Effect of Nocturnal Nasal Continuous Positive Airway Pressure on Blood Pressure in Obstructive Sleep Apnea

Lydia A. Bazzano, Zia Khan, Kristi Reynolds and Jiang He

Hypertension 2007, 50:417-423: originally published online June 4, 2007
doi: 10.1161/HYPERTENSIONAHA.106.085175
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Effect of Nocturnal Nasal Continuous Positive Airway Pressure on Blood Pressure in Obstructive Sleep Apnea

Lydia A. Bazzano, Zia Khan, Kristi Reynolds, Jiang He

Abstract—Obstructive sleep apnea (OSA) is a very common risk factor for hypertension, and continuous positive airway pressure (CPAP) has been widely used to treat OSA. We conducted a meta-analysis of randomized, controlled trials to evaluate the effects of CPAP on blood pressure, reported as either a primary or secondary end point, among patients with OSA. Studies were retrieved by searching Medline (January 1980 to July 2006), the Cochrane Database of Systematic Reviews, conference abstracts, and bibliographies of review and original articles. From 255 relevant reports, 16 randomized clinical trials were selected that compared CPAP to control among participants with OSA, had a minimum treatment duration of 2 weeks, and reported blood pressure changes during the intervention or control period. Data on sample size, participant characteristics, study design, intervention methods, duration, and treatment results were independently abstracted by 2 investigators using a standardized protocol. Data from 16 trials representing 818 participants were examined using a random-effects model. Mean net change in systolic blood pressure for those treated with CPAP compared with control was −2.46 mm Hg (95% CI: −4.31 to −0.62); mean net change in diastolic blood pressure was −1.83 mm Hg (95% CI: −3.05 to −0.61); and mean net change in mean arterial pressure was −2.22 mm Hg (95% CI: −4.38 to −0.05). Net reductions in blood pressure were not statistically different between daytime and nighttime. These results indicate that CPAP decreases blood pressure among those with OSA and may help prevent hypertension. **(*Hypertension*. 2007;50:417-423.)**

Key Words: continuous positive airway pressure ■ meta-analysis ■ randomized, controlled trial ■ sleep apnea syndromes ■ blood pressure

Hypertension is an important public health challenge worldwide. Its high prevalence and subsequent increased risk for developing cardiovascular diseases including heart attack, stroke, and chronic kidney disease have placed it as the leading risk factor for all-cause mortality and a major cause of life years–adjusted disability.[1] A recent study on the global burden of hypertension found that 26.4% of the adult population in 2000 had hypertension, and 29.2% were projected to have hypertension by the year 2025. This translates to ≈972 million persons, 333 million in economically developed countries and 639 million in economically developing countries, with hypertension in 2000. In 2025, 1.56 billion adults are expected to have hypertension.[2]

Obstructive sleep apnea (OSA) is a very common risk factor for hypertension. In 2003, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recognized sleep apnea as a common and identifiable cause of hypertension and suggested blood pressure (BP) screening among patients with OSA.[3] Although the prevalence varies by population and age group, it has been estimated that OSA affects ≈24% of middle aged men and 9% of middle-aged women.[4] In addition, the 5-year incidence was recently estimated to be 16% for mild-to-moderate and 7.5% for severe forms of OSA in the adult population.[5] Given the prevalence of OSA and its deleterious consequences, randomized, controlled trials have evaluated the use of continuous positive airway pressure (CPAP) to reduce BP among persons with OSA. Unfortunately, many of these trials were small in sample size and did not have sufficient statistical power to detect a modest but potentially important reduction in BP. We conducted a meta-analysis of randomized, controlled trials to evaluate the effects of CPAP on BP, reported either as a primary or secondary end point, among patients with OSA.

Methods

Study Selection

We conducted a literature search of the Medline database (from January 1980 through July 2006) using the medical subject headings *continuous positive airway pressure* or *positive-pressure respiration* AND *sleep apnea syndromes,* or *sleep apnea obstructive,* or *polysomnography*, or *sleep stages* AND *randomized controlled trial* (as medical subject heading or publication type) or *controlled clinical trial* (as medical subject heading or publication type). The search was restricted to human subjects who were >18 years of age. We also performed a search of the Cochrane Database of Systematic Reviews, conference

Received November 26, 2006; first decision December 27, 2006; revision accepted May 11, 2007.

From the Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine (L.A.B., K.R., J.H.), and Department of Medicine, Tulane University School of Medicine (L.A.B., Z.K., J.H.), New Orleans, La.

