Effect of Continuous Positive Airway Pressure on Blood Pressure
A Placebo Trial

Joel E. Dimsdale, Jose S. Loredo, Judi Profant

Abstract—This study examined the effect of continuous positive airway pressure (CPAP) treatment on blood pressure in patients with obstructive sleep apnea. Thirty-nine patients with sleep apnea were studied. Ambulatory blood pressure monitoring was obtained before and after patients were randomized to receive either 1 week of CPAP or placebo CPAP (CPAP administered at ineffective pressure). Blood pressure was examined over daytime hours (6 AM to 10 PM) and during nighttime hours (10 PM to 6 AM). Daytime mean arterial blood pressure decreased significantly but equally in both the active treatment group and the placebo treatment group ($P = 0.001$). Nighttime mean arterial pressure levels decreased to a much greater extent over time in the patients who received active CPAP treatment ($P = 0.032$). CPAP does appear to decrease nighttime blood pressure. However, the decrease in daytime blood pressure may reflect a nonspecific response (ie, placebo), since both the active treatment group and the placebo treatment group developed comparable decreases in blood pressure. *(Hypertension. 2000;35:144-147.)*

Key Words: apnea ■ blood pressure ■ blood pressure monitoring, ambulatory ■ placebo effect

Obstructive sleep apnea (OSA) is commonly associated with increased blood pressure (BP).1–4 Treatments for OSA are multiple, but, after weight loss, the most commonly used treatment is nocturnal continuous positive airway pressure (CPAP). The great majority of OSA patients can have their apnea successfully treated with this methodology.5

Because of the comorbidity of hypertension and OSA, many investigators have examined how CPAP affects BP levels.6–19 Table 1 summarizes these endeavors. As the table suggests, many of the studies report a beneficial effect of CPAP on BP. The studies suggest that CPAP acutely decreases nighttime BP in hypertensive OSA patients but not in normotensive patients and that longer-term use of CPAP decreases both nocturnal and diurnal BP. However, certain design aspects are striking. The studies generally have a small sample size (average of 14 patients per study), and most of them use neither randomization nor a control group. Most studies combined normotensives and hypertensives, and many hypertensives were studied while they were receiving antihypertensive treatment. Few studies examined patients in the absence of antihypertensive medication. Most studies did not describe how they dealt with data from patients who were noncompliant with the CPAP treatment.

Only half of the studies used ambulatory blood pressure monitoring (ABPM). ABPM techniques acquire a more complete and representative sample of BP readings than would be obtained by casual BP measurement in the physician’s office. In addition, ABPM allows examination of BP patterns in awake and in sleeping patients.

Most notably, only 1 study used a placebo control (an oral placebo) for CPAP, and that study found no effect of CPAP on 24-hour ambulatory BP.6 BP is notoriously influenced by nonspecific effects. The CPAP apparatus itself could be a very powerful stimulus for placebo responses. For this reason, we performed a double-blind placebo trial of CPAP versus placebo CPAP on BP as gauged by ABPM.

Methods

Patients were located by public advertisements and word-of-mouth referral. All patients signed written informed consent approved by the University of California at San Diego Institutional Review Board. Patients were eligible if they were between the ages of 30 and 65 years and were 100% to 170% of ideal body weight as determined by Metropolitan norms.20 Patients were ineligible if they had any major ongoing illness other than sleep apnea and hypertension.

Patients receiving antihypertensive medication had their medication slowly tapered and their BP status confirmed after a 3-week washout. Patients’ BP was screened repeatedly (3 times on 2 occasions) after they had been seated resting for at least 5 minutes. Individuals whose BP was <140/90 mm Hg were considered normotensive. Patients whose BP was >140/90 but <180/110 mm Hg were considered hypertensive and eligible to participate in this protocol.

Sleep was screened at home with a Nightwatch system, and individuals whose respiratory disturbance index (RDI) at home was >20 were considered provisionally to have OSA.

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From the Departments of Psychiatry (J.E.D.) and Medicine (J.S.L.), University of California at San Diego, and San Diego State University/University of California at San Diego Joint Doctoral Program in Clinical Psychology (J.P.).

