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Cardiovascular and metabolic effects of CPAP in obese males with OSA

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ABSTRACT: Obstructive sleep apnoea is associated with increased blood pressure and other features of the metabolic syndrome. The aim of the present study was to determine the relative effectiveness of continuous positive airway pressure (CPAP) in modifying these outcomes.

A randomised placebo-controlled blinded crossover trial comparing cardiovascular and metabolic outcomes after 6 weeks of therapeutic and sham CPAP was performed in 34 CPAP-naïve patients (mean±SD body mass and respiratory disturbance indices were 36.1±7.6 and 39.7±13.8, respectively).

Mean waking systolic and diastolic blood pressure fell by 6.7 and 4.9 mmHg, respectively, when compared with sham CPAP. No change was observed in glucose, lipids, insulin resistance or the proportion of patients with metabolic syndrome. In CPAP-compliant patients the fall in blood pressure was greater and the baroreceptor sensitivity improved significantly but no metabolic variable changed.

In obese Caucasians with untreated obstructive sleep apnoea, continuous positive airways pressure can improve baroreceptor responsiveness and reduce waking blood pressure within 6 weeks, but this treatment period was insufficient to modify insulin resistance or change the metabolic profile. The mechanisms underlying this difference in the time course of blood pressure and metabolic response to continuous positive airway pressure in obstructive sleep apnoea requires further exploration.

KEYWORDS: Baroreceptor sensitivity, blood pressure, insulin resistance, metabolic syndrome, obstructive sleep apnoea

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STATEMENT OF INTEREST
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Obstructive sleep apnoea (OSA) is a highly prevalent disorder [1] initially identified due to its association with snoring and daytime somnolence [2], but nowadays recognised as being associated with an increased cardiovascular morbidity [3] and, particularly, arterial hypertension [4]. Although initially dismissed as a chance association, a powerful epidemiological case based on controlling for other covariates of hypertension has established that OSA is an independent risk factor for this condition [5]. Similar problems have affected the interpretation of data about insulin resistance (IR), with early studies suggesting this was an epiphenomenon [6]. However, later studies in a variety of patient populations reported an independent effect of OSA on this variable [7–9], with evidence of decreasing insulin sensitivity as the severity of sleep apnoea increases [10]. The composite end-point of raised systemic blood pressure, fasting glucose and lipids, now defined as the metabolic syndrome [11] and itself related to the presence of IR, is significantly more prevalent in OSA sufferers naïve to continuous positive airway pressure (CPAP) treatment than in age- and weight-matched controls [12].

CPAP treatment abolishes the principal physiological abnormality in OSA, *i.e.* repetitive upper airway obstruction during sleep, reducing daytime sleepiness and improving health status in randomised placebo-controlled trials [13, 14]. The normal nocturnal fall in arterial blood pressure is reduced or absent in OSA and this can be restored by CPAP therapy, which also reduces waking blood pressure [15, 16]. Data about the effect of CPAP on the metabolic abnormalities are less robust, since, to date, studies have been uncontrolled and not all report whether body composition, an important determinant of metabolic outcome, changed during the trial period. Nonetheless, improvement in IR assessed by the insulin-clamp technique [17] has been observed, although in the latter study this effect was more evident in less obese patients.

To date, no study has investigated the relative time courses of the response to CPAP treatment and their impact on the number of individuals

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classified as having the metabolic syndrome. The present authors used the opportunity afforded by a delay in the funding of treatment in their area to conduct a prospective randomised crossover study of the effect of CPAP on the metabolic syndrome and its components. In order to confirm the physiological significance of any change in waking blood pressure or glucose, baroreceptor sensitivity (BRS) and IR were also measured. Finally, any change in these variables with CPAP to the degree of CPAP compliance and body habitus was reported.

