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SCIENTIFIC INVESTIGATIONS

Effects of Nocturnal Continuous Positive Airway Pressure Therapy in Patients with Resistant Hypertension and Obstructive Sleep Apnea

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Study Objective: To examine the long-term effects of continuous positive airway pressure (CPAP) therapy on blood pressure (BP) in patients with obstructive sleep apnea and resistant hypertension.

Methods: Study subjects were 98 patients with obstructive sleep apnea syndrome and hypertension who had 3 or more documented daytime BP measurements taken within 3 months of enrollment and every 3 months after CPAP initiation for 1 year. Resistant hypertension was defined as daytime BP of at least 140 mm Hg systolic or 90 mm Hg diastolic, despite the use of 3 or more antihypertensive medications. Patients in the resistant hypertension group (n = 42) were compared with subjects with controlled hypertension (n = 56).

Results: Mean difference in mean arterial pressure was -5.6 (95% confidence interval [CI] -2.0 to -8.7 mm Hg; p = 0.03) in the resistant group and -0.8 mm Hg (95% CI -2.9 to 3.3 mm Hg; p = 0.53) in patients with controlled BP at the end of follow up period. CPAP permitted de-escalation of antihypertensive treatment in 71% of subjects with resistant hypertension but did not significantly alter the antihypertensive regimen in the controlled group. Multivariate regression analysis showed that baseline BP (odds ratio 5.4, 95% CI 2.3 to 8.9; p = 0.01) and diuretic therapy (odds ratio = 3.2, 95% CI 1.8 to 6.1; p = 0.02), but not apnea-hypopnea index or hours of CPAP use, were independently associated with a decrease in mean arterial pressure after 12 months of CPAP therapy.

Conclusion: In this observational study, CPAP was associated with different effects on blood pressure control in hypertensive patients with sleep apnea. A beneficial response to CPAP therapy was found mainly in subjects with the most severe hypertensive disease.

Keywords: Sleep apnea, CPAP, hypertension, resistant

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Several studies have confirmed the relationship between obstructive sleep apnea syndrome (OSAS) and hypertension.[1,5] This relationship has long been recognized and has been attributed to the effects of hypoxemia,[6,8] hemodynamic effects of intrathoracic pressure changes,[9,10] interruptions in respiration,[11,12] or to disruption of sleep.[13,14,15]

Clinical trials of continuous positive airway pressure (CPAP) represent another line of investigation into the causal role of sleep apnea in hypertension.[16] Several studies have shown that CPAP reduces sympathetic activity,[17,18] decreases production of free-oxygen radicals and circulating levels of some markers of inflammation,[19,20] and reverses the endothelial dysfunction associated with OSAS.[21] Therefore, hypothetically, CPAP should improve blood pressure (BP) control in patients with OSAS. In recent years, conflicting results from several clinical studies[22,23,24,25] have shown either a clear improvement or only minor but insignificant reductions in BP measurements. However, most of these studies enrolled a relatively small number of participants or did not examine the long-term effects of CPAP therapy on BP in patients with OSAS. To date, there is still no clear agreement whether long-term CPAP therapy improves BP control in patients with OSAS and hypertension, and there is little evidence that the use of nocturnal positive pressure therapy can affect BP in patients suffering from OSA and resistant hypertension.

In this study, we examined whether treating OSA can lower BP in patients who remain hypertensive despite medical therapy. We also investigated whether CPAP therapy affects antihypertensive treatment among patients who are using CPAP for sleep disordered breathing.

METHODS

Study Design

This was a retrospective chart review study. We reviewed the medical records of all patients who had a polysomnography with CPAP study at the Veteran Affairs Medical Center in Oklahoma City and the University of Oklahoma Health Sciences Center.