Correspondence to Lydia A. Bazzano, Tulane University School of Public Health and Tropical Medicine, 1440 Canal St, SL-18, New Orleans, LA 70112-2715. E-mail lbazzano@tulane.edu

Hypertension **is available at http://www.hypertensionaha.org** **DOI: 10.1161/HYPERTENSIONAHA.106.085175**

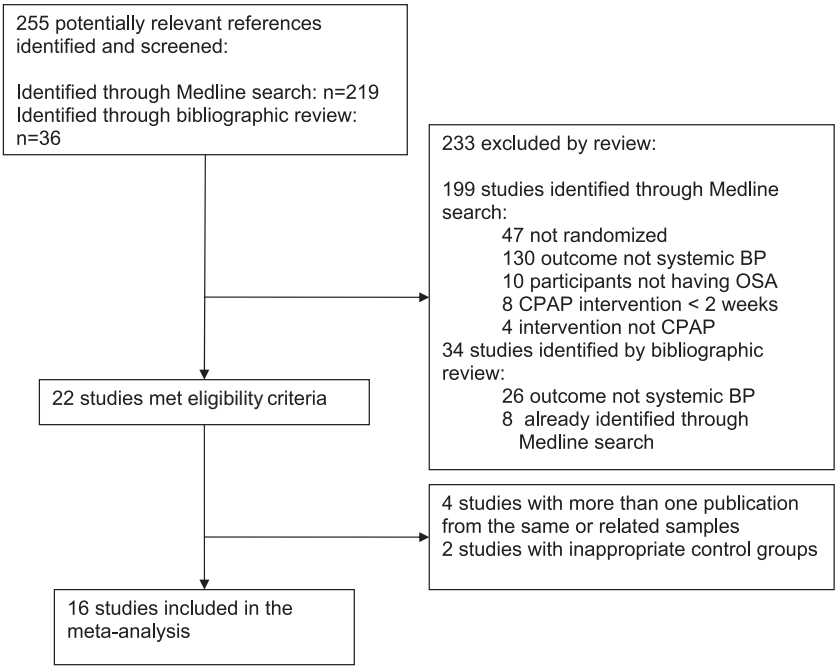

Figure 1. Flow diagram of articles identified and evaluated during the study selection process.

abstracts, and a manual search of references cited in the original published studies and in relevant review articles.[6–10]

The contents of 255 abstracts or full-text articles identified through the literature search were reviewed independently by 2 investigators in duplicate to determine whether they met eligibility criteria for inclusion. Where discrepancies between investigators occurred for inclusion or exclusion, a third investigator was involved to conduct additional evaluation of the study, and discrepancies were resolved in conference. Studies were eligible for inclusion if they met the following criteria: (1) design consisted of a randomized, controlled trial; (2) BP was reported by intervention and control groups or phases in crossover trials; (3) intervention consisted of CPAP; (4) duration of treatment was ≥2 weeks; (5) trial participants had OSA diagnosed by polysomnography; and (6) a control group or phase not receiving medical treatment that was expected to alter sleep pattern or physiology. The flow of studies in our analysis is depicted in Figure 1. Twenty-two studies met the eligibility criteria[11–32]; however, 6 studies were excluded[27–32]: 4 represented duplicate reports from the same or related samples, and 2 had inappropriate control groups (1 treated with theophylline and the other, atrial overdrive pacing).[28,31] We included a total of 16 trials representing data from 818 participants.[11–26]

Data Abstraction

All of the data were independently abstracted in duplicate by means of a standardized data collection form. We resolved discrepancies through discussion and reference to the original publication. If necessary, we contacted authors to request additional information where data were lacking. Study characteristics recorded were as follows: primary author's name, year and source of publication, country of origin, sample size, study design (factorial, parallel, or crossover trials), blinding (open, single, or double), type of control treatment (sham CPAP, pill, or other), method of outcome measurement (ambulatory BP monitoring or clinical BP), intervention (duration of treatment, average nightly use of CPAP, and average CPAP pressure), whether intention-to-treat analysis was used, and the change in BP in intervention and control groups or phases. Characteristics of the study population at the baseline were recorded as follows: distribution according to age and sex, baseline BP, baseline body mass index (BMI), and severity of OSA by apnea-hypopnea index.

Statistical Analysis

Mean systolic BP, diastolic BP, and mean arterial pressure (MAP) at baseline and at the end of the intervention and control periods (or phases) were used to calculate the mean net change in BP because of intervention with CPAP. For parallel trials, mean net change in BP was calculated as the difference (CPAP group minus control group) of the change (baseline minus follow-up) in mean values. For crossover trials, mean net change in BP was calculated as the difference (CPAP minus control group) in BP values at the end of the intervention and control phases.

Variance of the mean net change in BP for each trial was calculated using *P* values, CIs, SEs, or SDs. To calculate a pooled mean net change in BP, each study was assigned a weight, which was calculated as the reciprocal of the variance for the mean net change in BP (systolic BP, diastolic BP, or MAP, separately) in the trial.

