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CPAP and measures of cardiovascular risk in males with OSAS

M. Kohler*,+, J.C.T. Pepperell#,+, B. Casadei¶, S. Craig*, N. Crosthwaite*, J.R. Stradling*,§ and R.J.O. Davies*,§

ABSTRACT: Obstructive sleep apnoea syndrome (OSAS) has been associated with hypertension, stroke and myocardial ischaemia in epidemiological and observational studies. Continuous positive airway pressure (CPAP) is the treatment of choice for OSAS, but the impact of this intervention on established risk factors for cardiovascular disease remains incompletely understood.

A total of 102 males with moderate-to-severe OSAS were randomised to therapeutic (n=51) or subtherapeutic (n=51) CPAP treatment for 4 weeks to investigate the effects of active treatment on 24-h urinary catecholamine excretion, baroreflex sensitivity (BRS), arterial stiffness (augmentation index) and 24-h ambulatory blood pressure (ABP).

After 4 weeks of therapeutic CPAP, significant reductions were seen in urine normetanephrine excretion (from mean±SD 179.7±80.1 to 132.7±46.5 μmol·mol^{-1} creatinine) and augmentation index (from 14.5±11.3 to 9.1±13.8%) compared with the subtherapeutic control group. Furthermore, therapeutic CPAP significantly improved BRS (from 7.1±3.3 to 8.8±4.2 ms·mmHg^{-1}) and reduced mean arterial ABP by 2.6±5.4 mmHg.

In conclusion, treatment of obstructive sleep apnoea with continuous positive airway pressure may lower cardiovascular risk by reducing sympathetic nerve activity, ambulatory blood pressure and arterial stiffness and by increasing sensitivity of the arterial baroreflex.

KEYWORDS: Arterial stiffness, baroreflex, catecholamines, continuous positive airway pressure, obstructive sleep apnoea

Obstructive sleep apnoea syndrome (OSAS) is characterised by repetitive apnoea/hypopnoea during sleep associated with oxygen desaturations and sleep disruption. It has been estimated that 2–4% of the adult population in Western countries suffer from clinically significant OSAS, and it is becoming more prevalent as the average bodyweight of the population rises [1].

OSAS has been associated with hypertension, stroke and myocardial ischaemia in epidemiological and prospective observational studies [1, 2]. The pathophysiological mechanisms underlying the association between OSAS and cardiovascular disease are not fully understood, and indeed there may not be a causal relationship. During the actual repetitive episodes of apnoeas there is increased inspiratory effort, episodic hypoxaemia, recurrent arousals, reflex sympathetic activation, increased arterial stiffness and consequent marked transient increases in arterial blood pressure [3–5]. The prolonged repetitive rises in blood pressure are likely to induce excessive vascular shear stress, which has been shown to contribute to the formation of atherosclerotic plaques [6].

Sympathetic activity has been shown to be increased even in the daytime in patients with OSAS, both from measurements of circulating catecholamines and sympathetic nerve traffic. Augmented sympathetic activation may increase arterial stiffness and blunt baroreflex sensitivity (BRS), both of which may contribute to the development of arterial hypertension and to increased mortality [7–12].

Continuous positive airway pressure (CPAP) is the treatment of choice for patients with symptomatic OSAS, as it has been shown to improve daytime sleepiness, alertness and quality of life and to decrease blood pressure [13–15]. Whether CPAP treatment is effective in counteracting the autonomic imbalance and increased arterial stiffness in patients with OSAS remains a matter of debate.

The current authors have addressed this uncertainty by examining changes in 24-h urinary catecholamine excretion, BRS, arterial stiffness

AFFILIATIONS
*Oxford Centre for Respiratory Medicine, Churchill Hospital,
¶Dept of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, and,
#Dept of Respiratory Medicine, Musgrove Park Hospital, Taunton, UK.
+Both authors contributed equally to this study, and
§Both authors contributed as senior authors.

CORRESPONDENCE
M. Kohler
Oxford Centre for Respiratory Medicine
Oxford Radcliffe Hospitals
Churchill Hospital Campus
Headington
Oxford
OX3 7LJ
UK
Fax: 44 1865225221
E-mail: Malcolm.K@bluewin.ch

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and 24-h ambulatory blood pressure (ABP) in a double-blind, randomised controlled trial of therapeutic *versus* subtherapeutic CPAP in patients with symptomatic OSAS.

