Published in final edited form as:

J Hypertens. 2014 December ; 32(12): 2341–2350. doi:10.1097/HJH.0000000000000372.

Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis

Imran H. Iftikhar^a, Christopher W. Valentine^b, Lia R.A. Bittencourt^c, Debbie L. Cohen^d, Annette C. Fedson^e, Thorarinn Gíslason^f, Thomas Penzel^g, Craig L. Phillips^{h,i}, Lin Yu-sheng^j, Allan I. Pack^e, and Ulysses J. Magalang^k

^aDivision of Pulmonary, Critical Care, and Sleep Medicine, University of South Carolina, Columbia, South Carolina ^bDivision of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA ^cDisciplina de Medicina e Biologia do Sono, Departamento de Psicobiologia, Universidade Federal de São Paulo, São Paulo, Brazil ^dRenal and Hypertension Division, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA ^eDivision of Sleep Medicine, Center for Sleep and Circadian Neurobiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA ^fFaculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland ^gCenter of Sleep Medicine, Charité University Hospital, Berlin, Germany ^hDepartment of Respiratory and Sleep Medicine, Royal North Shore Hospital, St Leonards ⁱWoodcock Institute of Medical Research, University of Sydney, Sydney, New South Wales, Australia ^jDepartment of Internal Medicine, Taoyuan Chang Gung Memorial Hospital, Taiwan, Republic of China ^kDivision of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Abstract

Objective—To systematically analyze the studies that have examined the effect of continuous positive airway pressure (CPAP) on blood pressure (BP) in patients with resistant hypertension and obstructive sleep apnea (OSA).

Methods—Design – meta-analysis of observational studies and randomized controlled trials (RCTs) indexed in PubMed and Ovid (All Journals@Ovid). participants: individuals with resistant hypertension and OSA; interventions – CPAP treatment.

Results—A total of six studies met the inclusion criteria for preintervention to postintervention analyses. The pooled estimates of mean changes after CPAP treatment for the ambulatory (24-h) SBP and DBP from six studies were -7.21 mmHg [95% confidence interval (CI): -9.04 to -5.38 ; $P < 0.001$; I^2 58%) and -4.99 mmHg (95% CI: -6.01 to -3.96 ; $P < 0.001$; I^2 31%), respectively.

© 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Correspondence to Ulysses J. Magalang, MD, Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, The Ohio State University Wexner Medical Center, 201 Davis Heart and Lung Research Institute, 473 West 12th Avenue, Columbus, OH 43210, USA. Tel: +1 614 247 7701; fax: +1 614 293 4799; magalang.1@osu.edu.

Conflicts of interest

None of the authors have conflicts of interest with respect to this article.
This was not an industry-sponsored study.

The pooled estimate of the ambulatory SBP and DBP from the four RCTs showed a mean net change of -6.74 mmHg [95% CI: -9.98 to -3.49 ; $P < 0.001$; I^2 61%] and -5.94 mmHg (95% CI: -9.40 to -2.47 ; $P = 0.001$; I^2 76%), respectively, in favor of the CPAP group.

Conclusion—The pooled estimate shows a favorable reduction of BP with CPAP treatment in patients with resistant hypertension and OSA. The effects sizes are larger than those previously reported in patients with OSA without resistant hypertension.

Keywords

blood pressure; continuous positive airway pressure; meta-analysis; obstructive sleep apnea; resistant hypertension

INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder that is associated with increased risk of hypertension [1–3]. Treatment of OSA with continuous positive airway pressure (CPAP) is associated with a lower risk of incident hypertension [4]. Randomized controlled trials (RCTs) show that the reduction in blood pressure (BP) with CPAP therapy is significant, but modest with an average decrease in SBP of 2.6 mmHg and an average decrease in DBP of 2.0 mmHg [5].

Resistant hypertension, defined as BP that remains above the normal despite the concurrent use of three different antihypertensive medications including a diuretic or controlled BP that requires four or more medications [6], occurs in 9–13% of the general hypertensive population [7]. As hypertension affects about 77.9 million (one out of every three adults) in the United States, those with resistant hypertension represent a significant proportion of the population [8]. Resistant hypertension is a major public health burden because these individuals are at an increased risk for target organ damage and adverse cardiovascular outcomes including stroke, myocardial infarction, and congestive heart failure compared with those with more easily controlled hypertension [9,10].

The most common cause of resistant hypertension is OSA [11]. Among patients with resistant hypertension, the prevalence of OSA is reported to be 70–83% [12]. Several meta-analyses have shown consistently that CPAP treatment reduces BP in patients with OSA [5,13,14]. It has been suggested that CPAP treatment of OSA may have a more robust response in those with difficult-to-control hypertension [14]. However, the effects of CPAP on BP in patients with resistant hypertension have not been systematically examined. We therefore planned a systematic review and meta-analysis to assess whether CPAP reduces BP in patients with OSA and resistant hypertension.

METHODS

The investigators of this study are members of the Hypertension Working Group of the Sleep Apnea Genetics International Consortium (SAGIC).

Data sources

We searched in the databases of PubMed and Ovid (All Journals@Ovid) from inception to 30 July 2013 for observational studies and RCTs that specifically included participants with resistant hypertension and OSA. We also searched through the meeting abstracts of Associated Professional Societies of Sleep, American Thoracic Society and American College of Chest Physicians. Only one abstract was found relevant to our inclusion criteria. However, as the authors, the data, and the study population were the same as one of the published papers identified in our search from PubMed, we decided to include the published paper only [15].

