pressures (BPs) in patients with resistant hypertension and obstructive sleep apnea is not established. We aimed to evaluate it in a randomized controlled clinical trial, with blinded assessment of outcomes. Four hundred thirty-four resistant hypertensive patients were screened and 117 patients with moderate/severe obstructive sleep apnea, defined by an apnea–hypopnea index ≥15 per hour, were randomized to 6-month CPAP treatment (57 patients) or no therapy (60 patients), while maintaining antihypertensive treatment. Clinic and 24-hour ambulatory BPs were obtained before and after 6-month treatment. Primary outcomes were changes in clinic and ambulatory BPs and in nocturnal BP fall patterns. Intention-to-treat and per-protocol (limited to those with uncontrolled ambulatory BPs) analyses were performed. Patients had mean (SD) 24-hour BP of 129(16)/75(12) mm Hg, and 59% had uncontrolled ambulatory BPs. Mean apnea–hypopnea index was 41 per hour and 58.5% had severe obstructive sleep apnea. On intention-to-treat analysis, there was no significant difference in any BP change, neither in nocturnal BP fall, between CPAP and control groups. The best effect of CPAP was on night-time systolic blood pressure in per-protocol analysis, with greater reduction of 4.7 mm Hg (95% confidence interval, −11.3 to +3.1 mm Hg; P=0.24) and an increase in nocturnal BP fall of 2.2% (95% confidence interval, −1.6% to +5.8%; P=0.25), in comparison with control group. In conclusion, CPAP treatment had no significant effect on clinic and ambulatory BPs in patients with resistant hypertension and moderate/severe obstructive sleep apnea, although a beneficial effect on night-time systolic blood pressure and on nocturnal BP fall might exist in patients with uncontrolled ambulatory BP levels. (Hypertension. 2015;65:736-742. DOI: 10.1161/HYPERTENSIONAHA.114.04852.) • Online Data Supplement

Key Words: continuous positive airway pressure • obstructive sleep apnea • randomized controlled trial • resistant hypertension to conventional therapy

Obstructive sleep apnea (OSA) is a chronic disease characterized by recurrent upper airway collapse during sleep causing intermittent hypoxemia and sleep disruption.1 Its prevalence is relatively high in middle-aged populations, ranging from ≥4% to 24%, being higher in men and increasing with aging.2 Most important, it has been consistently demonstrated that OSA is a risk factor for several cardiovascular diseases, including hypertension, coronary and cerebrovascular diseases, heart failure, and atrial fibrillation.3-6 Continuous positive airway pressure (CPAP) is the treatment of choice for severe or symptomatic OSA.1,6,7 However, evidences of beneficial effects of CPAP treatment on cardiovascular outcomes are still scarce.7 In general hypertensive populations, CPAP treatment seems to provide only modest clinic blood pressure (BP) reductions of 2 to 3 mm Hg,8 and an even smaller effects on ambulatory BP levels.9 Resistant hypertension, defined10 as the failure to control clinic BP levels, despite the use of ≥3 antihypertensive drugs in optimal dosages, ideally including a diuretic, or achieving it with ≥4 drugs, is a rather common clinical condition with a prevalence of 12% to 15% of general treated hypertensives,11 and with a significantly worse cardiovascular prognosis.10,12 It has been demonstrated that resistant hypertensive patients had an extremely high prevalence of OSA, ≤80%;13,14 and it has been hypothesized that CPAP treatment may have more pronounced effects on BP reduction in resistant hypertension.6 Nevertheless, only 4 previous randomized controlled trials (RCT) evaluated it.15-18 Three of them15,16,18 had low sample sizes and the largest one17 evaluated CPAP treatment during only a 3-month period, which might have been insufficient for full CPAP effect on BP reduction.19 A recent meta-analysis20 of the first 3 studies15-17
still suggested only modest ambulatory BP reductions of 1.8 to 3.9 mm Hg on systolic blood pressure (SBP) and 2.5 to 3.5 mm Hg on diastolic blood pressure (DBP).

Therefore, we took advantage of an existing cohort of resistant hypertensive patients,12,14,21 and designed a parallel-group RCT to assess the effects of a 6-month CPAP treatment on clinic and ambulatory BP levels in mostly asymptomatic moderate/severe OSA patients with resistant hypertension.

Methods

Design Overview

The study was an uncentered open-label randomized parallel-group clinical trial with blinded outcomes assessment conducted at a tertiary-care university hospital. Patients with resistant hypertension, defined as uncontrolled clinic BP (≥140/90 mm Hg) using 3 antihypertensive drugs in full dosages or using ≥4 drugs regardless of clinic BP levels, ideally including a diuretic,15 and with moderate/severe OSA, defined as an apnea–hypopnea index ≥15 on a complete polysomnography,1 were randomly assigned to either CPAP or no therapy (control) during a 6-month period, whereas keeping unchanged their antihypertensive treatment. All participants gave a written informed consent and the local Ethics Committee had previously approved the study protocol. The study began as an observational cohort12,21 to establish OSA prevalence from September 2010 to December 2011; and the RCT began in January 2012, after trial registration, and ended in July 2014. An Expanded Methods section is available in the online-only Data Supplement, where the eligibility criteria, polysomnographic and BP measurement methods, the randomization procedure and patients’ follow-up are detailed.