METHODS

Subjects

The present authors studied untreated patients with a confirmed diagnosis of OSA recruited from the Sleep Disordered Breathing Clinic at the University Hospital Aintree (Liverpool, UK). Subjects were eligible if they were naïve to CPAP, not known to suffer from other medical conditions and were not receiving medication. If any abnormality was identified on a baseline ECG, or there was evidence of diabetes (fasting blood glucose $\geqslant$7.1 mmol·L^{-1}), renal, liver or cardiac disease they were excluded, as were patients with symptoms of peripheral neuropathy or a waking diastolic and systolic blood pressure $\geqslant$110 and $\geqslant$180 mmHg, respectively, a level of blood pressure which the present authors felt mandated treatment even if it had not yet begun. Patients with evidence of impaired fasting glucose, impaired glucose tolerance and dyslipidaemia in the absence of diabetes were not excluded. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. All subjects gave informed written consent.

Sleep diagnostic assessment

All subjects with OSA snored and reported excessive daytime sleepiness or two or more other features typical of the condition, which included impaired concentration, unrefreshing sleep, choking episodes during sleep, witnessed apnoeas, restless sleep, irritability/personality change, nocturia and decreased libido. Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), with a score $\geqslant$10 indicating a positive result [18]. Diagnosis was confirmed by overnight polysomnography (SleepLab 1000p system; Jaeger, Hoechlberg, Germany) using a standard montage of EEG, electrooculogram and electromyogram signals together with pulse oximetry, respiratory impedance and nasal airflow detected using thermistors. These studies were manually analysed by two technicians using computer software. Apnoea was defined as a cessation of airflow for $\geqslant$10 s accompanied by a $\geqslant$4% desaturation in the preceding 30 s. Hypopnoea was defined as a 50% reduction in airflow accompanied by a $\geqslant$4% desaturation and a reduction in chest wall movement. EEG arousals were not required to make the diagnosis of a respiratory event. Data were expressed as the respiratory disturbance index based on the mean number of apnoeas and hypopnoeas per hour slept, with an apnoea/hypopnoea index >15 events·h^{-1} confirming a positive diagnosis [19].

CPAP titration

CPAP titration was performed in the sleep laboratory using the Autoset^{TM} self-adjusting CPAP device (ResMed Autoscan, Sydney, Australia) [20]. Data were analysed by two experienced technicians using customised software. Optimal CPAP pressure used in the active limb of the study was defined as the pressure that abolished all apnoeas and the patient's snoring.

Protocol

After polysomnography and CPAP titration, subjects attended for baseline measurements of body composition and cardiovascular and metabolic variables related to the metabolic syndrome. They were then randomised to receive either therapeutic or identical sham CPAP (Aria LX; Respironics Inc., Pittsburgh, PA, USA), modified as previously described [21], for 6 weeks with CPAP pressure in the sham limb <1 cmH_2O. Machine pressures were confirmed using an electronic manometer. Subjects were told the sham treatment was a low-pressure alternative that might provide some symptomatic benefit. After reassessment, treatment was crossed-over with a final assessment 6 weeks later (fig. 1). Randomisation used a computer-generated sequence of random numbers and CPAP was provided by a technician unconnected with the study, so that both subject and investigators were blinded to treatment allocation. Standard advice and CPAP support was offered throughout the study. Compliance was measured electronically using a smartcard (Encore Pro®; Respironics Inc.). Data recorded on the smartcard was related to machine running time, as opposed to the time the mask was at pressure, due to the inability to detect subtherapeutic pressures in the mask. Adequate compliance was prospectively defined as a run time of $\geqslant$3.5 h·night^{-1} [22].

Body composition

Weight and percentage body fat were assessed using Tanita TBF-521 bioimpedance scales (Tanita Corp, Tokyo, Japan), and height was recorded. This method had previously been validated against a four-compartment model and was comparable to other prediction techniques, including conventional tetra-polar impedance, skin-fold thickness and body mass index (BMI)-based formulas [23]. BMI (kg·m^{-2}) was calculated as weight divided by height to the power of two. Neck circumference was measured at the level of the laryngeal prominence. Waist circumference was measured midway between the lower rib and iliac crest.

Cardiovascular variables

Waking blood pressure was measured between 08:00 and 11:00 h in the supine position after a 5-min rest and recorded as the mean of three measurements taken at 1-min intervals, according to the British Hypertension Society guidelines. An Omron automatic oscillometric digital blood pressure monitor (HEM-705CP; Omron Corporation, Tokyo, Japan) was used. Hypertension was defined, according to the British Hypertension Society guidelines, as a resting systolic and diastolic blood pressure of 140 and 90 mmHg, respectively.

