CPAP does not reduce blood pressure in non-sleepy hypertensive OSA patients

Short title: CPAP in non-sleepy hypertensive OSA patients

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Keywords cardiovascular risk, CPAP, hypertension, obstructive sleep apnoea.
Abstract

**Background:** OSA is associated with high cardiovascular morbidity and mortality. Several randomised controlled trials have shown that CPAP treatment of OSA reduces blood pressure. This randomised, sham-placebo controlled cross-over trial assesses whether CPAP produces a similar clinically significant fall in blood pressure in hypertensive OSA patients, but without hypersomnolence.

**Methods:** Thirty-five, non-sleepy, hypertensive patients with OSA were treated with CPAP for one month, randomised first to either therapeutic or sham-placebo (sub-therapeutic CPAP, about 1cm H2O pressure). The second months' alternative treatment followed a two-week washout period. 24h BP was measured before, and at the end of, the two treatment periods: Mean 24hr BP was the primary outcome variable.

**Results:** There was no overall significant difference in mean 24h BP: change in mean 24h BP on therapeutic CPAP -2.1mmHg (SD 8.1), and -1.1mmHg (SD 8.1) on sub-therapeutic CPAP; a difference of 0.7mmHg (95% CI +2.9 to -4.4). There was a small significant fall in Epworth Sleepiness Score (ESS), therapeutic (-1.4) versus sham (-0.3), difference -1.2 (95% CI -2.0 to -0.4), p< 0.02, but no change in objective sleepiness.

**Conclusion:** In non-hypersomnolent hypertensive patients with OSA, there is no significant fall in mean 24h blood pressure with CPAP, in contrast to the fall seen in hypersomnolent patients with OSA.
Introduction

Obstructive sleep apnoea (OSA) is common, with 2-4% of adult men, and about 1% of adult women having detectable sleep apnoea on overnight sleep study. Approximately 1% of UK men have moderate or severe disease, appropriate for treatment with nasal continuous positive airways pressure treatment (nCPAP). In OSA, recurrent upper airway closure causing transient asphyxia leads to sleep fragmentation with subsequent daytime hypersomnolence. Daytime hypersomnolence is associated with an increase in driving accidents and poor quality of life. Both day and nighttime blood pressure are often raised in OSA. The raised blood pressure is seen in community epidemiological and hospital based studies, and is independent of obesity (the commonest cause of OSA), and the other common risk factors for hypertension, which are also frequently present in this patient population.

Nasal continuous positive airways pressure (nCPAP) treatment is the most effective treatment for severe OSA. Randomised controlled trials have shown improvement of daytime sleepiness with nCPAP which is usually improved after the first night of treatment, and certainly after two weeks. Recent randomised controlled trials have shown that CPAP treatment of severe OSA reduces 24 hour blood pressure. In the Oxford randomised parallel controlled trial, there was a mean ambulatory blood pressure fall of 3.3mmHg (95% CI -5.3 to -1.3) with CPAP treatment relative to controls, with an even larger BP fall of 6.6mmHg in those on anti-hypertensive drugs. Patients with more severe disease (>30, >4% SaO2 dips/hr) had greater falls in blood pressure, and the blood pressure reduction appeared independent of baseline blood pressure. The mechanism for the hypertension of OSA is uncertain, but is likely to be related to increased sympathetic tone, and catecholamine excretion. Increased sympathetic tone may result from recurrent
nocturnal hypoxia (or hypercapnia), sleep fragmentation, or greater pleural pressure falls due to the increased inspiratory effort which develops during hypopnoeas and apnoeas.\textsuperscript{20}

Nasal CPAP is currently used to improve the daytime hypersomnolence of OSA\textsuperscript{21}. Depending on the definition used, between 1 and 5\% of UK adult men have detectable sleep apnoea on sleep study\textsuperscript{1}, with approximately 1\% having sufficient daytime symptoms to warrant treatment with CPAP\textsuperscript{2}. Therefore perhaps up to 4\% of UK adults have OSA which is detectable on sleep study, but without sufficient excess hypersomnolence to warrant CPAP therapy.

