Effects of Continuous Positive Airway Pressure Versus Supplemental Oxygen on 24-Hour Ambulatory Blood Pressure

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Abstract—Obstructive sleep apnea (OSA) is associated with recurrent episodes of nocturnal hypoxia and increased risk for development of systemic hypertension. Prior studies have been limited, however, in their ability to show reduction in blood pressure after continuous positive airway pressure (CPAP) therapy, and the effect of supplemental oxygen alone on blood pressure in OSA has not been evaluated. We performed a randomized, double-blind, placebo-controlled study comparing the effects of 2 weeks of CPAP versus sham-CPAP versus supplemental nocturnal oxygen on 24-hour ambulatory blood pressure in 46 patients with moderate-severe OSA. We found that 2 weeks of CPAP therapy resulted in a significant reduction in daytime mean arterial and diastolic blood pressure and nighttime systolic, mean, and diastolic blood pressure (all \( P < 0.05 \)). Although nocturnal supplemental oxygen therapy improved oxyhemoglobin saturation, it did not affect blood pressure. We conclude that CPAP therapy reduces both daytime and nighttime blood pressure in patients with OSA, perhaps through mechanisms other than improvement of nocturnal oxyhemoglobin saturation. (Hypertension. 2006;47:840-845.)

Key Words: apnea ■ blood pressure ■ oxygen

Obstructive sleep apnea (OSA) has been linked to a number of cardiovascular disorders, including coronary artery disease,2,3 cerebrovascular disease,4 cardiac arrhythmias,2 and sudden cardiac death.5 Patients with OSA not only experience dramatic swings in blood pressure during apneas and hypopneas at night,6 they are also at increased risk for daytime hypertension.7–28 Several different mechanisms have been proposed to explain this risk. Of these, heightened sympathetic activity17,29–34 and alterations in the renin-angiotensin-aldosterone system17,30 from exposure to recurrent nocturnal hypoxemia23,27,32,35–38 are the best supported.

Studies have shown varying ability of OSA therapy to lower blood pressure (BP).10,39–49 Some studies found a reduction only in nocturnal41,50 or in daytime BP44 with continuous positive airway pressure (CPAP) therapy. Several showed a decrease in both nocturnal and daytime BP with CPAP therapy,10,31,43–46,49,51,52 whereas other studies demonstrated no BP change.40,48,53,54

Several limitations exist in many of the prior studies that examined the effects of OSA treatment on BP. For instance, some studies used occasional BP measurements10,53 rather than 24-hour ambulatory BP monitoring (ABPM). The latter approach provides more detailed BP measurements and is of greater clinical and prognostic value.55–57 Other studies have lacked adequate CPAP placebo controls.10,31,43–46,49,51–54 Although some investigators have used an oral tablet as placebo,40,41 the substantial effort that patients make in using CPAP equipment may be more likely to elicit a placebo response or a nonspecific effect of therapy. Sham-CPAP, which is worn nightly like CPAP but delivers subtherapeutic pressure, is a preferable manner of performing placebo-controlled studies in OSA.58

Only 4 studies have been published to date that evaluated ambulatory BP response to sham-CPAP (or subtherapeutic CPAP) versus standard CPAP therapy. In one, Becker et al39 demonstrated dramatic reductions in mean arterial pressure (MAP) (≈10 mm Hg, day and night) with 9 weeks of CPAP versus subtherapeutic CPAP therapy. In another, Pepperell et al50 reported a more modest fall (≈2.5 mm Hg) in MAP (day and night) with 4 weeks of standard CPAP versus a 0.8-mm Hg rise with sham-CPAP therapy. However, in a third study, Barbe et al59 found no significant change in BP after 6 weeks of either sham- or standard CPAP therapy. Although these studies vary somewhat in their designs, all 3 allowed the subset of hypertensive patients in their studies to remain on antihypertensive medications. This makes their divergent results difficult to interpret, because use of antihypertensive medications has been reported by some authors as a positive predictor50 but by others...

Received November 15, 2005; first decision December 2, 2005; revision accepted January 24, 2006.

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Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000217128.41284.78

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a negative predictor of the potential blood pressure–lowering effects of CPAP therapy.