Statistical Analysis

Continuous data were described as mean (SD) or median (range) and categorical data as proportions. The primary outcomes were the changes in clinic and mean ambulatory 24-hour, daytime and nighttime BPs from baseline to end of 6-month CPAP treatment or control. Changes in the nocturnal BP fall and its patterns, particularly in the nondipping and riser patterns, were also primary outcomes. Sample size calculations were primarily made for 24-hour SBP changes. We aimed to detect a difference of ≥6 mm Hg in 24-hour SBP changes between CPAP and control groups, with an estimated SD of 12 mm Hg,15 an α error of 0.05 and a statistical power of 0.80. A total of 128 randomized patients (64 in each group) would be necessary. Indeed, with the actual number of patients (57 in CPAP and 60 in control groups) and the 13.5 mm Hg SD of the changes in 24-hour SBP in the CPAP group, we were able to show a minimum difference of ≥7.0 mm Hg in 24-hour SBP changes between CPAP and control groups, with an α error of 0.05 and a statistical power of 0.80.

Intergroup comparisons of changes in BPs were assessed by a general linear model with the allocation group as a fixed factor and adjusted for their respective baseline BP values. In a secondary analysis, models were further adjusted for age, sex, body mass index, presence of cardiovascular diseases, and antihypertensive treatment. No imputation was used because all patients had valid baseline and 6-month BP measurements, and also no adjustment for multiple testing was performed. Graphical analysis of residuals confirmed assumptions of linear regressions. A logistic regression analysis was used to estimate the odds of having a nondipping pattern and a riser pattern, and of having uncontrolled ambulatory BPs on the final ambulatory BP monitoring (ABPM) in the CPAP group in comparison with the control group, after adjustment for their respective baseline status. All primary analyses were by intention-to-treat. Two per-protocol analyses were performed: (1) after excluding patients in the CPAP group with less than optimal CPAP adherence and (2) limited to patients with uncontrolled ambulatory BP levels. Correlations between CPAP adherence and BP changes were also evaluated. All statistical analyses were performed with SPSS statistical package version 19.0 (SPSS Inc, Chicago, IL), and a 2-tailed P<0.05 was regarded as significant.