METHODS

Patients

Patients with possible obstructive sleep apnoea were referred to the Oxford Sleep Unit, (Oxford Centre for Respiratory Medicine, Oxford, UK) by general practitioners, ear, nose, and throat surgeons or other hospital consultants. Patients were eligible for the trial if they were CPAP-naïve males aged 20–75 yrs with excessive daytime sleepiness (Epworth Sleepiness Score (ESS) $\geqslant$10) [16] and proven obstructive sleep apnoea with >10 oxygen desaturations of >4% per h (oxygen desaturation index (ODI) >10 h^{-1}). All eligible patients were offered participation in the study, unless they required urgent CPAP therapy because of respiratory failure, driving or job issues. Data on blood pressure from 52 out of the 102 randomised patients had been used in a previously published study evaluating the effect of CPAP on ABP [15]. Measurements of urinary catecholamines, BRS and augmentation index were added to the previous protocol after receiving ethical approval and establishing the tests within the protocol. The study was approved by the Oxford research ethics committee (Oxford, UK; COREC No. 96.127) and written informed consent was obtained from all participants.

Sleep study, CPAP and assessment of sleepiness

OSAS was diagnosed from a 1-night in-hospital sleep study. Patients' body movements, cardiac frequency and pulse transit time (PTT) changes were recorded as measures of arousal from sleep. Pulse oximetry, snoring and increases in the respiratory swing in PTT were used as markers of breathing pattern and respiratory effort (Win-Visi monitoring system; Stowood Scientific Instruments, Oxford, UK) as previously described and validated [15, 17]. The results of the sleep study were scored automatically, with manual review to ensure accuracy of the data. OSAS was diagnosed from review of all data and severity was quantified as the number of oxygen desaturations >4% per h study (ODI).

After enrolment, patients were randomly assigned to either therapeutic or subtherapeutic CPAP and then underwent a second sleep study, during which respiratory polygraphy was repeated and CPAP was used according to randomisation. In patients assigned to therapeutic CPAP, the therapeutic pressure was determined from overnight use of the Sullivan Autoset-T auto-adjusting CPAP machine (ResMed, Abingdon, UK), from which mask pressure was recorded and synchronised with the sleep study signals. The record was reviewed the following morning, and the optimum pressure to prevent sleep apnoea, usually the 95th percentile of pressure overnight, was determined by a sleep technician. Patients assigned to subtherapeutic CPAP used a machine that delivered <1 cmH_2O pressure as previously described [15], which is insufficient to hold the pharynx open [13].

Patients remained blinded, whether they were receiving therapeutic or subtherapeutic CPAP, as did the investigators. The sleep nurses, who randomly assigned patients to the two groups, maintained the machines and assisted the patients, were not involved in outcome assessments.

Subjective sleepiness was assessed using the ESS, which assesses the tendency to fall asleep during eight typical daytime situations [16]. Objective sleepiness was measured with one sleep resistance challenge (the Oxford Sleep Resistance (Osler) test), which tests the subject's ability to stay awake in a darkened and sound-isolated room [18].

Patients were asked to refrain from caffeine and smoking on the day of examination. The sleep resistance challenge, pulse wave analysis and measurements of BRS were carried out on the same day and at the same time of day on the two occasions the patients were studied.

Urine catecholamines

Urine was collected for 24 h during normal daily activities at home. The adequacy of urine collections was evaluated by measures of volume and creatinine excretion. For analysis, 20 mL of urine were sampled and acidified with 0.5 mL 50% HCl. Urine normetanephrine was measured by high-performance liquid chromatography as previously described [19]. Results were corrected for creatinine excretion ($\mu mol \cdot mol^{-1}$ creatinine).

BRS

BRS was assessed using the bolus *i.v.* phenylephrine technique as previously described [20, 21]. Beat-by-beat arterial blood pressure was measured noninvasively by a finger cuff (Finapres, Ohmeda, CO, USA) [22]. For determination of the RR interval, a single-channel ECG was used (Hewlett-Packard 78342A; Hewlett-Packard, Palo Alto, CA, USA). Designated software (Foundation Salvatore Maugeri, Montescano, Italy) [21] was used to sample/digitise the finger blood pressure and ECG traces and detect systolic blood pressure and RR intervals, as well as for regression analysis. Phenylephrine (starting at 100 μg per bolus, increasing by 25-μg increments at 10-min intervals to a maximum of 200 μg per bolus) was administered *i.v.* with a minimum of three bolus injections to raise systolic arterial pressure by 15–40 mmHg.