Search strategy and selection criteria

We used the search terms, 'sleep apnea', 'hypertension', 'blood pressure' and 'continuous positive airway pressure' in both Ovid and PubMed. Figure 1 depicts a summary of our study selection process. Search terms used in PubMed are provided in the Supplementary data, <http://links.lww.com/HJH/A406>. We adhered to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines for all stages of the design, implementation, and reporting of this meta-analysis [16,17]. Altogether, 157 articles were found. We shortlisted the 57 studies from this initial search, as most were unrelated to our meta-analysis (such as case reports, letters, review articles or multiseried case reports). Full manuscripts of these 57 studies were obtained. These were divided among the investigators for review using the inclusion criteria below. All excluded studies were then reviewed for a second time by one of the investigators (I.H.I.). A total of 50 studies included participants who did not have resistant hypertension and these were excluded. One study that did include participants with resistant hypertension was excluded because of its retrospective design [18]. A total of six studies were finally included in our meta-analysis and the full manuscripts of these studies were reviewed by all investigators. There were no disagreements between the authors on the inclusion or exclusion of a study. We used the following inclusion criteria:

1. A study involving only adult human participants (age 18 years and older).
2. A study investigating the preintervention and post-intervention effect of CPAP on SBP and DBP.
3. A study comprising of participants with resistant hypertension and OSA.
4. We considered only prospective cohort studies either observational or RCTs. We did not include any case reports, retrospective studies or case-series reports.
5. We considered resistant hypertension in study participants if the participants were described to have BP above the goal in spite of the concurrent use of three antihypertensive agents of different classes (including a diuretic) at adequate doses [6].

Data abstraction

For this study, we extracted from each paper, the first author's name, year of publication, number of participants, preintervention and postintervention SBP and DBP measurements

with SDs, country of origin, study design, demographics [including mean age, BMI, sex distribution, presence of comorbidities and the apnea–hypopnea index (AHI)], and the method of BP measurement (ambulatory BP monitoring, or office BP). For the four RCTs, pre-CPAP and post-CPAP intervention data were extracted in a similar fashion [15,19–21]. Our primary outcome, defined *a priori*, was the 24-h SBP and DBP as recorded by the ambulatory blood pressure monitoring (ABPM). This measurement was given preference, because several studies have shown that ABPM is superior in predicting the target organ damage and cardiovascular events compared with office BP [22]. We abstracted the 24-h ABPM data for all included studies. Our secondary outcomes were the daytime and nocturnal SBP and DBP, for which separate analyses were performed. For the studies in which the SEM was reported, we calculated the SD based on the number of participants in the study and the reported SEM. All data were entered in mmHg. A study selected for inclusion in our meta-analysis did not report separate data for the 25 out of 44 study participants who met the criteria for resistant hypertension in the published manuscript. However, the data on these 25 patients were requested by us from the corresponding authors of the study and included in our analyses [19].

Quantitative data synthesis

The effect of CPAP was quantified by estimating the mean difference of outcomes (24-h ABPM and nocturnal mean SBP and DBP) before and after CPAP intervention. Data from the four RCTs on the effect of CPAP on SBP and DBP were also separately analyzed. This was analyzed by estimating and comparing the pooled means and SDs of the BP variables between control and intervention groups. The method by Follmann *et al.* [23] that assumes a correlation of 0.5 between preintervention and postintervention BP levels was adopted. Effect sizes and 95% confidence intervals (CIs) were estimated by pooling the available data using the Comprehensive Meta-Analysis (CMA) V2 software.

The CMA software was used which generates both random effects methods to account for variance between the studies as well as within the studies [24] and fixed effects methods to account for variance within the studies. We decided, *a priori*, to report all analyses in random effects model, as the study population to be analyzed in our meta-analysis was heterogeneous. The heterogeneity was separately assessed by I^2 statistics.

Heterogeneity was assessed with I^2 statistics [25]. For analyses with statistically significant results, but with moderate-to-high heterogeneity, prestated subgroup analyses were conducted to assess the effect of baseline Epworth Sleepiness Score (ESS), duration of CPAP intervention, method of BP measurement, trial design, geographical locations where studies were conducted and SBP/DBP of the participants at entry. To assess the risk of publication bias, a funnel plot of standard error and difference in means [26] was constructed for the pre-CPAP to post-CPAP analysis of 24-h SBP. We selected this analysis for conducting the assessment of publication bias, as this analysis incorporated all six studies that we included in our meta-analysis.

We also conducted meta-regression for the association of prestated variables of interest; ESS, AHI, BMI, and age at baseline. We used the mixed effects method (unrestricted maximum likelihood).

For the available data from studies (where such data was reported), we sought to conduct a meta-analysis of correlation and sample size for hours of CPAP use and change in BP. Sensitivity analyses were conducted for all analyses to evaluate the effects of each selected study on the overall results of the meta-analysis.

Publication bias was assessed with the construction of a funnel plot, and further assessed by Eggers test of the intercept and the Begg and Mazumdar rank correlation test [27]. A *P* value of less than 0.05 on these tests was considered statistically significant for the evidence of publication bias.

