Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea

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ABSTRACT Continuous positive airway pressure (CPAP) reduces blood pressure levels in hypertensive patients with obstructive sleep apnoea (OSA). However, the role of CPAP in blood pressure and the metabolic profile in women has not yet been assessed. In this study we investigated the effect of CPAP on blood pressure levels and the glucose and lipid profile in women with moderate-to-severe OSA.

A multicentre, open-label, randomised controlled trial was conducted in 307 women diagnosed with moderate-to-severe OSA (apnoea–hypopnoea index $\geqslant$15 events·h^{-1}) in 19 Spanish Sleep Units. Women were randomised to CPAP (n=151) or conservative treatment (n=156) for 12 weeks. Changes in office blood pressure measures as well as in the glucose and lipid profile were assessed in both groups.

Compared with the control group, the CPAP group achieved a significantly greater decrease in diastolic blood pressure (−2.04 mmHg, 95% CI −4.02–−0.05; p=0.045), and a nonsignificantly greater decrease in systolic blood pressure (−1.54 mmHg, 95% CI −4.58–1.51; p=0.32) and mean blood pressure (−1.90 mmHg, 95% CI −4.0–0.31; p=0.084). CPAP therapy did not change any of the metabolic variables assessed.

In women with moderate-to-severe OSA, 12 weeks of CPAP therapy improved blood pressure, especially diastolic blood pressure, but did not change the metabolic profile, compared with conservative treatment.

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Introduction

Although obstructive sleep apnoea (OSA) is a common disorder in women, with prevalence rates of 6–20% [1, 2], there is little evidence about the effects of treatment on the cardiovascular and metabolic outcomes of this sleep disorder in women. This may be because OSA has largely been considered a "male" disorder [3], thereby reducing the research on this topic in the female population. Accordingly, the growing evidence obtained in males has been applied to females, taking for granted that the response to OSA treatment would be similar in the two sexes. However, we know that OSA differs between men and women in terms of prevalence, pathophysiology, severity, polysomnography findings and clinical presentation [4–9], and previous population- and clinic-based studies have found that the female phenotype of OSA is strongly associated with age, obesity and hypertension, but not with excessive daytime sleepiness [2, 10].

Continuous positive airway pressure (CPAP) is the treatment of choice for patients with symptomatic OSA. High-quality evidence based on randomised controlled trials (RCTs) has demonstrated that CPAP reduces blood pressure [11–13]. Recent data suggest that it may also improve the glucose and lipid profile [14, 15]. These studies failed to examine sex differences, however, and they were conducted in either exclusively or predominantly male cohorts. Consequently, it remains unclear whether these positive effects of CPAP therapy can be translated to women or whether this population behaves and responds to treatment in a different way from males.

As hypertension may be a therapeutic target for CPAP therapy in female patients with OSA, in the present study we investigated the effect of CPAP on office blood pressure measures, as well as on the glucose and lipid profile of women diagnosed with moderate-to-severe OSA.

Methods

Design, settings and participants

This study is part of a larger study, designed to address the effect of CPAP on different clinical outcomes, in a population exclusively composed of women (ClinicalTrials.gov identifier: NCT02047071). The effect of CPAP on quality of life, the primary end-point of this trial, has been reported [16]. The present study deals with the secondary end-points: the effect on blood pressure levels and the metabolic profile.

We conducted a multicentre, open-label, RCT of parallel groups with final blind evaluation. Participants were enrolled in 19 Spanish Sleep Units between February 2014 and February 2015. The study was approved by the ethics committee of each participating centre. All the participants provided informed signed consent.

Women aged 18–75 years referred for suspicion of OSA and diagnosed with moderate-to-severe OSA (apnoea–hypopnoea index (AHI) $\geqslant$15 events·h^{-1}) were eligible for the study. Participants were enrolled on the basis of the presence of moderate-to-severe OSA and irrespective of cardiovascular comorbidities. Exclusion criteria are detailed in the supplementary material.