Because of the high incidence of cardiovascular complications in patients with OSA, some now advocate CPAP treatment for all these patients\textsuperscript{22}, regardless of daytime symptoms. The average patient with OSA has a 10 year cardiovascular risk of about 30\% (myocardial infarction and stroke risk combined), predicted from conventional risk factors\textsuperscript{23}. From large prospective studies, a blood pressure fall of 3.3mmHg would be expected to be associated with a 20\% stroke and 15\% coronary heart disease event rate risk reduction\textsuperscript{24}; thus the blood pressure falls seen with CPAP treatment have significant potential reductions in vascular risk. At present there is no data to support the extension of treatment to all-comers with just sleep study proven OSA, in the absence of daytime sleepiness: thus there is the potential to waste considerable resources.

This trial aimed to assess whether CPAP treatment produces a clinically significant fall in 24 hour blood pressure in hypertensive patients with OSA but without sufficient daytime symptoms to warrant CPAP therapy, of similar magnitude to that seen in symptomatic patients. This would establish if there is likely to be a cardiovascular benefit to treating hypertensive patients with OSA, even when they do
not have significant daytime hypersomnolence. The study was not designed to
determine the aetiology of any such blood pressure fall. The aim was to answer the
simple clinical question as to whether there is a blood pressure advantage to treating
non-hypersomnolent OSA patients.

Methods

Design and Setting

We performed a randomised sham-placebo controlled, cross-over study of
patients attending the Sleep and Respiratory Trials Units, Oxford Centre for
Respiratory Medicine, Oxford, UK. The unit is a regional referral centre and the
majority of referrals are for possible OSA. 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, had proven
obstructive sleep apnoea with more than 10 dips of >4% oxygen desaturation per hour
on overnight sleep study, and had no daytime hypersomnolence, with an Epworth
Sleepiness Score\textsuperscript{25} (ESS) <10. Subjects fulfilling these two criteria were then assessed
for hypertension. This was defined as either taking anti-hypertensive drugs, or a blood
pressure >140/90mmHg on 24h ambulatory blood pressure monitoring. The 24h
blood pressure recording was only performed on potential subjects if a casual clinic
blood pressure exceeded 140/90, and if they were not already on anti-hypertensive
drugs. Thus we recruited hypertensive patients, with significant sleep study OSA, but
without sufficient daytime hypersomnolence to warrant CPAP treatment.
Patients were excluded if they had respiratory failure, declined to participate, or were unable to give informed consent. A previous cardiovascular event, or the presence of any additional cardiovascular risk factors, were not determinants in offering or declining a patient entry to the trial. The study was approved by the Central Oxford Research Ethics Committee (C01.218), and all participants gave written informed consent.

**Procedures**

Obstructive sleep apnoea was diagnosed from a one night respiratory polysomnographic study, and has been described before\textsuperscript{13}. In brief, patients’ body movements, heart rate rises and transient pulse transit time (PTT) falls (BP rises) were recorded as measures of ‘autonomic arousal’ from sleep. The PTT signal and body movements recorded on video are robust markers of arousal and, along with arterial oxygen saturation, snoring and increases in the respiratory swing in PTT, are accurate in diagnosing and quantifying OSA severity\textsuperscript{26} (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 review of all data, including the video recording.

The severity of sleep apnoea was then quantified numerically as the number of dips in oxygen saturation of greater than 4% for every hour of the study. This index is one of the best predictors of response to nCPAP\textsuperscript{27}, correlates well with conventional apnoea-hypopnoea index (AHI) measurements, and is the most consistent index between repeat studies of patients with OSA\textsuperscript{28}.

24 hour blood pressure was measured with validated ambulatory recorders (TM 2420 or TM 2421 (Takeda A&D, Japan))\textsuperscript{29}. A trained nurse fitted an
appropriately sized cuff on the patients' non-dominant arm, which was worn for the subsequent 24 hours, during normal daily activities. Monitors were programmed to record blood pressure every 30 minutes, and subjects were instructed to switch the machine off whilst driving. Patients completed a diary card, and pressed the event marker to identify sleep and wake periods. When two or more readings occurred within the same half-hour (due to pressing the event marker), these were averaged to give one recording for that time period.

Patients assessed their subjective daytime sleepiness using the Epworth Sleepiness Score (ESS), a self completed questionnaire quantifying the tendency to fall asleep in various daytime situations\textsuperscript{25}. Objective sleepiness was measured with the Osler test (Stowood Scientific Instruments, Oxford, UK), a behavioural maintenance of wakefulness test (MWT), which assesses the subjects' ability to remain awake in a dark and sound isolated room, for up to 40 minutes\textsuperscript{30}. Even though patients were selected for the absence of subjective daytime symptoms, we expected that a number of subjects might be sleepy on objective measurements.