Both fixed-effects and DerSimonian and Laird random-effects models[33] were used to calculate the pooled mean net change in BP for CPAP compared with control groups. Significant heterogeneity between studies was not present on statistical testing. Although fixed-effect models yielded similar findings, results from the random-effects models are presented herein because of the different intervention regimens, durations, study participants, and methods of measurement represented in the original trials.

Prestated subgroup analyses were conducted to assess the influence of trial design, severity of OSA, CPAP intervention duration, baseline BMI, baseline BP, and study sample size on the mean net change in BP. We also conducted subgroup analyses by time of day during which BP was measured. The medians of each continuous characteristic were used to divide the studies into subgroups.

To assess the potential for publication bias, we constructed funnel plots for each outcome in which the mean net change was plotted against the study size.[34] In addition, Begg's rank correlation test[34,35] was used to examine the association between mean net change and its variance, and Egger's linear regression test,[36] which regresses *z* statistics on the reciprocal of the SE for each study, was also used to detect publication bias.

To assess the robustness of our pooled estimates, we excluded each trial in turn to evaluate the influence of that trial on the pooled estimate. We also conducted sensitivity analyses in which possible outliers were eliminated. All of the analyses were conducted in Stata 8.2 (Stata Corp).

Results

The characteristics of the 16 randomized, controlled trials and their participants are presented in Table 1. In total, data from 818 participants were included. Of those, 86.3% were men,

TABLE 1. Study Design and Baseline Characteristics of Participants in 16 Randomized, Controlled Trials of CPAP

Study	Total No.	Age	Male	BMI, kg/m^2	AHI, Events per h	Design*	Blinding	BP Measure†	Control‡	CPAP, wk	Baseline SBP, mm Hg	Baseline DBP, mm Hg
Englemann et al[18]	13	51.0 (10.8)	84.6	36.0 (9.4)	49 (32.4)	C	Open	Amb	Pill	3	...	...
Barbe et al[12]	54	53.0 (10.7)	90.7	29.0 (3.8)	55.4 (17.9)	P	Single	Amb	Sham	6	124.6 (10.4)	78.1 (7.5)
Faccenda et al[20]	68	50.0	80.9	30.0	35.0	C	Open	Amb	Pill	4	...	...
Monasterio et al[26]	125	53.5 (9.0)	85.7	29.4 (3.4)	20.5 (6.0)	P	Open	Manual	UC	24	128.8 (17.0)	82.4 (11.5)
Barnes et al[13]	28	45.5 (10.7)	85.7	30.9 (4.9)	12.9 (5.8)	C	Open	Amb	Pill	8	130.3 (10.5)	81.6 (7.5)
Pepperell et al[23]	118	50.6 (10.1)	100.0	35.0 (7.3)	...	P	Double	Amb	Sham	4	133.7 (17.0)	85.1 (8.8)
Becker et al[15]	32	53.4 (8.6)	90.6	33.4 (5.5)	63.8 (22.3)	P	Double	Amb	Sham	9	136.1 (15.3)	82.3 (14.1)
Kaneko et al[22]	24	55.6 (10.6)	87.5	31.4 (7.5)	41.2 (20.3)	P	Open	Manual	UC	4	127.0 (22.6)	61.0 (13.9)
Barnes et al[14]	110	47.0 (9.4)	79.8	31.1 (5.3)	21.3 (13.6)	C	Open	Amb	Pill	12	126.5 (10.5)	76.3 (8.4)
Coughlin et al[17]	25	...	...	...	...	C	...	Amb	Sham	6	...	...
Ip et al[21]	27	42.7 (8.9)	100.0	29.4 (5.7)	46.5 (14.8)	P	Open	Manual	UC	4	122.5 (11.9)	75.6 (11.9)
Mansfield et al[24]	40	57.6 (8.7)	95.0	33.4 (5.0)	25.8	P	Open	Manual	UC	12	...	...
Arias et al[29]	21	51.0 (13.0)	96.0	30.9 (4.0)	44.1 (29.3)	C	Double	Amb	Sham	12	122.2 (10.0)	76.4 (5.7)
Campos-Rodriguez et al[16]	68	56.7 (8.3)	60.2	34.8 (5.9.)	58.9 (23.2)	P	Double	Amb	Sham	4	131.2 (14.7)	78.0 (9.5)
Mills et al[25]	33	48.3 (10.4)	84.8	31.9 (6.3)	63.1	P	Single	Manual	Sham	2	152.2 (20.7)	83.4 (12.1)
Robinson et al[19]	32	54.0 (8.0)	88.5	33.2 (5.3)	28.1	C	Double	Amb	Sham	4	143.0 (17.3)	86.7 (11.1)