RESULTS

A total of seven studies [15,19–21,28–30] were initially shortlisted for the meta-analysis. However, one study [30] was excluded as BP was not measured by the ABPM methods. Figure 1 outlines our search strategy and selection process for including the six studies in our meta-analysis. The total number of study participants was 329, but the number included with each analysis varied because of different study designs. A total of 196, 193, and 171 study participants were analyzed for pre-CPAP to post-CPAP intervention analyses of ambulatory, daytime, and nocturnal BP, respectively. A total of 224 study participants for the RCT analyses of ambulatory and daytime BP and 174 for the RCT analyses of nocturnal BP were included. Characteristics of the study population in each trial are outlined in Table 1. Participants in all of the studies had a mean age of 55 and older, and had a mean BMI of 30 kg/m² or greater. The included studies enrolled participants who had OSA and resistant hypertension. Although the majority of the study participants were obese, those with other comorbidities were excluded. The duration of CPAP intervention ranged from 3 weeks to 6 months. There were two observational studies [28,29] and four RCTs [15,19–21]. We used the ABPM data for 24-h SBP and DBP analyses from the six studies in which these data were available [15,19–21,28,29]. A total of six studies [15,20,21,28–30] reported the nocturnal BP measurements, of which three were RCTs [15,20,21]. Three of the studies were from Spain [20,21,29], one from Russia [19], one from Brazil [15] and one from Canada [28]. Table 2 outlines the baseline AHI, ESS and CPAP compliance of study participants in different studies.

Effect on ambulatory blood pressure after continuous positive airway pressure intervention

The pooled estimate of the mean changes and the corresponding 95% CIs for ambulatory (24-h or office) SBP and DBP from six studies [15,19–21,28,29] were -7.21 (95% CIs: -9.04 to -5.38 ; $P < 0.001$; I^2 58%) and -4.99 (95% CIs: -6.01 to -3.96 ; $P < 0.001$; I^2 31%), respectively (Figs 2 and 3).

Effect on nocturnal blood pressure after continuous positive airway pressure intervention

The pooled estimate of mean changes and the corresponding 95% CIs for nocturnal SBP and DBP from five studies [15,20,21,28,29] were -6.79 mmHg [95% confidence interval (CI): -13.86 to 0.26 ; $P = 0.05$; I^2 96%] and -3.67 mmHg (95% CI: -8.05 to 0.71 ; $P = 0.10$; I^2 94%), respectively (Table 3).

Comparison of mean change in the ambulatory blood pressure between continuous positive airway pressure and control groups

The pooled estimate of the data from the four RCTs [15,19–21] showed a mean net change of -6.74 mmHg (95% CI: -9.98 to -3.49 ; $P < 0.001$; I^2 61%) and -5.94 mmHg (95% CI: -9.40 to -2.47 ; $P = 0.001$; I^2 76%) in the ambulatory SBP and DBP, respectively, in favor of the CPAP groups (Figs 4 and 5).

Comparison of mean change in nocturnal blood pressure between continuous positive airway pressure and control groups

The pooled estimate of the data from three RCTs [15,20,21] showed a mean net change of -2.08 mmHg (95% CI: -4.33 to 0.16 ; $P = 0.06$; I^2 0.0%) and -1.47 mmHg (95% CI: -3.22 to 0.28 ; $P = 0.10$; I^2 0.0%) in nocturnal SBP and DBP, respectively (Table 3). The results on SBP show a trend favoring the CPAP groups.

Separate analyses of daytime BP (pre-CPAP to post-CPAP intervention, based on six studies) showed statistically significant reductions in both SBP [-10.16 mmHg (95% CI: -10.16 to -4.81); $P < 0.001$] and DBP [-5.16 mmHg (95% CI: -7.61 to -2.71); $P < 0.001$]. Comparison of the mean change in daytime BP (between CPAP and control groups, based on four RCTs) also showed statistically significant reductions in both SBP [-5.32 mmHg (95% CI: -9.96 to -0.68); $P = 0.02$] and DBP [-4.80 mmHg (95% CI: -7.51 to -2.10); $P < 0.001$]. Supplementary figures S5–S8, <http://links.lww.com/HJH/A406> depict the results in forest plots for daytime BP analyses.

Exploring heterogeneity

To explore for the potential sources of heterogeneity, subgroup analyses was done based on the predefined variables. Heterogeneity in the analyses of pre-CPAP to post-CPAP 24-h SBP and DBP mean difference was found not to be associated with ESS less than 10, CPAP duration (<2 or >2 months), sample size greater than 20, pre-CPAP BP greater than 145/85 mmHg or studies including European participants (Table 4). Subgroup analyses based on the design (RCT versus non-RCT) of studies did not lead to heterogeneity in most of the subgroup analyses (Table 5). However, when the 24-h SBP and DBP data from RCTs were further analyzed based on their design, significant heterogeneity was noticed in the noncross-over trials (Table 5). The SBP and DBP subgroup analyses based on ESS, CPAP duration (<2 months), study sample size, geographical location and pre-CPAP BP did not reveal the heterogeneity (Table 5).

Meta-regression

Predefined meta-regression analyses was performed for pooled mean net change in SBP and DBP (both 24 h and nocturnal) based on pre to post CPAP analyses (Table 6). Meta-regression showed no relationship with either baseline age, BMI or ESS. However, significant relationship was observed between baseline AHI and pooled mean net change in 24-h DBP.