Pulse wave analysis

The shape of the pressure waveform of an artery provides a measure of arterial stiffness and can be assessed by the technique of pulse wave analysis [23]. Radial artery pulse waveforms were recorded using a pressure tonometer and dedicated software as previously described (SphygmoCor; AtCor Medical, Sydney, Australia) [24]. Briefly, mean values of ~10 radial pulse waves are used to generate a corresponding central aortic pressure waveform with a validated mathematical transfer function [25]. The software uses an algorithm to determine the aortic pressure waveform's inflection point which corresponds to the onset of the reflected wave coming back from peripheral arteries, and divides the aortic pressure wave into an early and late systolic peak. Augmentation index, which quantifies augmentation of central aortic pressure (due to the reflected component of the pulse pressure waveform) and typically increases with age as the arteries become less compliant [26], is then calculated as the difference between the second (P_2) and first systolic peak pressure (P_1), expressed as percentage of the central pulse pressure (P_P):

$$\text{Augmentation index (\%)} = ((P_2\text{-}P_1)/P_P) \times 100 \quad (1)$$

Essentially, the faster the pulse wave returned from the periphery, the stiffer the arteries, and the higher the calculated augmentation index.

A minimum of two sets of 10 radial artery pulse waveform readings were performed per patient until satisfactory operator indices, calculated by the software, were achieved, and the measurement with the highest operator indices was used for statistical analysis.

Blood pressure

For all patients, office blood pressure was measured in the sitting position with a standard digital automatic monitor (Omron Healthcare Company, Kyoto, Japan) at baseline and after 4 weeks of CPAP treatment. The mean value of three readings was used for analysis.

Validated recorders (TM 2420 and TM 2421; A&D Engineering, Milpitas, CA, USA) were used to measure 24-h ABP during usual daily activities [27]. Monitors recorded blood pressure every 30 min throughout the 24 h, and patients completed a diary card and pressed the event marker to identify the beginning of sleep and wake periods.

Follow-up

After baseline assessments, patients used their therapeutic or subtherapeutic CPAP machine (Sullivan 6; ResMed) for 4 weeks and then re-attended for repeat measurements of urine catecholamines, BRS, pulse wave analysis, blood pressure, ESS and the Osler test. Hour-meters on the CPAP machines were downloaded to calculate mean nightly use. At the end of the trial, CPAP pressure was retitrated in every patient to establish a therapeutic pressure for subsequent long-term use.

Data analysis

Data are expressed as mean$\pm$SD, unless otherwise stated. Baseline characteristics of patients were compared between the therapeutic and subtherapeutic group using independent t-tests. Differences between and within groups, measured at baseline and after 4 weeks, were assessed with two-way repeated-measures ANOVA on an intention-to-treat basis, with no change assumed when follow-up data were missing. When data were analysed as per protocol, all statistically significant differences persisted, and therefore data from this analysis are not shown. For comparison of frequencies, the Chi-squared test of independence was used. Pearson's correlation analysis was used to evaluate the correlation between blood pressure, BRS, augmentation index and urine catecholamines. A p-value <0.05 was considered to be statistically significant.

RESULTS

Trial profile and patients characteristics

Figure 1 shows the trial profile. Overall, 102 patients with a mean age of 48.4$\pm$10.1 yrs were randomised, 51 to therapeutic and 51 to subtherapeutic CPAP. The two groups were similar regarding age, body mass index, fat distribution, smoking status, prevalence of hypertension, proportion of patients on antihypertensive medication (and on β-blocking agents), diabetes and severity of OSAS, but the few subjects with coronary artery disease were only found in the therapeutic CPAP group (table 1).

Urine catecholamines

A total of 101 patients had their urine normetanephrine measured at baseline, and 96 at follow-up. Therapeutic CPAP reduced 24-h normetanephrine excretion significantly, compared with a nonsignificant increase in the subtherapeutic group. This reduction following therapeutic CPAP averaged 26% (table 2). Individual measurements of urine normetanephrine are shown in figure 2.

BRS

At baseline, 77 patients agreed to have their BRS measured, and 69 agreed at follow-up. In patients treated with therapeutic CPAP, BRS increased significantly compared with patients randomised to subtherapeutic CPAP. This increase following therapeutic CPAP averaged 24% (table 2; fig. 3). Just prior to actual BRS testing, heart rate and blood pressure were not significantly different between the therapeutic and subtherapeutic CPAP groups, both at baseline and follow-up.

Pulse wave analysis

At baseline, 72 patients agreed to have pulse wave analysis performed, and 62 agreed at follow-up. Mean change of augmentation index after 4 weeks of therapeutic CPAP was -5.4$\pm$11.0%, indicating a significant reduction in arterial stiffness, whereas augmentation index increased nonsignificantly by +2.0$\pm$8.0% with subtherapeutic CPAP (table 2; fig. 4).