Inclusion criteria were age at least 18 years of age, a diagnosis of OSAS, a history of hypertension on drug therapy, and 3 or more documented daytime BP measurements obtained within 3 months of enrollment and every 3 months for 6 months

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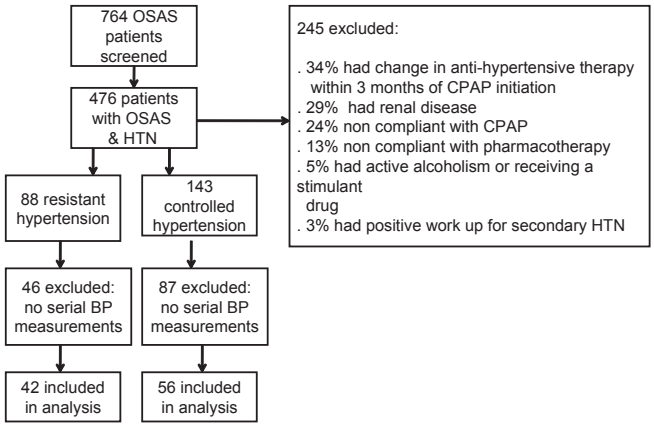

Figure 1—Enrollment chart. Patients may have had more than 1 reason for exclusion. OSAS refers to obstructive sleep apnea; BP, blood pressure; CPAP, continuous positive airway pressure; HTN, hypertension.

and then 1 year from CPAP initiation. Resistant hypertension was defined as a daytime blood pressure of at least 140 mm Hg systolic or at least 90 mm Hg diastolic, despite stable use of a combination of 3 or more antihypertensive medications. BP measurements were obtained from noninvasive measurements using a sphygmomanometer performed during routine examinations and monitoring of screened subjects.

Exclusion criteria were a documented history of noncompliance with drug treatment or CPAP therapy; use of medications that can raise BP; presence of any secondary form of hypertension, including renal insufficiency (defined as a serum creatinine level of at least 1.50 mg/dL); presence of renal artery stenosis; or positive results from a hormone work-up for secondary hypertension (defined as abnormal urine or serum catecholamine levels, plasma cortisol, rennin, aldosterone, or thyroid function tests). Other exclusion criteria were sustained excessive alcohol use and significant modification in drug regimen within 3 months of the study.

Sleep Studies

The diagnosis of OSAS was based on standard polysomnography performed using standard techniques and scoring criteria. Obstructive sleep apnea was defined as an apnea-hypopnea index (AHI) of at least 5 events per hour. Arousals were defined according to the recommendations of the American Sleep Disorders Association Atlas task force.[26] Sleep data were staged according to the system of Rechtschaffen and Kales.[27]

Data Analysis

Demographic characteristics, polysomnography data, comorbidities, and medications were recorded. Two groups of patients were identified at baseline. The first group consisted of patients with controlled hypertension on 2 or fewer drugs, whereas the second group included patients with resistant hypertension, as defined above. The primary outcome variable was change in mean arterial pressure at the end of the follow-up period. Secondary outcomes measured were change in systolic and diastolic BP as well as antihypertensive treatment among different patient groups at the end of follow-up period.

Statistical software (version 4.0; JMP; Cary, NC) was used for data processing and statistical analysis. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as a percentage. A 2-tailed *t* test for independent samples or a χ^2 test was used to compare baseline variables in the 2 groups. Changes in BP within groups were assessed using the paired t test.

Finally we constructed a multivariate logistic regression model to predict variables associated with change in BP in hypertensive patients. The dependent categorical variable was a decrement of 10% or more of the mean arterial pressure at 12 months, compared with baseline, whereas independent variables included in the model were age, comorbidities, weight change, medication use, baseline mean arterial blood pressure, baseline AHI, and hours of CPAP use.

RESULTS

Seven hundred sixty-four patients were screened for entry into the study. Ninety-eight subjects were found to be eligible after meeting the inclusion and exclusion criteria (Figure 1). Of those, 42 patients had resistant hypertension, as defined in the methods. Demographic characteristics and polysomnography data were similar in the two groups of patients. Patients with resistant hypertension (n = 42) had higher arterial pressure measurements and were receiving more antihypertensive agents, as was expected (Table 1).