Correlational analysis

Meta-analysis of correlation and sample size showed statistically significant correlation between hours of CPAP use and DBP response, with a pooled correlation of 0.26, with a *P* value of 0.003. This was based on the two studies with a total of 121 study participants in the CPAP arms [21,24].

Publication bias

The funnel plot showed visual evidence of the publication bias (Fig. 6).

Sensitivity analysis

In the sensitivity analyses, the exclusion of any study from the analyses did not change the pooled estimates of CPAP intervention on 24-h SBP, 24-h DBP, and the pooled estimates of mean net change between CPAP and control for 24-h SBP, 24-h DBP and nocturnal DBP. One study [15] appeared to be an outlier for the mean net change in nocturnal SBP between CPAP and control.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis that examined specifically the effects of CPAP treatment for OSA on BP in patients with resistant hypertension. The preintervention to postintervention analyses showed a significant mean reduction by -7.2 and -4.99 mmHg in the ambulatory SBP and DBP, respectively, whereas separate analyses from the RCTs showed a reduction in SBP and DBP by -6.74 and -5.94 mmHg, respectively. These effect sizes are greater than the reduction in BP reported with CPAP treatment in hypertensive OSA patients without resistant hypertension [5]. However, the nocturnal preintervention to postintervention analysis and the BP analysis from RCTs (in which such data were available) failed to reach statistical significance, although there were only three RCTs that reported this data.

Several prior meta-analyses have studied the effects of CPAP on BP in patients with OSA [5,13,14]. Most of these studies showed modest reductions in SBP and DBP in the 2–3 mmHg range. Studies included in these meta-analyses enrolled participants with OSA, who were either normotensive or hypertensive. In the most recent meta-analysis by Montesi *et al.* [31], however, a subgroup analysis showed that the effect of CPAP on BP is also in the same modest range (2–3 mmHg) even in hypertensive OSA patients. Therefore, the effect of CPAP on BP in patients with resistant hypertension appears to be greater. This is clinically important because patients with resistant hypertension are at an increased risk for target-organ damage and cardiovascular complications compared with those hypertensive patients with easy to control BP [6,9]. In our meta-analysis, we included only those trials that studied participants with resistant hypertension and our pooled estimates, more specifically the preintervention to postintervention analyses, showed a reduction in not just the ambulatory BP, but also the nocturnal BP measurements. Therefore, our findings provide additional rationale for a more aggressive screening for OSA in those with resistant hypertension as well as ensuring treatment compliance with nasal CPAP in those found to have OSA.

Two prior meta-analyses [5,13] of the studies that enrolled either normotensive or hypertensive participants showed conflicting findings in the effect of CPAP on nocturnal SBP. The results from our meta-analysis do show comparable reductions in nocturnal SBP in terms of the magnitude of change, statistical significance was not achieved. This is explained by our sensitivity analysis, which identified the study by Pedrosa *et al.* [15] as an outlier. This is because their study did not show a significant reduction in nocturnal SBP and DBP, a finding the authors themselves acknowledged was against their initial hypothesis and unexplained. This is an important finding as it has been previously suggested that nocturnal SBP may predict the future vascular events better than the diurnal measurements [32]. Similarly, in a separate study, Logan *et al.* [12] showed that resistant hypertension in patients with OSA is predominantly systolic and more pronounced at night. Excluding for the study by Pedrosa *et al.* [15], which did not show a decrease in nocturnal BP, the two studies by Martinez-Garcia *et al.* [21,29], and the ones by Lozano *et al.* [20] and Logan *et al.* [28] reported an increase in the number of study participants who recovered the normal nocturnal dipper BP pattern.

Our meta-analysis included patients who have or do not have subjective daytime sleepiness based on the ESSs (Table 2). Two previous studies by Barbe *et al.* [33] and Robinson *et al.* [34] suggest that CPAP treatment may not result in a significant BP reduction in those without daytime hypersomnolence. However, the study participants in both of these studies did not have resistant hypertension. At present, there is no clear evidence from the studies to suggest a similar association between daytime hypersomnolence and BP response to CPAP in patients with resistant hypertension. However, the results from our subgroup analyses (Tables 4 and 5) indicate that the participants with ESS less than 10, showed a similar statistically significant reduction in 24-h BP outcomes.

The data on correlation of BP change and hours of CPAP use was not universally available from all studies. On the basis of the two studies by Martinez-Garcia *et al.* [21,29], with a total of 121 participants, results of our meta-analysis show good correlation between hours of CPAP use and decrease in DBP. The latter study by Martinez-Garcia *et al.* also reported positive linear correlation between hours of CPAP use and decrease in 24-h SBP ($r=0.29$; $P=0.02$). However, the results are in contrast to that reported by Pedrosa *et al.* [15], who did not observe such a correlation in 19 study participants, a much smaller sample size.