BRS was measured under controlled environmental conditions using continuous blood pressure. ECG data were recorded with a Portapres Model II and three ECG limb leads (MP100 ECG acquisition module; BIOPAC Systems Inc., Santa Barbara, CA, USA). Breathing was standardised to 12 breaths·min^{-1} using auditory command software and confirmed using a Pneumotrace respiration transducer (World Precision) Instruments Ltd,

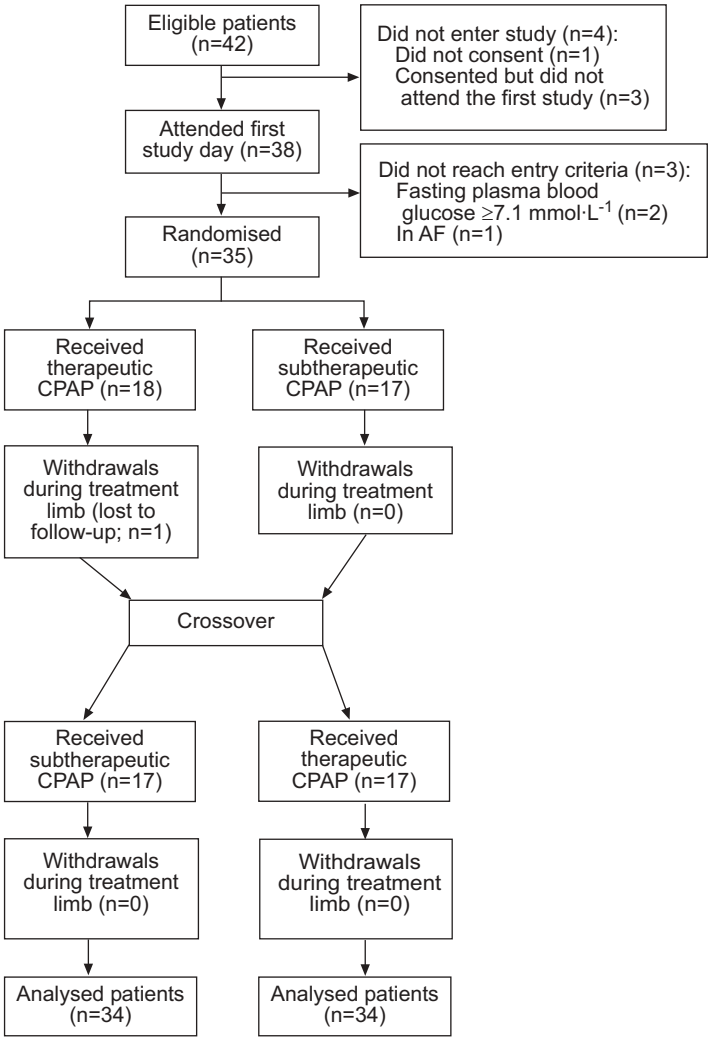

FIGURE 1. Flow chart showing the trial profile. AF: atrial fibrillation; CPAP: continuous positive airways pressure.

Aston, UK) to standardise the effects of respiratory sinus arrhythmia. BRS ($ms \cdot mmHg^{-1}$) was determined from the spontaneous fluctuations in a 300-s period of stationary blood pressure. ECG data were determined using a transfer function analysis, as the mean modulus between spectral values of blood pressure and heart rate variability in the mid-frequency band (0.07–0.14 Hz), with a coherence of 0.3 using the CARSPAN programme (Pro GAMMA, Groningen, the Netherlands) [24].

Metabolic variables

Insulin was quantified using a commercially available insulin assay. Fasting glucose was measured from whole blood using a glucose oxidase-based assay. IR was derived from the fasting glucose and insulin using the homeostasis model assessment (HOMA) calculation, previously validated against the hyperinsulinaemic euglycaemic clamp [25]. Fasting cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol concentrations were measured with a commercially available immunocolourimetric assay, while low-density lipoprotein cholesterol was derived using the Friedwald equation.

