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META-ANALYSIS

Impact of Continuous Positive Airway Pressure Therapy on Blood Pressure in Patients with Obstructive Sleep Apnea Hypopnea: A Meta-analysis of Randomized Controlled Trials

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Abstract Patients with untreated obstructive sleep apnea hypopnea (OSAH) are predisposed to developing hypertension, and therapy with continuous positive airway pressure (CPAP) may reduce blood pressure (BP). The purpose of this study was to assess the impact of CPAP therapy on BP in patients with OSAH. We performed a comprehensive literature search up to July 2006 [Medline, PubMed, EMBASE, Cochrane Database of Systematic Reviews (CDSR), Cochrane controlled trials register (CCTR), and Database of Abstract and Reviews of Effect (DARE)] to identify clinical studies and systemic reviews that examined the impact of CPAP on BP. Studies were included if they (1) were randomized controlled trials with an appropriate control group, (2) included systolic and diastolic BP measurements before and after CPAP/control in patients with OSAH, and (3) contained adequate data to perform a meta-analysis. To calculate pooled results, studies were weighted by inverse variances, with either a fixed or a random effects model used depending on the presence of heterogeneity (assessed with Q test). Ten studies met our inclusion criteria (587 patients): three studies were crossover (149 patients) and seven were parallel in design. Seven studies (421 patients) used 24-h ambulatory BP and three used one-time measurements. Two studies were of patients with heart failure (41 patients). Overall, the effects of CPAP were modest and not statistically significant; CPAP (compared to control) reduced systolic BP (SBP) by 1.38 mmHg (95% CI: 3.6 to –0.88, $p = 0.23$) and diastolic BP (DBP) by 1.52 mmHg (CI: 3.1 to –0.07; $p = 0.06$). Six of the trials studied more severe OSAH (mean AHI > 30/h, 313 patients); in these six trials, CPAP reduced SBP by 3.03 mmHg (CI 6.7 to –0.61; $p = 0.10$) and DBP by 2.03 mmHg (CI: 4.1 to –0.002; $p = 0.05$). There was a trend for SBP reduction to be associated with CPAP compliance. In unselected patients with sleep apnea, CPAP has very modest effects on BP. However, we cannot exclude the possibility that certain subgroups of patients may have more robust responses—this may include patients with more severe OSAH or difficult-to-control hypertension. Future randomized controlled trials in this area should potentially concentrate on these subgroups of patients.

Keywords Sleep · Apnea syndromes · Blood pressure · Meta-analysis

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Introduction

Obstructive sleep apnea hypopnea (OSAH) is characterized by recurrent episodes of partial or complete upper airway collapse during sleep resulting in sleep fragmentation and oxyhemoglobin desaturation. Patients with OSAH are predisposed to developing hypertension, presumably because of the sustained activation of the sympathetic nervous system in response to nocturnal hypoxemia and arousals [1, 2].

Continuous positive airway pressure (CPAP) is a well-established cost-effective treatment of OSAH [3]. CPAP acts as a pneumatic splint to the upper airway, keeping it patent during sleep and thus preventing apneas, hypoxemia, and sleep fragmentation [4, 5]. Several groups of investigators have found significant reductions in blood pressure (BP) with CPAP; however, other groups have demonstrated little to no effect. It is thus controversial whether CPAP reduces BP in patients with OSAH. Given the robust relationship between BP and future risks of cardiovascular events [6], we believe this is an important issue to address.

We performed a systematic review and meta-analysis of data from randomized controlled trials that have studied the effect of CPAP therapy on BP in patients with OSAH. The study objectives were to (1) assess the impact of CPAP therapy on BP in patients with OSAH and (2) identify any patient characteristics that might explain variations in the outcomes in the different studies.

Methods

Literature Search

We performed a systematic computerized search of Medline (1966-July 1, 2006), EMBASE (1980-July 1, 2006), Cochrane Database of Systematic Reviews (CDSR) (1996-2nd quarter 2006), Cochrane controlled trials register (CCTR) (1996-2nd quarter 2006), and the Database of Abstracts and Reviews of Effects (DARE) (1994-2nd quarter 2006) to identify all randomized controlled trials assessing the effect of CPAP therapy on BP in patients with OSAH. We used the following exploded search terms: (''sleep apnea syndromes'' or ''sleep apnea, obstructive'' or ''sleep disordered breathing'') AND (''continuous positive airway pressure'' or ''CPAP'' or ''positive pressure respiration'') AND (various markers: including hypertension BP (blood pressure) AND (clinical trial or randomized controlled trial). Bibliographies of retrieved articles, previous meta-analyses, and reviews were also used to identify any potentially relevant publications missed by our search. Abstracts, reviews, case reports, editorials, nonhuman studies, and non-English studies were excluded.