The change in augmentation index was not correlated with changes in 24-h urine normetanephrine excretion or change in BRS.

Office and ambulatory blood pressure

Office blood pressure was assessed in all 102 patients at baseline and in all 99 patients who finished the trial. A total of 62 patients agreed to have their 24-h ABP measured at baseline, and 53 at follow-up. Mean 24-h ABP fell by

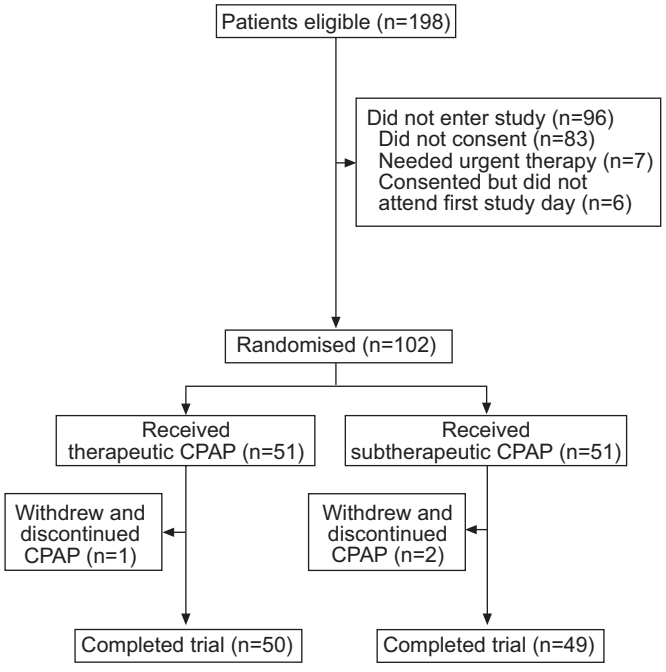

FIGURE 1. Trial profile. CPAP: continuous positive airway pressure.

TABLE 1 Patient characteristics

	Subtherapeutic CPAP	Therapeutic CPAP	p-value
Patients n	51	51	
Age yrs	48.7±10.6	48.1±9.5	0.77
Weight kg	111.3±22.0	115.5±25.1	0.37
BMI kg·m^{-2}	34.5±5.0	35.8±7.3	0.30
Neck circumference cm	44.6±3.3	45.1±4.0	0.54
Waist/hip circumference ratio	1.01±0.06	1.02±0.06	0.93
Current smokers %	17.7	21.6	0.62
Ex-smokers %	54.9	43.2	0.24
Hypertensive %	25.5	21.6	0.64
Patients on antihypertensive therapy %	25.5	21.6	0.64
Diabetics %	2.0	2.0	1.00
Patients with coronary artery disease %	0.0	7.4	0.04
Oxygen saturation dips >4% per hour of sleep	42.7±21.6	41.9±25.4	0.87
ESS at baseline	15.2±4.0	15.8±4.0	0.48
Osler test at baseline min	17.3±13.1	18.1±13.1	0.75
CPAP compliance at study end h·night^{-1}	3.9±2.5	4.7±2.1	0.08
Retitration CPAP pressure following study cmH_2O	10.1±1.6	10.0±1.9	0.72

Data are presented as mean±SD, unless otherwise stated. CPAP: continuous positive airway pressure; BMI: body mass index; ESS: Epworth Sleepiness Score; Osler: Oxford sleep resistance.

2.6 mmHg with therapeutic CPAP, whereas no significant change was found with subtherapeutic CPAP. Details of blood pressure measurements are given in table 2.

In the therapeutic CPAP group, no correlation was found between changes in mean 24-h blood pressure and those in BRS, urinary normetanephrines or augmentation index.

TABLE 2 Blood pressure (BP), baroreflex sensitivity (BRS), urine normetanephrine and augmentation index before and after treatment