Correspondence to Dr Joel E. Dimsdale, University of California at San Diego, La Jolla, CA 92093-0804. E-mail jdimsdale@ucsd.edu

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### TABLE 1. Studies of Effect of CPAP on BP

<table>
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<th>BP Measurement</th>
<th>Length of Treatment</th>
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<tr>
<td>Kellner C et al, 1993</td>
<td>n=10 (6/10 with HTN); RDI=28; age 54 y</td>
<td>BP measured every 30 min with Finapres overnight before and after CPAP</td>
<td>2–7 d</td>
<td>SBP decreased (P&lt;0.05); DBP decreased (P&lt;0.05); maximal BP decreased (P&lt;0.01). Conclusion: CPAP acutely lowers nocturnal BP</td>
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<tr>
<td>Naughton MT et al, 1995</td>
<td>n=9 healthy controls and 15 normotensive CHF patients</td>
<td>BP measured every minute for 75 minutes while awake before and during CPAP with automatic sphygmomanometer (Physio-Control Lifestat 200)</td>
<td>75 min at 0, 5, 7.5, 10 cm H2O CPAP pressure</td>
<td>No significant change in SBP or DBP in either group (normals or CHF)</td>
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<td>Engleman HM et al, 1996</td>
<td>n=13 OSA patients; age 51 y; RDI=49; 5 patients with HTN; 4 of them on medication</td>
<td>24-h ambulatory BP recording with Spacelabs 90207 every half hour for 24 h</td>
<td>Oral placebo treatment vs CPAP; CPAP average use 4 h/night for 3 wk</td>
<td>Nondippers’ (5) daytime MAP decreased (P&lt;0.01); 2/5 nondippers became dippers with CPAP CPAP did not alter BP in HTN patients</td>
</tr>
<tr>
<td>Guillemaint C et al, 1996</td>
<td>n=6 UARS patients with borderline HTN (untreated); age 40 y; RDI=2</td>
<td>BP measured every 30 min for 48 h with ABPM (model 630; Colin Medical Instruments)</td>
<td>≥30 d; 5/6 subjects compliant with CPAP</td>
<td>Daytime DBP decreased (P=0.05); SBP decreased (P=0.05) Night time BP: only DBP decreased (P=0.05)</td>
</tr>
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<td>Jennum P et al, 1989</td>
<td>n=13 OSA patients off anti hypertensive medication; 6/13 with HTN</td>
<td>BP measurement via A-line during sleep baseline and after CPAP</td>
<td>1 night</td>
<td>BP decreased (P&lt;0.05)</td>
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<tr>
<td>Ali NJ et al, 1992</td>
<td>n=8 obese OSA patients; normotensive</td>
<td>BP measured with Finapres while on CPAP during the same night for a 30-min period of non-REM sleep</td>
<td>&lt;1 night</td>
<td>BP fell slightly but not significantly with CPAP</td>
</tr>
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<td>Suzuki M et al, 1993</td>
<td>n=9 obese OSA patients; 5/9 with HTN on medication; RDI for HTN=49; RDI for normotensives=39</td>
<td>Up to 72-h ambulatory BP cuff monitoring with ABPM-630 Colin Medical Instruments</td>
<td>5 wk</td>
<td>HTN: BP fell (P&lt;0.04); daytime BP fell (P&lt;0.08); nighttime BP fell (P&lt;0.04) Normotensives: no change in BP with CPAP</td>
</tr>
<tr>
<td>Mayer J et al, 1991</td>
<td>n=12 HTN OSA patients; off medication; RDI=58</td>
<td>Nighttime BP by arterial line; daytime BP by BP cuff monitor</td>
<td>6 mo</td>
<td>Nighttime BP fell acutely (P&lt;0.001); daytime BP after 6 mo fell (P&lt;0.01). Conclusion: CPAP lowers nocturnal BP acutely and chronically lowers diurnal BP</td>
</tr>
<tr>
<td>Wilcox I et al, 1993</td>
<td>n=19 male OSA patients; 11/19 with HTN; off medications; RDI=56 at baseline</td>
<td>24-h ABPM with Oxford Medilog at 15-min intervals</td>
<td>Minimum of 8-wk follow-up on CPAP; 14/19 compliant with CPAP</td>
<td>Compliant subjects (HTN and non-HTN): BP decreased (P&lt;0.05); noncompliant patients (4) (CPAP&lt;4 h/night); BP remained unchanged</td>
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<tr>
<td>Worsno CJ et al, 1993</td>
<td>n=18 OSA patients; 7/18 with HTN; on medications; RDI=51</td>
<td>BP cuff readings with Dynmap</td>
<td>10 d</td>
<td>HTN patients: BP decreased (P&lt;0.04); normotensive OSA patients: no change in BP</td>
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<td>Davies RJO et al, 1994</td>
<td>n=11 male OSA patients; RDI=56; 6/11 with HTN; 3/6 HTN patients on medication</td>
<td>Ambulatory BP cuff measurements</td>
<td>3 mo</td>
<td>Daytime BP: no change in BP; nighttime BP decreased (P&lt;0.02). Conclusion: only nocturnal SBP showed a significant reduction with CPAP</td>
</tr>
<tr>
<td>Rauscher H et al, 1993</td>
<td>n=33 HTN OSA patients; controls were 27 OSA patients who refused CPAP; RDI=49 for treated and RDI=36 for controls; mean CPAP use 6 h/night; on medication</td>
<td>BP cuff measurements made in various places, eg, sleep lab, doctor’s office</td>
<td>512 d</td>
<td>10/33 HTN patients stopped or reduced medication; these patients also lost weight. 8/27 controls stopped or decreased medication; these patients also lost weight. Drop in BP was due to weight loss and not to CPAP</td>
</tr>
<tr>
<td>Akashiba T et al, 1995</td>
<td>n=31 OSA patients; 12/31 with HTN</td>
<td>BP during sleep was lowered; no clear lowering of daytime BP on CPAP</td>
<td>2 wk</td>
<td>Daytime SBP and DBP reduced</td>
</tr>
<tr>
<td>Akashiba T et al, 1993</td>
<td>n=5 HTN OSA patients; RDI=78</td>
<td>Ambulatory BP cuff measurements</td>
<td>10 d</td>
<td></td>
</tr>
</tbody>
</table>