Therapeutic nCPAP was generated using an automatic CPAP machine (Autoset Spirit, Resmed, Abingdon, UK)\textsuperscript{39}; the control arm used a fixed, sub-therapeutic pressure from the same machine, as previously described\textsuperscript{13}. Briefly, the sham-placebo (sub-therapeutic) CPAP machine delivers less than one cm water pressure, which is insufficient to hold open the pharynx. In all other respects, sham-placebo CPAP is identical to therapeutic CPAP. Patients were not aware which CPAP pressure they had received, and the nurse who assigned the patients to each treatment arm did not take part in outcome assessments. The investigators who assessed the study outcomes were not involved in randomisation or patient CPAP setup. A cross-
over design was chosen, as we did not expect a therapeutic effect on symptoms that might un-blind the patients.

Patients received our standard CPAP induction programme. Following baseline assessments, patients were randomised to the first treatment arm (either therapeutic or sub-therapeutic CPAP) for one month. Randomisation was by a series of pre-sealed and numbered opaque envelopes. The second randomised treatment period followed a two week ‘washout’. Twenty-four hour blood pressure, subjective and objective sleepiness were assessed before, and after each treatment period. CPAP compliance during both treatment periods, and residual AHI following therapeutic CPAP were measured from the machines' internal microprocessor. It was not possible to measure AHI after sub-therapeutic CPAP for technical reasons. Patients were instructed not to change their anti-hypertensive medication during the study period.

A specialist nurse team assisted patients with telephone advice for any CPAP difficulties during each treatment period, and masks were adjusted as necessary. At the end of the study, subjects were given the option to continue with CPAP long term. If they wished to continue, they were discharged with a fixed pressure machine, the pressure being derived from the study period on the therapeutic autoadjusting CPAP machine.

Sample Size

The study size was predicted from the results of our previous randomised parallel trial assessing the effect of therapeutic and sub-therapeutic CPAP on 24 hour ambulatory blood pressure. Results of this study suggested that a difference in mean 24 hour blood pressure of more than 5mmHg could be excluded with 26 patients crossing over (alpha = 0.05, power = 90%). Thus allowing for a 15% dropout rate, we
needed to recruit a minimum of 30 patients. The data are presented according to current recommendations (CONSORT)\textsuperscript{31}.

**Data Analysis**

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

The primary end point was change in mean blood pressure (1/3 systolic plus 2/3 diastolic), averaged over 24hr, after therapeutic or sub-therapeutic CPAP. Secondary analyses included change in systolic and diastolic blood pressure, and change in mean blood pressure during wake and sleep periods. Changes in blood pressure were assessed with paired t-tests. The correlation between the change in blood pressure and the two potential predictors, baseline BP and OSA severity were examined, as was any correlation with therapeutic CPAP compliance. All analyses were done with SPSS version 11.0.
Results

Figure 1 shows the trial profile. Of the 40 patients eligible for the trial (with > 10/hour, >4% oxygen desaturation dips on sleep study), with an Epworth Sleepiness Score <10, 5 did not have hypertension on 24h BP monitoring, leaving 35 entering the study. Twenty-seven of these subjects had drug-treated hypertension, the other 8 had hypertension confirmed on 24h BP monitoring. Seven subjects were taking two or more classes of anti-hypertensive drug, the other twenty were on a single drug. Similar numbers of patients were taking a beta blocker (n= 7), diuretic (n= 6), angiotensin converting enzyme inhibitor or angiotensin II blocker (n= 8), calcium channel blocker (n= 5). One patient was taking an alpha-blocker.

Eighteen patients received therapeutic CPAP, and 17 received sub-therapeutic CPAP for the first month. Two of the patients treated in the therapeutic CPAP arm first were withdrawn before completing the first months' treatment period, one because of intolerance of the blood pressure cuff, and one because the blood pressure data collected were inadequate. Following the two week ‘washout’ period, subjects were given the alternative treatment. Thus, in the second limb, 17 patients were treated with therapeutic CPAP, and 16 were treated with sub-therapeutic CPAP. One subject was withdrawn from the therapeutic CPAP arm during the second month, because of intolerance of the blood pressure cuff, leaving 32 patients completing both treatment arms of the study.