Procedures

Sleep study

Every woman underwent a diagnostic sleep study by means of an unattended, home respiratory polygraphy, using a device validated against polysomnography, and following the Spanish Society of

Pneumology and Thoracic Surgery Guidelines for OSA diagnosis and treatment [17]. A detailed description of the recording montage and sleep scoring procedures is given in the supplementary material.

Baseline visit

After OSA diagnosis, the participants completed a standardised protocol that included the following variables: age, menopausal status, anthropometric measures (body mass index (BMI), neck circumference and waist-to-hip ratio), smoking habit, physical activity, subjective sleep duration, subjective sleepiness measured by the Epworth Sleepiness Scale [18], cardiovascular risk factors and medication, and clinical complaints related to OSA.

Office blood pressure and metabolic measurements

Office blood pressure was measured with a sphygmomanometer, in the early morning, while the patient was seated for at least 5 min in a quiet environment. Blood pressure was measured three times at intervals of 5 min. For this study, the average of the second and third measures was used. Systolic blood pressure and diastolic blood pressure were assessed. Mean blood pressure was calculated as 1/3(systolic blood pressure)+2/3(diastolic blood pressure) [19].

Blood samples were collected after an overnight fast to measure glucose and lipid metabolism, which included glycated haemoglobin (HbA1c (%)), homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol ($mg{\cdot}dL^{-1}$), cholesterol subtypes (high- and low-density lipoprotein cholesterol) and triglycerides ($mg{\cdot}dL^{-1}$).

Both blood pressure and the metabolic profile were measured at the baseline visit and after 12 weeks of follow-up.

Randomisation and intervention

Women with AHI $\geqslant$15 $events{\cdot}h^{-1}$ were randomised to either CPAP or conservative treatment by using a computer-generated list of random numbers in the coordinating centre and stratified by centre.

All the women received dietary and sleep hygiene counselling. The participants were advised not to change their cardiovascular medication throughout the follow-up, except if dictated by clinical needs.

For those women randomised to CPAP therapy, the optimal pressure was titrated on a second night, using an auto CPAP device, according to a previous validation by the Spanish Sleep Network (see supplementary material) [20].

The women were reviewed at 4 and 12 weeks. At every medical appointment, objective adherence to CPAP and side-effects (for the CPAP group), changes in treatment, and re-evaluation of the exclusion criteria were assessed. At the last medical appointment, the blood pressure and metabolic measurements were repeated.

Study end-points

The end-points addressed in the present study correspond to the secondary end-points of the larger study and include changes in office blood pressure measurements, as well as changes in the glucose and lipid profile at 12 weeks compared with baseline, in the CPAP *versus* control group.

Statistical analysis

For more information on statistical analysis, see the supplementary material. Results are expressed as mean ±SD or median (first–third quartile) for continuous variables and number of patients with percentages for categorical variables.

The intergroup comparisons of the changes in blood pressure measures and the glucose and lipid profile were assessed by analysis of covariance with adjustments for baseline values, age, BMI and specific medication use. The analyses were performed on an intention-to-treat basis.

A sample size of 307 women (151 allocated to CPAP and 156 to conservative treatment) was calculated for the primary end-point of the original study (quality of life), but also for enough power to analyse other secondary end-points. Thus, this sample size would enable us to detect a change of at least 2 mmHg in blood pressure measures between the CPAP and control group, with an α error of 0.05 and a power of 80% (at least 140 participants would be needed in each group). This change of 2 mmHg is the average blood pressure reduction reported in meta-analyses which analysed RCTs in predominantly hypertensive male cohorts [12, 13, 21–23], and it is considered by international guidelines the expected decrease achieved by CPAP in men with OSA and simple hypertension [24, 25]. This sample size would also allow

us to detect a change of at least 0.5% in HbA1c between groups, with an α error of 0.05 and a power of 80% (at least 110 participants would be needed in each group) [26].

Two-tailed p-values <0.05 were considered significant. SPSS Statistics version 19.0 (IBM, Armonk, NY, USA) was used for data processing and analysis.

Results

571 women were referred to the participating centres for suspicion of OSA. Of these, 264 were excluded, mainly because they had AHI <15 events·h^{-1}, and 307 were finally randomised to the CPAP (n=151) and control (n=156) groups (figure 1). Only five women in each group did not complete the follow-up.