Values presented are mean (SD) or percent. AHI indicates apnea-hypopnea index; SBP, systolic BP; DBP, diastolic BP.
*P represents a parallel study design, and C represents a crossover study design.
†BP measure is recorded as clinical measurement using manual cuff (Manual) or as 24-hour ambulatory monitoring (Amb).
‡Control groups used placebo pills (Pill), subtherapeutic or sham CPAP treatment (Sham), or usual care (UC).

and the mean age was 51.3 years. The average BMI was 31.7 kg/m^2, and the average apnea-hypopnea index was 36.2 events per hour. Baseline mean systolic BP was 130.9 mm Hg, diastolic BP was 80.1 mm Hg, and MAP was 100.7 mm Hg. Fifteen of 16 studies reported mean systolic BP and diastolic BP after intervention and control, whereas 7 studies reported mean MAP. Eleven of 16 studies used ambulatory BP monitoring, whereas 5 used clinical BP measured with a manually inflated cuff. A parallel design was used in 9 trials, whereas crossover design was used in 7. Of the trials, 8 used sham or subtherapeutic CPAP in control groups, whereas 4 provided a pill, and another 4 provided usual care alone. Ten of the trials took place in European countries, 3 in Australia, 2 in North America, and 1 in China. Two of the trials used hypertension as an inclusion criteria, whereas 3 used hypertension as an exclusion criteria. The included trials varied in duration of intervention from 2 to 24 weeks.

Mean net changes and corresponding 95% CIs for systolic BP, diastolic BP, and MAP from each trial and pooled across trials are shown in Figures 2, 3, and 4, respectively. The mean net changes varied from −18.0 to 2.0 mm Hg for systolic BP; from −9.0 to 2.0 mm Hg for diastolic BP; and from −9.5 to 1.0 mm Hg for MAP. There was an intervention-related decrease in systolic BP in 12 of 15 trials, in diastolic BP in 11 of 15 trials, and in MAP in 5 of 7 trials. The pooled mean net change in systolic BP because of CPAP intervention was −2.46 mm Hg (95% CI: −4.31 to −0.62). For diastolic BP, the pooled mean net change because of CPAP intervention was −1.83 mm Hg (95% CI: −3.05 to −0.61), and for MAP the pooled mean net change was −2.22 mm Hg (95% CI: −4.38 to −0.05).

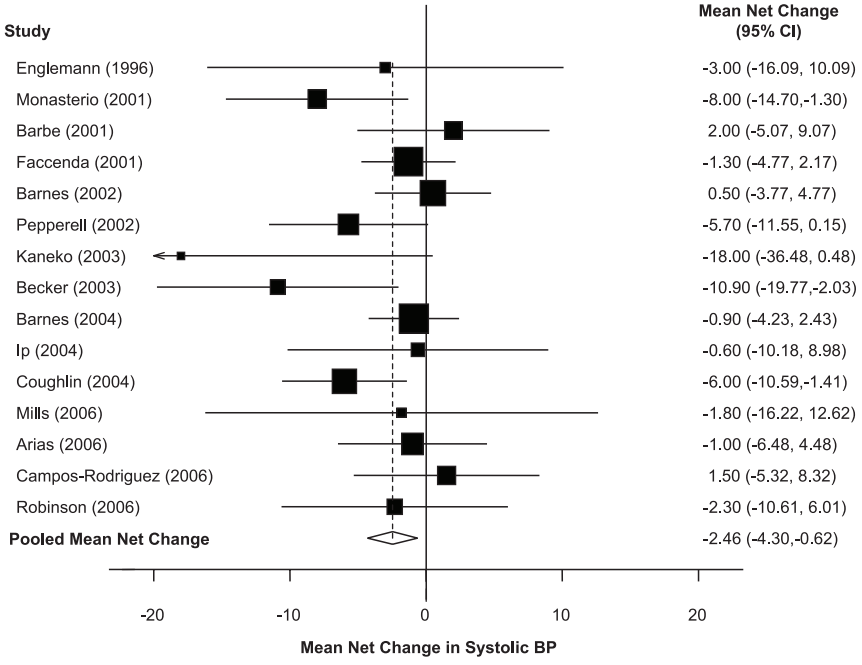

Figure 2. Mean net change in systolic BP and corresponding 95% CIs by trial and pooled.