HTN indicates hypertension; CHF, congestive heart failure; UARS, upper airway resistance syndrome; REM, rapid eye movement; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
Patients were admitted to the University of California at San Diego Clinical Research Center for a confirmatory overnight polysomnography (Nihon Koden, model 4412p). We recorded the following parameters: central and occipital electroencephalogram, bilateral electro-oculogram, submental and tibialis anterior electromyogram, ECG, nasal/oral airflow using thermistor, and respiratory effort using chest and abdominal inductance belts. Oxygen saturation was recorded with a pulse oximeter (Biox 3740). Individuals whose RDI was >15 were considered to have OSA. On the next night, patients were randomized to receive either CPAP or placebo CPAP. Patients receiving CPAP underwent standard CPAP titration with the use of a Devilbis CPAP machine and a comfortably fitting mask. Pressure in the mask started at 2 cm H2O and was increased over the night by 2-cm H2O increments until CPAP pressure was set at 2 cm H2O and was not advanced. All mock titration night. They wore a special mask that had 5 one-range.

Most respiratory events were controlled with CPAP while the patient was in the supine position and in the second or third rapid eye movement sleep period or until a pressure of 20 cm had been reached. Further pressure titration was then done in increments of 1 cm H2O on the basis of the presence of apnea, hypopnea, or snoring associated with arousals. The titration was considered ended when both patient groups complied with the treatment. After 7 days of home treatment, patients’ ambulatory BP was again studied with the use of the Spacelabs ambulatory monitor.

Data were analyzed with repeated-measures ANOVA with the use of SPSS software. If a significant effect was found for time alone, it would imply that CPAP did not have a specific effect on BP. If there was a significant interaction of time and treatment, it would imply that the group receiving a particular treatment (presumably CPAP) had a differential response to that treatment over time.