The metabolic syndrome was diagnosed according to the National Cholesterol Education Programme guidelines [10] by the presence of three or more of the following: waist circumference >102 cm; triglycerides ≥ 1.7 $mmol \cdot L^{-1}$; HDL cholesterol <1.04 $mmol \cdot L^{-1}$; systolic and diastolic blood pressure ≥ 130 and ≥ 85 mmHg, respectively; and fasting glucose ≥ 6.1 $mmol \cdot L^{-1}$.

Data analysis

The present authors' previous data suggest that ~80% of untreated male subjects with OSA have the metabolic syndrome. Assuming a minimum clinically significant reduction of 20% between groups, a sample size of 31 pairs would have 80% power to detect an absolute difference in proportions of 20% when the proportion of discordant pairs is expected to be 21% and the method of analysis is a McNemar's test of equality of paired proportions with a 0.05 two-sided significance level.

As the present study had a crossover design, the appropriate comparison for the effect of treatment was the difference between data at the end of each treatment period, rather than the change from individual baseline values. Data are presented as mean±SD, unless otherwise stated. Data were analysed on an intention-to-treat (ITT) basis, including all data obtained even if patients were known not to be complying with CPAP therapy. Data were also analysed using the *a priori* cut-point of 3.5 $h \cdot night^{-1}$ for reasonable CPAP compliance and for their relationship to baseline variables of interest. Normally distributed continuous random variables were compared using the mean difference, and 95% confidence interval (CI) for this difference, and paired t-tests. Categorical data were compared using the 95% CI for the difference in paired proportions and McNemar's Chi-squared test.

RESULTS

Trial profile

Four out of the 42 patients eligible to participate withdrew prior to the first study day (fig. 1). Three out of the 38 males who entered the study were excluded before randomisation due to hyperglycaemia (n=2; fasting plasma blood glucose ≥ 7.1 $mmol \cdot L^{-1}$) and atrial fibrillation (n=1). Of the 35 randomised patients, one withdrew during the first treatment period (CPAP limb) for personal reasons and was lost to follow-up. A total of 34 patients completed the trial and their baseline data, including the CPAP pressure used in the active limb of the study, are reported in table 1. Patients were predominantly obese and sleepy, with a raised percentage body fat, and most needed 10 cmH_2O CPAP to abolish their sleep-related breathing abnormalities. There was no significant change in weight, BMI, percentage body fat and fat distribution between the two treatment limbs ($p \geq 0.13$). There was also no evidence of either order or carry-over effect for any outcome variable ($p \geq 0.26$ for all of these comparisons).

Compliance

Mean (range) time on active CPAP was significantly higher than that on subtherapeutic CPAP (3.9 $h \cdot night^{-1}$ (0–7.4) *versus* 2.6 $h \cdot night^{-1}$ (0–7.5); $p<0.01$). Subjects who received CPAP first spent significantly more time on CPAP than the subtherapeutic alternative (3.9 (0–6.2) *versus* 1.9 (0–5.5); $p<0.01$). Subjects who received CPAP second used each treatment for a similar length

of time (4 (0–7.4) for active CPAP *versus* 3.3 (0–7.5) for subtherapeutic CPAP; p=0.22; data not shown).

ITT analysis

On an ITT analysis, subjective sleepiness, systolic, diastolic and mean arterial blood pressure were all significantly lower after 6 weeks of CPAP therapy compared with the sham treatment period and the increase in BRS approached significance (table 2, fig. 2). This reflected a reduction of blood pressure on active CPAP rather than any deterioration during the sham treatment period. No significant change was observed in any metabolic variable or in the number of subjects meeting the criteria for the metabolic syndrome between placebo and active CPAP trial periods. The CIs for the change with active CPAP are presented in table 2 for BRS, blood pressure and IR. To explore these relationships further, the present authors related the change in the variable between active and sham treatments to the baseline value of the variable at trial entry. No evidence was found of a relationship between the change in any variable and the initial value of that variable nor was the change in any variable related to the initial BMI or waist circumference.