	Subtherapeutic CPAP		Therapeutic CPAP		p-value[#]
	Baseline	Follow-up	Baseline	Follow-up	
Office mean BP mmHg	109.3±11.7	107.3±11.2	104.2±12.6	102.4±8.8	0.81
Office systolic BP mmHg	141.6±17.4	140.4±17.4	135.8±16.0	133.0±12.6	0.46
Office diastolic BP mmHg	92.9±11.4	90.8±10.2	89.3±10.8	87.0±8.9	0.96
24-h mean BP[¶] mmHg	105.1±10.9	105.7±10.5	99.6±9.6	97.0±9.9	0.02
24-h systolic BP[¶] mmHg	138.9±20.8	139.5±19.2	131.3±13.9	128.5±14.0	0.07
24-h diastolic BP[¶] mmHg	88.3±8.1	88.9±8.0	83.9±9.3	81.3±9.8	0.04
Wake mean BP mmHg	107.9±10.9	110.0±10.2	103.2±9.2	100.1±10.2	0.002
Wake systolic BP mmHg	142.6±21.5	145.4±20.0	135.9±14.0	133.1±14.6	0.02
Wake diastolic BP mmHg	90.7±7.9	92.3±7.5	86.9±8.9	83.8±10.1	0.005
Sleep mean BP mmHg	99.3±11.8	98.5±9.9	92.0±13.1	89.3±11.0	0.35
Sleep systolic BP mmHg	131.1±21.3	129.8±15.9	121.5±17.0	117.4±16.8	0.33
Sleep diastolic BP mmHg	83.4±9.4	82.7±8.8	77.3±12.5	75.2±10.3	0.51
BRS[+] ms·mmHg^{-1}	6.8±4.0	6.6±4.2	7.1±3.3	8.8±4.2	0.001
Urine normetanephrine[§] μmol·mol^{-1} creatinine	158.6±64.8	160.9±72.3	179.7±80.1	132.7±46.5	0.004
Augmentation[f] index %	12.2±13.6	14.2±14.9	14.5±11.3	9.1±13.8	0.001

Data are presented as mean±SD, unless otherwise stated. For both groups n=51. CPAP: continuous positive airway pressure. [#]: calculated by two-way ANOVA for repeated measurements and compares treatment effects; [¶]: 24-h BP was measured in 33 patients in the therapeutic, and in 29 in the subtherapeutic group; [+]: baroreflex sensitivity was measured in 34 patients in the therapeutic, and in 43 in the subtherapeutic group; [§]: urine normetanephrine was measured in 51 patients in the therapeutic, and in 50 patients in the subtherapeutic group; [f]: augmentation index was measured in 30 patients in the therapeutic, and 42 patients in the subtherapeutic group.

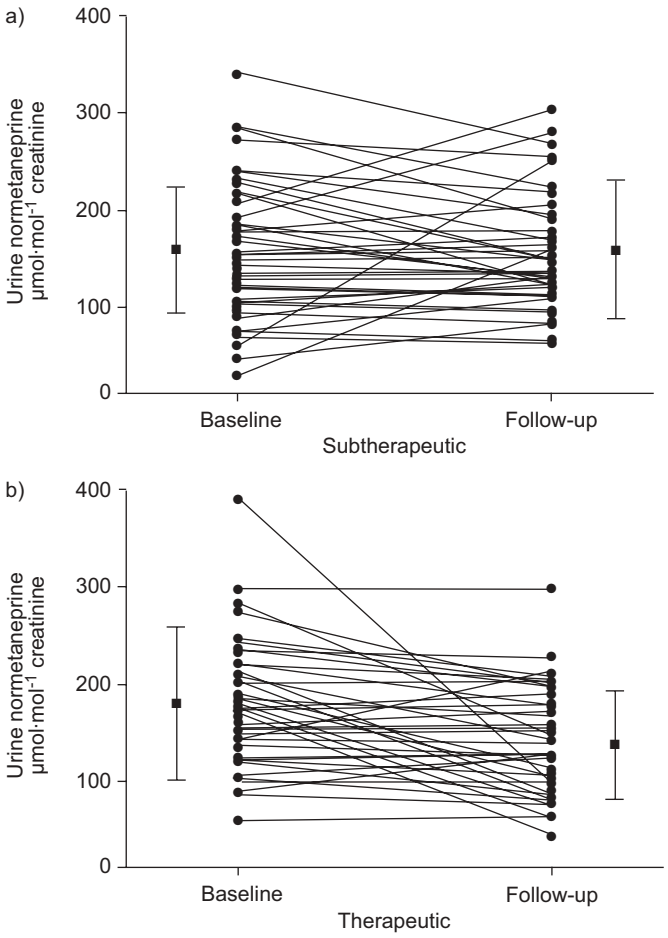

FIGURE 2. Individual urine normetanephrine levels at baseline and follow-up in a) the subtherapeutic continuous positive airway pressure (CPAP) group and b) the therapeutic CPAP group. Two-way ANOVA for repeated measurements revealed that therapeutic CPAP significantly reduced normetanephrine excretion compared with subtherapeutic CPAP ($p=0.004$). ■: mean; vertical bars: SD.