Table 1 shows the patients' characteristics at baseline. The subjects had significant sleep apnoea, with a median of 28.1 (IQ 18 to 38) > 4% oxygen saturation dips per hour, but no significant hypersomnolence, with a median baseline Epworth Sleepiness Score of 5.3 (IQ 3.0 to 7.0), and a median baseline MWT of 40 minutes, (IQ 40 to 40 minutes).
Table 2 shows the blood pressure data. There was no overall significant difference in mean 24h blood pressure. The change in mean 24h blood pressure on therapeutic CPAP was -2.1mmHg (-0.5 during waking hours, -2.9 during sleeping hours), and -1.1mmHg on sub-therapeutic CPAP (-1.2 awake, +0.1 asleep), a difference of 0.7mmHg (95% CI +2.9 to -4.4). There was no significant blood pressure fall on therapeutic or sub-therapeutic CPAP when the blood pressure was divided into 24h systolic and diastolic blood pressure, or into sleep and wake. Review of the Autoset CPAP microprocessor data showed resolution of oxygen desaturations with therapeutic CPAP (residual AHI 5.5, SD 3.7).

There was a small, significant difference in mean CPAP compliance between the two treatment arms. Mean CPAP use on therapeutic CPAP was 5.2 (SD 2.1) hours/night, and 4.3 (SD 2.4) hours/night on sub-therapeutic CPAP (p< 0.001). This was presumed to be because subjects felt symptomatically better on therapeutic CPAP, leading to increased overnight use. This fits with the small, but significant, fall in ESS (subjective sleepiness) seen on therapeutic CPAP of -1.4, versus -0.3 on sub-therapeutic CPAP (p< 0.02). However there was no change in maintenance of wakefulness test (MWT, p> 0.8), which was not surprising as the values were essentially normal at baseline. Only four of the 32 subjects failed to reach the full 40 minutes on MWT prior to therapeutic CPAP, and 5 failed after treatment. Seven subjects failed to reach the full 40 minutes prior to sub-therapeutic CPAP, and 2 failed after sub-therapeutic CPAP treatment (all non-significant).

Excluding those subjects with a poor CPAP compliance (<2 hours/night), did not significantly alter the blood pressure data. During the sub-therapeutic CPAP treatment arm, 6 subjects had a compliance <2 hours/night, and during the therapeutic
CPAP arm, 3 subjects had a compliance of <2 hours/night. These 3 subjects were also poor compliers on sub-therapeutic CPAP. With the poor CPAP compliers excluded from the data, the change in mean 24h blood pressure was -2.0mmHg and -1.4mmHg on therapeutic and sub-therapeutic CPAP respectively (difference -1.0, 95% CI +3.4 to -5.4).

The median baseline >4% oxygen saturation dip rate was 28.1/hour. There was no significant overall mean blood pressure change on therapeutic or sub-therapeutic CPAP depending on baseline OSA severity. For those in the bottom half of the group (defined as >4% oxygen saturation dip rate ≤ 28.0), the mean 24h blood pressure change was -3.3mmHg and +0.5mmHg on therapeutic and sub-therapeutic CPAP respectively; a difference of -3.8mmHg (95% CI -9.6 to +2.0). For those in the top half of the group (defined as >4% oxygen saturation dip rate ≥ 28.1), the change in mean 24h blood pressure was -0.8mmHg and +2.9mmHg on therapeutic and sub-therapeutic CPAP respectively; a difference of +1.5mmHg (95% CI +8.4 to -5.4).

There was no correlation between baseline OSA severity and blood pressure fall, showing that even at the most severe end of our patient population, there was no significant blood pressure fall, as seen in previous studies with symptomatic patients\textsuperscript{13-18}.

At the end of the study period, all of the 32 subjects elected to continue with CPAP, but by twelve months this had dropped to 28/32 (87.5%). The mean 95\textsuperscript{th} centile titration pressure was 10.4 (1.5) cm water. The main reason given by patients for continuing CPAP was the improvement in snoring on treatment.
Figure 1 – Trial profile

40 patients eligible

Excluded (n=5)
5 not hypertensive
(BP <140/90 on 24h measurement,
despite clinic measurement >140/90)

35 randomised

18 received therapeutic CPAP first

17 received sub-therapeutic CPAP first

1 intolerant of BP cuff
1 BP data inadequate

16 completed therapeutic CPAP

17 completed sub-therapeutic CPAP

2 week washout period

16 commenced second months' treatment (sub-therapeutic)

17 commenced second months' treatment (therapeutic)