Analysis of patients who averaged ⩾3.5 h·night^{-1} of CPAP use

In a subgroup analysis of subjects who averaged ⩾3.5 h·night^{-1} of CPAP use, subjective sleepiness, systolic, diastolic and mean arterial blood pressure were all significantly reduced following 6 weeks of CPAP therapy (table 3). In this subset the change in BRS now achieved statistical significance in the active treatment limb (p<0.04).

TABLE 1 Baseline characteristics of the patients studied

	Baseline characteristics
Subjects n	34
Age yrs	49.0±8.3
BMI kg·m^{-2}	36.1±7.6
Obesity	
Class I BMI 30–<35	10 (30)
Class II BMI ⩾35–<40	8 (24)
Class III BMI ⩾40	11 (32)
Waist cm	117.5±17.8
Body fat %	39.7±8.7
Fat mass kg	43.1±14.3
Neck cm	48.0 (43.0–45.0)
Hypertension#	27 (79)
RDI apnoea·h^{-1}	39.7±13.8
ESS	13.8±4.9
Treatment pressure cmH_2O	10.0 (8.0–10.0)
Smoke	12 (35)
Alcohol units·week^{-1}	
0–4	12 (35)
4–12	12 (35)
12–50	10 (30)

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; RDI: respiratory disturbance index; ESS: Epworth Sleepiness Scale. #: number of patients meeting British Hypertension Society definition of hypertension.

DISCUSSION

The present study is the first to evaluate the relative impact of CPAP over the first 6 weeks of treatment on both cardiovascular and metabolic outcome variables in OSA patients, most of whom were obese. It was established that changes in each outcome pursue a different time course, with waking blood pressure and BRS changing significantly and consistently after 6 weeks of treatment. In contrast, the metabolic variables, whether fasting glucose, lipids or IR, remained unchanged in the group as a whole irrespective of their compliance with treatment. These data, established in the rigorous setting of a randomised controlled crossover trial, have implications for the understanding of the pathogenesis of the complications associated with OSA and for clinical practice.

Patients included in the study were representative of those attending the present authors' clinical service and were diagnosed using relatively conservative definitions of apnoea and hypopnoea, which are comparable to those used in

TABLE 2 Effects of continuous positive airway pressure (CPAP) treatment on components of the metabolic syndrome

	CPAP	Placebo	Difference (95% CI)	p-value
Subjects n	34	34		
ESS	9.4±0.9	12.5±0.9	-3.1 (-4.5– -1.7)	<0.01
BP mmHg				
Systolic	135.7±2.0	142.4±2.4	-6.7 (-10.1– -3.3)	<0.01
Diastolic	86.8±0.15	91.7±1.6	-4.9 (-8.0– -1.8)	<0.01
Mean arterial	103.1±1.5	108.6±1.7	-5.5 (-8.2– -2.8)	<0.01
BRS ms·mmHg^{-1}	5.5±0.5	4.5±0.4	1.0 (-0.1–2.2)	0.07
Fasting glucose mmol·L^{-1}	4.7±0.1	4.8±0.1	-0.1 (-0.3–0.03)	0.11
Fasting insulin pmol·L^{-1}	15.5±1.6	18.1±2.0	-2.6 (-5.9–0.8)	0.13
HOMA IR	3.3±0.4	3.9±0.5	-0.6 (-1.3–0.1)	0.08
Cholesterol mmol·L^{-1}	5.5±0.1	5.7±0.1	-0.2 (-0.5–0.1)	0.29
Triglycerides mmol·L^{-1}	1.8±0.2	1.9±0.2	-0.1 (-0.5–0.2)	0.31
HDL mmol·L^{-1}	1.1±0.1	1.1±0.1	0.0 (-0.1–0.04)	0.30
LDL mmol·L^{-1}	3.6±0.1	3.7±0.1	-0.1 (-0.2–0.2)	0.83
Cholesterol HDL	5.2±0.2	5.3±0.2	-0.1 (-0.3–0.2)	0.73
Metabolic syndrome#	27 (79)	29 (85)	-0.08–0.20	0.63

Data are presented as mean±SEM or n (%), unless otherwise stated. Normally distributed continuous random variables were compared using the mean difference and 95% confidence interval (CI) of this difference. Categorical data were compared using the 95% CI for the difference in paired proportions. Paired t-tests were performed on normally distributed continuous random variables and McNemar's Chi-squared tests on categorical data. ESS: Epworth Sleepiness Scale; BP: blood pressure; BRS: baroreceptor sensitivity; HOMA: homeostasis model assessment; IR: insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein. #: diagnosed according to the National Cholesterol Education Programme criteria.