The box and whisker plots in Figure 2 illustrate that, in subjects with resistant hypertension, median mean arterial pressure and systolic BP moved toward lower values at 180 days, with a significant trend continuing at 12 months, whereas patients with controlled hypertension (n = 56) demonstrated no significant change over the same time period (Figure 3). No significant difference in diastolic measurements was seen in either group of patients. Mean difference in mean arterial pressure was -5.6 (95% confidence interval [CI] -2.0 to -8.7 mm Hg; p = .03) in the resistant hypertension group and -0.8 mm Hg (95% CI -2.9 to 3.3 mm Hg; p = .53) in patients with well-controlled BP at baseline. A trend toward a difference in the use of antihypertensive drugs was seen in the 2 groups of patients at end of the follow-up period (Table 2). In subjects with resistant hypertensive disease (n = 42), the antihypertensive drug regimen was unaltered in 12 patients (29%) but modified in 30 subjects (71%) by either dose reduction (n = 12) or by discontinuing 1 or more drugs (n = 18). Patients with controlled hypertension showed an overall stability in their treatment regimen. Only 6 patients (10%) required either escalation (n = 2) or change in their treatment (n = 4). Interestingly enough, 5 out of 14 subjects who were treated with a single agent at baseline were not taking any antihypertensive drugs at 12 months.

The results of multivariate regression analysis showed that predictors of a decrease in mean arterial pressure by 10% at 12 months were hypertension severity at baseline (odds ratio [OR] 5.4, 95% CI 2.3 to 8.9; p = 0.01) and diuretic therapy (OR = 3.2, 95% CI 1.8 to 6.1; p = 0.02) but not baseline AHI (OR = 1.4, 95% CI 0.60 to 3.8; p = 0.35) or hours of CPAP use (OR = 0.4, 95% CI 0.9 to 2.2; p = 0.42)

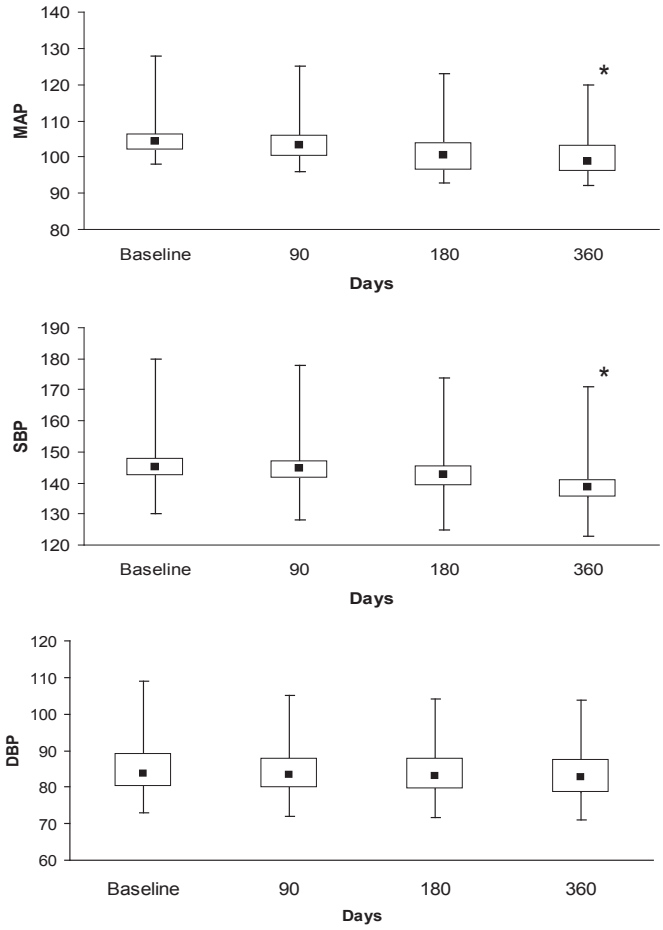

Figure 2—Box whisker plots showing a trend in blood pressure measurements in patients with resistant hypertension. MAP refers to mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure. *p < 0.05 compared with baseline.