Literature Selection

The following inclusion criteria were used: (1) The study populations were limited to adults with OSAH; (2) the studies included systolic and diastolic BP measurements before and after CPAP and control; (3) the studies were randomized controlled trials with a reasonable control group; and (4) the studies contained adequate data to perform a meta-analysis. All abstracts were reviewed by three independent assessors (MA, J. Fox, NTA) to determine whether they could potentially be included in the meta-analysis. These three investigators then reviewed the complete articles from these selected studies to determine if they met inclusion criteria.

Data Abstraction and Study Characteristics

Data abstracted from each paper included the year of publication, study design (crossover vs. parallel), number of subjects in each group, inclusion/exclusion criteria, gender distribution, mean age, mean body mass index (BMI), baseline and post-treatment apnea hypopnea index (AHI), mean applied CPAP pressure, use of antihypertensive medications, adherence with therapy, length of followup, baseline and post-treatment Epworth Sleepiness Scale Score (ESS), nature of BP measurement (i.e., 24-h vs. one-time measurement), and systolic/ diastolic BP measurements before and after therapy.

Quantitative Data Synthesis

We assessed whether there were significant differences between CPAP and control arms in terms of change of BP (i.e., post-BP - pre-BP measurements). The observed variability among the outcomes of the individual trials is commonly the result of two major sources. Within-trial variability is principally from variation among patients within each trial, measurement error in the trial, etc. When the total observed variation among the different trials can be fully accounted for by this within-trial variability, then trial effects may be combined by means of a ''fixed effects model.'' Under these conditions, the heterogeneity test (Q test) will be insignificant.

Another common source of variability of outcomes stems from differences (heterogeneity) between the trials. These differences may be the result of a number of potential differences among the studies, including protocol variations, patient populations, durations of treatment, technology used, and disease severity. Under these conditions, even an infinite number of patients in each trial would still result in variations in outcomes from the different trials. In this situation, the heterogeneity test (Q test) will generally be significant; indicating that in addition to the inevitable within-trial variation, there is evidence of significant between-trial variations that must be accounted for in the meta-analysis. Under these conditions, a ''random effects model'' is used. Using the random effects model leads to a less precise pooled estimate for the overall effect, with a wider confidence interval.

To calculate pooled results, studies were weighted by inverse variances, with either a fixed or a random effects model used depending on the presence of heterogeneity. In our study, a fixed effects model was used if significant heterogeneity was absent (Q test not significant, $p > 0.1$ because the Q test is relatively insensitive in detecting heterogeneity) [7]. If significant heterogeneity was present, the random effects model of DerSimonian and Laird was applied. We also performed subgroup analyses to assess whether there were any factors that were associated with variations in the magnitude of BP reduction.

We also used meta-regression to determine if a variety of variables (e.g., mean age, body mass index, baseline AHI, severity of hypersomnolence as assessed by baseline ESS, length of followup, CPAP pressure and compliance, antihypertensive use, and baseline blood pressure measurement) could account for differences in outcomes. All statistical analyses were performed using StataSE v8.

Results

Literature Search

Two hundred ninety-nine studies were identified from the computerized search and bibliographies. Review of the abstracts identified 68 potentially relevant studies. Review of these individual papers identified 18 randomized controlled trials that were considered appropriate for our analysis. Eight of these 18 studies were subsequently excluded because they did not report systolic and diastolic BP values, reported BP values divided into daytime and nighttime values without combining them together, or lacked sufficient data to perform meta-analysis [8–15].

Characteristics of Studies

The ten remaining trials studied a total of 587 patients [16–25]. Characteristics of the ten studies are shown in Table 1. All the studies enrolled relatively few patients (range = 17–125). Of note, three studies were crossover (149 patients) [16, 18, 25] and the remainder were parallel in design. Three of the studies used one-time measurements of blood pressure [17, 20, 21] (166 patients), while the rest used 24-h ambulatory blood pressure recordings. Two of the studies were of patients with heart failure (41 patients) [20, 21]. The duration of nine of ten studies was three months or less.

