Randomized Placebo-controlled Trial of Continuous Positive Airway Pressure on Blood Pressure in the Sleep Apnea–Hypopnea Syndrome

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Arterial blood pressure rises at apnea termination, and there is increasing evidence that the sleep apnea–hypopnea syndrome (SAHS) is associated with daytime hypertension but no randomized controlled trial evidence of whether SAHS treatment reduces blood pressure exists. We, therefore, conducted a randomized placebo-controlled cross-over study of the effects of 4 wk of continuous positive airway pressure (CPAP) or oral placebo on 24-h blood pressure in 68 patients (55 males, 13 females; median apnea–hypopnea index [AHI], 35) not receiving hypotensive medication. Ambulatory blood pressure was recorded for the last 48 h of each treatment. Epworth Sleepiness Score (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ) were also recorded. All patients were normotensive. There was a small decrease in 24-h diastolic blood pressure (placebo, 79.2 [SE 0.9] mm Hg; CPAP, 77.8 [SE 1.0] mm Hg; $p = 0.04$) with the greatest fall occurring between 2:00 A.M. and 9:59 A.M. The observed decrease in 24-h diastolic blood pressure was greater in two *a priori* groups, CPAP use $\geq$ 3.5 h per night (81.5 [SE 1.2] mm Hg; 79.6 [SE 1.2] mm Hg; $p = 0.03$) and those with more than twenty 4% desaturations per hour (82.4 [SE 2.1] mm Hg; 77.4 [SE 2.1] mm Hg; $p = 0.002$). Systolic pressure also fell in the latter group (133.1 [SE 2.8] mm Hg; 129.1 [SE 2.1] mm Hg; $p = 0.009$). Desaturation frequency was the best predictor of diastolic blood pressure fall with CPAP ($r = 0.38$; $p = 0.002$). Both ESS and FOSQ domains improved. Thus, CPAP can reduce blood pressure in patients with SAHS, particularly in those with nocturnal oxygen desaturation, but the decrease is small.

The sleep apnea–hypopnea syndrome (SAHS) occurs in 1–4% of the middle-aged population (1), causing sleepiness, daytime cognitive deficits, impaired mood, and road traffic accidents (2). Randomized placebo-controlled trials have shown that continuous positive airway pressure (CPAP) therapy significantly improves symptoms, sleepiness (3, 4), cognitive function, mood, and quality of life (5) while controlled trials suggest that CPAP significantly improves driving simulator performance (6).

Considerable uncertainty, however, remains about the effects of the sleep apnea–hypopnea syndrome on the cardiovascular system (7, 8). Apneas and hypopneas are immediately followed by acute rises in blood pressure coincident with the arousal from sleep (9). It is not clear, however, whether this episodic nocturnal hypertension results in sustained daytime hypertension or increased cardiovascular risk. About 50% of patients with the sleep apnea–hypopnea syndrome have daytime hypertension (9, 10) but many have other risk factors for hypertension, including obesity and alcohol consumption. Epidemiological studies, which have tried to factor out these confounders, have concluded that there is (11–14) or is not (15, 16) an independent association between sleep apnea and daytime hypertension. Intervention studies have shown that CPAP can normalize nocturnal blood pressure in patients with the sleep apnea–hypopnea syndrome (17), but the effect of CPAP on daytime blood pressure is unclear. Previous studies of the effects of CPAP on daytime blood pressure have been difficult to interpret because of the difficulty of matching controls (18–21) or, in the one case in which a randomized placebo-controlled design was used, were inadequately powered (22) with only 13 patients studied and no clear conclusion.

Studies of animal models have strongly suggested that sleep apnea may cause sustained hypertension (23, 24). They suggest that while arousal from sleep may cause transient nocturnal hypertension, sustained daytime hypertension occurs only if there is coexisting intermittent nocturnal hypoxemia and not if there is merely sleep fragmentation alone (24, 25).