Results

Study Population

Screening began in September 2010, and randomization began from January 2012 to December 2013, with the final follow-up examination completed in July 2014. Four hundred thirty-four patients with resistant hypertension were screened for OSA by complete polysomnography, and 229 patients (52.8%; 95% confidence interval [CI], 46.4%–60.0%) had moderate/severe OSA (apnea–hypopnea index, ≥15). One hundred four patients were excluded and 125 patients were randomized, 62 to CPAP and 63 to control groups. Five patients randomized to CPAP treatment did not receive the device (2 died and 3 withdrew consent); whereas 3 patients of the control group did not initiate the study (2 died before the beginning and 1 withdrew consent). Hence, there were a total of 57 patients in the CPAP group and 60 patients in the control group in the intention-to-treat analyses; all had baseline and 6-month valid ABPMs. Figure outlines the study flowchart and Table 1 shows the baseline characteristics of all 117 participants and of the CPAP and control groups. Patients had a mean (SD) age of 60.5 (8.2) years, 40% were men, with a mean body mass index of 33 kg/m². 46% had diabetes mellitus and 47% had previous cardiovascular diseases (mainly coronary heart disease). They were treated with a median of 5 antihypertensive drugs and had mean (SD) clinic BPs of 150 (27)/85 (16) mm Hg and ambulatory 24-hour BPs of 129 (16)/75 (12) mm Hg; 59% of them had uncontrolled ambulatory BP levels and 62% had a nondipping pattern of nocturnal BP decline. Mean apnea–hypopnea index was 41 per hour and 59% had severe OSA. There were no significant differences between CPAP and control
Table 1. Baseline Characteristics of All Patients and Randomized to Control and CPAP Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients (n=117)</th>
<th>Control Group (n=60)</th>
<th>CPAP Group (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, % men</strong></td>
<td>39.8</td>
<td>41.7</td>
<td>37.9</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>60.5 (8.2)</td>
<td>60.2 (8.4)</td>
<td>60.8 (8.0)</td>
</tr>
<tr>
<td><strong>Age &gt;65 y, %</strong></td>
<td>31.4</td>
<td>31.7</td>
<td>31.0</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>86.1 (16.8)</td>
<td>87.6 (18.4)</td>
<td>84.6 (15.1)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>33.4 (5.3)</td>
<td>33.8 (5.8)</td>
<td>32.9 (4.8)</td>
</tr>
<tr>
<td><strong>Obesity (BMI&gt;30 kg/m²), %</strong></td>
<td>68.6</td>
<td>65.0</td>
<td>72.4</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td>107 (11)</td>
<td>108 (12)</td>
<td>106 (10)</td>
</tr>
<tr>
<td><strong>Neck circumference, cm</strong></td>
<td>40 (4)</td>
<td>40 (4)</td>
<td>40 (4)</td>
</tr>
<tr>
<td><em><em>Increased neck circumference</em>, %</em>*</td>
<td>22.0</td>
<td>18.3</td>
<td>25.9</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus, %</strong></td>
<td>45.8</td>
<td>46.7</td>
<td>44.8</td>
</tr>
<tr>
<td><strong>Physical inactivity, %</strong></td>
<td>71.2</td>
<td>66.7</td>
<td>75.9</td>
</tr>
<tr>
<td><strong>Current smoking, %</strong></td>
<td>12.7</td>
<td>13.3</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>Dyslipidemia, %</strong></td>
<td>77.1</td>
<td>78.3</td>
<td>75.9</td>
</tr>
<tr>
<td><strong>Target organ damage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous cardiovascular disease, %</strong></td>
<td>46.6</td>
<td>48.3</td>
<td>44.8</td>
</tr>
<tr>
<td><strong>Coronary heart disease, %</strong></td>
<td>30.5</td>
<td>31.7</td>
<td>29.3</td>
</tr>
<tr>
<td><strong>Heart failure, %</strong></td>
<td>5.1</td>
<td>8.3</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease, %</strong></td>
<td>17.8</td>
<td>15.0</td>
<td>20.7</td>
</tr>
<tr>
<td><strong>Antihypertensive treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No. of drugs, median (range)</strong></td>
<td>5 (3–8)</td>
<td>5 (3–8)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>**No. of drugs at bedtime, median (range)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td><strong>Diuretics, %</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>ACE inhibitor, %</strong></td>
<td>63.6</td>
<td>66.7</td>
<td>60.3</td>
</tr>
<tr>
<td><strong>β-Blockers, %</strong></td>
<td>31.4</td>
<td>26.7</td>
<td>36.2</td>
</tr>
<tr>
<td><strong>Calcium channel blockers, %</strong></td>
<td>79.7</td>
<td>78.3</td>
<td>81.0</td>
</tr>
<tr>
<td><strong>Direct vasodilators, %</strong></td>
<td>40.7</td>
<td>41.7</td>
<td>39.7</td>
</tr>
<tr>
<td><strong>Central alpha agonists, %</strong></td>
<td>15.3</td>
<td>20.0</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Spironolactone, %</strong></td>
<td>47.5</td>
<td>46.7</td>
<td>48.3</td>
</tr>
<tr>
<td><strong>Blood pressures, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinic SBP</strong></td>
<td>150 (27)</td>
<td>150 (27)</td>
<td>151 (26)</td>
</tr>
<tr>
<td><strong>Clinic DBP</strong></td>
<td>85 (16)</td>
<td>83 (17)</td>
<td>86 (16)</td>
</tr>
<tr>
<td><strong>Ambulatory 24-h SBP</strong></td>
<td>129 (16)</td>
<td>130 (16)</td>
<td>127 (16)</td>
</tr>
<tr>
<td><strong>Ambulatory 24-h DBP</strong></td>
<td>75 (12)</td>
<td>76 (12)</td>
<td>75 (11)</td>
</tr>
<tr>
<td><strong>True (uncontrolled) RH, %</strong></td>
<td>59.0</td>
<td>58.3</td>
<td>59.6</td>
</tr>
<tr>
<td><strong>Nondipping pattern, %</strong></td>
<td>62.4</td>
<td>56.7</td>
<td>68.4</td>
</tr>
<tr>
<td><strong>Riser pattern, %</strong></td>
<td>14.5</td>
<td>13.3</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>PSG results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AHI</strong></td>
<td>41 (21)</td>
<td>39 (18)</td>
<td>44 (24)</td>
</tr>
<tr>
<td><strong>Severe apnea (AHI &gt;30), %</strong></td>
<td>58.5</td>
<td>58.3</td>
<td>58.6</td>
</tr>
<tr>
<td><strong>Mean SaO₂ during sleep, %</strong></td>
<td>93 (2)</td>
<td>93 (2)</td>
<td>92 (2)</td>
</tr>
<tr>
<td><strong>Lowest SaO₂ during sleep, %</strong></td>
<td>78 (10)</td>
<td>77 (11)</td>
<td>78 (10)</td>
</tr>
<tr>
<td><strong>Time with SaO₂ &lt;90%, min (median (range))</strong></td>
<td>9 (0–306)</td>
<td>8 (0–306)</td>
<td>11 (0–204)</td>
</tr>
<tr>
<td><strong>Epworth Sleepiness Scale (points)</strong></td>
<td>11 (6)</td>
<td>12 (6)</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD) or proportions, except for number of antihypertensive drugs and time spent with SaO₂ <90%, which are presented as median (range). ACE indicates angiotensin-converting enzyme; AHI, apnea–hypopnea index; AR, angiotensin-II receptor; BMI, body mass index; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; PSG, Polysomnography; RH, resistant hypertension; SaO₂, oxygen arterial saturation; and SBP, systolic blood pressure.

*Increased neck circumference: >41 cm in women and >43 cm in men.
groups. Polysomnographic data and antihypertensive treatment were identical between CPAP and control groups.

Median use of CPAP was 4.8 hours per night and 15 patients (26%), including 5 who interrupted CPAP use during the first month of treatment because of poor adaptation, used CPAP for ≤4 hours per night. The mean (SD) CPAP pressure was 7.3 (1.8) mm Hg and the residual apnea–hypopnea index after CPAP application during titration was 3 per hour. Patients had a mean Epworth Sleepiness Scale score of 11 points, identical between CPAP and control groups, and after 6-month treatment, there was a mean reduction of 3.4 points (95% CI, 1.9–5.0; P<0.001) in the CPAP group and a mean reduction of 0.4 points (95% CI, −0.4 to 1.3; P=0.32) in the control group.