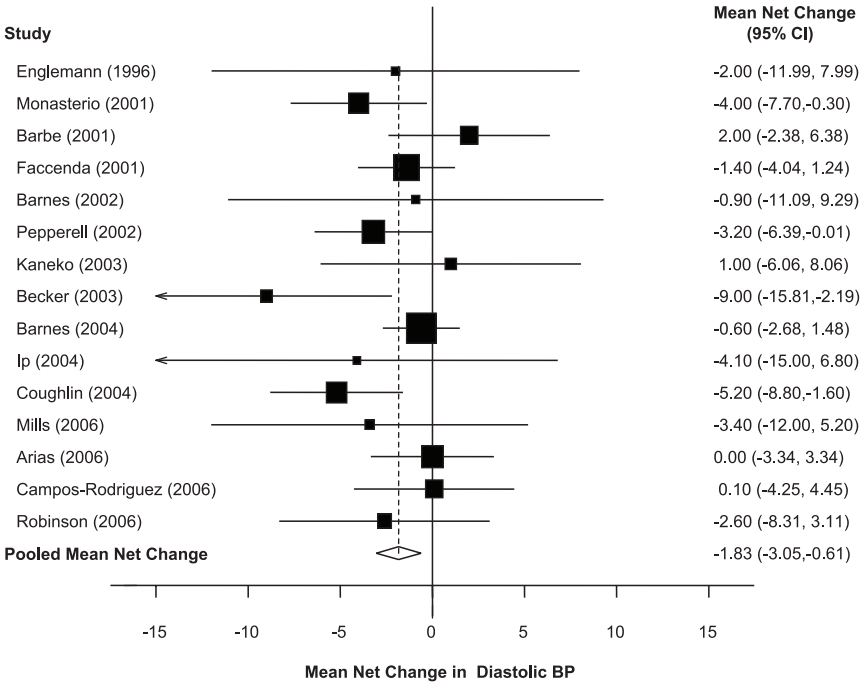

Figure 3. Mean net change in diastolic BP and corresponding 95% CIs by trial and pooled.

Table 2 presents subgroup analyses by time of day when BP was measured. There was a trend toward lower BP in CPAP intervention groups, though the mean net reduction in BP only reached customary statistical significance for nighttime MAP. Net reductions in systolic, diastolic, and pulse pressure were not statistically significantly different between daytime and nighttime measures. We also conducted subgroup analyses by study design, severity of OSA, treatment duration, baseline BMI, baseline BP, and trial sample size. These results are presented in Table 3. A statistically significant mean net reduction in BP was seen more often among studies with participants who had higher baseline BP levels, higher BMI, and more severe OSA. We also examined the effect of different control treatments on our results. When restricted to trials that provided sham CPAP as a control treatment (8 of 16 trials), we found significant reductions for both systolic and diastolic BP (−3.10 and −2.24, respectively). Among trials using pills or usual care as the control treatment, we did not see a statistically significant reduction in systolic or diastolic BP; however, only 4 trials using pill as control treatment and 3 trials using usual care as control treatment reported systolic and diastolic BP. In Figure 5, we present the average nightly hours of CPAP use plotted against mean net change in systolic BP for each study. Increasing hours of CPAP use were associated with greater mean reduction in systolic BP.

We examined the potential for publication bias by plotting sample sizes versus mean net change in systolic BP, diastolic BP, and MAP among the trials included in our meta-analysis

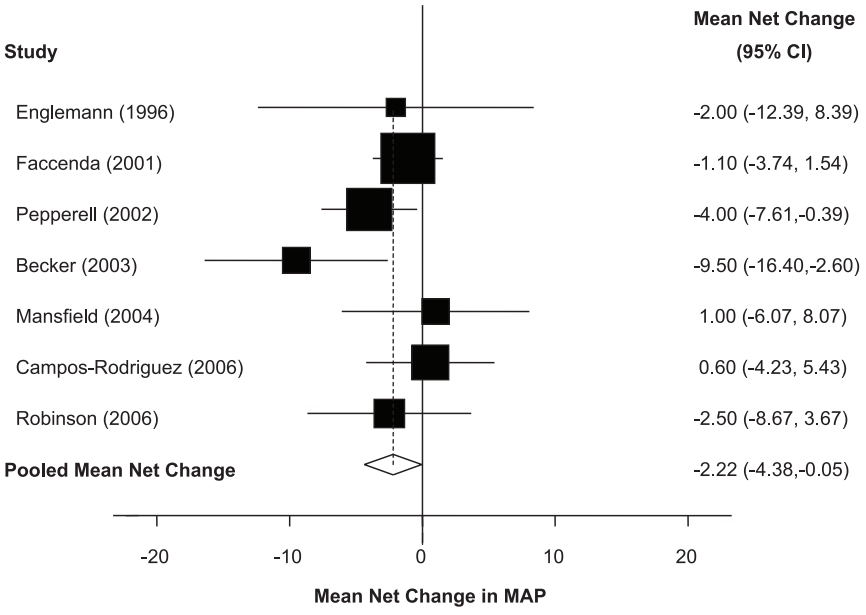

Figure 4. Mean net change in MAP and corresponding 95% CIs by trial and pooled.