The high prevalence of OSA among patients with resistant hypertension seems to be multifactorial, but the exact reasons are unclear. It is possible that both OSA and resistant hypertension share common mechanistic links. It has been postulated that overnight rostral fluid shift with fluid volume displacement from the legs to the neck plays an important role in the genesis of upper airway obstruction [35]. The phenomenon of overnight rostral fluid shift is more pronounced in patients with resistant hypertension than in those with controlled hypertension [35]. It is known that hyperaldosteronism and the associated fluid retention play a major mechanistic role in the development of resistant hypertension [36]. Similarly, although based on the preliminary evidence, aldosterone has also been implicated in the increased severity of OSA seen in patients with resistant hypertension [37,38]. Thus, it is possible that a common pathway between OSA and resistant hypertension could be the fluid retention.

Additionally, OSA alone can cause poorly controlled BP through several different mechanisms. Increased sympathetic tone [39], endothelial dysfunction [40], and salt and water dysregulation [6] have all been implicated as potential mechanisms for the increase in BP in OSA. Finally, another common link may be obesity, as this is a risk factor for both conditions [6].

Our meta-analysis has several strengths. First, we analyzed ambulatory and nocturnal BP data separately and also included separate analyses of these outcomes based on the RCTs. Second, our meta-analysis had enough power to detect a BP-lowering effect of CPAP in the included studies. Third, our meta-analysis included studies involving different geographic locations and ethnicities, allowing some degree of generalizability for our findings. Fourth, we performed sensitivity analyses to identify studies that could have caused a significant shift in the results. As expected in the nocturnal SBP and DBP analysis, the study by Pedrosa *et al.* [15] was the outlier, predominantly responsible for the statistical nonsignificance of results.

There are limitations to our study. It is possible that potential confounding factors in addition to CPAP treatment could have affected our findings. Most important of these include concomitant use of the antihypertensive medications, obesity and other life-style factors such as the use of alcohol and smoking. The small sample size and the short duration of follow-up for most included studies are other important limitations of our meta-analysis. Finally, visual assessment of the funnel plot revealed publication bias. However, this is because of the fact that we excluded the study by Zhang and Li [30], as it did not provide 24-h BP data. This was clearly evident, as including the office BP data from this study clearly did not reveal the publication bias.

Despite these limitations, the results of our meta-analysis argue strongly that OSA contributes to the resistance to medication treatment in patients with resistant hypertension because of the large effect size of CPAP treatment on BP reduction. This is important from an epidemiological standpoint at a population level. Even modest reductions in BP (especially DBP) of 2 mmHg [41] or 5 mmHg [42] have been associated with a significant decrease in the risk for stroke and coronary heart disease.

In conclusion, among patients with OSA and resistant hypertension, the pooled estimate shows a relatively large effect size on BP reduction with CPAP treatment. This supports the idea of more aggressive screening for OSA in those with resistant hypertension as well as ensuring treatment compliance in those found to have OSA. Our findings also support the notion that patients with OSA and resistant hypertension represent an extreme and unique phenotype compared with those OSA patients who do not develop hypertension. This may be the result of less common gene variants with large effect. Further research and RCTs involving a larger number of study participants, followed over a longer period of time, are warranted to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors greatly appreciate the assistance of Alexander Y. Litvin (from the Russian Cardiology Research and Production Complex, Moscow, Russian Federation) in providing the specific data from their study in the participants with resistant hypertension.

Financial support: This study was supported by the NHLBI award P01 HL094307 (A.I.P.), HL093463 (U.J.M.) and UL1TR000090 of the Ohio State University Center for Clinical and Translational Science.

Abbreviations

ABPM	ambulatory blood pressure monitoring
AHI	apnea–hypopnea index
BP	blood pressure
CI	confidence interval
CPAP	continuous positive airway pressure
ESS	Epworth Sleepiness Score
I^2	marker for statistical heterogeneity
mmHg	millimeters of mercury
OSA	obstructive sleep apnea
RCT	randomized controlled trial

References

1. 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. [PubMed: 10805822]
2. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med*. 1997; 157:1746–1752. [PubMed: 9250236]
3. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Sleep Heart Health Study*. *JAMA*. 2000; 283:1829–1836. [PubMed: 10770144]
4. Marin JM, Agusti A, Villar I, Forner M, Nieto D, Carrizo SJ, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. *JAMA*. 2012; 307:2169–2176. [PubMed: 22618924]
5. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension*. 2007; 50:417–423. [PubMed: 17548722]
6. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation*. 2008; 117:e510–e526. [PubMed: 18574054]
7. Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension*. 2011; 57:1076–1080. [PubMed: 21502568]
8. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. *Circulation*. 2013; 127:e6–e245. [PubMed: 23239837]