### Outcomes

Table 2 presents the intention-to-treat analyses of the differences between CPAP and control groups about clinic and ambulatory BP changes during follow-up. There were no significant differences between CPAP treatment and control on BP reductions, after adjustments for their respective baseline values. About ambulatory BPs, the best effect of CPAP was on night-time SBP, with a greater reduction of nearly 2 mm Hg and an increase in 1% on relative nocturnal SBP fall in comparison with the control group. A secondary analysis with further adjustments for age, sex, body mass index, presence of cardiovascular disease, and antihypertensive treatment, did not change any of the results. There was no influence of spironolactone use on BP reduction difference between CPAP and control groups, although a slightly nonsignificant better response to CPAP was observed in patients using spironolactone (−2.8 versus −0.2 mm Hg for night-time SBP).

Table 3 shows the effects of CPAP on adverse nocturnal BP dipping patterns and on ambulatory BP control. CPAP treatment nonsignificantly decreased 7% the odds of having a nondipping pattern and 43% of having a riser pattern; and also decreased 27% the odds of having uncontrolled ambulatory BP levels in comparison with the control group after adjustment for their respective baseline ABPM dipping and control status.

On a per-protocol analysis, excluding the 15 patients with less than optimal CPAP adherence did not change significantly any of the results. There was also no significant association between hours of CPAP use and any BP change.

Table 4 presents the per-protocol analyses of the differences between control and CPAP groups on BP changes limited to patients with uncontrolled ambulatory BP levels. Although the differences in BP changes were increased, favoring greater reductions in the CPAP group, none achieved statistical significance. The best effect of CPAP remained on night-time SBP levels, with greater reduction of nearly 5 mm Hg and greater increase of 2.2% on nocturnal SBP fall, in comparison with the control group.

### Discussion

This controlled RCT demonstrates that CPAP treatment provides no significant reduction on clinic and ambulatory BPs in the whole group of patients with resistant hypertension and moderate/severe OSA; but may provide a modest, yet clinically relevant, night-time SBP reduction of nearly 5 mm Hg associated with an increase of 2.2% in nocturnal SBF fall in the subgroup of patients with uncontrolled ambulatory BP levels.

This is the fifth RCT on the effects of CPAP treatment on BP in patients with resistant hypertension and OSA, and the largest one of the uncenter trials.15,16,18 The first RCT15 randomized 29 resistant hypertensive patients (20 with uncontrolled ambulatory BPs) to 3-month CPAP treatment and 35 patients (21 with uncontrolled BPs) to control group; and observed no significant BP reduction in the whole study group. The best CPAP effect was a borderline significant 3.1 mm Hg reduction on night-time DBP (P=0.05). However, in the subgroup with uncontrolled ambulatory BP levels, there were a significant reduction on

### Table 2. Effect of 6-Month CPAP Treatment on Clinic and Ambulatory Blood Pressures on Intention-To-Treat Analysis

<table>
<thead>
<tr>
<th>Blood Pressures</th>
<th>Control Group (n=60)</th>
<th>CPAP Group (n=46)</th>
<th>Adjusted* Difference Between CPAP and Control Mean (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BPs, mm Hg</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Clinic</td>
<td>148.8 (27.5)</td>
<td>148.0 (25.1)</td>
<td>151.4 (26.0)</td>
<td>146.3 (25.0)</td>
</tr>
<tr>
<td>24 h</td>
<td>130.5 (16.5)</td>
<td>130.1 (16.7)</td>
<td>126.7 (16.4)</td>
<td>127.5 (15.9)</td>
</tr>
<tr>
<td>Daytime</td>
<td>132.2 (16.4)</td>
<td>132.6 (16.7)</td>
<td>129.5 (16.9)</td>
<td>130.5 (16.1)</td>
</tr>
<tr>
<td>Night-time</td>
<td>121.6 (18.1)</td>
<td>123.4 (16.2)</td>
<td>119.2 (17.5)</td>
<td>120.4 (17.9)</td>
</tr>
<tr>
<td>Nocturnal fall (%)</td>
<td>8.0 (8.0)</td>
<td>6.7 (8.4)</td>
<td>7.8 (7.6)</td>
<td>7.7 (7.9)</td>
</tr>
<tr>
<td>Diastolic BPs, mm Hg</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Clinic</td>
<td>83.3 (16.6)</td>
<td>80.7 (17.1)</td>
<td>86.5 (15.9)</td>
<td>82.3 (15.4)</td>
</tr>
<tr>
<td>24 h</td>
<td>75.7 (12.1)</td>
<td>75.2 (11.8)</td>
<td>74.7 (11.5)</td>
<td>74.5 (10.9)</td>
</tr>
<tr>
<td>Daytime</td>
<td>72.2 (12.0)</td>
<td>77.0 (12.4)</td>
<td>76.7 (12.1)</td>
<td>76.6 (10.9)</td>
</tr>
<tr>
<td>Night-time</td>
<td>69.0 (12.0)</td>
<td>70.0 (11.7)</td>
<td>69.2 (11.0)</td>
<td>69.8 (12.1)</td>
</tr>
<tr>
<td>Nocturnal fall (%)</td>
<td>10.4 (9.8)</td>
<td>8.7 (10.0)</td>
<td>9.4 (8.3)</td>
<td>9.0 (9.0)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CI, confidence interval; and CPAP, continuous positive airway pressure.