TABLE 2. Effect of CPAP Intervention on BP by Time of Day

	Day			Night		
Outcome	No. of Trials	Mean Net Change	95% CI	No. of Trials	Mean Net Change	95% CI
SBP	9	−3.00	−5.90 to 0.51	6	−2.29	−5.44 to 0.87
DBP	9	−1.60	−3.45 to 0.25	7	−1.01	−2.98 to 0.97
MAP	7	−2.05	−4.67 to 0.57	6	−3.30*	−5.82 to −0.81

Mean net change between treatment and control groups. SBP indicates systolic BP; DBP, diastolic BP.
*Three trials reporting nighttime MAP did not report either nighttime SBP or DBP and, thus, are not included in those analyses.

(data not shown). There was no evidence to suggest publication bias. In addition, there was no evidence of publication bias in plots of variance or by statistical testing using Begg's rank correlation test and Egger's linear regression tests. No statistically significant heterogeneity was detected among all of the BP outcomes.

In sensitivity analyses, the exclusion of any one study from the analysis did not alter the pooled effect of CPAP intervention on systolic BP, diastolic BP, or MAP. Two trials appeared to be outliers for mean net change in systolic BP,[15,22] and 1 trial appeared to be an outlier for mean net change in diastolic BP and MAP.[15] We conducted additional sensitivity analyses with these trials excluded and found no change in the statistical significance of our results, though effect estimates were slightly attenuated. In additional sensitivity analyses, we excluded studies in which participants had comorbid heart failure. Two trials, including 64 of 818 participants, were excluded. The pooled mean difference in systolic BP (95% CI) was −2.26 (−3.98 to −0.53); diastolic BP was −1.92 (−3.19 to −0.66); and MAP was −2.53 (−4.89 to −0.18).

Discussion

OSA is a common disorder that is likely to increase in prevalence in tandem with recent increases in obesity in the general population.[37] It is a very common identifiable cause of hypertension cited in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[3] Our results show that

TABLE 3. Effect of CPAP Intervention on BP by Subgroup of Baseline Characteristics or Study Design

	Mean Net Change in Blood Pressure					
	SBP			DBP		
Subgroup	No. of Studies	Mean Net Change	95% CI	No. of Studies	Mean Net Change	95% CI
AHI						
≥42.7	7	−1.22	−4.28 to 1.83	7	−1.15	−3.71 to 1.41
<42.7	6	−2.01	−4.65 to 0.64	6	−1.38	−2.78 to 0.03
SBP						
≥129.6	6	−2.57	−6.18 to 1.04	6	−2.82	−4.97 to −0.68
<129.6	6	−2.16	−5.51 to 1.20	6	−0.72	−2.26 to 0.82
DBP						
≥79.9	6	−4.36	−8.14 to −0.58	6	−3.79	−5.80 to −1.78
<79.9	6	−0.57	−2.93 to 1.80	6	−0.10	−1.58 to 1.39
BMI						
≥31.4	7	−4.36	−8.27 to −0.45	7	−2.55	−4.58 to −0.52
<31.4	7	−1.08	−2.86 to 0.70	7	−0.94	−2.22 to 0.34
Study design						
Parallel	8	−4.03	−7.95 to −0.11	8	−2.20	−4.48 to 0.08
Crossover	7	−1.61	−3.35 to 0.13	7	−1.44	−2.74 to −0.14
CPAP duration						
≥6 weeks	7	−2.82	−5.76 to 0.12	7	−2.16	−4.51 to 0.19
<6 weeks	8	−2.09	−4.50 to 0.31	8	−1.78	−3.40 to −0.15
Sample size						
≥32	9	−2.49	−4.87 to −0.11	9	−1.81	−3.34 to −0.27
<32	6	−2.56	−5.94 to 0.82	6	−2.06	−4.36 to 0.24

Mean net change between treatment and control groups. SBP indicates systolic BP; DBP, diastolic BP; AHI, apnea-hypopnea index. Cut points of continuous variables were based on the median value among the studies included.

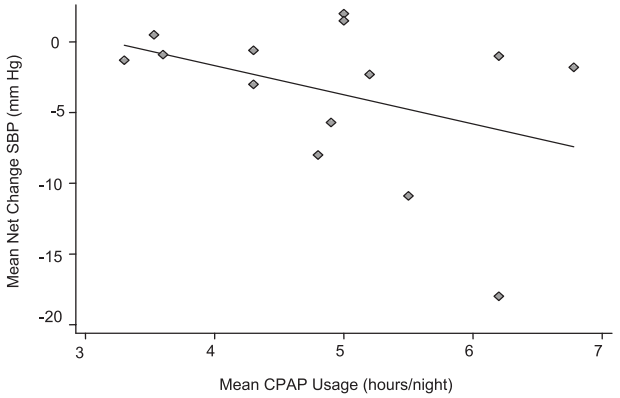

Figure 5. Mean net change in systolic BP and corresponding average nightly use of CPAP in each trial (r^2=0.40; P=0.13).

treating persons with OSA with therapeutic CPAP significantly reduces systolic and diastolic BP and nighttime MAP. With an estimated 15 million Americans affected by sleep apnea,[10] and given the individual and public health burden of hypertension and its associated comorbidities, the results of this study have far-reaching clinical and public health implications.