We have, therefore, carried out a randomized placebo-controlled trial of CPAP therapy on 24-h blood pressure in patients with the sleep apnea–hypopnea syndrome. At the same time we have also examined the effects of CPAP on subjective sleepiness and quality of life.

METHODS

Patients

Consecutive patients referred to the sleep center were considered for inclusion, provided they had at least two major symptoms of SAHS and an apnea–hypopnea index (AHI) $\geq$ 15 on polysomnography using our previously described techniques (26) recorded on a computerized system (*S* system; Compumedics, Melbourne, Australia). Hypopnea was defined as a $\geq$ 50% reduction in thoracoabdominal movement sum signal (27). Exclusion criteria included problems with sleepiness when driving, living more than 50 miles from the center, shift work, diabetes, or the taking of medication that would alter blood pressure. One hundred and seven patients were approached and 78 agreed to participate in the study, the remainder declining because of work or family commitments. None of these patients had taken part in any of our previous studies (Figure 1).

Weight and height were measured to allow calculation of body mass index (kg/m^2). The Epworth Sleepiness Scale (ESS; 28) and the Sleep-specific Quality of Life Scale—Functional Outcomes of Sleep Questionnaire (FOSQ; 29) were completed at the start of the study to allow familiarization, and at the end of each treatment limb.

ESS: Subjects score themselves, on a scale of 0–3, on how easily they would fall asleep in eight different situations, giving an overall score between 0 and 24; the higher the score the sleepier the individual.

FOSQ: The FOSQ is a sleep-specific questionnaire developed to reflect the impact of sleep disorders and excessive sleepiness on activities of daily living. It focuses on five different domains: General Productivity, Social Outcomes, Activity Level, Vigilance, and Sexual Relationships and Intimacy. The optional questions on intimacy and sexual relationships were excluded in this study. The questionnaire comprises 26 questions set at a 10-yr-old reading level, which takes approximately 15 min to complete. Each question has a four-point scale with an appropriate column to be checked. The results are processed to give a mean-weighted item score for each of the four sub-

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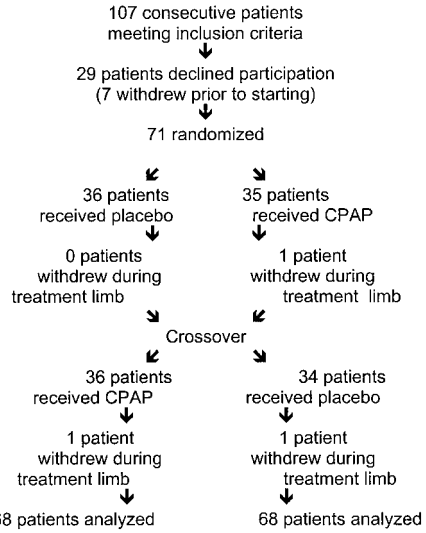

Figure 1. Trial profile.

groups (ex4), which when added together produce a global score. The lower the score the more dysfunctional the individual secondary to sleepiness.

Ambulatory Blood Pressure Monitoring

Patients were fitted with a lightweight microprocessor to collect the BP data via an arm cuff (Ultralite ABPM; SpaceLabs Medical, Redmond, WA) at the end of each treatment limb. The ambulatory blood pressure monitoring (ABPM) module is a small unit weighing 347 g, which is carried on a belt or shoulder strap, connecting to the arm cuff via a rubber hose. A cuff of appropriate size was fitted to the nondominant upper arm, with instructions provided on how to readjust, if necessary. Subjects were asked to continue their normal daily activities, recording these in a diary. The monitor was worn during the whole 48 h, removing it only for bathing. The monitor recorded systolic blood pressure (Psyst), diastolic blood pressure (Pdias), and mean arterial pressure ($\overline{Pa}$).

Protocol

All patients underwent a full-night CPAP titration study using an automated pressure setting device (Auto Set; ResMed, Sydney, Australia). The following morning the patient was randomized, using a balanced block design, to receive either CPAP or an oral capsule for the first limb, and crossed over after 1 mo to the alternative treatment for the second limb. The capsule was a placebo, which patients were told, with the permission of the local ethics committee, might improve the tone in the upper airway muscles. The CPAP units used for home therapy were Sullivan V Elites (ResMed), which were downloaded at the end of the treatment period to obtain a real-time record of the time when the patient was using the device at the appropriate pressure (time at pressure).

