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

Daniel Norman, José S. Loredo, Richard A. Nelesen, Sonia Ancoli-Israel, Paul J. Mills, Michael G. Ziegler and Joel E. Dimsdale

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

Print ISSN: 0194-911X. Online ISSN: 1524-4563

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

Daniel Norman, José S. Loredo, Richard A. Nelesen, Sonia Ancoli-Israel, Paul J. Mills, Michael G. Ziegler, Joel E. Dimsdale

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*s <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,[1] 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 activity[17,29–34] and alterations in the renin-angiotensin-aldosterone system[17,30] from exposure to recurrent nocturnal hypoxemia[7,23,27,32,33,35–38] 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 nocturnal[41,50] or in daytime BP[44] 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 measurements[10,53] 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.[10,31,43–46,48,49,51–54] 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 al[39] 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 al[50] 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 al[59] 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 predictor[50] but by others

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

From the Departments of Medicine (D.N., J.S.L., M.G.Z.), and Psychiatry (R.A.N., S.A.-I., P.J.M., J.E.D.), School of Medicine, University of California San Diego, San Diego, Calif.

Correspondence to Daniel Norman, Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California San Diego Medical Center, 200 West Arbor Dr, San Diego, CA 92103-8383. E-mail d1norman@ucsd.edu

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

a negative predictor[60] 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.[61] 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 Gillin Laboratory of Sleep and Chronobiology 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 H_2O, then CPAP pressure was increased by 1- to 2-cm H_2O 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 H_2O 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 electomyogram, 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 (Spo_2) 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 (Alliance, Healthdyne Technologies Model 505). In the placebo and oxygen groups, the CPAP unit was modified as follows: the CPAP machine was set at 3-cm H_2O 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 H_2O on end-expiration, and 0-cm H_2O 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. χ^2 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 Spo_2, and mean level of Spo_2 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

TABLE 1. Subject Characteristics at Baseline

Factor	Placebo (n=15)	CPAP (n=18)	Oxygen (n=13)	*P* Value
Age, y	49.3±2.7	49.7±2.5	44.2±2.4	NS
BMI, kg/m^2	29.9±1.3	31.5±1.4	29.5±1.3	NS
Epworth sleepiness scale	12.0±1.7	12.0±1.3	12.2±1.5	NS
AHI (from home screening device), events/h	59.2±9.3	66.1±8.8	56.6±9.4	NS
SBP, mm Hg	122.5±3.3	135.1±3.8	132.5±3.6	0.042*
MAP, mm Hg	91.2±2.5	98.1±2.5	94.9±2.2	NS
DBP, mm Hg	75.6±2.5	79.6±1.7	76.0±1.7	NS
Gender, n (%)				
Male	13 (87)	15 (83)	9 (69)	NS
Female	2 (13)	3 (17)	4 (31)	NS
Ethnicity, n (%)				
White	10 (67)	11 (61)	8 (62)	NS
Black	1 (7)	2 (11)	3 (23)	NS
Hispanic	2 (13)	2 (11)	1 (8)	NS
Asian	0 (0)	2 (11)	1 (8)	NS
Other	2 (13)	1 (6)	0 (0)	NS

Data are presented as either No. of subjects and frequencies (%) or mean±SE. BMI indicates body mass index. SBP and DBP, average systolic and diastolic BP, respectively, obtained from each patient during initial outpatient screening evaluation; NS, not significant. *P* values are obtained from 1-way ANOVA or χ^2 analysis.

*CPAP group had significantly higher SBP at baseline than placebo group. Groups did not significantly differ at baseline in other characteristics.

was observed, post hoc 1-way ANOVA was performed to look for significant effects over time within each treatment group.

Despite randomization, the groups differed in their baseline systolic BPs (see Table 1). Therefore, we further analyzed the data using repeated-measures 2-way ANCOVA. Thus we controlled for baseline (eg, measured by manual cuff during initial outpatient subject screening) systolic, mean, or diastolic BP when we looked for the respective group×time effect on 24-hour ambulatory systolic, mean, and diastolic BP. In all cases, $P<0.05$ was used as the cutoff value for statistical significance.

Results

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, pretreatment AHI, Epworth Sleepiness Scale scores, gender, and ethnicity. Although the groups did not differ significantly in their mean arterial and diastolic BP, the CPAP group had higher systolic BP than the placebo group at the time of initial screening ($P=0.042$).