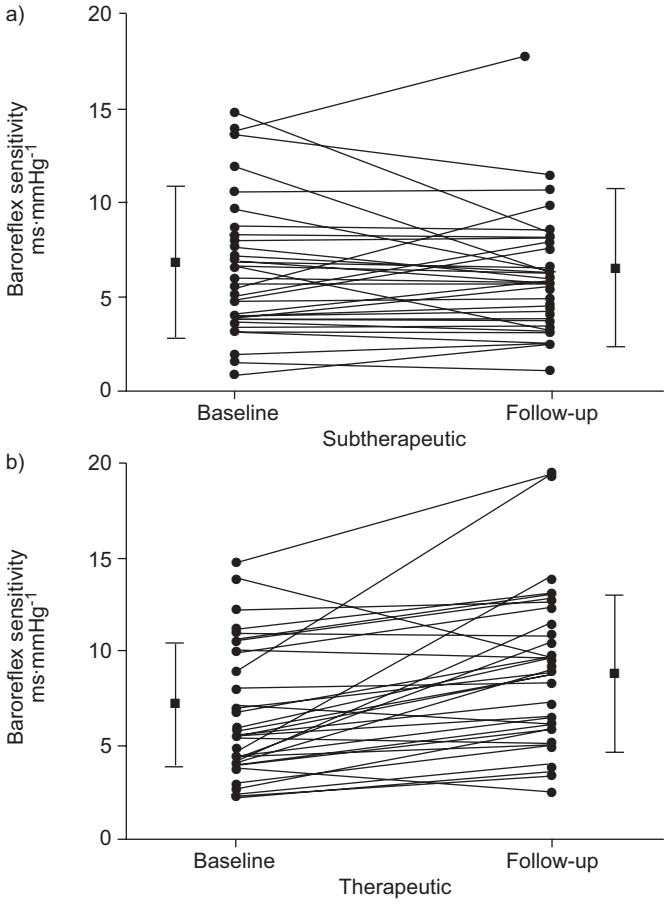

FIGURE 3. Individual baroreflex sensitivity at baseline and after 4 weeks of a) subtherapeutic continuous positive airway pressure (CPAP) and b) therapeutic CPAP. ANOVA showed that therapeutic CPAP significantly increased baroreflex sensitivity compared with subtherapeutic CPAP ($p=0.001$). ■: mean; vertical bars: SD.

Measures of sleepiness and CPAP compliance

Therapeutic CPAP significantly reduced the ESS from 15.8 ± 4.0 to 6.8 ± 5.1 (difference -8.6, 95% confidence interval (CI) -10.2– -7.1; $p<0.0001$) and improved objective sleepiness measured by the Osler test from 18.1 ± 13.1 to 26.8 ± 12.9 min (difference 8.7 min, 95% CI 4.5–12.9; $p=0.009$). Subjective sleepiness measured by ESS also improved with subtherapeutic CPAP, from 15.2 ± 4.0 to 11.9 ± 5.9 (difference -3.3, 95% CI -4.6– -2.0; $p<0.0001$). However, subtherapeutic CPAP had no significant effect on objective sleepiness (17.3 ± 13.1 and 18.3 ± 14.3 min; difference 1.0 min, 95% CI -2.7–4.7; $p=0.58$). Compliance with CPAP did not differ between the two groups (table 1). The present data show a clear difference in the change of objective sleepiness between the two groups, despite a placebo effect on ESS.

In the therapeutic CPAP group, the improvement of objective sleepiness assessed by the Osler test was correlated with 24-h diastolic blood pressure fall ($r= -0.48$, 95% CI -0.72– -0.14; $n=29$; $p=0.008$), but not with change in BRS, urine normetanephrine excretion or augmentation index.

DISCUSSION

The present authors have performed a large randomised controlled trial on the effects of CPAP on daytime BRS and arterial stiffness in patients with OSAS, and found a significant improvement in these parameters after 4 weeks of active treatment. Furthermore, therapeutic CPAP treatment decreased 24-h urine normetanephrine excretion, consistent with a reduction in sympathetic nerve activity, and mean 24-h ABP. These beneficial changes may explain the increased survival found in OSAS patients treated with CPAP in a recently published observational study [12].