* Differences between CPAP and control groups were adjusted for their respective baseline values. Negative values mean greater reductions, whereas positive values mean greater increases on CPAP group in relation to control group.
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24-hour DBP (4.9 mm Hg; P=0.027) and borderline significant reductions on 24-hour SBP (7.6 mm Hg; P=0.074) and on daytime DBP (3.6 mm Hg; P=0.072). The best response was observed in those patients who adhered to CPAP for >5.8 hours per night. The second RCT16 randomized 19 resistant hypertensives to 6-month CPAP treatment and 16 to control group, all with uncontrolled ambulatory BPs; and demonstrated significant reductions only on daytime BP levels (6.5 mm Hg for SBP and 4.5 mm Hg for DBP; both P<0.05) in the CPAP group, without significant effects on 24-hour or night-time BPs. In this study, changes in BPs were not associated with CPAP adherence. The third RCT,17 the largest and unique multicenter one, randomized 98 resistant hypertensive patients to 3-month CPAP treatment and 96 to control arm, all with uncontrolled ambulatory BPs. It reported significant reductions on 24-hour mean BP (3.1 mm Hg; P=0.02) and on 24-hour DBP (3.2 mm Hg; P=0.005), but only a borderline reduction on 24-hour SBP (3.1 mm Hg; P=0.10) in the intention-to-treat analysis. This was the only study, like ours, that adjusted the differences between CPAP and control changes in BPs to their respective baseline values, which decreases the effect of the regression to the mean phenomenon that may occur after serial measurements. The authors also reported that CPAP treatment was associated with higher odds of reversing the adverse baseline nondipping pattern into normal dipping (odds ratio, 2.4; 95% CI, 1.2–5.1) and positive correlations between time of CPAP use and BP reductions. On per-protocol analysis of patients with better CPAP adherence (≥4 hours per night), there were significant reductions on most ambulatory BPs, most notably on night-time BPs (7.1 mm Hg for SBP and 4.1 mm Hg for DBP; both P=0.003). However, in this study,17 20 patients did not have valid final ABPMs and missing values were imputed. Recently, another small unicenter RCT was reported as a research letter.18 It randomized 22 patients to 8-week CPAP treatment and 23 to sham-CPAP and observed an impressive 10 mm Hg 24-hour SBP reduction in the CPAP group. Our results mainly agreed with the first15 and third trials17 by showing a predominant CPAP effect on night-time SBP levels and on nocturnal SBP fall and nondipping/riser

Table 3. Effect of 6-Month CPAP Treatment on Prevalences of Nondipping Patterns and on Ambulatory Blood Pressure Control On Intention-To-Treat Analysis

<table>
<thead>
<tr>
<th>Ambulatory BP Parameters</th>
<th>Control Group (n=60)</th>
<th>CPAP Group (n=57)</th>
<th>Odds Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 Mo</td>
<td>Baseline 6 Mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of nondipping pattern</td>
<td>34 (56.7%)</td>
<td>39 (65.0%)</td>
<td>39 (68.4%)</td>
<td>39 (68.4%)</td>
</tr>
<tr>
<td>Prevalence of riser pattern</td>
<td>8 (13.3%)</td>
<td>13 (21.7%)</td>
<td>9 (15.8%)</td>
<td>8 (14.0%)</td>
</tr>
<tr>
<td>Prevalence of uncontrolled ambulatory BP</td>
<td>35 (58.3%)</td>
<td>43 (71.1%)</td>
<td>34 (59.6%)</td>
<td>38 (66.7%)</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CI, confidence interval; and CPAP, continuous positive airway pressure.
*Logistic regression was adjusted for their respective baseline dipping patterns and ambulatory BP control status.

Table 4. Effect of 6-Month CPAP Treatment on Clinic and Ambulatory Blood Pressures in Per-Protocol Analysis of Patients With True (Uncontrolled)–Resistant Hypertension