Results

Table 2 summarizes the sample characteristics. Thirty-nine individuals were studied. Individuals randomized to the 2 treatments were comparable in age, pretreatment RDI, and screening systolic BP; however, patients randomized to receive CPAP were heavier (P<0.05). The mean mask pressure required among the CPAP group was 10.1 cm H2O; placebo CPAP patients all received CPAP at a pressure of 2 cm H2O administered through a mask with numerous air holes to produce a large air leak. Both patient groups complied equivalently with the CPAP treatment over the 1-week interval of home treatment (>5 hours per night for each group). Patients receiving CPAP demonstrated a significantly greater drop in RDI than was observed in patients assigned to the placebo CPAP group (time×CPAP interaction, P=0.001) (Table 2).

ABPM revealed a main effect for time on daytime mean arterial pressure (F=7.96, df=2, P=0.001) (Figure 1). The daytime BP of both groups declined equivalently over the 1-week trial (ie, there was no effect specific to the CPAP group per se). At nighttime, there was a time-by-group interaction such that the BP of patients receiving CPAP fell considerably more over time than the BP of patients assigned to placebo CPAP (F=3.62, df=2, P=0.032) (Figure 2).

Discussion

The treatment of sleep apnea is rapidly evolving. Medications have had limited value compared with weight loss, various surgical procedures, and CPAP.21 For the vast majority of patients, CPAP is an effective treatment of the apnea per se if the patient complies with the treatment. Our results suggest, however, that the effects of CPAP on BP are not so straightforward. Had we not administered a placebo version of CPAP, we would have concluded that CPAP has a robust BP-lowering effect. That conclusion is not strongly supported by our data. Whereas CPAP lowered daytime mean arterial pressure, so did placebo CPAP. There is very little acclimatization effect to wearing an ABPM cuff; that is, BP does not noticeably

![Figure 1. Effect of CPAP on daytime mean arterial pressure.](http://hyper.ahajournals.org/)

Mean arterial pressure was measured during daytime with ABPM before treatment (day 0), after 1 day, and after 7 days of treatment with either CPAP or placebo CPAP. There was a non-specific time effect for lowering BP across both treatments (P=0.001).
fall on a second 24-hour ABPM study. We interpret the uniform decrease of BP in our study to a nonspecific effect of treatment, ie, a placebo effect. Patients were observed closely by our research staff, and all patients used impressive-looking CPAP machinery while sleeping. The combination of professional attention and expectations from the machinery may well have lowered daytime BP. In this sense, the placebo effects of CPAP on BP join a long list of other treatments that have beneficial although nonspecific effects.

However, it is not accurate to attribute all of the effects of CPAP on BP to a placebo effect. We did observe a differential effect of CPAP on nocturnal BP. In the absence of the waking conscious awareness of the treatment (in which treatment had a beneficial effect on both groups), only the patients receiving effective CPAP lowered their nighttime BP.

We specifically examined weight and hypertension to assess whether our findings would materially change after controlling for these variables. Because of the difference in weight between the treatment and placebo groups, we repeated the analyses using body mass index as a covariate. The study still failed to reveal a specific time-by-treatment effect on BP lowering after controlling for BMI. We also reanalyzed the data using screening blood pressure (hypertension versus normotension) as a grouping factor to determine whether CPAP effects for only a 1-week interval because we were data beyond a 1-week trial. Our patients all had substantial time interval; indeed, Figure 1 suggests this, but we have no evidence to suggest that CPAP had a greater BP-lowering effect in hypertensive patients.

The study has a number of limitations. We examined CPAP effects for only a 1-week interval because we were uneasy about imposing a lengthy placebo CPAP treatment on patients who had OSA. It is possible that the BP-lowering effects of CPAP become even more apparent over a longer time interval; indeed, Figure 1 suggests this, but we have no data beyond a 1-week trial. Our patients all had substantial levels of apnea (average RDI was 48.1), but in other ways they were relatively healthy. We excluded patients with other major illnesses requiring treatment, such as those with congestive heart failure, a history of myocardial infarction, or morbid obesity. Perhaps such latter patients may obtain substantially greater benefits with CPAP treatment.

Nonetheless, our study provides a cautionary note, demonstrating the value and importance of a placebo arm in medical research. Even though CPAP is effective in treating apnea, whether it benefits daytime BP is not clear.

Acknowledgment
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References
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