9. Cuspidi C, Macca G, Sampieri L, Michev I, Salerno M, Fusi V, et al. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. *J Hypertens*. 2001; 19:2063–2070. [PubMed: 11677373]
10. Isaksson H, Ostergren J. Prognosis in therapy-resistant hypertension. *J Intern Med*. 1994; 236:643–649. [PubMed: 7989899]
11. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*. 2011; 58:811–817. [PubMed: 21968750]
12. Logan AG, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens*. 2001; 19:2271–2277. [PubMed: 11725173]
13. Haentjens P, Van Meerhaeghe A, Moscariello A, De Weerd S, Poppe K, Dupont A, et al. 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. *Arch Intern Med*. 2007; 167:757–764. [PubMed: 17452537]
14. Alajmi M, Mulgrew AT, Fox J, Davidson W, Schulzer M, Mak E, et al. Impact of continuous positive airway pressure therapy on blood pressure in patients with obstructive sleep apnea hypopnea: a meta-analysis of randomized controlled trials. *Lung*. 2007; 185:67–72. [PubMed: 17393240]
15. Pedrosa RP, Drager LF, de Paula LK, Amaro AC, Bortolotto LA, Lorenzi-Filho G. Effects of obstructive sleep apnea treatment on blood pressure in patients with resistant hypertension: a randomized trial. *Chest*. 2013; 144:1487–1494. [PubMed: 23598607]
16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–2012. [PubMed: 10789670]
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; 151:264–269. W64. [PubMed: 19622511]
18. Dernaika TA, Kinasewitz GT, Tawh MM. Effects of nocturnal continuous positive airway pressure therapy in patients with resistant hypertension and obstructive sleep apnea. *J Clin Sleep Med*. 2009; 5:103–107. [PubMed: 19968040]
19. Litvin AY, Sukmarova ZN, Elfimova EM, Aksenova AV, Galitsin PV, Rogozha AN, et al. Effects of CPAP on 'vascular' risk factors in patients with obstructive sleep apnea and arterial hypertension. *Vasc Health Risk Manag*. 2013; 9:229–235. [PubMed: 23690688]
20. Lozano L, Tovar JL, Sampol G, Romero O, Jurado MJ, Segarra A, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. *J Hypertens*. 2010; 28:2161–2168. [PubMed: 20577130]
21. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, Lloberes P, Diaz de Atauri MJ, Somoza M, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *JAMA*. 2013; 310:2407–2415. [PubMed: 24327037]
22. Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med*. 2006; 354:2368–2374. [PubMed: 16738273]
23. Follmann D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *J Clin Epidemiol*. 1992; 45:769–773. [PubMed: 1619456]
24. Sutton, AAK.; Jones, D.; Sheldon, T.; Song, F. *Methods for meta-analysis in medical research*. Wiley Series in Probability and Statistics. New York: NY: John Wiley & Sons Inc; 2000.
25. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods*. 2006; 11:193–206. [PubMed: 16784338]
26. Sterne JA, Egger M, Smith GD. Systematic reviews in healthcare: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001; 323:101–105. [PubMed: 11451790]
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50:1088–1101. [PubMed: 7786990]

28. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, et al. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. *Eur Respir J*. 2003; 21:241–247. [PubMed: 12608436]
29. Martinez-Garcia MA, Gomez-Aldaravi R, Soler-Cataluna JJ, Martinez TG, Bernacer-Alpera B, Roman-Sanchez P. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. *Eur Respir J*. 2007; 29:951–957. [PubMed: 17301092]
30. Zhang XL, Li YQ. Efficacy of continuous positive airway pressure therapy upon resistant hypertension in patients with obstructive sleep apnea hypopnea syndrome. *Zhonghua Yi Xue Za Zhi*. 2009; 89:1811–1814. [PubMed: 19953923]
31. Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. *J Clin Sleep Med*. 2012; 8:587–596. [PubMed: 23066375]
32. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, et al. 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. [PubMed: 10450715]
33. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, et al. 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. [PubMed: 11388814]
34. Robinson GV, Smith DM, Langford BA, Davies RJ, Stradling JR. Continuous positive airway pressure does not reduce blood pressure in nonsleepy hypertensive OSA patients. *Eur Respir J*. 2006; 27:1229–1235. [PubMed: 16455835]
35. Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. *Hypertension*. 2010; 56:1077–1082. [PubMed: 21060007]
36. Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P. Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension*. 2002; 40:892–896. [PubMed: 12468575]
37. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, et al. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens*. 2010; 24:532–537. [PubMed: 20016520]
38. Gonzaga CC, Gaddam KK, Ahmed MI, Pimenta E, Thomas SJ, Harding SM, et al. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med*. 2010; 6:363–368. [PubMed: 20726285]
39. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995; 96:1897–1904. [PubMed: 7560081]
40. Atkeson A, Yeh SY, Malhotra A, Jelic S. Endothelial function in obstructive sleep apnea. *Prog Cardiovasc Dis*. 2009; 51:351–362. [PubMed: 19249441]
41. Cook NR, Cohen J, Hebert PR, Taylor JO, Hennekens CH. Implications of small reductions in diastolic blood pressure for primary prevention. *Arch Intern Med*. 1995; 155:701–709. [PubMed: 7695458]
42. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990; 335:765–774. [PubMed: 1969518]

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

FIGURE 2.

Forest plot for the mean change in 24-h SBP with the corresponding 95% confidence interval (CI).

FIGURE 3. Forest plot for the mean change in 24-h DBP with the corresponding 95% confidence interval (CI).

FIGURE 4.

Forest plot for the mean change in 24-h SBP from the randomized controlled trials with the corresponding 95% confidence interval (CI).

FIGURE 5. Forest plot for the mean change in 24-h DBP from randomized controlled trials with the corresponding 95% confidence interval (CI).

FIGURE 6.
Funnel plot for the assessment of publication bias.