Forty-eight hours before the end of each limb, the patients were fitted with the ABPM module. The monitors were fitted in the early evening to all patients, and programmed to record every 30 min for 48 h. Patients were asked to abstain from caffeine-containing products during this time. Data gathered before 6:00 P.M. on the second evening were discarded to allow for acclimatization. The analysis was performed with the second 24 h of data (6:00 P.M. to 6:00 P.M.). All data were manually checked for artifact by an observer who was blinded to the treatment status of the patient.

All patients gave written informed consent to participation in the study, which was approved by the Lothian Ethics of Medical Research Committee.

Data Analysis

The ESS, FOSQ, and blood pressure data (grouped into 4-h means) were analyzed by repeated measures analysis of variance, using the general linear model (SPSS for Windows, version 9, 1998; SPSS, Chicago, IL). When this showed significant difference, MANOVA was used to identify time points when blood pressure altered with CPAP use. Data were analyzed on an intention to treat basis, including all data obtained even if patients were known not to be complying with CPAP therapy. A subanalysis was also performed, using an *a priori* agreed cut point of 3.5 h per night for reasonable CPAP compliance (3). Because of the animal data indicating the importance of intermittent hypoxemia in the pathogenesis of hypertension in sleep apnea (23, 24), we also used an *a priori* cut point of twenty 4% desaturations per hour to indicate those patients with significant nocturnal hypoxemia. Pearson correlation analysis was performed on data that had been shown to be normally distributed.

RESULTS

Of the 78 patients (65 males, 13 females) who agreed to participate, 7 withdrew prior to randomization for personal reasons and 71 started the study. Of the 71, 3 withdrew during the study (1 in the placebo limb and 2 in the CPAP limb). Sixty-eight (55 males, 13 females) completed the trial (Table 1) and their data are reported. Mean CPAP time at pressure in the 4 wk of the study was 3.3 h per night (range, 0 to 8.1 h per night). Capsule counting showed the patients missed a median of 0 tablets (95th percentile, 1.4 tablets) over the month on placebo. There was no significant change in weight between the two limbs ($p > 0.8$). There was no evidence of either order or carryover effects ($p > 0.3$).

Over the 24-h period, on an intention to treat analysis, there was no significant change in systolic pressure but a significant 1.5-mm Hg reduction in diastolic blood pressure on CPAP therapy ($p = 0.04$; Table 2). Analysis of the 4-h time blocks showed that diastolic blood pressure was significantly lower in the 2:00 A.M. to 5:59 A.M. ($p = 0.03$) and 6:00 A.M. to 9:59 A.M. ($p = 0.02$) blocks; there were no other significant changes ($p > 0.1$). These data are available in the online data supplement to this article at www.atsjournals.org. There were no significant changes in either heart rate (placebo, 77 [SE

TABLE 1

DEMOGRAPHICS OF 68 PATIENTS STUDIED

	Median	Range
Age, yr	50	29–72
AHI/h slept	35	15–129
4% Desaturation index/h slept	7	0–128
EEG arousals/h slept	42	12–129
BMI, kg/m^2	30	21–53
Neck, cm	40	33–55
Waist, cm	104	81–145
Hips, cm	108	93–160
ESS, ex24	15	6–24
Partner ESS	14	4–24

Definition of abbreviations: AHI = apneas + hypopneas per hour slept; BMI = body mass index (kg/m^2); EEG = electroencephalogram; ESS = Epworth Sleepiness Score.

