The Impact of Continuous Positive Airway Pressure on Blood Pressure in Patients With Obstructive Sleep Apnea Syndrome

Evidence From a Meta-analysis of Placebo-Controlled Randomized Trials

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Background: Continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea syndrome (OSAS) might lower blood pressure, but evidence from clinical studies is inconsistent, perhaps as a result of small sample size or heterogeneity in study design. This study aimed to assess whether CPAP reduces ambulatory blood pressure in patients with OSAS, to quantify the effect size with precision, and to identify trial characteristics associated with the greatest blood pressure reductions.

Methods: We identified randomized controlled trials of CPAP vs placebo in patients with OSAS specifically reporting 24-hour ambulatory mean blood pressure (MBP).

Results: We included a total of 572 patients from 12 randomized controlled trials. According to a random-effects model, the pooled estimate of the effect of the CPAP intervention was a net decrease of 1.69 mm Hg in 24-hour MBP (95% confidence interval, −2.69 to −0.69). Statistical heterogeneity was moderate (I² = 41%). Pre-defined metaregression analyses estimated that 24-hour MBP would decrease by 0.89 mm Hg per 10-point increase in apnea-hypopnea index at entry (P = .006), by 0.74 mm Hg for each increase of 10 arousal events per hour slept (P = .008), and by 1.39 mm Hg for each 1-hour increase in effective nightly use of the CPAP device (P = .01).

Conclusions: Among patients with OSAS, CPAP reduces 24-hour ambulatory MBP, with greater treatment-related reductions in ambulatory MBP among patients with a more severe degree of OSAS and a better effective nightly use of the CPAP device. These reductions in blood pressure are likely to contribute to a better prognosis in terms of adverse cardiovascular events.

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sizes, different degrees of severity of OSAS, presence or absence of daytime sleepiness, associated arterial hypertension, concomitant medication therapy, or comorbid conditions.

We therefore planned a systematic review and meta-analysis to assess whether CPAP reduces blood pressure in patients with OSAS, to quantify the effect size with precision, and to identify trial characteristics associated with the greatest blood pressure reductions.

**METHODS**

**SEARCH STRATEGY AND DATA EXTRACTION**

We searched for English and non-English articles using MEDLINE (Ovid and PubMed) and EMBASE (from January 1981, and the Cochrane Randomised Controlled Trials Register, with the last computerized search undertaken in August 2006. The search terms were *obstructive sleep apnea* and *blood pressure*. The MEDLINE search was limited to randomized controlled trials, *humans*, and all adults >19 years old. The computerized search was supplemented by a manual search of the bibliographies of all retrieved articles. Potentially relevant articles were assessed for inclusion against prespecified eligibility and exclusion criteria. Data were independently extracted by 2 of us (P.H. and A.V.M.) and checked for accuracy in a second review. Consensus was achieved for all data.

**ELIGIBILITY**

We included RCTs published in full that reported net changes in ambulatory arterial blood pressure in patients with OSAS receiving CPAP treatment vs placebo. Studies were required to report 24-hour ambulatory blood pressure as a separate outcome. If a particular patient population was reported in more than 1 publication, we selected the article that provided the most complete data set. Reviews, observational studies, uncontrolled trials, RCTs in which 24-hour blood pressure was not reported as a separate outcome in all treatment arms, and RCTs in which patients had any ongoing illness other than OSAS and arterial hypertension were excluded.

**DATA**

The outcome of primary interest was the net change in 24-hour ambulatory MBP in patients receiving CPAP treatment compared with patients receiving placebo. Secondary outcomes were changes in 24-hour ambulatory systolic blood pressure (SBP), 24-hour diastolic blood pressure (DBP), and nighttime and daytime MBP, SBP, and DBP. The following data were abstracted: the first author’s name; the publication year; the country of origin; the number, mean age, mean body mass index, and sex of the participants; the presence or absence of hypertension and the use of antihypertensives, based on the information as provided in the primary studies; the study design details, including whether the design was parallel or crossover, study duration, and method of placebo intervention; whether ambulatory 24-hour blood pressure monitoring was the primary outcome of interest; AH1 at entry (AH1 values of 5–14.9 indicate mild OSAS; ≥15–29.9, moderate OSAS; and ≥30, severe OSAS); the number of arousal events per hour slept (arousal index); daytime sleepiness at entry, as measured by the Epworth Sleepiness Scale (range, 0–24; a higher score indicates more severe daytime sleepiness); the degree of sleep hypoxemia (% oxygen desaturation index per hour slept and the mean and nadir arterial oxygen saturation levels); the effective nightly use of a CPAP device (hours per night); and the number of patients who withdrew from the study.