Characteristics of the studies

TABLE 1

Author	Year	Type of study	Number of participants	Age (SD)	Sex (male)	BMI (SD)	Duration of intervention (used in this meta-analysis)	Method of BP measurement
Logan <i>et al.</i> [28]	2003	Observational	11	57 (2)	90%	34.4 (2.4)	2 months	ABPM
Martinez-Garcia <i>et al.</i> [29]	2007	Observational	23 ^a	68.1 (7.8)	52.2%	35.1	3 months	ABPM
Lozano <i>et al.</i> [20]	2010	RCT	20 (CPAP)	59.2 (8.7)	75.9%	30 (4.3)	3 months	ABPM
			21 (Control)					
Pedrosa <i>et al.</i> [15]	2013	RCT	19 (CPAP)	57 (2) ^b	74% ^b	36 (31–41) ^c	6 months	ABPM
			16 (Control)					
Litvin <i>et al.</i> [19]	2013	RCT (cross-over design)	25 (CPAP)	55.5 (9.6)	77.27%	37.7 (7.8)	3 weeks	Office
			25 (Control)					
Martinez-Garcia <i>et al.</i> [21]	2013	RCT	98 (CPAP)	56.0 (9.5)	68.6%	34.1 (5.4)	3 months	ABPM
			96 (Control)					

ABPM, ambulatory blood pressure monitoring; CPAP, continuous positive airway pressure; RCT, randomized controlled trial.

^aOut of 39 participants, 33 completed study and out of these 23 showed good CPAP tolerance.

^bData expressed as mean and standard error of mean.

^cData expressed as median and interquartile range.

TABLE 2

Baseline AHI, ESS and CPAP compliance

Author	AHI	ESS	CPAP compliance
Logan <i>et al.</i> [28]	45.3 ± 10.1	–	–
Martinez-Garcia <i>et al.</i> [29]	40 ± 9.7 ^a	7.4 ± 5.1 ^a	4 h ^a
Lozano <i>et al.</i> [20]	52.67 ± 21.5	6.2 ± 3.34	5.6 ± 1.5 h
Pedrosa <i>et al.</i> [15]	36 (24–51) ^b	12 ± 1	6:01 ± 0:20 h
Litvin <i>et al.</i> [19]	63.4 ± 26.3	–	5.1 ± 1.6 h
Martinez-Garcia <i>et al.</i> [21]	41.3 (18.7)	8.9 (4.0)	5 ± 1.9 h

AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score.

^aData represents the 23 study participants included from this study.

^bData shown in median and interquartile range.

TABLE 3

Nocturnal blood pressure data

	No. of studies	Mean change (mmHg)	95% CI, <i>P</i> value
Mean difference in SBP after CPAP	5	−6.79	−13.86 to 0.26, <i>P</i> =0.05
Mean difference in DBP after CPAP	5	−3.67	−8.05 to 0.71, <i>P</i> =0.10
Mean net change in SBP between CPAP and control	3	−2.08	−4.33 to 0.16, <i>P</i> =0.06
Mean net change in DBP between CPAP and control	3	−1.47	−3.22 to 0.28, <i>P</i> =0.10

CIs, confidence intervals; CPAP, continuous positive airway pressure.

TABLE 4

Subgroup analyses of 24-h blood pressure data (preintervention to postintervention)

Subgroup	SBP			DBP		
	No. of studies	Mean net change	95% CI, <i>P</i> value	No. of studies	Mean net change	95% CI, <i>P</i> value
ESS						
<10	3	-5.29	-7.36 to -3.22, <i>P</i> 0.001; <i>I</i> ² 0%	3	-4.10	-5.95 to -2.25, <i>P</i> <0.001; <i>I</i> ² 0%
>10	1	-6.50	-7.98 to -5.01, <i>P</i> <0.001; <i>I</i> ² 0%	1	-4.50	-5.35 to -3.64, <i>P</i> <0.001; <i>I</i> ² 0%
CPAP duration						
<2 months	2	-9.47	-11.88 to -7.06, <i>P</i> 0.001; <i>I</i> ² 30%	2	-6.08	-7.57 to -4.59, <i>P</i> 0.001; <i>I</i> ² 8%
>2 months	4	-6.04	-7.28 to -4.79, <i>P</i> <0.001; <i>I</i> ² 0%	4	-4.36	-5.14 to -3.57, <i>P</i> <0.001; <i>I</i> ² 0%
Study sample size						
<20	2	-8.37	-12.28 to -4.45, <i>P</i> <0.001; <i>I</i> ² 86%	2	-4.94	-6.07 to -3.80, <i>P</i> <0.001; <i>I</i> ² 76%
>20	4	-6.07	-7.81 to -4.33, <i>P</i> 0.001; <i>I</i> ² 0%	4	-5.14	-7.47 to -2.82, <i>P</i> 0.001; <i>I</i> ² 43%
Study design						
Non-RCT	2	-9.62	-12.86 to -6.39, <i>P</i> <0.001; <i>I</i> ² 23%	2	-4.75	-7.67 to -1.83, <i>P</i> =0.001; <i>I</i> ² 46%
RCT	4	-6.31	-7.46 to -5.16, <i>P</i> 0.001; <i>I</i> ² 0%	4	-4.98	-6.36 to -3.59, <i>P</i> 0.001; <i>I</i> ² 35%
Geographical location						
Asia	1	-8.00	-11.24 to -4.75, <i>P</i> <0.001; <i>I</i> ² 0%	1	-7.60	-10.84 to -4.36, <i>P</i> <0.001; <i>I</i> ² 0%
Europe	3	-5.29	-7.36 to -3.22, <i>P</i> 0.001; <i>I</i> ² 0%	3	-4.10	-5.95 to -2.25, <i>P</i> 0.001; <i>I</i> ² 0%
America	2	-8.37	-12.83 to -4.45, <i>P</i> 0.001; <i>I</i> ² 86%	2	-4.94	-6.07 to -3.80, <i>P</i> 0.001; <i>I</i> ² 47%
Baseline SBP/DBP						
<145/<85	2	-9.62	-12.86 to -6.39, <i>P</i> <0.001; <i>I</i> ² 23%	2	-4.60	-9.09 to -0.12, <i>P</i> =0.04; <i>I</i> ² 46%
>145/>85	4	-6.31	-7.46 to -5.16, <i>P</i> <0.001; <i>I</i> ² 0%	4	-5.04	-6.16 to -3.93, <i>P</i> <0.001; <i>I</i> ² 44%