A fourth study, by Dimsdale et al,61 examined the effects of 1 week of CPAP versus sham-CPAP on OSA patients not on antihypertensives. That study demonstrated that, although 1 week of CPAP lowered nighttime BP, sham-CPAP was as effective as standard CPAP therapy in lowering daytime BP. One wonders, however, if the nonspecific effects of sham-CPAP might fade over time. This randomized study, therefore, was designed to examine the differential effects of 2 weeks of CPAP versus 2 weeks of sham-CPAP on 24-hour ambulatory BP in a group of patients with OSA who were not on antihypertensive medications. In addition, because recurrent nocturnal hypoxia is thought to have an integral role in the development of hypertension in OSA, a third treatment arm was added, using sham-CPAP with supplemental oxygen, to study the effects of nocturnal oxygen supplementation on 24-hour ambulatory BP.

Methods

Subjects
Subjects were recruited through public advertisements and word-of-mouth referral. Men and women between 25 and 65 years of age who were free from major illnesses other than hypertension and within 100% to 170% of ideal body weight (by Metropolitan Life tables)62 were evaluated. Subjects who had previously tried CPAP therapy or who had undergone pharyngeal surgery for OSA were excluded. All of the subjects provided written informed consent before study participation. The study protocol was approved by the University of California San Diego Human Research Protections Program.

Experimental Protocol
Subjects were first screened for OSA with an unattended home sleep study (Stardust home monitoring system, Respironics Inc). Those with an apnea-hypopnea index (AHI; average number of apneas plus hypopneas per hour of sleep) ≥20 were given a provisional diagnosis of OSA and eligible for further testing, including medical history, physical examination, and Epworth Sleepiness Scale questionnaire. Patients on antihypertensive medications were tapered off their medication over a supervised 3-week washout period. All of the subjects then underwent repeated BP screening (3 cuff measurements on each of 2 occasions) after resting seated for 5 minutes. Individuals whose BP was consistently >170/105 mm Hg were excluded from the protocol, placed back on their BP medications, and referred to their primary care physician for further therapy. ABPM (described below) was then performed for a 24-hour period on a weekday on an outpatient basis before treatment randomization.

Subjects were then admitted to the General Clinical Research Center (GCRC) for 2 nights. On the first night, all of the subjects underwent attended polysomnography to confirm the diagnosis and further assess the severity of their OSA. Individuals whose AHI was >15 during the attended polysomnogram were considered to have OSA and remained in the study. Subjects with OSA were randomized in a double-blind manner into 1 of 3 treatment groups: CPAP, placebo, and oxygen. On the second night, subjects randomized to the CPAP treatment group underwent a polysomnogram with standard CPAP titration. These subjects were allowed to fall asleep while on a CPAP of 4-cm H2O, then CPAP pressure was increased by 1- to 2-cm H2O increments until respiratory events were controlled with the patient supine through the second or third period of rapid eye movement sleep. Subjects randomized to the placebo and oxygen treatment groups underwent a mock titration night using room air (placebo group) or 3 L/min of supplemental oxygen (oxygen group) while using modified CPAP equipment that delivered <1 cm of H2O pressure. After the “titration” night, subjects were sent home with their assigned treatment equipment. Subsequent telephone calls and home visits ensured proper equipment setup and compliance.

On completion of the 2-week treatment period, while on their assigned therapy, subjects underwent another weekday outpatient 24-hour ABPM. They then returned to the General Clinical Research Center, where a final attended polysomnogram was performed with subjects still on their assigned therapy. All of the home CPAP units had a hidden compliance clock. The compliance data were downloaded at the end of the treatment period to determine average hours of use per night.

ABPM
Ambulatory BP was recorded using a Spacelabs model 90207 recorder. Once the cuff was appropriately sited, the skin borders were marked with ink so that the cuff could be repositioned in case of movement. The cuff was programmed to inflate every 15 minutes between 6:00 AM and 10:00 PM (“daytime”) and every 30 minutes between 10:00 PM and 6:00 AM (“nighttime”). Standard manufacturer criteria for artifact rejection were used in evaluating BP measures.