<table>
<thead>
<tr>
<th>Blood Pressures</th>
<th>Control Group (n=35)</th>
<th>CPAP Group (n=34)</th>
<th>Adjusted* Difference Between CPAP and Control Mean (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>6 Mo Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BPs, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>155.8 (24.8)</td>
<td>157.9 (23.7)</td>
<td>−6.1 (−17.5 to +5.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>24 h</td>
<td>139.1 (14.0)</td>
<td>137.7 (16.2)</td>
<td>-3.2 (−9.3 to +2.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Daytime</td>
<td>140.9 (15.2)</td>
<td>139.6 (16.9)</td>
<td>−1.4 (−7.6 to +4.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Night-time</td>
<td>133.2 (14.0)</td>
<td>131.1 (14.5)</td>
<td>−4.7 (−11.3 to +3.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Nocturnal fall</td>
<td>5.1 (8.5)</td>
<td>5.5 (9.0)</td>
<td>2.2 (−1.6 to +5.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diastolic BPs, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>85.9 (18.1)</td>
<td>84.2 (19.5)</td>
<td>-1.1 (−8.7 to +6.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>24 h</td>
<td>80.5 (12.2)</td>
<td>79.6 (12.6)</td>
<td>−1.9 (−6.1 to +2.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Daytime</td>
<td>82.0 (12.4)</td>
<td>81.1 (13.4)</td>
<td>−1.6 (−6.0 to +2.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Night-time</td>
<td>75.2 (11.5)</td>
<td>74.3 (12.3)</td>
<td>−1.0 (−5.9 to +3.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>Nocturnal fall</td>
<td>7.8 (10.7)</td>
<td>7.9 (10.6)</td>
<td>0.2 (−4.4 to +4.7)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CI, confidence interval; and CPAP, continuous positive airway pressure.
*Differences between CPAP and control groups were adjusted for their respective baseline values. Negative values mean greater reductions, whereas positive values mean greater increases on CPAP group in relation to control group.
patterns, but with lesser magnitude of reductions than these previous studies. However, some important differences from these previous RCTs should be noted. First, our study evaluated the effect of a 6-month CPAP treatment. This may be important because a previous retrospective observational study had suggested that the full beneficial effect of CPAP may only seem after 6 months of treatment. Only the smallest RCT assessed the effect of a 6-month CPAP treatment. The 3 other RCTs evaluated shorter treatments. Second, this was the group of patients with resistant hypertension most intensively treated before CPAP beginning. In previous RCTs, patients were treated by a median of 3 to 4 antihypertensive drugs and none of them reported the use of mineralocorticoid receptor blockers, which are currently the drug of choice to be added to antihypertensive treatment of uncontrolled resistant hypertensive patients. In our study, patients were treated by a median of 5 antihypertensive drugs (2 at bedtime), and almost half of them were using spironolactone. This is the plausible reason why we had a relatively high proportion of patients with controlled ambulatory BP levels (41%) and their ambulatory BP levels were lower than those reported in previous RCTs. It also probably explains the lesser effect of CPAP on ambulatory BP levels in our study in comparison with the previous ones. Finally, all our patients had valid baseline and final ABPM examinations and no missing values imputation was used.

Although nonsignificant in our study because of lower statistical power of the per-protocol analysis limited to patients with uncontrolled ambulatory BPs (indeed, in this analysis with 35 controls and 34 patients with CPAP, with the actual 17 mmHg SD of night-time SBP changes, we were only able to show differences >11 mmHg, with a 0.80 power and 0.05 α error; a difference of ±5 mmHg had only a 0.22 statistical power to be demonstrated); the greater night-time SBP reduction of CPAP treatment, ranging from 4.7 mmHg in our data to 7.1 mmHg in the per-protocol analysis of the HIPARCO trial, may be clinically relevant to improve cardiovascular prognosis. It has been consistently demonstrated that night-time BPs are better cardiovascular risk predictors than daytime or clinic BPs, both in general hypertensives, and in patients with resistant hypertension. We had previously demonstrated that each 5 mmHg increase in night-time SBP augmented 8% (95% CI, 3%–12%) the risk of major cardiovascular disease occurrence, and that the presence of nondipping or riser patterns more than doubled the risk of cardiovascular mortality, even after adjustment for 24-hour SBP levels. Hence, it is plausible to hypothesize that even these rather modest night-time SBP reductions and improvements on nocturnal BP fall patterns induced by CPAP treatment may be translated into future cardiovascular protection. Although some reports from uncontrolled observational studies have suggested that cardiovascular risk may be reduced by CPAP treatment, currently there is no adequately powered RCT designed to examine whether CPAP treatment offers protection for hard cardiovascular outcomes. One previous RCT did not demonstrate significant cardiovascular benefits of CPAP treatment, but it was limited by insufficient statistical power. Such studies are urgently needed.

This study has some limitations that warrant discussion. First, it had a nonblinded design and no placebo was offered to the control arm. Indeed, only one of the previous RCTs, the shortest 8-week one, was blinded and had a placebo-controlled arm. Otherwise, all outcomes were assessed in a blinded manner. The sham-CPAP, the commonest used CPAP-placebo, because of excessive air leaking and low pressures along with the persistence of snoring and recurring apneas, frequently leads the patient to realize that he is not receiving the effective treatment. Moreover, it may cause discomfort and poor adherence, which may result in BP elevations, suggesting that sham-CPAP fails to function as true placebo. Second, as previously discussed, the per-protocol analysis was underpowered to show the prespecified outcome of 6 to 7 mmHg SBP differences between CPAP and control groups. Furthermore, the sample size was primarily calculated for 24-hour SBP changes and there were no multiple testing adjustments for the other outcomes. However, this study has some strengths that should be emphasized. CPAP treatment was carried on a longer period of 6 months, all patients had no missing data and the RCT was conducted on a well-characterized cohort of resistant hypertensive patients under intensive currently recommended antihypertensive treatment.

**Perspectives**

This controlled RCT provides evidence that a 6-month CPAP treatment did not reduce clinic and ambulatory BPs in patients with resistant hypertension and moderate/severe OSA in relation to a control group on a stable intensive antihypertensive treatment. However, it suggests that in the specific subgroup of patients with uncontrolled ambulatory BP levels, CPAP treatment may modestly reduce night-time SBP and improve nocturnal BP fall patterns. Whether these potential benefits of CPAP treatment could have effect on improving cardiovascular prognosis should be the focus of future long-term randomized clinical trials.