ABPM, ambulatory blood pressure monitoring; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score; *I*², heterogeneity analysis; RCT, randomized controlled trial. America groups one study from Canada and one from Brazil.

TABLE 5

Subgroup analyses of 24-h ABPM blood pressure data from the RCTs

Subgroup	SBP			DBP		
	No. of studies	Mean net change	95% CI, <i>P</i> value	No. of studies	Mean net change	95% CI, <i>P</i> value
ESS						
<10	2	-4.10	-7.59 to -0.62, <i>P</i> =0.02; <i>I</i> ² 0%	2	-3.50	-6.36 to -0.64, <i>P</i> =0.01; <i>I</i> ² 0%
>10	2	-9.60	-11.79 to -7.40, <i>P</i> 0.001; <i>I</i> ² 0%	2	-8.26	-10.84 to -5.68, <i>P</i> 0.001; <i>I</i> ² 38%
CPAP duration						
<2 months	1	-6.30	-10.67 to -1.92, <i>P</i> 0.01; <i>I</i> ² 0%	1	-5.90	-10.49 to -1.31, <i>P</i> =0.01; <i>I</i> ² 0%
>2 months	3	-6.72	-11.22 to -2.23, <i>P</i> 0.01; <i>I</i> ² 72%	3	-5.83	-10.31 to -1.36, <i>P</i> =0.01; <i>I</i> ² 83%
ABPM						
3	3	-6.72	-11.22 to -2.23, <i>P</i> 0.01; <i>I</i> ² 72%	3	-5.83	-10.31 to -1.36, <i>P</i> =0.01; <i>I</i> ² 83%
Study sample size						
<20	1	-9.60	-11.79 to -7.40, <i>P</i> 0.001; <i>I</i> ² 0%	1	-9.00	-10.26 to -7.73, <i>P</i> 0.001; <i>I</i> ² 0%
>20	3	-4.95	-7.68 to -2.23, <i>P</i> 0.001; <i>I</i> ² 0%	3	-4.17	-6.60 to -1.74, <i>P</i> 0.01; <i>I</i> ² 0%
Study design						
Cross-over	1	-6.30	-10.67 to -1.92, <i>P</i> 0.01; <i>I</i> ² 0%	1	-5.90	-10.49 to -1.31, <i>P</i> =0.01; <i>I</i> ² 0%
Noncross-over	3	-6.72	-11.22 to -2.23, <i>P</i> 0.01; <i>I</i> ² 72%	3	-5.83	-10.31 to -1.36, <i>P</i> =0.01; <i>I</i> ² 83%
Geographical location						
Asia	1	-6.30	-10.67 to -1.92, <i>P</i> 0.01; <i>I</i> ² 0%	1	-5.90	-10.49 to -1.31, <i>P</i> =0.01; <i>I</i> ² 0%
Europe	2	-4.10	-7.59 to -0.62, <i>P</i> 0.02; <i>I</i> ² 0%	2	-3.50	-6.36 to -0.64, <i>P</i> =0.01; <i>I</i> ² 0%
America	1	-9.60	-11.79 to -7.40, <i>P</i> 0.001; <i>I</i> ² 0%	1	-9.00	-10.26 to -7.73, <i>P</i> 0.001; <i>I</i> ² 0%
Baseline SBP/DBP						
<145/<85	2	-4.10	-7.59 to -0.62, <i>P</i> =0.02; <i>I</i> ² 0%	2	-3.50	-6.36 to -0.64, <i>P</i> =0.01; <i>I</i> ² 0%
>145/>85	2	-8.51	-11.55 to -5.47, <i>P</i> 0.001; <i>I</i> ² 42%	2	-8.26	-10.84 to -5.68, <i>P</i> 0.001; <i>I</i> ² 38%

ABPM, ambulatory blood pressure; CI, confidence interval; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score; *I*², heterogeneity analysis; RCT, randomized controlled trial. America groups one study from Canada and one from Brazil.

TABLE 6

Meta-regression of pre-CPAP to post-CPAP blood pressure data using mixed effects regression (unrestricted maximum likelihood)

Explanatory variable (baseline)	SBP		DBP	
	No. of studies	<i>P</i> value	No. of trials	<i>P</i> value
AHI	6	0.47	6	0.02 ^a
ESS	4	0.57	4	0.80
Age	6	0.65	6	0.20
BMI	6	0.78	6	0.85

AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score.

^aIndicates statistical significance.