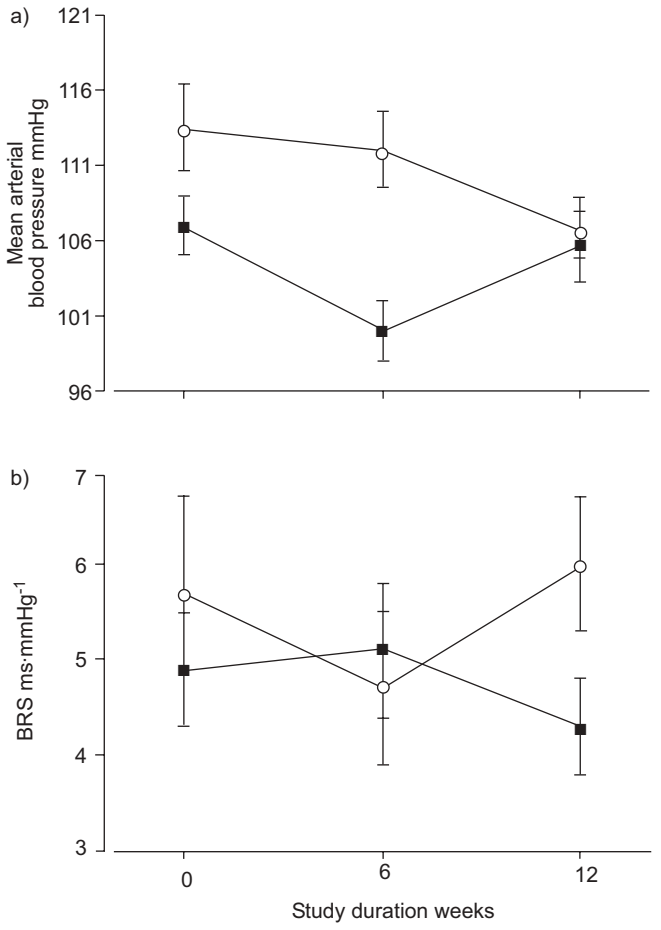

FIGURE 2. Effect of continuous positive airway pressure (CPAP) on a) mean arterial blood pressure and b) baroreceptor sensitivity (BRS). ○: baseline-placebo-CPAP; ■: baseline-CPAP-placebo. The whiskers represent SEM.

patients studied without polysomnographically confirmed OSA [14, 15]. Trial patients were selected to be free from medication and to be either normotensive or unwilling to use treatment at the levels of blood pressure included at recruitment. The change in waking blood pressure, measured under standardised conditions to minimise pressor factors, was both statistically and clinically significant. As shown in figure 2, there was a fall in blood pressure in those receiving active therapy first, while blood pressure remained constant in those patients where placebo CPAP was administered second, producing a reverse pattern. These differences in waking blood pressure after CPAP treatment were similar to those identified in the present study when comparing a different group of OSA patients studied before therapy began with a group of age and weight-matched controls [12]. In these studies it was found that, using the same methodology, the standardised measurement of waking blood pressure identified important differences between groups and treatments. This reduction in blood pressure is greater than that previously reported on CPAP when measuring blood pressure at hourly intervals throughout the daytime [15, 16]. This is possibly due to the fact that blood pressure was estimated at the same time of day in each patient.? Data from large prospective studies suggest that a reduction in blood pressure of 5.5 mmHg, as

TABLE 3 Effects of continuous positive airways pressure (CPAP) treatment on components of the metabolic syndrome in subjects who demonstrated adequate compliance ($\geqslant$3.5 h·night^{-1})