Nocturnal nasal CPAP therapy for OSA is a relatively new therapy, introduced only in the mid-1980s. This meta-analysis is one of the first to systematically review trials with a focus on estimating the effect of CPAP therapy on BP among those with OSA. In our analysis of 16 randomized trials, we found a pooled mean net change of −2.46 mm Hg in systolic BP, −1.83 mm Hg in diastolic BP, and −2.22 mm Hg in MAP among those using CPAP therapy compared with those in control groups. The results of this study provide evidence that CPAP treatment reduces BP levels in persons with OSA.

This meta-analysis has several strengths that lend confidence to our findings. First, we selected only randomized, controlled trials for inclusion in this analysis. Second, we had a high power to detect a BP-lowering effect of CPAP among the pooled trials. Third, there was no significant evidence of heterogeneity among the studies. Fourth, our sensitivity analysis showed no significant change in overall systolic BP, diastolic BP, or MAP because of the influence of any one study. Sensitivity analyses also showed no significant change with apparent outliers removed. Finally, there was no evidence of publication bias by graphical methods or rank correlation and linear regression testing.

This study also has several limitations. First, our sample population may limit generalizability of the results. The majority of participants in the included studies were overweight-to-obese men in middle age. Hence, additional analyses should be conducted among different demographic groups and ethnicities to confirm these results. Second, another limitation of this study may be the relatively short duration of CPAP therapy, ranging from 2 to 24 weeks. Longer treatment may be associated with different effects on systemic arterial pressure. Additional studies are warranted to evaluate longer treatment and its possible effects. Third, intermittent noninvasive BP measurement techniques used in these trials may not capture surges in BP with each apnea and their suppression with CPAP. Continuous measurement techniques, such as finger arterial BP monitoring (Finapres), may be better suited to such measures. Thus, the impact of CPAP on nocturnal BP may be underestimated in this study.

Our findings are consistent with several pathophysiological mechanisms that have been proposed regarding the role of OSA in the development of hypertension. In persons without sleep apnea, sleep is associated with a sleep stage–related decrease in sympathetic tone of muscles, vasculature, and heart rate.[38] The rapid eye movement stage of sleep is associated with an increase in sympathetic drive.[38] In persons with sleep apnea, repetitive apneic episodes result in hypoxemia and hypercapnia that are associated with chemoreflexive sympathetic vasoconstriction of peripheral vessels. At the termination of the apneic episode, hyperventilation increases venous return and cardiac output in the face of increased systemic resistance, setting the stage for elevated BP.[39] Increased sympathetic output may be carried over from night to day, and this effect is abolished by CPAP treatment.[32] Moreover, the use of CPAP to abolish obstructions at night greatly reduces left ventricular transmural pressure.[40] This represents an important benefit, which may prevent or reduce ventricular hypertrophy, aortic dilation, and provocation of atrial fibrillation in the future. Hypoxemia is also associated with increased endothelin release, another potent vasoconstrictor, which has sustained hypertensive effects that last beyond the duration of sleep.[40] In addition to increased endothelin release, evidence suggests that OSA is linked with more extensive endothelial dysfunction because of impaired NO release and endothelium-mediated vasodilatory responses.[38] Variability in hemodynamic response may also play a role in the pathophysiology of hypertension associated with OSA. Persons with sleep apnea have been shown to have increased BP variability.[38,41] Increased BP variability has been linked with end-organ damage.[42,43] By reducing the number of nocturnal apneic episodes, CPAP therapy may attenuate the cascade of physiological mechanisms that leads to acute and chronic BP elevation.

Perspectives

This meta-analysis provides evidence that effective CPAP treatment does indeed reduce BP levels in patients with OSA. Additional concurrent measures to reduce the severity of OSA include weight loss, avoidance of alcohol before bedtime, and sleeping in the lateral positions. The effect of these approaches for BP reduction should be examined among patients with OSA. Given our results, CPAP should be considered a potentially important part of the current strategy to reduce BP and prevent hypertension among those with OSA.