The rate of compliance with therapy among the 3 treatment groups was similar (6.0±2.4, 6.7±1.2, and 6.5±1.2 hours/night for the placebo, CPAP and oxygen groups, respectively; $P=0.315$). Table 2 demonstrates the measures of oxygenation pretherapy and post-therapy from attended inpatient polysomnography. The groups did not differ from each other in any of the measures of oxygenation before initiation of therapy. After treatment, both the CPAP and oxygen groups had a significantly higher mean nocturnal Spo_2 and average Spo_2 nadir during desaturations compared with the placebo group. Both of these groups also demonstrated significant

TABLE 2. Measures of Oxygenation Pretreatment and Posttreatment From Attended Inpatient Polysomnography

Measure	Time	Placebo	CPAP	Oxygen
AHI (from attended study), events/h	PreTx	53.9±29.8	66.1±29.1	60.7±29.6
	PostTx	50.1±32.1	3.4±3.0*†	43.6±32.8*‡
ODI, events/h	PreTx	25.9±27.7	38.3±33.9	34.8±32.1
	PostTx	31.9±33.0	1.3±1.9*†	15.7±24.8*
% time in bed with SpO_2 <90%	PreTx	3.5±7.2	7.5±14.6	3.2±6.3
	PostTx	3.3±4.5	0.1±0.3†	1.1±2.9
Mean nocturnal SpO_2	PreTx	94.0±2.9	92.7±4.5	93.6±4.8
	PostTx	92.1±3.8	95.6±3.1†	96.2±3.3*†
Average SpO_2 nadir during desaturations	PreTx	89.9±5.3	88.4±5.8	90.1±5.8
	PostTx	90.1±3.0	93.6±3.1*†	93.2±3.2*†

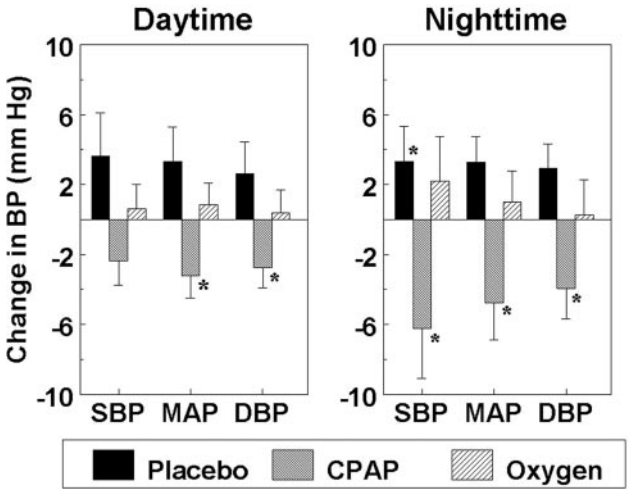
Data are presented as mean±SD. PreTx indicates pretreatment; PostTx, posttreatment. The groups did not differ from each other on any of the above parameters before therapy.

*$P<0.05$ compared with pretreatment value; †$P<0.05$ compared with placebo group; ‡$P<0.05$ compared with CPAP group.

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



Change in 24-hour ABPM in each of the 3 treatment groups after 2 weeks of therapy. Daytime BP was measured from 6:00 AM to 10:00 PM. Nighttime BP values were measured from 10:00 PM to 6:00 AM. Change is measured from mean pretreatment minus post-treatment values. Bars represent mean±SE. *Significant changes over time ($P<0.05$).

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.[61] 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,[64–66] as opposed to repeated arousals from sleep.[67,68] 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.[69]

Prior experiments have demonstrated that BP after apneic events rises even when hypoxemia is blunted through oxygen administration[70,71] and that CPAP, but not supplemental oxygen, can lower BP variability during sleep.[72] 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,[31] 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,[73] or primarily,[74] diastolic hypertension during the day. Thus, the lesser reduction of daytime 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 ≤1 year after the institution of CPAP.[75] 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.[76]

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 (but not statistically significant) increase in BP with supplemental oxygen therapy. Although we cannot completely rule out the possibility that a threshold of nocturnal Spo_2 exists, beyond which improvement in BP would start to appear, these findings argue that a larger sample size would not result in more robust BP effects of supplemental oxygen therapy.

Perspectives

Our results confirm the BP-lowering effects of CPAP therapy for OSA and suggest that potential improvements in BP could be added to the long list of motivating factors for patients to pursue CPAP therapy. In addition, they raise mechanistic questions regarding the complex link between nocturnal hypoxia and persistent BP elevations in OSA. Additional studies may be directed to further examining this link, as well as to the effects of CPAP therapy over longer periods of time.