	CPAP	Placebo	Difference (95% CI)	p-value
Subjects n	23	23		
ESS	9.2±1.2	13.1±1.0	-3.9 (-5.7– -2.1)	<0.01
BP mmHg				
Systolic	133.7±2.5	142.2±2.8	-8.5 (-12.7– -4.3)	<0.01
Diastolic	86.6±1.9	93.3±1.7	-6.7 (-10.9– -2.5)	<0.01
Mean arterial	102.3±1.9	109.6±2.0	-7.3 (-10.8– -3.8)	<0.01
BRS ms·mmHg^{-1}	6.1±0.6	4.7±0.3	1.4 (0.1–2.7)	<0.04
Fasting glucose mmol·L^{-1}	4.6±0.1	4.7±0.1	-0.1 (-0.3–0.1)	0.31
Fasting insulin pmol·L^{-1}	13.8±1.6	15.5±2.2	-1.7 (-4.8–1.4)	0.29
HOMA IR	2.8±0.3	3.2±0.5	-0.4 (-1.1–0.3)	0.22
Cholesterol mmol·L^{-1}	5.4±0.2	5.7±0.2	-0.3 (-0.6–0.02)	0.07
Triglycerides mmol·L^{-1}	1.7±0.2	1.9±0.3	-0.2 (-0.7–0.3)	0.33
HDL mmol·L^{-1}	1.1±0.1	1.2±0.1	-0.1 (-0.2–0.03)	0.15
LDL mmol·L^{-1}	3.5±0.1	3.7±0.2	-0.2 (-0.5–0.1)	0.66
Cholesterol HDL	5.0±0.2	5.1±0.3	-0.1 (-0.4–0.2)	0.62
Metabolic syndrome#	16 (70)	19 (83)	-0.04–0.30	0.25

Data are presented as mean±SEM or n (%), unless otherwise stated. Normally distributed continuous random variables were compared using the mean difference and 95% confidence interval (CI) of this difference. Categorical data were compared using the 95% CI for the difference in paired proportions. Paired t-tests were performed on normally distributed continuous random variables and McNemar's Chi-squared tests on categorical data. ESS: Epworth Sleepiness Scale; BP: blood pressure; BRS: baroreceptor sensitivity; HOMA: homeostasis model assessment; IR: insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein. #: diagnosed according to the National Cholesterol Education Programme criteria.

seen in the present study, would be associated with a stroke risk reduction of ~30% and coronary heart disease event risk reduction of 20% [26]. Thus the changes observed provide a rationale for the reduced incidence of cardiovascular disease previously reported in effectively treated OSA patients in a 7-yr follow-up study [27]. This improvement in blood pressure in the present sleepy apnoeic patients contrasts with the lack of response to CPAP in patients without excessive daytime sleepiness, a finding recently confirmed in a randomised controlled clinical trial which used the same sham methodology employed in the present study [28]. Whether metabolic variables were altered in these less common nonsleepy OSA patients has not been reported but would usefully complement the present data were it to become available.

The change in BRS did not reach statistical significance in the ITT population, reflecting the greater measurement variability of this test compared with standardised blood pressure

recording and possibly a smaller impact of CPAP on 24-h blood pressure, as suggested by the ambulatory blood pressure data [15, 16]. The present data also suggest that reduction in BRS is not the only mechanism determining morning blood pressure change in OSA patients after 6 weeks of treatment and are in keeping with recent reports that obesity and OSA have independent effects on adrenergic activation [29]. However, the changes in blood pressure seen in those patients who complied with treatment were larger and the increase in BRS reached statistical significance in this group. Depressed BRS is known to be an independent marker of poor prognosis after an acute myocardial infarction [30]. Although the changes observed before treatment were relatively modest, their correction may translate to an important additional protective benefit if maintained over a longer period.