Sympathetic activity

Elevated levels of circulating plasma norepinephrine and urine catecholamine metabolites have been demonstrated during sleep and resting waking periods in patients with OSAS [28, 29]. It has been suggested that hypoxia and frequent periodic arousals from sleep may underlie the increased sympathetic nervous activity in the presence of OSAS, although arousals seem to be more significant [10, 30]. Consistent with a reduction of sympathetic nerve activity, the present authors found that 4 weeks of CPAP

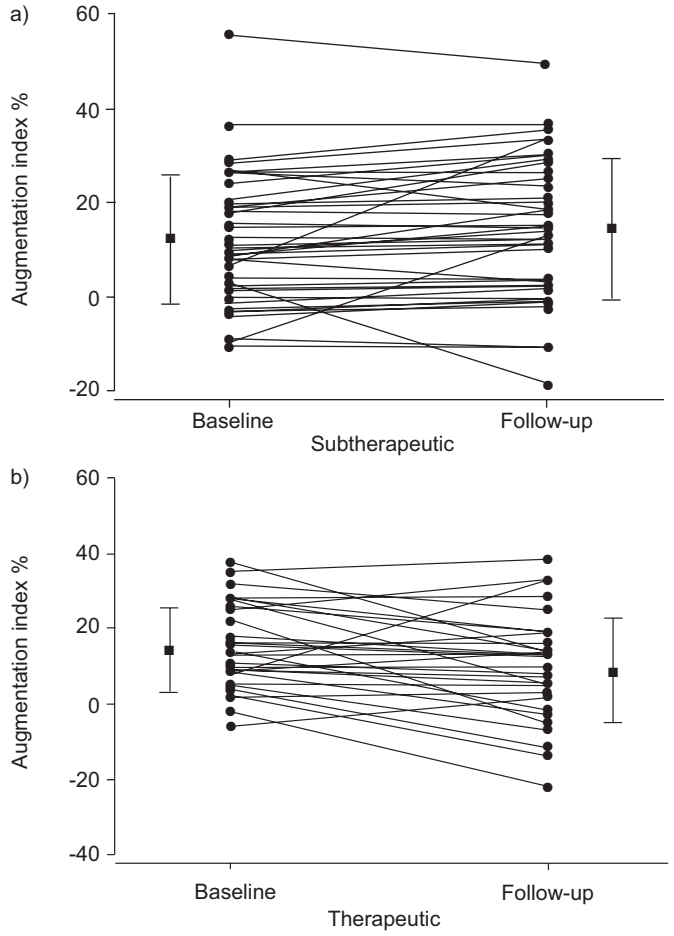

FIGURE 4. Individual augmentation index assessed by pulse wave analysis at baseline and follow-up in a) the subtherapeutic continuous positive airway pressure (CPAP) group and b) the therapeutic CPAP group. ANOVA showed that therapeutic CPAP significantly decreased augmentation index compared with subtherapeutic CPAP ($p=0.001$). ■: mean; vertical bars: SD.

therapy decreased 24-h urine normetanephrine excretion by 26%. This finding is supported by results from an uncontrolled study from HEDNER *et al.* [31], who found significantly decreased levels (32–54%) of urine vanylmandelic acid and metanephrines after 20.5 (range 14–26) months of CPAP in patients with severe OSAS. Furthermore, in agreement with the current study, ZIEGLER *et al.* [32] found a 26% reduction in 24-h urine norepinephrine after 7 days of CPAP in a randomised controlled trial including 38 patients with moderate-to-severe OSAS. The observed effect of CPAP on urinary catecholamines is comparable to that achieved by weight-reducing gastroplasty (reduction of the body mass index from 38.6 to 28.5 $kg \cdot m^{-2}$ produces a 23% decrease in norepinephrine excretion) [33] or by endurance training programmes of >4 weeks' duration (reduction of plasma norepinephrine 29%) [34]. In addition to potential beneficial effects on heart rhythm disturbances, which have been associated with enhanced sympathetic activity, CPAP might also have a direct effect on vascular properties, since the level of sympathetic nerve activity has been shown, for example, to be associated with femoral artery wall thickness in healthy humans [35].

BRS

Reduced vagal activity and relative sympathetic predominance have been shown to be associated with sudden death and poor prognosis in patients after myocardial infarction. [21, 36] BRS, a well-established index of cardiac vagal responsiveness [37], has been shown to be depressed during sleep in patients with severe OSAS, and uncontrolled short-term trials have suggested an improvement of nocturnal BRS with CPAP treatment [7–9]. In the present study, BRS measured during daytime increased by 24% after 4 weeks of therapeutic CPAP, indicating that the beneficial effect of treatment on the cardiac sympatho-vagal balance is not limited to the sleep period. It should be noted that this improvement in BRS after CPAP is comparable in size to the effect seen after several months of endurance training in patients with mild hypertension [38]. The increase of BRS in response to CPAP might contribute to the improved survival found in OSAS patients treated with CPAP, compared with untreated patients [12], as decreased vagal tone and increased sympathetic activity may lead to arrhythmias and a peak in sudden death from cardiac causes during the sleeping hours in patients with OSAS [39].