Acknowledgments

This work was supported by National Institutes of Health grants HL 44915, K23 HL04056, and RR00827.

References

1. Doherty LS, Kiely JL, Swan V, McNicholas WT. Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest*. 2005;127:2076–2084.
2. Koehler U, Dubler H, Glaremin T, Junkermann H, Lubbers C, Ploch T, Peter JH, Pomykaj T, von Wichert P. Nocturnal myocardial ischemia and cardiac arrhythmia in patients with sleep apnea with and without coronary heart disease. *Klin Wochenschr*. 1991;69:474–482.
3. Schafer H, Koehler U, Ewig S, Hasper E, Tasci S, Luderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. *Cardiology*. 1999;92:79–84.
4. McArdle N, Riha RL, Vennelle M, Coleman EL, Dennis MS, Warlow CP, Douglas NJ. Sleep-disordered breathing as a risk factor for cerebrovascular disease: a case-control study in patients with transient ischemic attacks. *Stroke*. 2003;34:2916–2921.
5. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med*. 2005;352:1206–1214.
6. Morgan BJ, Dempsey JA, Pegelow DF, Jacques A, Finn L, Palta M, Skatrud JB, Young TB. Blood pressure perturbations caused by subclinical sleep-disordered breathing. *Sleep*. 1998;21:737–746.
7. Akashiba T, Kurashina K, Minemura H, Yamamoto H, Horie T. Daytime hypertension and the effects of short-term nasal continuous positive airway pressure treatment in obstructive sleep apnea syndrome. *Intern Med*. 1995;34:528–532.
8. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A. Association of hypertension and sleep-disordered breathing. *Arch Intern Med*. 2000;160:2289–2295.
9. Carlson JT, Hedner JA, Ejnell H, Peterson LE. High prevalence of hypertension in sleep apnea patients independent of obesity. *Am J Respir Crit Care Med*. 1994;150:72–77.
10. Dhillon S, Chung SA, Fargher T, Huterer N, Shapiro CM. Sleep apnea, hypertension, and the effects of continuous positive airway pressure. *Am J Hypertens*. 2005;18:594–600.
11. Dart RA, Gregoire JR, Gutterman DD, Woolf SH. The association of hypertension and secondary cardiovascular disease with sleep-disordered breathing. *Chest*. 2003;123:244–260.
12. Fletcher EC. The relationship between systemic hypertension and obstructive sleep apnea: facts and theory. *Am J Med*. 1995;98:118–128.
13. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med*. 1985;103:190–195.
14. Garcia-Rio F, Pino JM, Alonso A, Arias MA, Martinez I, Alvaro D, Villamor J. White coat hypertension in patients with obstructive sleep apnea-hypopnea syndrome. *Chest*. 2004;125:817–822.
15. Hla KM, Young TB, Bidwell T, Palta M, Skatrud JB, Dempsey J. Sleep apnea and hypertension. A population-based study. *Ann Intern Med*. 1994;120:382–388.
16. Isaksson H, Svanborg E. Obstructive sleep apnea syndrome in male hypertensives, refractory to drug therapy. Nocturnal automatic blood pressure measurements–an aid to diagnosis? *Clin Exp Hypertens A*. 1991;13:1195–1212.
17. Hoffmann M, Bybee K, Accurso V, Somers VK. Sleep apnea and hypertension. *Minerva Med*. 2004;95:281–290.
18. Jeong DU, Dimsdale JE. Sleep apnea and essential hypertension: a critical review of the epidemiological evidence for co-morbidity. *Clin Exp Hypertens A*. 1989;11:1301–1323.
19. Kiselak J, Clark M, Pera V, Rosenberg C, Redline S. The association between hypertension and sleep apnea in obese patients. *Chest*. 1993;104:775–780.
20. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkila K. Snoring as a risk factor for hypertension and angina pectoris. *Lancet*. 1985;1:893–896.
21. Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J*. 1984;108:373–376.
22. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. *BMJ*. 2000;320:479–482.
23. Lavie P, Yoffe N, Berger I, Peled R. The relationship between the severity of sleep apnea syndrome and 24-h blood pressure values in patients with obstructive sleep apnea. *Chest*. 1993;103:717–721.