Polysomnography
Overnight polysomnography was recorded with a Grass Heritage (model PSG36-2), that recorded the following parameters: ECG, central and occipital electroencephalogram, bilateral electrooculogram, submental and tibialis anterior electromyogram, nasal airflow using a nasal cannula and pressure transducer, naso-oral airflow using a thermistor, and respiratory effort using chest and abdominal piezoelectric belts. Oxyhemoglobin saturation (SpO2) was monitored using a pulse oximeter (Biox 3740; Ohmeda). Sleep staging was scored according to the criteria of Kales and Rechtschaffen.63 Apneas were defined as decrements in airflow ≥90% from baseline for a period ≥10 seconds. Hypopneas were defined as decrements in airflow ≥50% but <90% from baseline for a period ≥10 seconds. The number of apneas and hypopneas per hour of sleep were calculated to obtain the AHI. Respiratory events were derived primarily from the nasal cannula-pressure transducer. The oxygen desaturation index (ODI) was defined as the total number of episodes of oxyhemoglobin desaturation ≥3% from the immediate baseline, ≥10 seconds but <3 minutes in duration, divided by the total sleep time.

Treatment Apparatus
The equipment used in all 3 of the treatment groups appeared identical, consisting of a CPAP unit (Aria LX CPAP System, Respironics Inc), a heated humidifier (Fisher and Pykel HC100), and an oxygen concentrator (Atlantic Healthcare Technologies Model 505). In the placebo and oxygen groups, the CPAP unit was modified as follows: the CPAP machine was set at 3-cm H2O pressure and a 3-mm-diameter pressure restrictor was placed downstream. A special nasal mask with 10 quarter-inch drilled holes was used to allow for adequate air exchange with the environment. Resultant CPAP pressures at the mask were 0.5-cm H2O on end-expiration, and 0-cm H2O on inspiration. The oxygen concentrators contained a hidden switch that allowed for delivery of 3 L/min of supplemental oxygen (fraction of inspired oxygen, 32% to 34% at the CPAP mask) for the oxygen group or room air for the CPAP and placebo groups. The noise level of the 3 treatment conditions was not perceptibly different.

Statistical Analysis
Data were analyzed using SPSS version 12.0 software (SPSS Inc). One-way ANOVA was used to evaluate for differences between groups in CPAP compliance rates and in baseline demographic characteristics. χ2 analysis was performed for baseline characteristics containing nominal data. Repeated-measures 2-way ANOVA was used to examine treatment group×time effects on polysomnographic measures (AHI, ODI, mean nocturnal SpO2, and mean level of SpO2 desaturation with respiratory events) and on ABPM measures (systolic, mean, and diastolic BP during night (10:00 PM to 6:00 AM) and day (6:00 AM to 10:00 PM)). When a significant group×time effect
Forty-six subjects were randomly assigned into 3 treatment groups. Table 1 summarizes the subjects’ baseline characteristics. The groups were comparable in age, body mass index, and diastolic BP, the CPAP group had a significantly higher mean nocturnal SpO2 and average SpO2 nadir during desaturations compared with the placebo group. Both of these groups also demonstrated significant reductions in ODI and AHI compared with their baseline values; however, the magnitude of change was smaller in the oxygen than the CPAP group and not enough to differentiate the former group from placebo.

The Figure shows the effect of treatment on the various 24-hour ambulatory BP parameters. After controlling for baseline systolic, mean, and diastolic BP values, there were significant time×treatment effects on 24-hour ambulatory systolic (F = 4.84; P = 0.01), mean (F = 5.45; P = 0.01), and diastolic (F = 4.45; P = 0.02) BP at nighttime and on mean (F = 5.34; P = 0.01) and diastolic (F = 3.64; P = 0.04) BP during daytime.

Post hoc analysis demonstrated that 2 weeks of CPAP therapy resulted in a 6-, 5-, and 4-mm Hg decline, respectively, in nighttime systolic, mean, and diastolic BP and
3-mm Hg declines in daytime mean and diastolic BP (all $P<0.05$). In the placebo group, there was a 3-mm Hg rise in nighttime systolic BP ($P<0.05$). In the oxygen group, no significant changes were observed in any of the BP parameters.

**Discussion**

Our study demonstrated that 2 weeks of CPAP therapy significantly lowered nighttime diastolic, mean, and systolic BP and daytime mean and diastolic BP in patients with OSA. A smaller (2 mm Hg) reduction in daytime systolic BP was observed with CPAP therapy but fell short of statistical significance. Whereas supplemental oxygen therapy successfully improved many indices of nocturnal SpO$_2$, it did not result in a lowering of daytime or nighttime BP. Two weeks of placebo-CPAP therapy did not result in a significant change in daytime BP and actually raised nighttime systolic BP.