Results of Pooled Analysis

For both systolic and diastolic BP, fixed effects models were used whenever no significant heterogeneity was noted and random effect models were otherwise used. Compared with control, therapy with CPAP reduced systolic BP (SBP) minimally (1.38 mmHg) and this was not statistically significant (95% CI: 3.6 to –0.88; $p = 0.23$, fixed effects model). Similarly, diastolic BP (DBP) was not significantly reduced (pooled result = 1.52 mmHg reduction, CI: 3.11 to –0.07; $p = 0.06$, fixed effects model).

Subgroup Analysis

Parallel studies Because of issues related to carryover effects, crossover studies may not accurately represent the effectiveness of therapy. Therefore, we also reperformed the analysis excluding the three crossover studies. When the crossover studies were excluded, CPAP resulted in a larger reduction of SBP (3.18 mmHg, CI: 6.7 to –0.34; $p = 0.08$, fixed effects model) and DBP of 1.94 mmHg (CI:3.9 to –0.01; $p = 0.05$, fixed effects model) with a trend to significance. However, the severity of OSAH in two of these studies was relatively mild (mean AHI = 12.9 and 21.3 events/h), which might also account for the reduced CPAP effect seen in them (see below).

Severe disease Because a previous study suggested that more severe OSAH may be associated with an increased BP response to CPAP [19], we performed a subgroup analysis using only trials with severe OSA (i.e., mean AHI > 30/h, 313 patients). When only these six trials were considered [19–24], the effects of CPAP on BP were of greater magnitude. That is, CPAP reduced

Table 1 Summary of eight studies that have examined the effect of CPAP on blood pressure[a]

Study date	First author	No. patients	Mean age	Mean AHI	Systolic BP reduction (mmHg)	Diastolic BP reduction (mmHg)	Duration of CPAP	% using antihypertensive medications	Control group
2002	Barnes[c]	28	45.5	12.9	–0.5	0.9	8 weeks	N/a	Pill placebo
2001	Monasterio	125	54	20	2[e]	1	6 month	N/a	Conservative treatment
2004	Barnes[c]	89	47	21.3	0.9	0.6	3 month	N/a	Pill placebo
2006	Robinson[c]	32	54	28.1[b]	-0.4	1.2	1month	77	Subtherapeutic CPAP
2002	Pepperell	118	50.6	37[b]	3.4	3.3	1 month	19	Subtherapeutic CPAP
2005	Usui[d]	17	53.5	40.4	19.9[e]	8.5	1 month	100	Standard treatment of heart failure
2003	Kaneko[d]	24	55.6	41.2	16[e]	1	1 month	100	Standard treatment of heart failure
2001	Barbe	54	53	55	1	1	6 weeks	15–30[f]	Subtherapeutic CPAP
2006	Campos-Rodriguez	68	56.7	58.9	0.9	0.7	4 weeks	100	Subtherapeutic CPAP
2003	Becker	32	53.4	63.8	10.6	11.3	9 weeks	47	Subtherapeutic CPAP

AHI = apnea hypopnea index; N/a: not available

[a] Studies are arranged in increasing order of disease severity. For BP reduction, a positive value indicates that CPAP reduced BP more than the control group

[b] A desaturation index rather than AHI (used as AHI for regression)

[c] Crossover studies

[d] Studies with heart failure patients

[e] One time measure of blood pressure

[f] Six patients were receiving β blockers, seven angiotensin-converting enzyme inhibitors, and three diuretics. It is unclear how many patients were receiving multiple medications. For the regression analysis, the midpoint (22.5%) was used

SBP by 3.03 mmHg (CI: 6.7 to –0.61; $p = 0.10$, fixed effects model) and DBP by 2.03 mmHg (CI: 4.1 to –0.002; $p = 0.05$, fixed effects model) with trends to significance.

Two of the studies included only patients with OSAH and heart failure; these two studies also relied on one-time BP measurements as opposed to 24-h measurements [20, 21]. We reanalyzed the studies after excluding these two studies, as BP in patients with heart failure may respond differently than those without heart failure. When the eight studies that examined patients with OSAH and no heart failure were considered, CPAP reduced SBP (pooled SBP result = 1.10 mmHg, CI: 3.4 to –1.2, $p = 0.81$, fixed effects model) and DBP (pooled result = 1.47 mmHg, CI: 3.1 to –0.14, $p = 0.61$, fixed effects model) minimally and nonsignificantly.

Metaregression

In univariate analysis, mean compliance with CPAP (hours per night, reported in 9 studies) was significantly associated with a trend to an increased effect of CPAP on SBP ($p = 0.06$) but not on DBP ($p = 0.24$). Otherwise, use of antihypertensives, mean ESS, age, BMI, AHI, post-CPAP AHI, baseline BP, and duration of CPAP were not associated with extent of BP reduction (data not shown, $p > 0.1$).

