

Predictors of blood pressure fall with continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA)

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ABSTRACT

Background: Obstructive sleep apnoea (OSA) is associated with high cardiovascular morbidity and mortality. Randomised controlled trials have shown that, on average, treatment of OSA with continuous positive airway pressure (CPAP) reduces blood pressure (BP) by 3–5 mm Hg, although with considerable variation between individuals. No predictors of the change in BP with CPAP have been convincingly identified. This prospective study aimed to determine predictors of BP change, which might provide an insight into the aetiology of the raised BP seen in untreated OSA.

Methods: Eighty-six patients with daytime hypersomnolence warranting treatment with CPAP were recruited. 24 h mean BP (24 hMBP), subjective sleepiness, fasting venous blood samples and anthropometric measurements were assessed at baseline and after 6 months of CPAP treatment.

Results: The mean (SD) 24 hMBP fell at 6 months from 101.0 (10.3) mm Hg to 96.1 (9.1) mm Hg (change -4.92 mm Hg (95% CI -2.8 to -7.1)). The Epworth Sleepiness Score (ESS) fell from a median of 16 (IQR 12–18) to 4 (2–7) with a mean fall of 9.7 (95% CI 8.6 to 10.8). Several factors correlated with the fall in 24 hMBP but, after allowing for the baseline 24 hMBP, only the fall in ESS and the body mass index (BMI) remained significant independent predictors ($p = 0.006$ and 0.007 , respectively). There was also a correlation between the fall in 24 hMBP and the fall in pulse rate ($r = 0.44$, $p < 0.001$). Baseline severity of OSA, overnight hypoxia, caffeine intake or being on antihypertensive drugs were not independent predictors of a fall in 24 hMBP.

Conclusion: Improvement in hypersomnolence and the BMI are independent correlates of the fall in 24 hMBP following CPAP therapy. Markers of initial OSA severity did not predict the fall in 24 hMBP. This suggests that sleep fragmentation and its effects may be more important than hypoxia in the pathogenesis of the hypertension associated with human sleep apnoea.

Obstructive sleep apnoea syndrome (OSAS) is a common problem^{1,2} and randomised controlled trials have shown improvement of daytime sleepiness with continuous positive airway pressure (CPAP).^{3–5} Recurrent upper airway collapse leads to transient asphyxia and hypoxia which cause sleep fragmentation and daytime hypersomnolence. A raised blood pressure (BP) is seen in epidemiological⁶ and hospital-based studies⁷ of OSA; it is independent of obesity (the most common cause of OSA) and the other common risk factors for hypertension which are also frequently present in this patient population.

Recent randomised controlled trials have shown that CPAP treatment of severe symptomatic OSA reduces 24 h BP at 4 weeks.^{8–13} In the Oxford randomised parallel controlled trial,⁸ there was a small fall in 24 h mean ambulatory BP of 3.3 mm Hg (95% confidence interval (CI) -5.3 to -1.3) with CPAP treatment relative to control subjects in whom there was no such reduction. Patients with more severe disease (characterised either from the sleep study or by degree of sleepiness) had greater falls in BP. However, the reduction in BP was not seen in all patients, a number of whom had a rise in BP following CPAP treatment. It is not clear if this variation is simply regression to the mean or the result of true differences in physiological response. If there are true patient differences in the BP response to CPAP, this will affect the individual potential cardiovascular benefit.^{14,15} The mechanism for the hypertension of OSA is uncertain, but is likely to be related to increased sympathetic tone and catecholamine excretion.¹⁶ Increased sympathetic tone¹⁷ may result from recurrent nocturnal hypoxia (and/or hypercapnia) or sleep fragmentation. Alternatively, greater falls in pleural pressure (due to the increased inspiratory efforts which develop during obstructive hypopnoeas or apnoeas) generate large transient falls in arterial BP with each inspiration^{18,19} and thus may provoke sympathetic activation to defend the BP.

There are no comprehensive studies on the predictors of the fall in BP with successful CPAP treatment of OSA, although recent data suggest that prior daytime hypersomnolence is important for the BP lowering effect of CPAP.^{11,20} We have therefore studied predictors of the change in BP with CPAP treatment of symptomatic OSA.

METHODS

Design and setting

We performed a prospective cohort study of 86 patients attending the Sleep and Respiratory Trials Unit, Oxford Centre for Respiratory Medicine, Oxford, UK. The Sleep Unit is a regional referral centre and the majority of referrals are for possible OSAS. About one-third of patients are from the immediate Oxford area. Referrals are made from general practitioners (36%), ear, nose and throat surgeons (41%) and other hospital consultants (23%).