The general baseline characteristics of both groups were comparable, except for age and BMI (table 1). Women in the CPAP group were older and slightly less obese than those in the control group, but there were no differences in other anthropometric features, baseline blood pressure values, glucose and lipid parameters, number and type of antihypertensive medication, and number of lipid-lowering and oral antidiabetic drugs (tables 1 and 2). At the end of the follow-up, no significant change in weight was observed in either the CPAP or control groups. Adherence data are detailed in the supplementary material.

Only 96 women (31.2%) satisfied the hypertension criteria (systolic blood pressure ⩾140 mmHg or diastolic blood pressure ⩾90 mmHg) at entry. Similarly, the proportion of women with HbA1c ⩾6.5% was low (41 women (13.3%)). There were no differences between the CPAP and control group with regard to baseline prevalence of hypertension (p=0.512), diabetes mellitus (p=0.597) or hypercholesterolaemia (p=0.477).

Effect of CPAP therapy on blood pressure measurements

In the intention-to-treat analysis, after 12 weeks of follow-up, the CPAP group achieved a significantly greater decrease in diastolic blood pressure (−2.04 mmHg, 95% CI −4.02–−0.05; p=0.045), and a nonsignificantly greater decrease in systolic blood pressure (−1.54 mmHg, 95% CI −4.58–1.51; p=0.321) and mean blood pressure (−1.90 mmHg, 95% CI −4.0–0.31; p=0.084), compared with the control group (table 3 and figure 2). The results of the per-protocol analysis did not significantly differ from those of the intention-to-treat analysis (supplementary table E1 and figure 2).

The decrease observed in blood pressure values was greater in certain subgroups of women, although in most cases it did not reach statistical significance (figure 3). In the subgroup of 96 women who showed high systolic blood pressure or diastolic blood pressure at baseline, CPAP reduced systolic blood pressure,

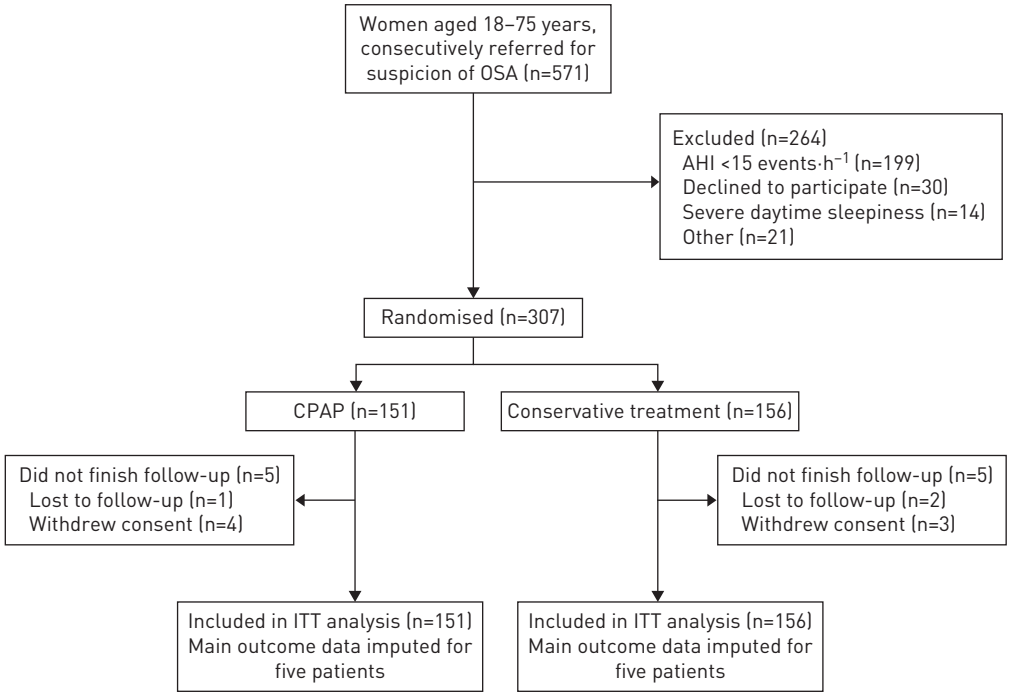

FIGURE 1 Flowchart of the study. OSA: severe obstructive sleep apnoea; AHI: apnoea–hypopnoea index; CPAP: continuous positive airway pressure; ITT: intention-to-treat.