Discussion

In our meta-analysis, CPAP therapy resulted in a small and nonsignificant decrease in BP when all studies were included. Patients with more severe disease (mean AHI > 30 events/h) had a larger decrease in BP response which approached significance.

There are a number of strengths to our study. First, by pooling the results of multiple studies, the statistical power to detect a difference was increased and the confidence intervals of our estimates were reduced. Second, we were able to analyze differences in the studies using metaregression to better understand the potential effect of various patient characteristics on the BP response to CPAP.

Nevertheless, we acknowledge that there are also a number of limitations to our study. First, the nature of the control group varied according to the study. Control groups included subtherapeutic CPAP, conservative treatment, a pill placebo, and standard care. Second, as in all meta-analyses, one potential weakness of the study is the possibility of publication bias. If negative studies were not published, an overestimate of the effect of CPAP would result. We doubt this was the case because our overall result was negative. Third, followup was relatively short in the majority of these studies, with only one study longer than nine weeks. As such, it is unclear whether BP effects are maintained or increase with time. Indeed, a recent study by West et al. [26] suggests that BP changes may not be sustained in patients treated with CPAP. Fourth, our severe OSAH subgroup was defined *post hoc* and study means rather than data from individual patients were used. As such, our findings need to be interpreted cautiously.

Despite these limitations, our data suggest that CPAP is not useful in reducing BP in unselected patients with OSAH. However, CPAP may be useful in reducing BP in certain groups of patients. For instance, in our analysis there was a trend for studies with patients with more severe OSAH to have a greater BP response. This could be because these patients have more substantial physiologic abnormalities with greater degrees of nocturnal hypoxemia and sympathetic nervous system activation. Indeed, the degree of BP reduction seen in the studies with patients with more severe disease lies between the effects seen with ACE inhibitors (5 and 2 mmHg) and angiotensin receptor blockers. (2 and 1 mmHg). In a recent meta-analysis [6], ACE inhibitors reduced the risk of stroke by 28%, major cardiovascular events by 22%, and cardiovascular death by 20%, whereas angiotensin receptor blockers reduced the risk in the same categories by 21%, 10%, and 4%, respectively. Risk reduction in this study was directly related to blood pressure reduction; therefore, it seems reasonable to extrapolate at least an intermediate effect on risk reduction for CPAP in patients with severe OSAH.

In our study baseline BP values and percentage of patients using antihypertensive drugs were not associated with the BP response to CPAP. This was somewhat surprising because we had expected that patients with increased BP or who are using medications would have had a greater response to treatment. One potential explanation is that the range of mean baseline BP in our study was fairly narrow and on the ''lower'' side (i.e., 125–143 mmHg for SBP, 61–87 mmHg for DBP). As such, we cannot exclude the possibility that patients with substantial hypertension may experience a large reduction in BP with CPAP; indeed, a previous nonrandomized study demonstrated a reduction in BP of 11 mmHg in patients with difficult-to-control hypertension treated with CPAP [27].

However, considering only the effect of CPAP on blood pressure may be a gross underestimate of the potential cardiovascular benefits of CPAP therapy. The benefits of CPAP are likely due to not only BP reductions but also to a host of other effects. Preliminary studies have demonstrated improvements in endothelial function, inflammation, oxidative stress, and cholesterol levels in patients with OSAH treated with CPAP therapy [28–30]. Furthermore, a recent large prospective observational cohort study by Marin et al. [31] demonstrated a substantial effect of CPAP on cardiovascular outcomes. These investigators followed healthy men, patients with untreated OSAH, and treated patients for the development of incident cardiovascular disease (i.e., stroke, myocardial infarction, revascularization). Patients with untreated severe OSAH had a significantly increased risk of developing both fatal (odds ratio = 2.87) and nonfatal (odds ratio = 3.17) cardiovascular disease compared with healthy controls; treated patients did not have an increased risk of events suggesting that CPAP therapy eliminates the excess cardiovascular risk of patients with severe OSAH. Although the possibility of confounding by indication cannot be completely excluded given the observational design of the study, the large effect that persisted after controlling for a variety of potential confounders would make this unlikely.

Conclusion

In unselected patients with OSAH, CPAP has little effect on blood pressure. However, it is possible that certain subgroups of patients (e.g., patients with severe OSAH or with difficult-to-control BP) may respond more. Future randomized controlled trials in this area should concentrate on more severe patients or on patients with substantial hypertension.

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