Patients

Patients were eligible for the trial if they were aged over 18 years and were on the routine waiting list

for CPAP treatment. Subjects had proven OSA on overnight sleep study, with sufficient daytime hypersomnolence to warrant treatment with CPAP. A particular overnight rate of dips in arterial oxygen saturation (SaO_2) of $>4\%$ and baseline Epworth Sleepiness Score (ESS) were not entry criteria in offering recruitment of patients to the trial, thus providing a full spread of severity. The trial recruited all subjects with OSA whom the usual clinic doctor had felt warranted a trial of CPAP for daytime symptoms. A control arm was not included as this was not a trial of whether CPAP lowered BP which has been established in previous trials.^{8–13} Furthermore, in our previous study no effect of placebo CPAP on BP was seen.⁸ Patients were excluded if they had diurnal ventilatory failure, declined to participate or were unable to give informed consent. The presence of hypertension, a previous cardiovascular event or any additional cardiovascular risk factor were not determinants in offering or declining a patient for entry to the trial.

Procedures

OSA was diagnosed from a one night respiratory polysomnographic study, as described previously.⁸ In brief, patients' body movements, heart rate rises (>6 beats/min) and falls in transient pulse transit time (PTT) (reflecting BP rises) were recorded as markers of arousal from sleep. The PTT signal and body movements derived from video signals are robust markers of arousal and—together with SaO_2 , snoring and increases in the respiratory swing in PTT²¹—are accurate in diagnosing and quantifying OSA severity²² (Win-Visi Monitoring System, Stowood Scientific Instruments, Oxford, UK). The results of the sleep study are scored automatically, with manual review to ensure data accuracy. OSA was diagnosed from a review of all data including the video recording.

The severity of OSA was then quantified numerically as the number of dips in SaO_2 of $>4\%$ for every hour of the study (oxygen desaturation index, ODI), mean nocturnal SaO_2 and time spent below $90\% \text{SaO}_2$. The ODI is one of the best predictors of response to CPAP,²³ correlates well with conventional apnoea-hypopnoea index (AHI) measurements²⁴ and is the most consistent index between repeat studies of patients with OSA.²⁵ The average degree of inspiratory effort overnight was estimated from the oscillations in PTT,²¹ which had been shown to influence morning BP in an epidemiological study.¹⁹

Blood pressure across 24 h was measured with validated ambulatory recorders (TM 2420 or TM 2421 (Takeda A&D, Japan)).²⁶ A trained nurse fitted an appropriately sized cuff on the patient's non-dominant arm, which was worn for the subsequent 24 h during normal daily activities. The monitors were programmed to record BP every 30 min, and subjects were instructed to switch the machine off while driving. The mean BP (one-third systolic and two-thirds diastolic) averaged over the whole 24 h was calculated (24 hMBP). Patients completed a diary card and were asked to press the event marker to identify sleep and wake periods. When two or more readings occurred within the same 30 min (due to pressing the event marker), these were averaged to give one recording for that time period. Mean 24 h pulse rate was also determined.

Patients assessed their subjective daytime sleepiness using the ESS, a self-completed questionnaire which quantifies the tendency to fall asleep in various daytime situations.²⁷ Nasal CPAP was provided for home use using an automatic CPAP machine (Autoset Spirit, Resmed, Abingdon, UK).²⁸ Patients received our standard CPAP induction programme and were seen for a routine appointment at 1 month. Fasting venous blood samples were taken and 24 h BP and subjective sleepiness

were assessed before starting CPAP and after 6 months of treatment. A detailed drug and caffeine consumption history²⁹ and anthropometric measurements were made at both study visits.

A specialist nursing team assisted patients with telephone or outpatient advice for any difficulties with CPAP during the study and masks were adjusted as necessary. Adherence to CPAP over the last 5 months of treatment and the residual AHI were measured from the internal microprocessors of the machines.

Blood samples

Fasting venous blood samples were taken before starting CPAP for measurement of steady state fasting glucose and insulin levels. This allowed a subsequent Homeostasis Model Assessment (HOMA) of beta cell function (%B) and insulin sensitivity (%S) as percentages of a normal reference population. These measures correspond with estimates of beta cell function and insulin sensitivity derived from other models such as the euglycaemic hyperinsulinaemic clamp and the oral glucose tolerance test.³⁰

Sample size

The study population size was chosen to be similar to our previous study in which a significant fall in BP had been found following CPAP treatment.⁸ It is also recommended that there should be 10 subjects per predictive variable in a multiple linear regression model.³¹ A sample size in excess of 60 subjects would allow the simultaneous exploration of a maximum of six variables, should bivariate analysis suggest that this was required.