Prior work from our laboratory demonstrated a decline of MAP only at nighttime from 1 week of CPAP versus sham-CPAP therapy. The similar reductions seen in the previous study in daytime MAP with both CPAP and sham-CPAP were thought to reflect a nonspecific or placebo effect, and it was hypothesized that this effect would likely fade over time. In keeping with this hypothesis, the current results demonstrate that 2 weeks of CPAP lowered daytime and nighttime BP, whereas the daytime-BP-lowering effects of sham-CPAP were not evident over the longer time course used in this study. Interestingly, sham-CPAP actually raised nocturnal SBP over the 2-week course of this study. Although not likely to be clinically significant over the short term, we speculate that this finding may be because of sleep disturbance and arousals that result from the use of noise-generating machinery and CPAP mask, without the usual benefits of effective OSA therapy.

Participants in the supplemental oxygen therapy arm of our study did not demonstrate any improvements in BP. This finding seems to contradict results from animal models of OSA that have suggested that development of daytime systemic hypertension is related to recurrent nocturnal hypoxia, as opposed to repeated arousals from sleep. Our findings also do not support prior human studies suggesting that oxygen desaturation, rather than frequency of arousals from sleep, is associated with higher odds ratios for systemic hypertension.

Prior experiments have demonstrated that BP after apneic events rises even when hypoxemia is blunted through oxygen administration and that CPAP, but not supplemental oxygen, can lower BP variability during sleep. Together, these results suggest that repeated oxyhemoglobin desaturation may be a necessary component for the development of hypertension in patients with OSA, but that improving SpO$_2$ alone, without treating airway obstruction and arousal, may not be enough to reverse these effects on BP.

Whereas this study showed a reduction of daytime mean and diastolic BP and all of the nighttime parameters with CPAP therapy, a significant reduction in daytime systolic pressure was not observed. These findings mirror those of Minemura et al., whose uncontrolled study demonstrated nighttime and daytime reductions in diastolic BP but only nighttime reduction in systolic BP with CPAP therapy. Some have suggested that OSA may predispose to both systolic and diastolic hypertension at night, but initially, or primarily, diastolic hypertension during the day. Thus, the lesser reduction of nighttime systolic BP with CPAP may reflect how OSA does not have as profound an effect on daytime systolic as it does on diastolic BP. Alternatively, it remains possible that a more significant decline in daytime systolic BP could take place over longer courses of therapy, because sympathetic nerve activity has been demonstrated (in an uncontrolled study) to decline for $\leq$1 year after the institution of CPAP. Nevertheless, a decline in systolic BP with CPAP therapy, even if limited to nighttime, may still have significant long-term implications, because nighttime systolic BP has proven to be an important predictor of risk for cardiovascular morbidity.

This study has several limitations. A heterogeneous group of OSA patients were included as participants. Subjects were of both genders, across a wide spectrum of ages and ethnic groups, had varying degrees of sleep apnea, and had a large spread in baseline BP. Although this heterogeneity meant that sample sizes were too small to permit meaningful subgroup analyses, the subjects were more reflective of, and, thus, more generalizable to, a typical patient population seen in a sleep clinic, who may receive counseling regarding potential BP effects of CPAP therapy. Further studies, containing larger sample sizes, may focus specifically on the BP effects of CPAP on hypertensive versus nonhypertensive patients with OSA.

Another potential limitation that must be considered when a treatment results in no significant change is whether the magnitude of the intervention (or sample size) was large enough to detect a change. Although supplemental oxygen was not as successful as CPAP therapy in improving all indices of nocturnal oxyhemoglobin desaturation, it did result in significant improvement in many measures. If correcting nocturnal oxygen desaturation alone was sufficient to reverse the effects of OSA on BP, one would expect at least a trend toward BP improvement in the oxygen therapy group. To the contrary, our results demonstrated either no change or a slight increase in BP with supplemental oxygen therapy.
References


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*Hypertension.* 2006;47:840-845; originally published online April 3, 2006;
doi: 10.1161/01.HYP.0000217128.41284.78

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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