Sources of Funding

L.A.B. was supported by a Building Interdisciplinary Research Careers in Women's Health Scholarship (K12-HD43451) cofunded by the Office of Research on Women's Health and the Office of Dietary Supplements of the National Institutes of Health (Bethesda, Md). K.R. was partially supported by grant P20-RR17659 from the National Center for Research Resources of the National Institutes of Health.

Disclosures

None.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347–1360.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005; 365:217–223.
3. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42: 1206–1252.
4. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.
5. Tishler PV, Larkin EK, Schluchter MD, Redline S. Incidence of sleep-disordered breathing in an urban adult population: the relative importance of risk factors in the development of sleep-disordered breathing. *JAMA*. 2003;289:2230–2237.
6. 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.
7. Giles TL, Lasserson TJ, Smith BJ, White J, Wright J, Cates CJ Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev*. 2006:CD001106.
8. Mohsenin V. Is sleep apnea a risk factor for stroke? A critical analysis. *Minerva Med*. 2004;95:291–305.
9. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA*. 2003;290: 1906–1914.
10. Wolk R, Shamsuzzaman AS, Somers VK. Obesity, sleep apnea, and hypertension. *Hypertension*. 2003;42:1067–1074.
11. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. *Eur Heart J*. 2006;27:1106–1113.
12. 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.
13. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, Trinder J, Saunders NA, Douglas McEvoy R, Pierce RJ. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;165:773–780.
14. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, Pierce RJ. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. *Am J Respir Crit Care Med*. 2004; 170:656–664.
15. 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.
16. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel J, Merino-Sanchez M, Gonzalez-Benitez MA, Beltran-Robles M, Almeida-Gonzalez C. Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebo-controlled trial. *Chest*. 2006;129:1459–1467.
17. Coughlin S, Mugarza J, Mawdsley L, Wilding J. Continuous positive airways pressure treatment reduces the cardiovascular risk factors associated with obstructive sleep apnea [abstract]. Presented at the *American Thoracic Society 100th International Conference*, May 21–26, 2004, Orlando, FL; C99 Poster: 111.
18. 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.
19. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in non-sleepy hypertensive OSA patients. *Eur Respir J*. 2006;27:1229–1235.
20. 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.
21. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. *Am J Respir Crit Care Med*. 2004;169:348–353.
22. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley TD. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *N Engl J Med*. 2003;348:1233–1241.
23. 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.
24. Mansfield DR, Gollogly NC, Kaye DM, Richardson M, Bergin P, Naughton MT. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med*. 2004;169:361–366.
25. Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. *J Appl Physiol*. 2006;100:343–348.
26. 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.
27. Norman D, Loredo JS, Nelesen RA, Ancoli-Israel S, Mills PJ, Ziegler MG, Dimsdale JE. Effects of continuous positive airway pressure versus supplemental oxygen on 24-hour ambulatory blood pressure. *Hypertension*. 2006;47:840–845.
28. Orth MM, Grootoonk S, Duchna HW, de Zeeuw J, Walther JW, Bauer TT, Schultze-Werninghaus G, Rasche K. Short-term effects of oral theophylline in addition to CPAP in mild to moderate OSAS. *Respir Med*. 2005;99:471–476.
29. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. *Circulation*. 2005;112:375–383.
30. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. *Thorax*. 2005;60:781–785.
31. Unterberg C, Luthje L, Szych J, Vollmann D, Hasenfuss G, Andreas S. Atrial overdrive pacing compared to CPAP in patients with obstructive sleep apnoea syndrome. *Eur Heart J*. 2005;26:2568–2575.
32. Usui K, Bradley TD, Spaak J, Ryan CM, Kubo T, Kaneko Y, Floras JS. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol*. 2005;45:2008–2011.
33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
34. Begg C. Publication bias. In: Cooper H, Hedges L, eds. *The Handbook of Research Synthesis.* New York, NY: Russell Sage Foundation; 1994: 399–409.
35. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101.
36. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
37. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol*. 2005;99:1592–1599.
38. Hoffmann M, Bybee K, Accurso V, Somers VK. Sleep apnea and hypertension. *Minerva Med*. 2004;95:281–290.
39. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96: 1897–1904.
40. Tkacova R, Rankin F, Fitzgerald FS, Floras JS, Bradley TD. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. *Circulation*. 1998;98: 2269–2275.
41. Noda A, Okada T, Hayashi H, Yasuma F, Yokota M. 24-Hour ambulatory blood pressure variability in obstructive sleep apnea syndrome. *Chest*. 1993;103:1343–1347.
42. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G. Prognostic value of 24-hour blood pressure variability. *J Hypertens*. 1993;11:1133–1137.
43. Palatini P, Penzo M, Racioppa A, Zugno E, Guzzardi G, Anaclerio M, Pessina AC. Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. *Arch Intern Med*. 1992;152: 1855–1860.