Data analysis

The data are presented as mean (SD) unless non-normally distributed, and then as median and interquartile range (IQR).

The change in 24 hMBP between baseline and at 6 months was the primary outcome measure and dependent variable, with all other measurements being potential independent predictors which were assessed with linear modelling techniques (stepwise multiple linear regression), using SPSS Version 14.0. Potential interactions between independent predictors were explored using additional interactive terms in the multiple linear regression.

Table 1 Baseline characteristics of study patients (n = 86)

	Baseline	At 6 months
Age (years)	54.3 (11.0)	
M/F	74/12	
BMI (kg/m^2)*	35.6 (32.0–40.0)	35.5 (31.9–39.9)
Neck size (cm)	44.9 (4.0)	44.5 (3.90)
ESS*	16.0 (12.0–18.0)	4.0 (2.0–7.0)
24 hMBP (mm Hg)	101.0 (10.3)	96.1 (9.1)
SaO_2 dips $>4\%$ /h of study*	32.7 (18.3–49.8)	
Mean overnight % SaO_2 *	92.6 (90.8–93.8)	
Minutes spent $<90\% \text{SaO}_2$ *	55.0 (18.3–120.0)	
No with known type 2 diabetes	16/86	
No on antihypertensive drugs	47/86	
CPAP compliance (h/night)		4.8 (2.2)

Data given as mean (SD) or *median (interquartile range) when not normally distributed.

BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Score; 24 hMBP, mean 24 h blood pressure; SaO_2 , arterial oxygen saturation.

Table 2 Correlates (r) of 6-month fall in 24 hMBP (bivariate analysis)

	Correlation coefficient (r)	95% CI	p Value
Baseline ESS	-0.23	-0.002 to -0.44	0.045
Change in ESS	0.39	0.18 to 0.57	<0.001
Baseline 24 hMBP	-0.60	-0.43 to -0.73	<0.001
Time below SaO ₂ 90%	-0.25	-0.02 to -0.45	0.047
Baseline BMI	-0.39	-0.18 to -0.57	<0.001
Baseline waist/height ratio	-0.37	-0.16 to -0.55	<0.001
Change in pulse rate	0.44	0.24 to 0.61	<0.001
Compliance	-0.04	-0.26 to 0.19	0.75
Change in caffeine consumption	-0.002	-0.25 to 0.21	0.86

BMI, body mass index; ESS, Epworth Sleepiness Score; 24 hMBP, mean 24 h blood pressure; SaO₂, arterial oxygen saturation.

RESULTS

Eighty-six subjects were recruited to the study. Their baseline characteristics are shown in table 1; 86% had ESS scores >9, 92% had >4% SaO₂ dips/h of >10, 55% were known to be hypertensive and were taking one or more antihypertensive drugs (nitrates (n = 5), α blockers (n = 5), angiotensin converting enzyme inhibitors or angiotensin II blockers (n = 32), calcium channel blockers (n = 19), diuretics (n = 19), β blockers (n = 20)). Only two subjects had 24 hMBP values over 110 mm Hg and were not already known to be hypertensive and already on antihypertensive medication. Four subjects failed to complete the study: three withdrew before the 1-month visit (one because of intolerance of the BP cuff and two because of intolerance of the CPAP mask) and one subject died before the 6-month visit. Of the remaining 82 subjects, complete data for all variables were available for 72. The median CPAP pressure (95th centile from the Autoset download) was 11.3 (IQR 10.1–12.5) cm H₂O. The median AHI derived from the Autoset download was 6.1 (IQR 3.4–9.2), indicating good control of the OSA and similar to previous studies.³² The mean (SD) compliance over the last 5 months of CPAP usage was 4.8 (2.2) h/night; 13 patients used CPAP for <2.5 h/night.

The change in 24 hMBP at 6 months was -4.92 mm Hg (95% CI -2.8 to -7.1); mean (SD) -5.35 (10.45) during waking hours and -3.82 (12.43) during sleeping hours. The mean improvement in ESS was -9.7 (95% CI -8.6 to -10.8) at 6 months, similar to previous studies.⁵

The change in mean 24 hMBP at 6 months (a fall is negative) correlated most strongly with the baseline 24 hMBP (r = -0.60, table 2). Using an illustrative post hoc analysis of patients above and below the median value for baseline 24 hMBP (100 mm Hg) showed that subjects with a baseline value \geq 100 mm Hg experienced a mean (SD) 6 month fall in 24 hMBP of -9.2 (9.5) mm Hg compared with a mean (SD) fall of -0.7 (8.3) mm Hg in those with a baseline 24 hMBP <100 mm Hg (mean difference 8.54 mm Hg (95% CI 4.4 to 12.7), p<0.001).