24. Millman RP, Redline S, Carlisle CC, Assaf AR, Levinson PD. Daytime hypertension in obstructive sleep apnea. Prevalence and contributing risk factors. *Chest*. 1991;99:861–866.
25. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*. 2000;283:1829–1836.
26. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med*. 2000;342:1378–1384.
27. Phillips BG, Somers VK. Hypertension and obstructive sleep apnea. *Curr Hypertens Rep*. 2003;5:380–385.
28. Narkiewicz K, Wolf J, Lopez-Jimenez F, Somers VK. Obstructive sleep apnea and hypertension. *Curr Cardiol Rep*. 2005;7:435–440.
29. Fletcher EC. Sympathetic over activity in the etiology of hypertension of obstructive sleep apnea. *Sleep*. 2003;26:15–19.
30. Goodfriend TL, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: theory and therapy. *Hypertension*. 2004;43:518–524.
31. Minemura H, Akashiba T, Yamamoto H, Akahoshi T, Kosaka N, Horie T. Acute effects of nasal continuous positive airway pressure on 24-hour blood pressure and catecholamines in patients with obstructive sleep apnea. *Intern Med*. 1998;37:1009–1013.
32. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens*. 1997;15:1613–1619.
33. Phillips BG, Somers VK. Neural and humoral mechanisms mediating cardiovascular responses to obstructive sleep apnea. *Respir Physiol*. 2000;119:181–187.
34. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96:1897–1904.
35. Lavie P, Silverberg D, Oksenberg A, Hoffstein V. Obstructive sleep apnea and hypertension: from correlative to causative relationship. *J Clin Hypertens*. 2001;3:296–301.
36. Loredo JS, Clausen JL, Nelesen RA, Ancoli-Israel S, Ziegler MG, Dimsdale JE. Obstructive sleep apnea and hypertension: are peripheral chemoreceptors involved? *Med Hypotheses*. 2001;56:17–19.
37. Mendelson WB. Sleepiness and hypertension in obstructive sleep apnea. *Chest*. 1992;101:903–909.
38. Pankow W, Nabe B, Lies A, Becker H, Kohler U, Kohl FV, Lohmann FW. Influence of sleep apnea on 24-hour blood pressure. *Chest*. 1997;112:1253–1258.
39. Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. *Circulation*. 2003;107:68–73.
40. Engleman HM, Gough K, Martin SE, Kingshott RN, Padfield PL, Douglas NJ. Ambulatory blood pressure on and off continuous positive airway pressure therapy for the sleep apnea/hypopnea syndrome: effects in "non-dippers". *Sleep*. 1996;19:378–381.
41. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;163:344–348.
42. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized, controlled trial. *Sleep*. 2004;27:934–941.
43. Hla KM, Skatrud JB, Finn L, Palta M, Young T. The effect of correction of sleep-disordered breathing on BP in untreated hypertension. *Chest*. 2002;122:1125–1132.
44. Jennum P, Wildschiodtz G, Christensen NJ, Schwartz T. Blood pressure, catecholamines, and pancreatic polypeptide in obstructive sleep apnea with and without nasal Continuous Positive Airway Pressure (nCPAP) treatment. *Am J Hypertens*. 1989;2:847–852.
45. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, Bradley TD. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. *Eur Respir J*. 2003;21:241–247.
46. Lies A, Nabe B, Pankow W, Kohl FV, Lohmann FW. Hypertension and obstructive sleep apnea. Ambulatory blood pressure monitoring before and with nCPAP-therapy. *Z Kardiol*. 1996;85(suppl 3):140–142.
47. Berger M, Oksenberg A, Silverberg DS, Arons E, Radwan H, Iaina A. Avoiding the supine position during sleep lowers 24 h blood pressure in obstructive sleep apnea (OSA) patients. *J Hum Hypertens*. 1997;11:657–664.
48. Marrone O, Salvaggio A, Bonsignore MR, Insalaco G, Bonsignore G. Blood pressure responsiveness to obstructive events during sleep after chronic CPAP. *Eur Respir J*. 2003;21:509–514.