1 intolerant of BP cuff

16 completed the study

16 completed the study
Table 1 - Baseline patient characteristics

<table>
<thead>
<tr>
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<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>54 (8)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>31/4</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>33.2 (5.3)</td>
</tr>
<tr>
<td>Neck Size (cm)</td>
<td>43.9 (4.0)</td>
</tr>
<tr>
<td>Epworth Sleepiness Score</td>
<td>Median 5.3</td>
</tr>
<tr>
<td></td>
<td>(IQ 3.0 to 7.0)</td>
</tr>
<tr>
<td>Osler Test (min)</td>
<td>Median 40</td>
</tr>
<tr>
<td></td>
<td>(IQ 40 to 40)</td>
</tr>
<tr>
<td>Oxygen saturation dips &gt; 4% (per hour of sleep)</td>
<td>Median 28.1</td>
</tr>
<tr>
<td></td>
<td>(IQ 18.0 to 38.0)</td>
</tr>
<tr>
<td>Drugs/no drugs for hypertension</td>
<td>27/8</td>
</tr>
</tbody>
</table>

CI = Confidence Interval
IQ = Interquartile Range
## Table 2 - Blood pressure results

<table>
<thead>
<tr>
<th></th>
<th>Sub-therapeutic CPAP</th>
<th>Therapeutic CPAP</th>
<th>Difference in BP change (95% CI, negative figures = therapeutic lower)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>24 hour mean blood pressure (mmHg)</td>
<td>105.1 (12.1)</td>
<td>103.9 (12.7)</td>
<td>103.4 (11.6)</td>
<td>101.4 (12.5)</td>
</tr>
<tr>
<td>Wake period mean blood pressure (mmHg)</td>
<td>108.8 (13.0)</td>
<td>107.6 (13.7)</td>
<td>106.1 (13.6)</td>
<td>105.6 (13.2)</td>
</tr>
<tr>
<td>Sleep period mean blood pressure (mmHg)</td>
<td>98.0 (14.8)</td>
<td>97.8 (13.6)</td>
<td>96.0 (11.5)</td>
<td>93.3 (12.3)</td>
</tr>
<tr>
<td>24h systolic blood pressure (mmHg)</td>
<td>143.0 (17.3)</td>
<td>139.3 (17.6)</td>
<td>140.3 (16.1)</td>
<td>137.0 (16.3)</td>
</tr>
<tr>
<td>24h diastolic blood pressure (mmHg)</td>
<td>86.7 (11.1)</td>
<td>86.8 (11.6)</td>
<td>85.3 (11.2)</td>
<td>84.2 (11.7)</td>
</tr>
</tbody>
</table>

Results are mean (SD)
* p of the difference of the differences
Discussion

This study has shown no overall difference in the primary endpoint of mean 24h ambulatory blood pressure in patients with moderate to severe OSA, but without daytime hypersomnolence, when treated with therapeutic CPAP. Further analysis has shown no change in systolic and diastolic blood pressures, and no change during sleep and awake periods. This is in contrast to the blood pressure fall seen in hypersomnolent patients with OSA treated with CPAP\textsuperscript{13,14,15,17} It also suggests that hypersomnolence might in some way be important for the pathogenesis of the hypertension of sleep apnoea. These data further suggest that there is unlikely to be a cardiovascular benefit through reducing 24hr BP to treating non-hypersomnolent hypertensive patients with OSA (despite their high baseline cardiovascular risk), as has been suggested by some\textsuperscript{22}.

The potential limitations of this study include the likely heterogenous population of subjects studied, in terms of the cause of their hypertension. There might be a sub-group of patients on particular anti-hypertensive drugs that behave differently. To answer this question will need a much larger study. The treatment period was short, but comparable to the treatment period in Pepperell et al's study\textsuperscript{13} (to aid data comparison), where treatment with sub-therapeutic CPAP in hypersomnolent patients for greater than one month would have been unethical. It is possible that a longer period of treatment might have led to an eventual fall.

The mechanism for the sustained rise in blood pressure with OSA is uncertain, but is likely to be secondary to increased sympathetic tone and catecholamine excretion\textsuperscript{20}. The cause of the increased sympathetic tone is not established, but this data could suggest that it may be indirectly related to the hypersomnolence, with both perhaps due to sleep fragmentation. Hypoxia, hypercapnia and pleural pressure
fluctuation are also possible alternative causes\textsuperscript{32,33}, but the absence of a blood pressure fall in this patient group (despite resolution of these consequences), indirectly suggests that sleep fragmentation may be the more important mechanism.