Table 1—Patient Characteristics at Baseline

	Controlled hypertension (n = 56)	Resistant hypertension (n = 42)	p Value
Age, y	56.1 ± 1.4	61.8 ± 8.9	NS
BMI, kg/m^2	37.7 ± 7.1	38.5 ± 10.2	NS
Men/women, no.	54/2	41/1	NS
Smoker, no. (%)	12 (23)	10 (21)	NS
Co-occurring medical condition, no. (%)			
Diabetes	14 (25)	9 (21)	NS
Dyslipidemia	19 (34)	15 (38)	NS
COPD	8 (14)	5 (12)	NS
CAD	13 (23)	13 (31)	NS
ESS, score	12.7 ± 6.0	13.0 ± 6.5	NS
Creatinine level, mg/dL	1.02 ± 0.4	1.04 ± 0.35	NS
AHI, no./h	58.8 ± 32.2	60.1 ± 36.2	NS
CPAP use, h	6.1 ± 0.9	6.5 ± 1.2	NS
Blood pressure, mm Hg			
Systolic	128 ± 8.3	146 ± 8.4	0.03
Diastolic	79.8 ± 6.4	84.8 ± 7.2	0.06
Mean arterial	96.2 ± 5.7	105 ± 5 .7	0.02
Antihypertensive use, no. (%)			
ACE inhibitor	25 (44)	37 (88)	0.01
Diuretic	30 (53)	33 (78)	0.02
β blocker	29 (52)	27 (64)	0.01
Calcium-channel blocker	10 (18)	18 (43)	0.02
Other agent	3 (5)	9 (21)	0.03
Antihypertensive drugs[a]	1.5 ± 0.5	3.4 ± 0.8	0.01
Follow-up, days	368 ± 25	344 ± 32	NS

Data are presented as mean ± SD, unless otherwise indicated. BMI refers to body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; ACE, angiotensin converting enzyme inhibitor. [a]Antihypertensive drugs refers to the number of drugs used per person.

DISCUSSION

Several trials have investigated the effect of CPAP on BP in patients with OSAS. CPAP has been reported to lower nighttime and daytime BP in hypertensive individuals with OSAS.[28] The use of CPAP therapy was also been associated with reduction in systolic and, to a lesser extent, diastolic BP in patients with resistant hypertension after 8 weeks of therapy.[29] Conversely, Campos-Rodriguez and colleagues reported no significant changes in systolic, diastolic, daytime, or nighttime BP in patients with well-controlled hypertension.[30] More recently, investigators from the same group followed 55 hypertensive patients with sleep apnea for 24 months after CPAP initiation.[31] A modest but statistically significant decrease in mean arterial pressure (-4.4; 95% CI, -7.9 to -0.9 mm Hg) at the end of follow-up period was observed on an intention-to-treat analysis. Noting that hypertension was relatively well controlled with drug therapy in this cohort of patients, the researchers found that the subjects with higher baseline BP and better compliance with CPAP showed the most significant improvement with treatment.

In this retrospective study, we provide several new observations on the effect of CPAP therapy in patients with OSAS and hypertension. First, the use of CPAP therapy was accompanied by a reduction in daytime BP in patients with resistant hypertension; this reduction was first apparent at 6 months after treatment initiation and was sustained after 12 months of therapy. Second, CPAP therapy permitted deescalation of antihypertensive drug therapy in a significant proportion of patients with resistant hypertension. Third, the effects of CPAP therapy on BP regulation appear to be less noticeable in hypertensive patients controlled on drug regimen.

This study differs from the previous investigations because we examined specifically the long-term effect of CPAP therapy in a particular group of patients with hypertension and found a different effect of CPAP on BP control in patients with resistant versus well-controlled hypertension. We did not observe a measurable significant change in arterial pressure after 3 months of CPAP had elapsed in patients with resistant hypertension. These results are consistent with the findings by Campos-Rodriguez and colleagues in their 2 studies because achieving a significant reduction in BP may take longer than a few months. This could be explained by the effect of CPAP on the mechanisms underlying hypertension. Although, the reversal of sustained sympathetic activation may be seen shortly after CPAP application, control of other neuronal, humoral,

Table 2—Antihypertensive Therapy and Body Mass Index at Baseline and 1 Year After Initiation of CPAP

	Controlled Hypertension		Resistant Hypertension	
Antihypertensive agent use, no (%)	**Baseline**	**12 months**	**Baseline**	**12 months**
ACE inhibitor	25 (44)	24 (43)	37 (88)	34 (81)
Diuretic	30 (53)	28 (50)	33 (78)	30 (71)
β blocker	29 (52)	30 (53)	27 (64)	25 (59)
Calcium-channel blocker	10 (18)	8 (14)	18 (43)	13 (31)[a]
Other	3 (5)	2 (3)	9 (21)	4 (9)[a]
Antihypertensive drugs[b]	1.5 ± 0.5	1.4 ± 0.6	3.4 ± 0.8	2.8 ± 0.05
BMI, kg/m^2	37.7 ± 7.1	36.2 ± 9.1	38.5 ± 10.2	37.8 ± 9.9