49. Mayer J, Becker H, Brandenburg U, Penzel T, Peter JH, von Wichert P. Blood pressure and sleep apnea: results of long-term nasal continuous positive airway pressure therapy. *Cardiology*. 1991;79:84–92.
50. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. *Lancet*. 2002;359: 204–210.
51. Sanner BM, Tepel M, Markmann A, Zidek W. Effect of continuous positive airway pressure therapy on 24-hour blood pressure in patients with obstructive sleep apnea syndrome. *Am J Hypertens*. 2002;15: 251–257.
52. Suzuki M, Otsuka K, Guilleminault C. Long-term nasal continuous positive airway pressure administration can normalize hypertension in obstructive sleep apnea patients. *Sleep*. 1993;16:545–549.
53. Monasterio C, Vidal S, Duran J, Ferrer M, Carmona C, Barbe F, Mayos M, Gonzalez-Mangado N, Juncadella M, Navarro A, Barreira R, Capote F, Mayoralas LR, Peces-Barba G, Alonso J, Montserrat JM. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. *Am J Respir Crit Care Med*. 2001;164:939–943.
54. Saarelainen S, Hasan J, Siitonen S, Seppala E. Effect of nasal CPAP treatment on plasma volume, aldosterone and 24-h blood pressure in obstructive sleep apnoea. *J Sleep Res*. 1996;5:181–185.
55. Krakoff LR. Ambulatory blood pressure monitoring can improve cost-effective management of hypertension. *Am J Hypertens*. 1993;6: 220S–224S.
56. White WB, Schulman P, McCabe EJ, Dey HM. Average daily blood pressure, not office blood pressure, determines cardiac function in patients with hypertension. *JAMA*. 1989;261:873–877.
57. Verdecchia P. Prognostic value of ambulatory blood pressure: current evidence and clinical implications. *Hypertension*. 2000;35:844–851.
58. Farre R, Hernandez L, Montserrat JM, Rotger M, Ballester E, Navajas D. Sham continuous positive airway pressure for placebo-controlled studies in sleep apnoea. *Lancet*. 1999;353:1154.
59. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agusti AG. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. a randomized, controlled trial. *Ann Intern Med*. 2001;134:1015–1023.
60. Borgel J, Sanner BM, Keskin F, Bittlinsky A, Bartels NK, Buchner N, Huesing A, Rump LC, Mugge A. Obstructive sleep apnea and blood pressure: interaction between the blood pressure-lowering effects of positive airway pressure therapy and antihypertensive drugs. *Am J Hypertens*. 2004;17:1081–1087.
61. Dimsdale JE, Loredo JS, Profant J. Effect of continuous positive airway pressure on blood pressure: a placebo trial. *Hypertension*. 2000;35: 144–147.
62. Metropolitan Life Foundation. Metropolitan height and weight tables. *Stat Bull Metop Insur Co.* 1983;64.
63. Kales A, Rechtschaffen A, University of California Los Angeles. Brain Information Service. National Institute of Neurological Diseases and Blindness. Neurological Information Network. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Bethesda, MD: National Institute of Neurological Diseases and Blindness, Neurological Information Network; 1968.
64. Fletcher EC, Lesske J, Culman J, Miller CC, Unger T. Sympathetic denervation blocks blood pressure elevation in episodic hypoxia. *Hypertension*. 1992;20:612–619.
65. Fletcher EC, Lesske J, Qian W, Miller CC, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension*. 1992;19:555–561.
66. Lesske J, Fletcher EC, Bao G, Unger T. Hypertension caused by chronic intermittent hypoxia–influence of chemoreceptors and sympathetic nervous system. *J Hypertens*. 1997;15:1593–1603.
67. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. *J Clin Invest*. 1997;99:106–109.
68. Bao G, Metreveli N, Fletcher EC. Acute and chronic blood pressure response to recurrent acoustic arousal in rats. *Am J Hypertens*. 1999;12: 504–510.
69. Redline S, Min N, Shahar E, Rapoport D, O'Connor G. Polysomnographic predictors of blood pressure and hypertension: is one index best? *Sleep*. 2005;28:1122–1130.
70. Garpestad E, Parker JA, Katayama H, Lilly J, Yasuda T, Ringler J, Strauss HW, Weiss JW. Decrease in ventricular stroke volume at apnea termination is independent of oxygen desaturation. *J Appl Physiol*. 1994; 77:1602–1608.
71. Ringler J, Basner RC, Shannon R, Schwartzstein R, Manning H, Weinberger SE, Weiss JW. Hypoxemia alone does not explain blood pressure elevations after obstructive apneas. *J Appl Physiol*. 1990;69: 2143–2148.
72. Ali NJ, Davies RJ, Fleetham JA, Stradling JR. The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. *Chest*. 1992;101:1526–1532.
73. Sharabi Y, Scope A, Chorney N, Grotto I, Dagan Y. Diastolic blood pressure is the first to rise in association with early subclinical obstructive sleep apnea: lessons from periodic examination screening. *Am J Hypertens*. 2003;16: 236–239.
74. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. *Thorax*. 2000;55:736–740.
75. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. *Circulation*. 1999;100: 2332–2335.
76. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.