TABLE 1 Baseline characteristics of the women included in the study

	Whole group	Control group	CPAP group	p-value
Subjects	307	156	151	
Age years	57.1±10.1	55.5±10.3	58.8±9.6	0.005
BMI kg·m^{-2}	33.7 (29.0–38.5)	33.8 (29.6–39.1)	33.5 (28.9–37.6)	0.033
Neck circumference cm	37.5 (35.0–40.0)	38.0 (36.0–40.4)	37.0 (35.0–40.0)	0.109
Waist-to-hip ratio	0.90 (0.86–0.94)	0.90 (0.86–0.95)	0.90 (0.85–0.94)	0.209
Menopause	238 (77.5)	117 (75.0)	121 (80.1)	0.339
Physical activity <30 min·day^{-1}	160 (52.1)	83 (53.2)	77 (51.0)	0.732
Sleep duration h·day^{-1}	7.0 (6.0–8.0)	7.5 (6.0–8.0)	7.0 (6.0–8.0)	0.363
Smoking current or former	129 (42.0)	74 (47.4)	55 (36.4)	0.064
Apnoea hypopnoea index events·h^{-1}	32.0 (22.6–48.5)	31.0 (20.3–46.8)	35.1 (24.3–50.0)	0.431
Oxygen desaturation index events·h^{-1}	32.9 (22.1–49.5)	30.2 (21.0–49.0)	34.5 (23.3–49.7)	0.662
ESS score	9.8±4.4	9.4±4.6	10.2±4.2	0.142
Systolic blood pressure mmHg	130.8±18.00	129.8±18.43	131.8±17.53	0.335
Diastolic blood pressure mmHg	80.2±10.64	80.4±10.51	79.9±10.81	0.696
Mean blood pressure mmHg	96.7±11.7	96.80±11.77	97.14±11.70	0.541
Fasting glucose mg·dL^{-1}	105.65±25.94	103.55±21.48	107.82±29.78	0.150
HbA1c %	5.85±0.80	5.86±0.77	5.85±0.83	0.949
HOMA-IR	4.67±3.83	4.86±3.97	4.47±3.68	0.375
Total cholesterol mg·dL^{-1}	205.27±36.65	203.77±35.91	206.82±37.45	0.468
LDL cholesterol mg·dL^{-1}	124.11±33.04	123.96±32.21	124.25±33.98	0.940
HDL cholesterol mg·dL^{-1}	55.22±16.58	54.36±15.16	56.10±17.93	0.361
Triglycerides mg·dL^{-1}	134.30±65.29	133.80±60.67	134.82±69.94	0.891

Data are expressed as n, mean±SD, median (first–third quartile) or n (%), unless otherwise stated. CPAP: continuous positive airway pressure; BMI: body mass index; ESS: Epworth Sleepiness Scale; HbA1c: glycated haemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

diastolic blood pressure and mean blood pressure by 1.90, 2.56, and 2.20 mmHg, respectively, compared with the control group. In the subgroup of 173 women with severe OSA (AHI ⩾30 events·h^{-1}), CPAP achieved decreases of 2.98, 2.50 and 2.68 mmHg in systolic blood pressure, diastolic blood pressure and mean blood pressure, respectively, compared with the control group. The greatest changes were found in the group of sleepy women (n=142), in whom CPAP reduced the blood pressure measures by >3 mmHg compared with the control group, including a significant reduction of −3.26 mmHg (95% CI −6.28–−0.23; p=0.035) in diastolic blood pressure.