**Sources of Funding**

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**Disclosures**

None.

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Novelty and Significance

What Is New?

• The effect of continuous positive airway pressure treatment on clinic
and ambulatory blood pressure (BP) reduction in patients with resistant
hypertension and sleep apnea has been scarcely investigated by ade-
quately powered controlled trials.

What Is Relevant?

• A 6-month continuous positive airway pressure treatment has no signifi-
cant effect on clinic and ambulatory BP reductions in resistant hypo-
tensives with moderate/severe sleep apnea. However, a beneficial effect
on night-time systolic blood pressure and on nocturnal BP fall might exist
in the subgroup of patients with uncontrolled ambulatory BP levels.
This modest reduction on nocturnal BPs and improvement in dipping patterns
may have favorable effect on cardiovascular prognosis.

Summary

In patients with resistant hypertension and moderate/severe sleep
apnea, a 6-month continuous positive airway pressure treatment
provides no significant reduction on clinic and ambulatory BPs; but
may provide a modest, yet clinically relevant, night-time systolic
BP reduction of nearly 5 mm Hg associated with an increase of
2.2% in nocturnal systolic BP fall in the subgroup of patients with
uncontrolled ambulatory BP levels.
Effects of Continuous Positive Airway Pressure Treatment on Clinic and Ambulatory Blood Pressures in Patients With Obstructive Sleep Apnea and Resistant Hypertension: A Randomized Controlled Trial

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Title: EFFECTS OF CPAP TREATMENT ON CLINIC AND AMBULATORY BLOOD PRESSURES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND RESISTANT HYPERTENSION: A RANDOMIZED CONTROLLED TRIAL.


Expanded Methods

Supplementary References
Expanded Methods

Design overview

The study was an unicenter open-label randomized parallel-group clinical trial with blinded outcomes assessment conducted at a tertiary-care university hospital. Patients with resistant hypertension, defined as uncontrolled clinic BP (≥140/90mmHg) using 3 anti-hypertensive drugs in full dosages or using ≥4 drugs regardless of clinic BP levels, ideally including a diuretic, and with moderate/severe OSA, defined as an apnea-hypopnea index (AHI) ≥15 on a complete polysomnography, were randomly assigned to either CPAP or no therapy (control) during a 6-month period, while keeping unchanged their anti-hypertensive treatment. All participants gave a written informed consent and the local Ethics Committee had previously approved the study protocol. The study began as an observational cohort to establish OSA prevalence from September 2010 to December 2011; and the RCT began in January 2012, after trial registration, and the last patient was randomized in December 2013 and follow-up ended in July 2014.

Eligibility

Adult patients with resistant hypertension aged up to 74 years were consecutively recruited from the Hypertension outpatient clinic. Exclusion criteria were pregnancy, concomitant life-threatening diseases, significant cognitive impairment, poor anti-hypertensive treatment adherence, other secondary causes of hypertension (including renal artery stenosis and surgical primary aldosteronism; patients with possible bilateral adrenal hyperplasia, based on adrenal CT scan results, were all treated with spironolactone, but were not excluded), advanced renal failure (defined by a CKD-EPI-formula estimated glomerular filtration rate <30 ml/min/1.73m²), major cardiovascular events occurrence on the previous 6-months, severe hypersomnia requiring treatment (defined by an Epworth Sleepiness Scale [ESS] >18), and current or previous CPAP use.

Study procedures

At initial screening visit, all eligible patients completed a standardized protocol that included clinical and anthropometric data, and the Berlin and ESS questionnaires, both validated for Portuguese language. Treatment adherence was assessed by a specific questionnaire at baseline and by monthly pill count during the 6-month follow-up period.

Polysomnography

All eligible patients underwent a full-night in-hospital attended complete diagnostic polysomnography (PSG), recorded in BrainNet BNT 36 device and analyzed by Poliwin XP software (EMSA, Brazil), as previously described. During all PSG studies, airflow, respiratory effort, and oxyhemoglobin saturation were monitored. Electrocardiogram, electroencephalogram, electrooculogram, and submental/anterior tibial electromyogram were simultaneously recorded with surface electrodes according to the American Academy of Sleep Medicine standards. Sleep stages, oxygen desaturation, breathing events, and periodic limb movement were scored by an experienced physician blinded to other patients’ data. Apnea and hypopnea episodes were respectively defined as a ≥90% and ≥30% decrease of airflow for at least 10s associated with oxyhemoglobin desaturation ≥4%. Obstructive and central apneas were diagnosed according to the presence or absence of accompanying respiratory effort. The AHI was calculated as the number of apnea-hypopnea events per hour of sleep. The presence of OSA was defined by an AHI ≥5 events/hour and each severity category by
following criteria: mild OSA with AHI 5-14.9 events/hour, moderate OSA with AHI 15-29.9 events/hour, and severe OSA with AHI ≥30 events/hour.² Mean and lowest arterial oxygen saturation (SaO₂) during sleep and time spent with SaO₂ < 90% were also registered. Patients with predominant central apneas were excluded.