**STATISTICAL ANALYSES**

For parallel trials, net change in blood pressure was calculated as the mean difference (active treatment minus placebo) of the change (follow-up minus baseline). For crossover trials, net change in blood pressure was calculated as the mean difference between the end of the active treatment and placebo periods. To calculate the pooled effects, each study was assigned weights consisting of the reciprocal of the total variance for net change in blood pressure. Missing variances for net changes in blood pressure were calculated from confidence intervals, P values, or individual variances for intervention and placebo groups (parallel trials) or intervention or placebo periods (crossover trials). For parallel trials in which variance for paired differences during the trial was reported separately for each trial arm, we calculated a pooled variance for net blood pressure change using standard methods. Missing variances for paired differences were calculated from variances at baseline and at the end of follow-up. The method of Follmann et al.36 assumes a correlation coefficient of 0.5 between initial and final blood pressure levels.

Estimates of the mean effect of CPAP treatment on blood pressure and the corresponding 95% confidence intervals (CIs) were calculated using the inverse variance fixed-effect model and the DerSimonian and Laird random-effects model.34,35

The results were examined for heterogeneity by visually examining forest plots and using formal statistical tests for heterogeneity and trial inconsistency.36 Between-study heterogeneity was assessed using the Cochran Q test, P<.10 indicating significance, and formally quantified by the I² statistic, with values less than 25% indicating low, 25% to 50% indicating moderate, and greater than 50% indicating high heterogeneity.36,37

To explain anticipated heterogeneity among trial findings, we identified, a priori, potential sources of heterogeneity. Because the treatment effect might vary according to risk factors for and severity of OSAS, we plotted the effect size of each trial against, in turn, age (years), sex (percentage male), body mass index (calculated as weight in kilograms divided by height in meters squared), prevalence of arterial hypertension (percentage), number of arousal events per hour slept (arousal index), degree of sleep hypoxemia (oxygen desaturation index and mean and nadir arterial oxygen saturation levels), daytime sleepiness (measured by the Epworth Sleepiness Scale), effective nightly use of a CPAP device (hours per night), and total duration of the study (weeks). We also performed formal random-effects metaregression analyses. We further postulated that the findings of the trials would be affected by the following study characteristics: crossover vs parallel design, whether ambulatory 24-hour blood pressure monitoring was the primary outcome of interest, and type of control treatment (sham CPAP vs oral tablet).

To evaluate the effect of each selected study on the overall results of the meta-analysis, we performed a 1-way sensitivity analysis, also defined a priori. Potential publication bias was explored by funnel plot,10 indicating significance, and the test of Egger et al.36

**RESULTS**

**STUDIES IDENTIFIED**

*We identified 49 candidate RCTs,18–30,40–76 including 44 by means of the electronic search strategy* and 5 from the bibliographies of all references.

References 20, 21, 23–30, 40–44, 46–72, 74, 76.
they studied the effect of antihypertensive medication in OSAS patients or compared the effect of a dental device vs placebo); 5 did not consider blood pressure as a separate outcome variable; and 2 did not report 24-hour blood pressure. Three trials reported data on the same population, and only one of these was included for the meta-analysis. Thus 12 RCTs of CPAP vs placebo, all published in English, were included in this review (Figure 1, Table 1, and Table 2). Automated ambulatory 24-hour blood pressure monitoring was the primary outcome measure in 8 trials. The ethnicity of the individuals involved was 100% white in all but 1 trial. Only 1 trial reported data on smoking status, and 2 reported data on alcohol consumption.