TABLE 2 Baseline use of antihypertensive, antidiabetic and lipid-lowering medication in randomised patients

	Whole group	Control group	CPAP group	p-value
Subjects	307	156	151	
Drugs per patient				
Antihypertensive drugs	1.0±1.13	1.07±1.17	0.93±1.09	0.269
Lipid-lowering drugs	0.38±0.55	0.41±0.58	0.34±0.51	0.299
Antidiabetic drugs	0.23±0.53	0.26±0.55	0.20±0.50	0.341
Patients				
Antihypertensive medication	168 (54.7)	90 (57.7)	78 (51.7)	0.172
Diuretic	85 (27.7)	47 (30.1)	38 (25.1)	0.331
Calcium channel blockers	42 (13.7)	22 (14.1)	20 (13.2)	0.827
β-Blockers	35 (11.4)	22 (14.1)	13 (8.6)	0.130
Angiotensin-converting enzyme inhibitor	53 (17.3)	26 (16.6)	27 (17.8)	0.778
Angiotensin II receptor blockers	91 (29.6)	49 (31.4)	42 (27.8)	0.514
Lipid-lowering medication	106 (34.5)	56 (35.9)	50 (33.1)	0.632
Antidiabetic medication	61 (19.9)	34 (21.8)	27 (17.9)	0.475

Data are expressed as n, mean±SD or n (%), unless otherwise stated. CPAP: continuous positive airway pressure.

TABLE 3 Changes in blood pressure measurements between randomised groups in the intention-to-treat analysis

	CPAP treatment[#]			Conservative treatment[¶]			Adjusted intergroup difference (95% CI)[+]	p-value
	3 months	Baseline	Intragroup difference	3 months	Baseline	Intragroup difference		
Systolic blood pressure mmHg	126.11±17.11	131.83±17.53	5.72±1.29	126.16±17.59	129.85±18.43	3.69±1.20	−1.54 (−4.58–1.51)	0.321
Diastolic blood pressure mmHg	75.44±10.29	79.95±10.81	4.51±0.84	77.88±11.00	80.42±10.51	2.54±0.71	−2.04 (−4.02– −0.05)	0.045
Mean blood pressure mmHg	92.24±11.31	97.14±11.70	4.91±0.91	93.88±12.13	96.80±11.77	2.93±0.79	−1.90 (−4.0–0.31)	0.084

CPAP: continuous positive airway pressure. The results are expressed as changes in the CPAP *versus* the control group at 12 weeks compared with baseline. [#]: n=151; [¶]: n=156; [+]: adjusted for baseline values, body mass index, age and medication use.

TABLE 4 Changes in glucose and lipid profile between randomised groups in the intention-to-treat analysis

	CPAP treatment[#]			Conservative treatment[¶]			Adjusted intergroup difference (95% CI)[+]	p-value
	3 months	Baseline	Intragroup difference	3 months	Baseline	Intragroup difference		
Fasting glucose mg·dL^{-1}	106.90±31.28	107.82±29.78	0.92±1.39	105.31±24.12	103.55±21.48	1.76±1.00	−1.45 (−4.75–1.84)	0.387
HbA1c %	5.90±0.85	5.85±0.83	0.04±0.02	5.84±0.76	5.86±0.77	0.01±0.03	0.07 (−0.01–0.14)	0.096
HOMA-IR	4.60±4.61	4.47±3.68	0.13±0.30	4.98±4.60	4.86±3.97	0.12±0.28	−0.05 (−0.86–0.76)	0.902
Total cholesterol mg·dL^{-1}	203.45±37.71	206.82±37.45	−3.37±2.17	200.56±36.15	203.77±35.91	−3.21±2.28	0.29 (−5.62–6.21)	0.922
HDL cholesterol mg·dL^{-1}	55.87±14.02	56.10±17.93	0.23±1.03	55.10±16.0	54.36±15.16	0.74±0.88	−0.76 (−3.12–1.6)	0.527
LDL cholesterol mg·dL^{-1}	122.19±34.47	124.25±33.98	2.06±2.06	118.79±33.8	123.96±32.21	5.17±2.54	3.14 (−2.92–9.20)	0.309
Triglycerides mg·dL^{-1}	130.83±70.14	134.82±69.94	3.99±3.52	131.32±56.55	133.80±60.67	2.48±2.95	−0.54 (−9.20–8.11)	0.902

CPAP: continuous positive airway pressure; HbA1c: glycated haemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein. The results are expressed as changes in the CPAP *versus* the control group at 12 weeks compared with baseline. [#]: n=151; [¶]: n=156; [+]: adjusted for baseline values, body mass index, age and medication use.