Arterial stiffness

Augmentation index, a measure of central arterial stiffness and pressure wave reflection, independently predicts cardiovascular events in high-risk populations [40]. In the current study, augmentation index decreased significantly from 14.5 to 9.1% after 4 weeks of CPAP therapy. This considerable reduction is comparable in size to the effect seen after 12 weeks of exercise training in patients with coronary artery disease [41] or after 6 weeks of eprosartan (600 mg daily) in patients with never-treated arterial hypertension [42]. The mechanism responsible for this fall in augmentation index is at present a subject of speculation. A decrease in sympathetic activity may contribute to the observed reduction in arterial stiffness; however, the change in urine normetanephrine excretion with CPAP did not correlate with the change in augmentation index in the present study. Alternatively, augmentation index has been shown to increase with the plasma level of asymmetric dimethylarginine (an endogenous inhibitor of endothelial nitric oxide synthase), suggesting that improved endothelial function secondary to a higher bioavailability of nitric oxide may be a further beneficial effect of CPAP [43].

Blood pressure measurements

The current results on 24-h ABP showed a significant fall of 2.6 mmHg in mean blood pressure after 4 weeks of therapeutic CPAP, in agreement with other randomised controlled trials [44]. It is important to point out that the data presented on 24-h ABP has been included in a previously published study evaluating the effect of CPAP on ABP [15], and therefore the current report does not provide new cases for meta-analyses.

The reductions were similar for systolic and diastolic ABP during wake times, but the reductions seen during sleep failed to achieve statistical significance. This discrepancy may be explained by the observation that nocturnal blood pressure measurements with automatic inflation devices produce electroencephalic evidence of arousals from sleep, and probably underestimate the true reduction in blood pressure during sleep [45].

Interestingly, therapeutic CPAP did not significantly lower office blood pressure when compared to subtherapeutic CPAP in current study, a finding similar to that of MONASTERIO *et al.* [46], who did not observe a reduction in office blood pressure after 6 weeks of CPAP in patients with mild OSAS. These findings are likely to be due to difficulties in detecting small changes in blood pressure with the less reproducible office measurements [47], often ascribed to variable ''white coat'' effects [47]. The significant correlation found in the present study between the improvement in sleepiness and the reduction in blood pressure supports a possible consequence of recurrent arousals from sleep.

Study limitations

There are some limitations of the current study which have to be mentioned. According to common clinical practice [48], a single titration night was used to determine the required level of CPAP to abolish OSAS, and the sleep study was not repeated at the end of the trial to ascertain that patients were optimally treated. Therefore, the study design did not allow the impact of therapeutic CPAP on arousal frequency to be quantified, which might have enabled an exploration of the possibility that arousal frequency is a major determinant of sympathetic activity in patients with OSA. However, the large improvement in objective sleepiness in the therapeutic CPAP group strongly suggests that patients in the active CPAP group were adequately treated.

The current study used an ODI $>10\ h^{-1}$ associated with excessive daytime sleepiness (ESS>10) instead of the more commonly used apnoea/hypopnoea index (AHI) to define OSAS. However, there is good evidence that equivalence exists between the two measures of OSAS severity [49], and indeed ODI is at least as reproducible as the AHI between repeated nights [50]. Furthermore, oscillations in oxygen levels may be more pertinent to the vascular effects of OSA than apnoeic events [51] and therefore the current authors believe that the use of an ODI rather than an AHI does not limit the interpretation of their data.

Only males with moderate-to-severe OSAS were included in the present study, and the findings might therefore not be applicable to females, or patients with milder forms of OSAS. Therefore, further randomised controlled studies are needed to prove that CPAP does produce the same benefits on measures of cardiovascular risk in females, or patients with mild OSAS.

CONCLUSIONS

In a randomised controlled trial of therapeutic *versus* subtherapeutic continuous positive airway pressure in male patients with moderate to severe obstructive sleep apnoea syndrome, the present authors have shown that active treatment is associated with a significant decrease in 24-h urinary catecholamine excretion, arterial stiffness and ambulatory blood pressure, as well as with an improvement in baroreflex sensitivity. These findings suggest that treatment of symptomatic obstructive sleep apnoea syndrome patients with continuous positive airway pressure may have a positive impact on patients' survival by effectively reducing a number of well-established risk factors for cardiovascular disease.

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