The change in mean 24 hMBP at 6 months also correlated significantly with the baseline ESS but more so with the change in ESS (table 2). Using a post hoc threshold for illustrative

purposes, the 30 subjects with a change in ESS \geq 9 experienced a mean (SD) fall in 24 hMBP of -7.34 (9.83) mm Hg, and the 42 subjects with a change in ESS <9 experienced a mean (SD) change in 24 hMBP of -1.37 (8.93) mm Hg (mean difference 5.97 mm Hg (95% CI 1.5 to 10.5), p<0.01).

Measures of general and central obesity (but not other components of the metabolic syndrome such as the HOMA measure of insulin sensitivity) correlated significantly with the change in 24 hMBP at 6 months (table 2). One measure of baseline OSA severity—the time below 90% SaO₂—significantly predicted the change in 24 hMBP at 6 months in single regression, but overnight ODI and mean SaO₂ did not. There was also no correlation between the change in 24 hMBP and the change in reported caffeine consumption or CPAP compliance (table 2). No correlation was found between the change in 24 hMBP at 6 months and the estimate of overnight inspiratory effort from the PTT data or the measure of autonomic arousals during sleep (pulse rate rises per hour of sleep study) during the diagnostic sleep study. There was also no correlation between change in 24 hMBP and subject age.

The use of stepwise multiple linear regression analysis to first allow for baseline 24 hMBP showed that only the fall in ESS and BMI independently correlated with the fall in 24 hMBP between baseline and 6 months (table 3). The β coefficient from the multiple linear regression for the fall in ESS was 0.51 so, for each 1 point reduction in ESS, the predicted reduction in 24 hMBP was 0.51 mm Hg. The inclusion of all independently predictive variables (baseline 24 hMBP, fall in ESS, BMI) gave a linear modelling coefficient (r) of 0.70, together accounting for 49% (r²) of the variance in 24 hMBP change after 6 months of CPAP therapy. No increases in correlations were seen if log transformations of ODI and time below 90% SaO₂ were used in the linear regression modelling instead.

The change in 24 hMBP at 6 months also correlated significantly with the fall in pulse rate measured from the 24 h BP monitor (table 2), possibly indicating a reduction in sympathetic activation as part of the explanation for the 24 hMBP reduction.

Taking antihypertensive drugs did not predict the change in 24 hMBP: the mean (SD) fall in 24 hMBP in the 39 subjects

Table 3 Multiple linear regression analysis: fall in MBP between baseline and 6 months is the dependent variable

Independent variable	r	95% CI	r ²	p Value	β coefficient	95% CI
Baseline MBP	0.60	0.43 to 0.73	0.36	<0.001	-0.60	-0.39 to -0.75
Change in ESS	0.66	0.51 to 0.77	0.44	0.006	0.51	0.17 to 0.84
Baseline BMI	0.70	0.56 to 0.80	0.49	0.007	-0.28	-0.07 to -0.49

BMI, body mass index; ESS, Epworth Sleepiness Score; MBP, mean blood pressure.

taking any antihypertensive drug was -4.33 (11.2) mm Hg, and for the 35 subjects not taking antihypertensive drugs it was -5.57 (8.2) mm Hg (mean difference 1.24 mm Hg (95% CI 5.84 to -3.37), $p = 0.59$). Patients taking β blockers ($n = 20$) did not experience a significantly different change in 24 hMBP from those not taking β blockers (-3.8 (12.9) mm Hg vs -5.1 (9.3) mm Hg; mean difference 1.30 mm Hg (95% CI 7.53 to -4.94), $p = 0.23$). Inspection of the five subjects who had a rise in 24 hMBP after CPAP of >10 mm Hg showed that four were on antihypertensives but they were not consistently different in any other way.