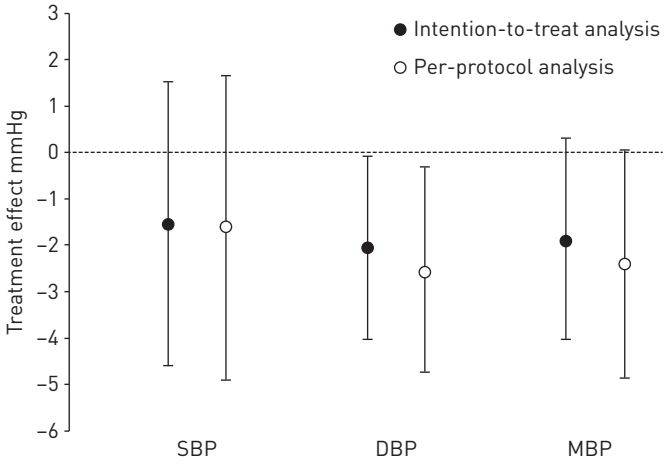

FIGURE 2 Effect of continuous positive airway pressure (CPAP) treatment on blood pressure measurements. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure. Adjusted treatment effects and 95% confidence intervals (adjusted by baseline values, age, body mass index and antihypertensive medication) of CPAP *versus* conservative treatment at the end of follow-up compared with baseline. Intention-to-treat analysis: SBP −1.54 mmHg (95% CI −4.58–1.51; p=0.32), DBP −2.04 mmHg (95% CI −4.02–−0.05; p=0.045) and MBP −1.90 mmHg (95% CI −4.0–0.31; p=0.084). Per-protocol analysis: SBP −1.67 mmHg (95% CI −5.12–1.79; p=0.34), DBP −2.61 mmHg (95% CI −4.84–−0.37; p=0.022) and MBP −2.32 mmHg (95% CI −4.75–0.10; p=0.061).