TABLE 2

MEAN BLOOD PRESSURE OVER 24 h IN ALL 68 PATIENTS

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	126.9	1.3	128.2	1.2	−1.3	−3.3 to 0.7	0.19
Pdias, mm Hg	77.8	1.0	79.2	0.9	−1.5	−3.0 to −0.1	0.04
$\overline{Pa}$, mm Hg	94.4	1.0	95.5	0.9	−1.0	−2.6 to 0.6	0.20

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

TABLE 3

MEAN BLOOD PRESSURE IN PATIENTS USING CPAP ⩾ 3.5 h PER NIGHT*

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	129.9	2.1	131.0	1.8	−1.1	−3.6 to 1.4	0.41
Pdias, mm Hg	79.6	1.2	81.5	1.2	−1.9	−3.7 to −0.1	0.03
$\overline{Pa}$, mm Hg	96.1	1.4	97.7	1.2	−1.0	−3.1 to 1.0	0.30

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

* n = 32.

1.1], CPAP 76 [SE 1.2]; p = 0.4) or pulse pressure (p = 0.8) with CPAP.

Thirty-two patients used their CPAP machines for more than the *a priori* cut point of 3.5 h per night on average and showed a mean decrease in 24-h diastolic blood pressure (Table 3). There was no significant change in 24-h systolic blood pressure in this group. In the 14 patients with 4% desaturation frequencies above 20 per hour on the baseline sleep studies, CPAP therapy produced highly significant falls in 24-h systolic, diastolic, and mean arterial pressures (Table 4).

Using intention to treat data for all 68 patients, the decrease in 24-h diastolic blood pressure between placebo and CPAP was significantly correlated with the frequency of 4% desaturations in the baseline sleep study (r = 0.35; p = 0.002) and with AHI (r = 0.23; p = 0.032). Multiple regression analysis showed that desaturation frequency was the only independent predictor of drop in diastolic blood pressure with CPAP (r = 0.38; p = 0.02).

There was a significant drop in ESS with treatment (Table 5; $p < 0.001$). The FOSQ data (Table 5) show that three of the four different domains improved significantly with CPAP, as did the overall total.

DISCUSSION

This study shows that CPAP results in a significant fall in 24-h diastolic blood pressure, but when analyzed in all patients on an intention to treat basis, the fall in diastolic pressure is only 1.5 mm Hg. However, the falls in blood pressure were greater in those patients with intermittent nocturnal hypoxemia in whom systolic pressure over 24 h dropped by 4.0 mm Hg and diastolic pressure by 5.0 mm Hg.

Potential problems with this study include the type of placebo used, the lack of a washout period, dropouts, the 1-mo treatment duration, the large number of potential comparisons, and the fact that the patients were normotensive. Normotension was not an entry criterion, but it was requred that no patients be receiving hypotensive therapy, and none proved to be hypertensive on entry. We excluded patients taking hypotensive drugs to avoid any confounding effects of hypotensive medication, and did not feel ethically justified to stop hypotensive therapy for the duration of a study in known hypertensives. CPAP therapy is relatively obtrusive and could conceivably have an effect merely due to "machine mystique," which was not found in our tablet placebo. One study has used a CPAP set at a subtherapeutic pressure to investigate daytime function in SAHS (4). Interestingly, the magnitude of the placebo effect with sham CPAP on symptoms in that study was similar to that found by our group with placebo tablets (ESS, Jenkinson and coworkers [4] baseline 15, sham CPAP 13; Engleman and coworkers [5] baseline 13, placebo tablet 11), suggesting that there is no specific "machine mystique" effect of a sham CPAP placebo that our tablet lacks. Furthermore, we used a tablet that was actively "sold" to our patients as an agent that might be effective, with ethics committee agreement, on the basis of the following points.

1. A CPAP machine set at subtherapeutic pressure might keep the patient awake, thus, falsely raising blood pressure and predisposing to finding benefit from real CPAP.
2. We were concerned that patients would use sham CPAP less than active CPAP, as they would not perceive any symptomatic benefit to counterbalance the inconvenience, and thus a true placebo benefit might not be obtained at the end of the study limbs when the key measurements were made.
3. At the time the study was designed, there were reports that subtherapeutic CPAP might cause dangerous hypoxemia (30).
4. A CPAP unit set at minimum pressure might stabilize the airway sufficiently to treat some episodes of upper airway narrowing.
5. Sham CPAP has also to be "sold" to patients as potentially active therapy.