META-ANALYSIS OF THE PRIMARY END POINT

Twelve RCTs involving 572 subjects were included in the primary analysis of net change in the 24-hour MBP (Figure 2). The decrease in the 24-hour MBP ranged from −0.30 to −10.50 mm Hg. In 4 trials, these MBP reductions were statistically significant. The pooled estimate of the effect of intervention with CPAP was a net decrease of 1.69 mm Hg (95% CI, −2.69 to −0.69; P < .001) using a DerSimonian and Laird random-effects model (Figure 2). Statistical heterogeneity between the RCTs was moderate (I² = 41%), indicating that additional factors could affect the

Table 1. Design Characteristics of the Trials Included in the Meta-analyses

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<tr>
<th>Source</th>
<th>Site</th>
<th>Study Design</th>
<th>Study Duration, wk</th>
<th>Actively Treated Group</th>
<th>Placebo-Treated Group</th>
<th>Effective CPAP Use, h/Night†</th>
<th>Sample Size‡</th>
<th>Dropout Rate, %</th>
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<td>68</td>
<td>13</td>
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<td>Multicenter study, Spain</td>
<td>Parallel</td>
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Abbreviations: CPAP, continuous positive airway pressure; ellipses, no data available.
*The 12 CPAP randomized controlled trials are those providing data on 24-hour mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), or allowing to calculate these values based on the following equation: MBP = SBP/3 + (2/3 × DBP).†Effective nightly CPAP use was measured objectively by using a timer built into each CPAP device.
†In parallel study, the virgule (/) denotes treatment/control group; each value indicates the number of patients who completed the protocol with complete outcome data for 24-hour MBP, SBP, and DBP.
Table 2. Patients’ Characteristics of the Trials Included in the Meta-analyses

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<tr>
<th>Source</th>
<th>Mean Age, y</th>
<th>Mean BMI</th>
<th>Male, %</th>
<th>AHI at Entry</th>
<th>AI at Entry</th>
<th>ESS Score at Entry</th>
<th>ODI at Entry</th>
<th>Mean SaO2</th>
<th>Nadir SaO2</th>
<th>Hypertensive, % of Subjects</th>
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Abbreviations: AHI, apnea-hypopnea index (defined as the sum of the number of apneas plus hypopneas per hour slept); AI, arousal index (defined as the number of arousal events per hour slept); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index (calculated as the number of oxygen desaturations of 4% or more per hour slept); SaO2, arterial oxygen saturation; ellipses, no data available.

*The 12 continuous positive airway pressure randomized controlled trials are those providing data on 24-hour mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), or allowing to calculate these values based on the following equation: MBP = SBP/3.

†A higher score indicates more severe daytime sleepiness.

Figure 2. Random-effects meta-analysis for the primary outcome of interest (net change in 24-hour mean blood pressure [MBP]). Net change was calculated as the difference of the baseline minus the follow-up levels of blood pressure for the intervention and control groups (parallel trials) or the difference in blood pressure levels at the end of the intervention and control treatment periods (crossover trials). The size of the circle corresponds to the weight of the study. CI indicates confidence interval.

Efficacy of intervention with CPAP in reducing the 24-hour MBP. The largest reductions in blood pressure were observed in 2 small trials (sample sizes of 3225 and 3328 participants, respectively), which included participants with a very severe degree of OSAS (mean AHI at entry, 64.225 and 66.128).

META-ANALYSES OF THE SECONDARY END POINTS

The 24-hour SBP and DBP data involved similar magnitudes of effect for the net changes in blood pressure, but statistical heterogeneity was lower for SBP (Table 3). In the daytime MBP, SBP, and DBP data, the effect size was larger, with similar statistical heterogeneity. There was also a significant reduction in nighttime MBP and SBP, but a statistically nonsignificant decrease in nighttime DBP.

EXPLORING HETEROGENEITY

Predefined metaregression analyses estimated that the 24-hour MBP would decrease by 0.89 mm Hg per 10-point increase in the AHI at entry (P = 0.06; adjusted R2 = 34%; Figure 3A), by 0.74 mm Hg for each increase of 10 arousal events per hour slept (P = 0.08; adjusted R2 = 33%; Figure 3B), and by 1.39 mm Hg for each 1-hour increase in effective nightly use of the CPAP device (P = 0.1; adjusted R2 = 7%; Figure 3C). We found no relationship between...
Higher Epworth Sleepiness Scale scores at entry and net change in the 24-hour ambulatory MBP (8 trials; 467 individuals; P = .54).