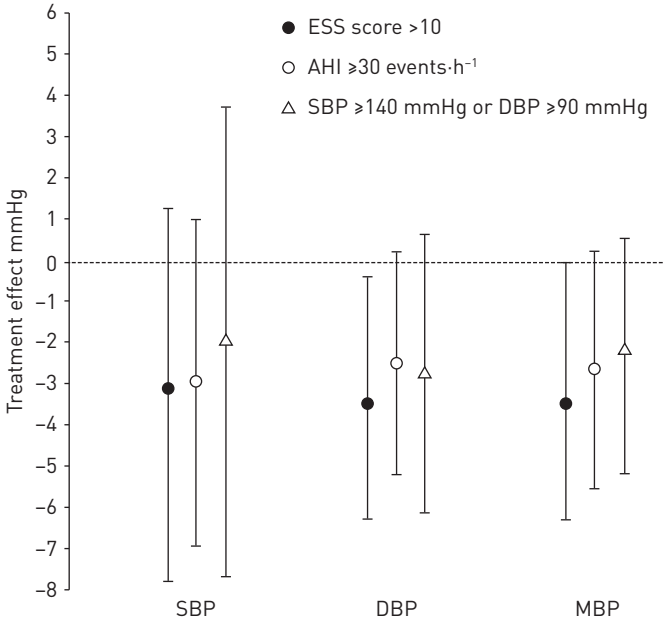

FIGURE 3 Effect of continuous positive airway pressure (CPAP) treatment on blood pressure measurements in the subgroups of women with high blood pressure, severe obstructive sleep apnoea (OSA) and excessive daytime sleepiness. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure. Adjusted treatment effects and 95% confidence intervals (adjusted by baseline values, age, body mass index and antihypertensive medication) of CPAP *versus* conservative treatment at the end of follow-up compared with baseline in the intention-to-treat analysis. Women with excessive daytime sleepiness (Epworth Sleepiness Scale (ESS) score >10): SBP −3.11 mmHg (95% CI −7.84–1.62; p=0.195), DBP −3.26 mmHg (95% CI −6.28–−0.23; p=0.035) and MBP −3.30 mmHg (95% CI −6.62–0.01; p=0.051). Women with severe OSA (apnoea–hypopnoea index (AHI) ⩾30 events·h^{-1}): SBP mmHg −2.98 (95% CI −6.92–0.97; p=0.138), DBP −2.5 mmHg (95% CI −5.18–0.18; p=0.067) and MBP −2.68 mmHg (95% CI −5.54–0.17; p=0.066). Women with high blood pressure (SBP ⩾140 mmHg or DBP ⩾90 mmHg): SBP −1.90 mmHg (95% CI −7.70–3.91; p=0.51), DBP −2.56 mmHg (95% CI −6.02–0.90; p=0.145) and MBP −2.2 mmHg (95% CI −5.30–0.20; p=0.180).

Effect of CPAP therapy on the glucose and lipid profile

12 weeks of CPAP therapy did not change any of the metabolic variables assessed, including fasting glucose, HbA1c, HOMA-IR, total cholesterol, cholesterol subtypes or triglycerides, compared with the conservative treatment group. The results were similar in the intention-to-treat and per-protocol analyses (table 4, and supplementary figures E1 and E2).

Discussion

To the best of our knowledge, this is the first RCT to address the effect of CPAP therapy on the blood pressure values and metabolic profile in a large cohort of women with moderate-to-severe OSA. We have found that, compared with conservative treatment, 12 weeks of CPAP therapy reduces blood pressure measures, especially diastolic blood pressure, and that this decrease is within the range reported in other large RCTs conducted in predominantly male hypertensive cohorts. Moreover, this improvement may be larger in some subgroups of women, particularly those with daytime sleepiness. 12 weeks of CPAP therapy did not, however, change the glucose and lipid profile of this sample.

Although there is growing and compelling evidence that shows a beneficial effect of CPAP on blood pressure in hypertensive patients with OSA, all this research was conducted in predominantly or exclusively male cohorts where women were underrepresented [11, 13]. One very recent meta-analysis of seven studies with a total of 794 patients reported that all the trials predominantly recruited male patients, with a mean percentage of 74% male [12]. Similarly, the effect of CPAP on glucose and lipid metabolism has also been assessed in cohorts in which women usually accounted for <30–40% of the whole sample [14, 27–30]. Given that OSA differs between women and men, it cannot be taken for granted that the findings obtained in males can be translated to women. In fact, women may have a different cardiovascular risk profile to men, as suggested by studies which have observed that women had more OSA-related endothelial dysfunction [31, 32], higher levels of high-sensitivity troponin T and a higher risk of incident heart failure or death than men [33].

In our study we observed that 12 weeks of CPAP therapy improves diastolic blood pressure, and to a lesser extent mean blood pressure and systolic blood pressure, compared with conservative treatment of OSA. Although only diastolic blood pressure achieved a statistically significant decrease, the reductions of 1.54–2.04 mmHg in blood pressure values fall within the range of 1.5–2.5 mmHg reported in most meta-analyses of RCTs conducted in hypertensive male cohorts [12, 13, 21–23]. Remarkably, these reductions were achieved even though our cohort mainly comprised nonhypertensive patients. In fact, when we analysed a subgroup of participants that satisfied hypertension criteria at entry, the reductions achieved in all blood pressure measurements were larger (1.90–2.56 mmHg) than those observed for the whole group, although they did not reach statistical significance, due, at least in part, to the loss of power associated with the smaller sample size. Even though the reductions achieved in our sample may be considered modest, international guidelines have pointed out that reductions in blood pressure levels of ~2–3 mmHg have a clinically significant benefit, and are associated with a 4–8% reduction in future stroke and coronary heart disease risk [34, 35].