Although we did not include a formal washout period, no measurements were made until 26 d after cross-over. Thus, it is unlikely there would be any carryover effects, especially as in the dog model of sleep apnea, blood pressure normalizes within 1–3 wk of apnea termination (24). Further, any carryover effect would bias against the positive findings in our study. We believe the dropout rate of 3 of the 71 patients randomized, while undesirable, was acceptable and will not have influenced the blood pressure results reported. Patients used CPAP for 4 wk and thus the data from this study cannot be extrapolated to long-term treatment. However, early CPAP use predicts later CPAP use and 95% of those patients using CPAP for more than 4 h at 1–3 mo after CPAP initiation are still using CPAP 7 yr later (31). This suggests that at least in our good user group, sustained treatment is likely.

TABLE 4

MEAN BLOOD PRESSURE IN PATIENTS WITH MORE THAN TWENTY 4% DESATURATIONS PER HOUR*

	CPAP		Placebo		Differences		
	Mean	SEM	Mean	SEM	Mean	95% CI	p Value
Psyst, mm Hg	129.1	2.1	133.1	2.8	−4.0	−7.0 to −4.0	0.009
Pdias, mm Hg	77.4	2.1	82.4	2.1	−5.0	−7.3 to −2.4	0.002
$\overline{Pa}$, mm Hg	95.2	1.8	98.6	1.9	−3.4	−6.3 to −0.6	0.012

Definition of abbreviations: CI = confidence interval; $\overline{Pa}$ = mean arterial pressure; Pdias = diastolic blood pressure; Psyst = systolic blood pressure; SEM = standard error of the mean.

* n = 14.

TABLE 5

EFFECTS OF CPAP

FOSQ Domain (ex4)	CPAP (mean SEM)	Placebo	p Value
General Productivity	3.2 (0.2)	3.1 (0.2)	0.070
Social Outcomes	3.3 (0.1)	3.0 (0.2)	0.010
Activity Level	3.0 (0.1)	2.7 (0.2)	0.004
Vigilance	2.9 (0.1)	2.7 (0.2)	0.029
Total (ex16)	12.4 (0.5)	11.6 (0.7)	0.010
ESS (ex24)	10.1 (0.7)	12.5 (0.8)	0.001

Definition of abbreviations: ESS = Epworth sleepiness scale; FOSQ = functional outcomes of sleep questionnaire; SEM = standard error of the mean.

The study generated a large amount of data, with 13,056 blood pressure recordings (68 × 2 limbs × 48 times [systolic + diastolic]) and thus has potential for finding significant differences due to multiple comparisons. We have adopted a conservative statistical approach, using only intention to treat or two *a priori* subgroup analysis along with conservative data analysis. Furthermore, the data are internally consistent, showing significant changes in the whole population that are larger in the subgroups, in whom greater benefit was predicted. Thus, we believe the number of data points is a strength of our study.

We excluded patients receiving treatment for hypertension, lest this interfere with the effects of CPAP on blood pressure. We did not think it was ethical to withdraw antihypertensive therapy from treated patients for a placebo-controlled trial of an unproven therapy for hypertension. Data from hypertensive populations do not show any "threshold" diastolic pressure below which decreases in pressure were not associated with decreases in stroke and myocardial risk (32). Thus, we believe including normotensive patients was valid.

The mechanism of the blood pressure increases in SAHS is not well understood; however, it has been postulated that the sympathetic nervous system plays an integral part. Previous studies have shown an increase in sympathetic nerve traffic in SAHS which is reduced with treatment acutely (33); this is borne out also in long-term use (34). The latter study did not show a significant reduction in blood pressure or heart rate at 6 mo; however, their patient group included only 11 patients. A further study looked at the acute effects of CPAP on blood pressure in two groups: one group was treated with CPAP and the other group had "sham" CPAP as a placebo. The two groups showed significant reductions in blood pressure, and the authors suggested that the placebo effect was strong; however, recordings were taken after only 1 wk of therapy (35).