In contrast, no significant changes were observed in fasting glucose or lipids over the 6 weeks of CPAP treatment and hence there was no significant change in the number of patients classified as having the metabolic syndrome. This is disappointing since differences in HDL cholesterol were identified as being an important factor distinguishing cases and controls in the present cross-sectional comparison. Recently data obtained in the course of two other randomised parallel group trials of CPAP therapy found a trend to reduction in nonfasting total cholesterol after 1 month of treatment, which became significant when patients were reclassified according to their use of therapeutic CPAP [31]. At the same time, a large population-based study found a small but significant improvement in HDL cholesterol after 6 months of CPAP therapy most evident in those with abnormal initial values [32]. Replicating this effect in a randomised controlled trial is likely to be extremely difficult.

The evidence about the role of CPAP in reducing IR in OSA is conflicting [33, 34], although the present study is the first randomised controlled trial data to report using this end-point. An effect of CPAP treatment on IR has been reported in uncontrolled studies of type-2 diabetics with OSA [35] and in OSA in patients with a mean lower BMI [17]. There is always a risk of regression to the mean in data like these, although the randomised blinded treatment allocation used lessens the impact of this. The observations by IP *et al.* [7], who used insulin clamping to determine insulin sensitivity, are particularly relevant to the present findings. The magnitude of response to CPAP in this uncontrolled interventional study was inversely related to the initial BMI. The patients included in the present study were more obese than those in the study by BROOKS *et al.* [35] and no relationship was observed between any measure of body fat and the subsequent IR assessed indirectly. Indeed, calculation of the BMI of the subgroup studied after 3 months of CPAP with a BMI >30 in the data reported by BROOKS *et al.* [35] suggests it is similar to the data in the present trial and the changes in insulin sensitivity at 3 months are largely due to improvements in those individuals with a BMI close to 30 $kg \cdot m^{-2}$. This suggests that there may be a threshold level of obesity where excess body fat is the principal determinant of insulin sensitivity irrespective of the presence of sleep apnoea or its severity. This would be compatible with the large data set provided by IP *et al.* [7], where obesity was the major determinant of IR measured according to the HOMA method with a proportionately smaller effect from OSA. Clearly, longer periods of study will be required to investigate whether changes in IR occur in obese subjects and to determine whether the presence of clinical diabetes changes the responsiveness to therapy. Obesity rather than OSA has been shown to drive other relationships that were initially thought to be a feature of OSA, such as raised serum C-reactive protein levels [36]. However, the present data do demonstrate that important changes in cardiovascular variables occur relatively rapidly and independently of changes in metabolic outcomes or baseline conditions.

Compliance with CPAP is a potentially important confounding variable. As sham CPAP was used rather than a placebo tablet, machine run time was accepted as the surrogate measure of compliance instead of mask pressure. Previous studies have reported a good relationship between these measures and the fall in ESS on active treatment was significantly greater than that on placebo, which may explain the better compliance with active rather than sham therapy in those individuals who received active therapy first. The better compliance with placebo therapy during the second treatment limb may reflect a carry-over effect of successful earlier treatment. However, no other carry-over or order effects were observed. Although individuals who use CPAP for >3.5 $h \cdot night^{-1}$, which was close to the median CPAP use of 4.2 h, showed greater changes in blood pressure and BRS, still there was no significant difference in the metabolic variables or the number and the criteria for the metabolic syndrome. Whether longer periods of compliant therapy will be more successful cannot be addressed in the present study.

In summary, in the present randomised blinded crossover trial in obese Caucasians symptomatic from OSA, significant changes have been confirmed in waking arterial blood pressure within 6 weeks of commencement of continuous positive airway pressure treatment and these are greatest in patients who comply best with continuous positive airway pressure therapy. Baroreceptor sensitivity also improves but, in the present group of relatively obese symptomatic patients, no evidence was found of an improvement in insulin resistance or change in serum lipids over the treatment period and hence no change in the number of individuals classified as having the metabolic syndrome. These data suggest that, while a reduction in sympathetic activation is likely when obstructive sleep apnoea is treated [37] and helps explain the altered cardiovascular responses, this is not sufficient to modify the degree of insulin resistance in the patients over this time frame and other mechanisms predominate to drive insulin resistance in these circumstances. The present results emphasise the need to offer multiple modalities of treatment to obese obstructive sleep apnoea patients if their cardiovascular risk profile is to be successfully modified.

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