DISCUSSION

This prospective study has shown that baseline 24 hMBP, treatment-related improvements in hypersomnolence (as measured by the ESS) and obesity measurements best predict 24 hMBP changes following CPAP treatment for 6 months. The subjects studied were typical of those of an OSA population with moderate to severe disease, and were similar to those assessed in our previous randomised controlled trial examining the effect of CPAP treatment of OSA on 24 hMBP, with a median baseline ESS of 16.0, a median baseline $>4\%$ dip rate of 32.8/h (16 and 33, respectively, in the previous study) and similar compliance with CPAP.^{5,8}

Initial 24 hMBP strongly predicts the change in 24 hMBP after CPAP for OSA; if the starting 24 hMBP was <100 mm Hg there was almost no fall with CPAP (mean (SD) -0.7 (8.3) mm Hg). This would be expected for several reasons—particularly regression to the mean—and was thus allowed for in the multiple linear regression modelling before exploring the effect of other factors. However, if any beneficial effects of CPAP on 24 hMBP are actually greater in those with an initially higher 24 hMBP, then we will have overcorrected and obscured this effect. This possibility was explored using an interactive term: initial 24 hMBP multiplied by change in ESS. However, the minimal improvement in variance explained ($r^2 = 0.701$ vs 0.699) was not significant, implying that most of the effect of initial 24 hMBP is likely to have been regression to the mean.

This study therefore suggests that the daytime fall in 24 hMBP following CPAP treatment relates more closely to hypersomnolence than the degree of OSA (quantified from the ODI, nocturnal hypoxia or an estimate of overnight inspiratory effort). This result agrees with two recent studies: our sham-placebo controlled crossover study in non-sleepy hypertensive patients with sleep study proven OSA in whom there was no fall in BP with CPAP²⁰ and the similar study by Barbe *et al.*¹¹ It does not, however, support the hypothesis that overnight inspiratory effort (from a PTT-based method of its estimation) might influence the daytime BP.^{19,21}

The mechanism for the diurnal rise in BP with OSA is uncertain but is likely to be secondary to an increase in sympathetic activation and catecholamine excretion. Hypersomnolence is a marker of sleep fragmentation, and those subjects with greater sleep fragmentation may have more frequent and greater nocturnal catecholamine release leading to daytime hypertension. Thus, resolution of the hypersomnolence may be a co-correlate and marker of the reduction in sympathetic stimulation resulting from effective CPAP therapy that leads to a fall in BP. This is supported by recent studies showing reduced adrenergic activity following CPAP.^{16,17,33} The fall in 24 hMBP at 6 months in the current study correlated significantly with the fall in pulse rate, also implying reduced sympathetic activation. Choi *et al* have shown that cardiac

dysfunction in OSA correlated with sleepiness, independent of indices of OSA severity.³⁴

Although hypoxia, hypercapnia and pleural pressure fluctuations are also possible causes of hypertension in OSA, these data suggest that sleep fragmentation may be the more important mechanism. Norman *et al.*³⁵ failed to demonstrate a fall in mean 24 h ambulatory BP with nocturnal oxygen supplementation compared with CPAP in patients with OSA despite an improvement in oxyhaemoglobin saturation. This suggests that recurrent intermittent hypoxia is less likely to be the cause of the hypertension associated with OSA in humans.

The fall in mean 24 hMBP also correlated with one of the features of the metabolic syndrome—obesity—including waist to height ratio and baseline BMI. A more direct marker of the metabolic syndrome—insulin resistance using the HOMA model—did not, however, predict the fall in 24 hMBP. Correlation analysis showed that the effect of BMI was due partly to its relationship with ESS. The mechanism for the residual independent relationship between obesity and the change in 24 hMBP following CPAP is uncertain, but these data suggest that individuals with greater obesity have slightly more to gain in terms of a fall in BP with CPAP. It is possible that central obesity is acting as a surrogate marker for increased sympathetic tone, since it is thought that the hypertension of the metabolic syndrome is likely to be due in part to increased sympathetic tone via raised insulin resistance.³⁶

No baseline measures of OSA severity predicted the change in 24 hMBP following CPAP. The failure of ODI to predict may seem counterintuitive, given that arousals result from respiratory events. However, the correlation between respiratory events and arousals is not good, with only a proportion of respiratory events leading to arousal and with considerable interindividual variability.³⁷ Sleepiness may therefore reflect the more disturbing arousals and perhaps the more important ones for adrenergic stimulation and diurnal increases in BP. Alternatively, the daytime hypersomnolence itself may in some unknown way be an important factor in driving raised BP rather than the number of arousals per se. Interestingly, poor sleep and sleepiness for reasons other than OSA have also been shown to raise BP.^{38,39}

In conclusion, this prospective study of patients with moderate to severe OSA has shown that, after correction for the baseline 24 hMBP, reduction in daytime sleepiness and measures of obesity are the best predictors of the reduction in 24 hMBP following CPAP therapy for 6 months. We therefore hypothesise that sleep fragmentation may be particularly important in the pathogenesis of the diurnal hypertension of human sleep apnoea by stimulating adrenergic activity.

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