Data are presented as mean ± SD, unless otherwise indicated. CPAP refers to continuous positive airway pressure; ACE, angiotensin converting enzyme inhibitor; BMI, body mass index. [a]$p < 0.05$; [b]Antihypertensive drugs refers to the number of drugs used per person.

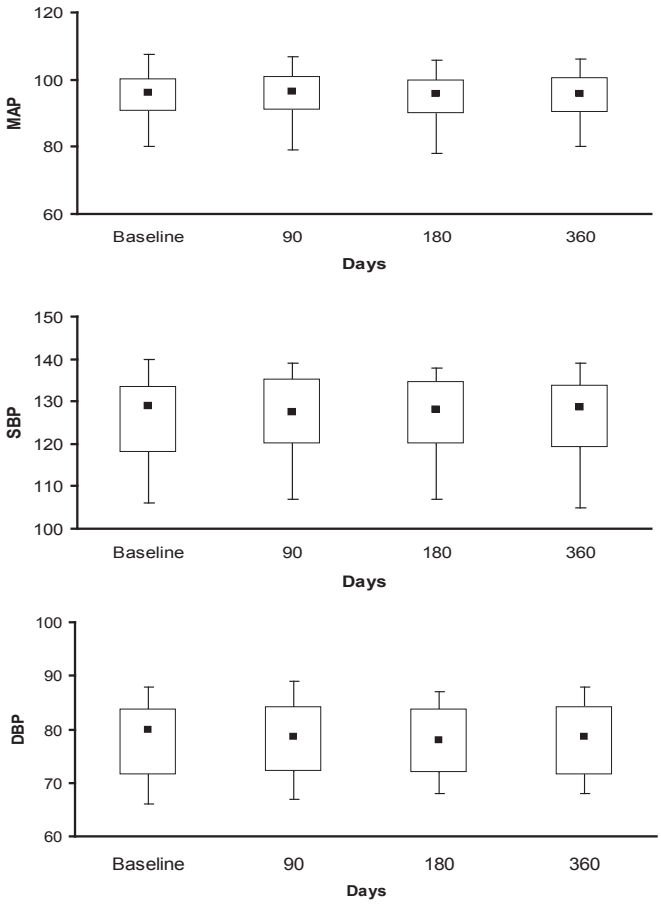

Figure 3—Box whisker plots showing a trend in blood pressure measurements in patients with controlled hypertension. MAP refers to mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

and vascular factors may take a longer time to be brought under control.[32]

The trend in antihypertensive therapy examined in this study further supports the beneficial effect of CPAP in this patient population. There is general agreement derived from meta-analyses of the benefits of antihypertensive treatment. A reduction of mean arterial BP by 5% to 10% in hypertensive patients has the potential to reduce stroke incidence by at least 40%.[33,34] Although CPAP alone is unlikely to achieve such reduction in BP, our study showed a positive impact of CPAP on arterial BP. particularly in patients with uncontrolled hypertensive disease.

A few limitations of this study should be noted. Given the retrospective nature of our study, compliance with pharmacotherapy and CPAP were assessed by clinical data obtained from review of patients' charts. We also recognize that BP measurements were recorded during clinic visits and did not follow the American Heart Association guidelines for definition of resistant hypertension because no ambulatory recordings were available to include in this analysis. We did exclude secondary causes for hypertension, with the exception of obesity; however, patients kept a relatively constant body mass index during the entire observation period, and, as assess using multivariate analysis, weight change was not associated with a decrement in BP measurements at the end of the follow-up period.

In summary, we conclude that the long-term use of CPAP therapy is associated with improved BP control in patients with OSAS and resistant hypertension, as reflected by a reduction in mean arterial pressure and a decreased trend in the use of antihypertensive therapy. Randomized larger trials in this particular group of patients are needed to confirm these results.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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