Nonsignificant trends toward greater treatment-related reductions in the 24-hour MBP were noted in trials with a parallel study design (P = .06) and in those where the 24-hour MBP was the primary outcome measure (P = .053). None of the other a priori variables was significantly different (Table 4), but some of these analyses of explanatory variables involved only a very small number of trials.

**SENSITIVITY ANALYSIS**

One-way sensitivity analyses demonstrated that the overall effect size and its statistical significance were consistent across the studies and did not depend on any single study (data not shown). The I² value ranged from 26% to 46%, indicating moderate heterogeneity.

**PUBLICATION BIAS**

A funnel plot of effect size vs precision was not perfectly symmetrical, mainly owing to 2 small trials on the left of the summary estimate of the effect size (Figure 4). This asymmetry may arise from study factors other than publication bias; ie, participants in 1 small trial (sample size of 32) had a very severe degree of OSAS (mean AHI at entry, 64.2) and a high proportion with arterial hypertension (66%); that trial reported the greatest reduction in blood pressure and the widest 95% CI. The use of a continuous beat-to-beat blood pressure measurement device (Portapres; Finapres Medical Systems, Amsterdam, the Netherlands) not causing arousal from sleep rather than the standard blood pressure cuff for continuous noninvasive blood pressure monitoring may also have contributed to the large decrease in blood pressure. The other small trial included 33 patients with an even more severe degree of obstructive sleep apnea (AHI at entry, 66.1) and was the only trial to include black and Hispanic Americans.

Formal statistical tests for publication bias, including the rank-correlation test of Begg and Mazumdar (z = −1.509; P = .13) and the test of Egger et al (intercept, −1.217; 90% CI, −2.418 to 0.016; P = .09), were not significant.

**COMMENT**

The present review shows that treatment with CPAP causes a small but significant decrease in 24-hour arterial MBP (−1.69 mm Hg). Even a small decrease in blood pressure may lead to a clinically important reduction in the cardiovascular risk of a population. Among patients treated for hypertension, 1- to 2-mm Hg mean differences in blood pressure are associated with reduced odds of stroke, major cardiovascular events,
and heart failure.²⁷ Moreover, several quantitative reviews indicate that lowering blood pressure is more important in reducing adverse cardiovascular events than the specific medication used.²⁷-⁸¹

Table 4. Metaregression Analyses and Categorical Meta-analyses

<table>
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<th>Explanatory Variable</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>P Value</th>
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<td>.39</td>
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<td>% of Patients with hypertension</td>
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<td>.62</td>
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Abbreviations: AHI, apnea-hypopnea index; AI, arousal index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; SaO₂, arterial oxygen saturation.

*See Figure 3A.
†See Figure 3B.
‡See Figure 3C.

Figure 3. Scatterplots of the effect sizes (net change in 24-hour ambulatory mean blood pressure [MBP]) by the apnea-hypopnea index (AHI) at entry (A), arousal index at entry (arousal events per hour) (B), and effective nightly use of the continuous positive airway pressure (CPAP) device (hours per night) (C). Squares represent the net change in 24-hour ambulatory MBP and error bars represent 95% confidence intervals. Numbers alongside each square relate to the reference numbers for the trials as detailed in Figure 2. The trend line is based on the series of effect sizes (squares). A metaregression that included 572 individuals (12 trials) estimated the 24-hour ambulatory MBP to decrease by 0.089 mm Hg (0.89 mm Hg) per 1-point (10-point) increase in AHI at entry (A: slope β = –0.089; P = .006; adjusted R² = 34%). A metaregression that included 248 individuals (6 trials) estimated the 24-hour ambulatory MBP to decrease by 0.74 mm Hg per increase of 10 arousal events (B: slope β = –0.074; P = .008; adjusted R² = 33%). A metaregression that included 542 individuals (10 trials) estimated the 24-hour ambulatory MBP to decrease by 1.383 mm Hg per 1-hour increase in effective use of the CPAP device (C: slope β = –1.383; P = .01; adjusted R² = 7%).

Figure 4. Funnel plot of the net change in 24-hour ambulatory mean blood pressure for all 12 trials in the meta-analysis.