**BP measurements**

Clinic BP was measured twice on two occasions with suitably sized cuffs, with patients in the sitting position, using a digital BP monitor (HEM-907 XL, Omron Healthcare, Kyoto, Japan). The mean between the 4 readings were registered. Ambulatory BP monitoring (ABPM) was recorded using Mobil O graph (version 12) equipment (DYNAMAPA, Cardios LTDA., São Paulo, Brazil), approved by the British Society of Hypertension.⁹ All patients were using their prescribed anti-hypertensive medications during ABPM. A reading was taken every 15 minutes throughout the day and every 30 minutes at night. The nighttime period was ascertained for each individual patient from registered diaries. Parameters evaluated were mean 24-hour, daytime and nighttime systolic (SBP) and diastolic BP (DBP). The nocturnal BP fall was calculated as \( \frac{(\text{daytime BP} - \text{nighttime BP})}{\text{daytime BP}} \times 100 \), and patients were classified according to the dipping pattern as: dippers (nocturnal reduction ≥10%) or non-dippers (nocturnal reduction <10%). Riser pattern (or reversed dipping) was defined as a nocturnal reduction <0%. Patients were also divided into controlled ambulatory BP (24-hour BP <130/80 mmHg) or uncontrolled ambulatory BP (24-hour BP ≥130/80 mmHg).¹,¹⁰,¹¹ ABPM data were assessed by an independent observer blinded to other patients’ data.

**Random allocation**

Eligible patients were randomized to either CPAP or control groups by a central telephone line connected to a specific randomizing software (www.randomizer.org). Randomization was stratified by gender, age (>60 / ≤60 years) and OSA severity (AHI >30 / ≤30) in blocks of 4 patients. The randomization centre only revealed the allocation group after the investigator provided the full data of an eligible patient, which guaranteed the allocation concealment of the randomization procedure.

**CPAP titration**

Patients randomized to CPAP group underwent a second in-hospital attended complete PSG to titrate optimal CPAP pressure. No titration was performed on split-night PSG examinations. CPAP titration was performed manually by the PSG technician and the optimal CPAP pressure was evaluated by the same independent sleep specialist who assessed the initial PSGs, based on visual inspection of the raw data recording with no significant leaks.

**Follow-up**

Patients assigned to CPAP group received the equipment (Rem-Star Pro, Philips Respironics, Eindhoven, the Nederlands) and were followed-up in a CPAP clinic with weekly visits during the first month and monthly visits thereafter until completion of the 6-month period, whereas control group patients were followed-up with monthly visits in the hypertension clinic. Both groups had direct all-time contact with their researchers for any problem-solving issue. CPAP adherence was assessed by its own digital storage device, using a specific software (EncorePro, Philips Respironics), which recorded the proportion of nights and the time per night the device was used, the presence of leaks and the residual AHI. If the AIH increased for ≥5, the titrated CPAP pressure was increased by 1mmHg weekly until AIH <5. For calculation of CPAP adherence, the time per night of CPAP use was multiplied by the
proportion of nights it was used, and an optimal adherence was defined by ≥4h of CPAP use per night, without leaks and a residual AHI <5/h. All patients repeated 24-hour ABPM under the same initial protocol after the 6-month period.

**Main outcome measures**

The primary outcomes were the changes in clinic and mean ambulatory 24-hour, daytime and nighttime BPs from baseline to end of 6-month CPAP treatment or control. Changes in the nocturnal BP fall and its patterns, particularly in the non-dipping and riser patterns, were also primary outcomes.

**Statistical Analysis**

Continuous data were described as means (SD) or medians (range) and categorical data as proportions. Sample size calculations were primarily made for 24-hour SBP changes. We aimed to detect a difference of 6 mmHg or more in 24-hour SBP changes between CPAP and control groups, with an estimated SD of 12 mmHg, an α error of 0.05 and a statistical power of 0.80. A total of 128 randomized patients (64 in each group) would be necessary. Indeed, with the actual number of patients (57 in CPAP and 60 in control groups) and the 13.5 mmHg SD of the changes in 24-hour SBP, we were able to show a minimum difference of 7.0 mmHg in 24-hour SBP changes between CPAP and control groups, with an α error of 0.05 and a statistical power of 0.80.

Intergroup comparisons of changes in BPs were assessed by a general linear model with the allocation group as a fixed factor and adjusted for their respective baseline BP values. In a secondary analysis, models were further adjusted for age, gender, body mass index (BMI), presence of cardiovascular diseases and anti-hypertensive treatment. No imputation was used because all patients had valid baseline and 6-month BP measurements, and also no adjustment for multiple testing was performed. Graphical analysis of residuals confirmed assumptions of linear regressions. A logistic regression analysis was used to estimate the odds of having a non-dipping pattern and a riser pattern, and of having uncontrolled ambulatory BPs on the final ABPM in the CPAP group in comparison to the control group, after adjustment for their respective baseline status. All primary analyses were by intention-to-treat (ITT). Two per-protocol analyses were also carried on: one after excluding patients in the CPAP group with less than optimal CPAP adherence, and the second limited to patients with uncontrolled ambulatory BP levels. Correlations between CPAP adherence and BP changes were also evaluated. All statistical analyses were performed with SPSS statistical package version 19.0 (SPSS Inc., Chicago, Il., USA), and a 2-tailed p-value <0.05 was regarded as significant.

**Supplementary References**