This study is the first randomized controlled trial to show that CPAP can reduce blood pressure in SAHS compared with placebo. The previous trials of the effect of CPAP on blood pressure have not only produced conflicting results (16–21, 35), but most have not been randomized (18–21, 36) and variably controlled (18, 35). The only exception was our previous but underpowered study (22).

Our current study found a fall in diastolic blood pressure with CPAP over the time periods 2:00 to 9.59 A.M. Patients were asleep for much of this time and this fall in blood pressure on CPAP during sleep is compatible with acute studies showing that CPAP abolishes nocturnal blood pressure rises by preventing apneas (18–22, 33, 35–38). Our patients' median reported waking time was 7:00 A.M. (95% CI 6:45 to 7:30 A.M.). Thus, significant decreases in diastolic pressure were found at times encompassing both sleep and the first few hours of wakefulness. However, it must be stressed that the 4-hourly analysis did not find any significant decrease in blood pressure with CPAP during most of the waking day.

What is the clinical significance of the changes in blood pressure found in this study? Investigations using conventional antihypertensive agents in non-SAHS populations indicate that a 5-mm Hg decrease in diastolic blood pressure is associated with a 42% decrease in stroke and a 14% decrease in coronary heart disease within a 5-yr period (39). A similar decrease in diastolic blood pressure results in a 31% decrease in stroke and 21% decrease in coronary heart disease, a mean of 10 yr after starting therapy (32). Our hypoxemic patients had a 5-mm Hg decrease in diastolic pressure and thus CPAP therapy in SAHS patients with nocturnal hypoxemia would seem justified on the grounds of pressure reduction alone. Whether the reduction of 1.5 mm Hg in diastolic blood pressure seen in the overall patient group is clinically useful is difficult to determine and might need further evaluation with longer term trials. These could possibly be done in asymptomatic patients, as there is overwhelming evidence of the efficacy of CPAP on symptoms and daytime function (3–5) and long-term placebo-controlled studies of symptomatic patients would not be ethical. However, in clinical practice, the assessment of the value of CPAP therapy in individual patients must include consideration of the symptomatic, cognitive, mood, quality of life (3) and driving (2) benefits as well as any possible hypotensive effect.

This study also suggests that SAHS results in increased 24-h blood pressure profiles, thus confirming the animal studies (23, 24) and some (11–14), but not all (15, 16), of the epidemiological studies. This intervention study has the advantage over epidemiological studies of not having confounders to make interpretation of causality difficult. The study is also compatible with the observation in animal models that nocturnal hypoxemia predisposes to higher blood pressures and probably ultimately hypertension (23, 24).

The significant improvements in ESS seen with CPAP confirm previous work (26). The FOSQ data extend the previous observations (5, 40) of improved quality of life with CPAP as judged by the general quality-of-life questionnaire, the medical outcomes short form 36 (SF-36). This is the first randomized controlled trial to report improvements in sleep-specific quality of life measures with CPAP. These improvements with CPAP confirm the efficacy of CPAP both in this study and in general CPAP use.

Overall, the use of CPAP in this study, while disappointing, was similar to that in our previous studies (3, 5, 22), in which use has been prospectively documented in all patients presenting with a wide range of SAHS severity. CPAP was used as the best of the currently available patient acceptable interventions at abolishing nocturnal events. Although we did not perform further sleep studies during the treatment limbs in these patients, all patients had had CPAP titration studies in our center after study enrolment, which showed a reduction in their apneas and hypopneas to a mean of 6 (SE 1) per hour slept. All studies of CPAP were carried out at that pressure and were completed within 3 mo of the titration study.

The results from this study show that 24-h blood pressure can be lowered by treatment. However, it is hoped that future developments will make treatment of SAHS better used and, thus, perhaps increase the blood pressure reduction obtained.

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