Our approach has a number of novel aspects compared with previous systematic reviews and meta-analyses.⁸²-⁸⁵ in particular, the focus on 24-hour blood pressure as the key outcome, and the inclusion of metaregression modeling. Thus, we were able to take advantage of the complete spectrum of blood pressure results from 4 RCTs,²⁷-³⁰ among the largest in this research area, published after April 2006.

In our prespecified metaregression analyses, greater CPAP treatment-related reduction in 24-hour arterial MBP was observed when OSAS...
was more severe or when the effective nightly use of the CPAP device was higher. Previous subgroup analyses had shown that blood pressure reduction is more pronounced in more severe sleep apnea, \textsuperscript{21,23} even in normotensive subjects. \textsuperscript{21} Compliance with CPAP treatment may be particularly poor in OSAS patients with a low AHI. This might explain why 2 trials in OSAS patients with the lowest AHIs did not show any effect on blood pressure. \textsuperscript{24,26} There was no relationship between changes in the 24-hour MBP and the widely used Epworth Sleepiness Scale score for daytime sleepiness.

Publication bias typically excludes trials that fail to report statistically significant differences. Our findings are unlikely to be biased by this tendency: the 95% CIs for 8 of the 12 individual estimates for net change in the 24-hour MBP included unity. Statistically nonsignificant results may get published in this field because of the relative popularity of research on OSAS. Alternatively, most of the included trials reported data on other outcome measures that were significantly associated with active CPAP treatment, including neurophysiological function and mood, quality of life, compliance, and patient preferences.

This review has a number of strengths. Eligible RCTs had to have been published as full-length original articles in peer-reviewed journals and to have used 24-hour automated ambulatory blood pressure monitoring. Ambulatory measurement of blood pressure is superior to single office measurements of average pressures,\textsuperscript{86} is not influenced by a placebo treatment,\textsuperscript{87} and accurately predicts left ventricular hypertrophy,\textsuperscript{88} and cardiovascular risk.\textsuperscript{30,58} All trials were conducted within the past decade, minimizing any effect of secular trends and changes in medical practice. To avoid a further source of variability between trials, we excluded trials reporting the effects of dental devices on 24-hour blood pressure.\textsuperscript{26,67}

A key feature of our systematic review is the metaregression analysis exploring the relationship between net change in 24-hour ambulatory MBP and several continuous variables considered potential sources of heterogeneity. These metaregression analyses were not limited by insufficient power.\textsuperscript{43,55}

These strengths, however, are balanced by some potential limitations. One of the most recent trials,\textsuperscript{27} which found no significant reduction in blood pressure, is the only trial that used autotitration CPAP. Also, ambulatory blood pressure monitoring is more difficult in persons with large arms, and patients who are more obese may have a more severe degree of sleep apnea. It is possible that trials limited to ambulatory blood pressure monitoring might select patients with a less severe degree of OSAS. Duration of OSAS before inclusion; the percentage of hypertensive, overweight, and obese subjects; smoking status; alcohol use (especially before bedtime); and concomitant (antihypertensive) medication therapy may also have confounded the extent of net blood pressure reduction. A meta-analysis of individual-level data using common definitions and cutoff points would allow adjustments for such confounding variables and estimation of effects in identically defined subgroups of patients.

Data obtained from individual patients separately analyzed for normotensive and hypertensive OSAS patients might answer the following important questions: What is the effect size in normotensive OSAS? What is the effect size in hypertensive OSAS patients? Does OSAS severity influence the effect in normotensive and hypertensive subjects? Clarifying the effect of CPAP treatment on hypertension also would support clinical decisions: When confronted with an OSAS patient with hypertension, should one simply treat OSAS and expect the hypertension to improve, or should one concurrently start specific antihypertensive treatment?

Economic evaluation also is needed because of the cost implications related to the widespread prevalence of OSAS in industrialized countries and because obesity, one of the strongest risk factors for OSAS, is more prevalent in these countries.

In conclusion, among OSAS patients, CPAP reduces 24-hour ambulatory MBP, with greater treatment-related reductions in ambulatory MBP among patients with a more severe degree of OSAS and a better effective nightly use of the CPAP device. These reductions in blood pressure are likely to contribute to a better prognosis in terms of adverse cardiovascular events.

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