Hypersomnolence is a marker of sleep fragmentation, so it follows that this patient population may have had less severe sleep fragmentation than in the previous studies on hypersomnolent patients\textsuperscript{13,14,15,17}. Rees et al have shown considerable inter-individual variation in the degree to which patients with OSA experience cortical electroencephalographic (EEG) arousal with each apnoea\textsuperscript{34}. It is possible that the previously studied patients represented a population more susceptible to the cortical effects of apnoeas, with a higher proportion leading to EEG arousal, and hence causing sleep fragmentation and daytime hypersomnolence.

This current group of subjects had a median >4\% oxygen saturation dip rate of 28.1. Our previously studied OSA population had a baseline median >4\% oxygen saturation dip rate of 33\textsuperscript{13}. In these earlier subjects, the majority of the blood pressure fall with therapeutic CPAP was in those subjects with >33, >4\% oxygen saturation dips/hour. In this currently studied population, there was no relationship between baseline OSA severity and blood pressure fall. Our subjects with the most severe OSA (the top 50\% of the group, i.e. those with >28.1, >4\% oxygen saturation dips/hour), also showed no fall in BP, indicating no dependence on baseline >4\% oxygen saturation dip rate. This confirms it is unlikely we have missed an effect seen only at the severe end of the spectrum.

Philipson et al's studies using a dog model of OSA\textsuperscript{35,36}, suggest that recurrent intermittent hypoxia is the more likely mechanism for the sustained hypertension of OSA, rather than sleep fragmentation\textsuperscript{37} - which is the more likely explanation for the transient blood pressure rises seen following each apnoea. Studies in rats\textsuperscript{38} also
suggest that hypoxia may be the causal link, although blood pressure elevation is seen in only some rat strains after exposure to chronic episodic hypoxia for 35 days. In these studies, the blood pressure remained abnormally elevated for some time, in the absence of ongoing hypoxia; with evidence of adrenergic and renin-angiotensin system over-activity as mechanisms for the blood pressure rise. No human studies have thus far addressed this issue. Our current data suggests that hypoxia may not be the linking mechanism, but that an alternative hypothesis, recurrent arousals sufficient to produce daytime sleepiness, may be possible.

This current data is in accordance with that of Barbe et al\textsuperscript{16}, who did not show a blood pressure fall (24 hour ambulatory measurements) with therapeutic CPAP after 6 weeks treatment compared to sham (sub-therapeutic) CPAP. This multicentre Spanish trial studied a more severe group of patients (mean AHI around 55), with no hypertension or daytime hypersomnolence (mean ESS 7.0). No change in subjective or objective sleepiness measures were seen in this study.

Becker et al\textsuperscript{14} and Faccenda et al\textsuperscript{15} showed significant blood pressure falls with CPAP compared to placebo (either sham CPAP or tablet respectively), but the subjects studied were hypersomnolent (median ESS around 14.2 and 15 respectively). Becker et al studied more severe patients, with a mean AHI of around 63; Faccenda et al’s subjects had a mean AHI of 35, similar to the patients studied here.

The literature suggests that the greatest blood pressure falls with CPAP are seen in those patients with hypersomnolence who are taking anti-hypertensive drugs\textsuperscript{13,14,15}. Despite 77\% of our subjects being on anti-hypertensive drugs, there was no fall in blood pressure, thus further suggesting that we should have seen a fall in BP if non-hypersomnolent patients with OSA behave similarly to the hypersomnolent.
Thus, although the power of this study in non-sleepy patients with OSA was limited, we believe that the previous literature would have predicted a much larger BP fall with CPAP in these relatively severe, largely compliant, hypertensive patients mostly on anti-hypertensive medications; and this we did not see.

**Conclusion**

This study in hypertensive patients with obstructive sleep apnoea, but without daytime hypersomnolence, has not demonstrated a significant blood pressure fall with CPAP therapy, as would have been predicted from the available literature on patients with hypersomnolence. This suggests that sleep fragmentation may be important in the pathogenesis of hypertension in human sleep apnoea as well as hypersomnolence. If this is the case, then this potential link needs further exploration using more sophisticated measures of arousal and sleep fragmentation and a range of both hypersomnolent and non-hypersomnolent patients. At present, based on this study and that of Barbe et al\textsuperscript{16}, treating non-hypersomnolent patients with OSA for potential effects on blood pressure, and therefore possibly cardiovascular risk, cannot be supported.

**Acknowledgements**

The British Heart Foundation (study number PG/01/171/13395) provided funding.
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