Several studies have reported that in addition to patients with high blood pressure values, CPAP might be more effective in those with more severe OSA [13, 22, 25]. When we separately assessed a subgroup of 173 women with AHI $\geqslant$30 events·h^{-1}, the effect of CPAP on blood pressure values was stronger, achieving decreases of 2.5–2.98 mmHg in blood pressure measurements, compared with conservative treatment. Although these improvements did not reach statistical significance, they suggest that women with more severe OSA may be a target in whom CPAP can be particularly effective.

Although some studies have reported that sleepy patients would achieve greater blood pressure reductions with CPAP [36], a large RCT of nonsleepy, hypertensive OSA patients demonstrated a statistically significant benefit in diastolic blood pressure and a nearly significant benefit in systolic blood pressure after 1 year of follow-up [37]. Furthermore, data from different meta-analyses have not shown excessive daytime sleepiness to be an independent predictor of CPAP efficacy in hypertensive patients [13, 22, 23]. Interestingly, although the association between excessive daytime sleepiness and OSA in women is controversial [38, 39], in our study sleepy women were the subgroup in which we found the largest blood pressure reductions, with >3 mmHg in all blood pressure values, reaching statistical significance for diastolic blood pressure. Whether the presence of excessive daytime sleepiness in women is a marker of better response to CPAP needs to be confirmed in prospective studies.

The role of CPAP in glucose metabolism in OSA patients is controversial, but recent data suggest that either very high adherence or long follow-up periods are essential to show any benefit. Martinez-Ceron *et al.* [14] have shown that 6 months, but not 3 months of CPAP treatment significantly reduced HbA1c levels in 50 patients with OSA, type 2 diabetes mellitus and baseline HbA1c $\geqslant$6.5% compared with

conservative therapy. Pamidi *et al.* [28] randomised 39 participants with OSA and pre-diabetes to receive either 8 h nightly CPAP or oral placebo for 2 weeks, and found that CPAP treatment improved glucose metabolism compared with placebo. However, a recent multicentre study in 298 participants with type 2 diabetes (HbA1c 6.5–8.5%) and OSA who were randomised to CPAP or usual care for 6 months did not find any improvement in HbA1c levels, even when analyses were restricted to those with poorer baseline glycaemic control, more severe sleep apnoea or those who were adherent to CPAP [27]. In our study we did not observe any changes in either group in HbA1c or insulin resistance measured by HOMA-IR, which suggests a lack of effect of CPAP therapy on the glycaemic profile of nonselected OSA women. We cannot rule out, however, that the low prevalence of women with high HbA1c at entry (only 13.3% had values >6.5%), the short follow-up of only 3 months and the merely average CPAP adherence in our series may have influenced the final results.

Several studies report conflicting results regarding the role of CPAP in the lipid metabolism. One study that analysed 613 OSA patients who were not taking lipid-lowering medications observed no effect of CPAP on 2-year fasting lipid changes [30]. Chirinos *et al.* [40] randomised 181 OSA patients to receive treatment with CPAP, weight loss intervention or CPAP plus weight loss intervention. After 24 weeks of follow-up, the group receiving CPAP alone did not show any improvement in cholesterol or triglyceride levels, whereas those assigned to weight loss or the combined interventions had reductions in serum triglyceride levels, but not in cholesterol levels. Concurrent with the aforementioned evidence, we did not observe that 3 months of CPAP therapy had any effect on lipid metabolism in women with moderate-to-severe OSA compared with conservative treatment.

Our study has some limitations. First, we analysed a nonselected sample of women in whom the enrolment criterion was moderate-to-severe OSA, regardless of comorbidities. As a result, most women had normal baseline blood pressure, glucose and lipid values, so, although our sample size has enough power to demonstrate reductions in blood pressure and HbA1c measurements, it is less likely to achieve significant improvements in patients with baseline values within the normal range, due to a possible floor effect. Second, the follow-up period of 3 months may have been insufficient to achieve improvements in some of the variables assessed, particularly the metabolic profile. However, a longer follow-up could have provoked ethical issues, since active treatment was withheld from patients in the control group. Third, the use of office instead of ambulatory blood pressure monitoring, which is the recommended method for blood pressure monitoring in OSA patients, has disadvantages. Office blood pressure is usually higher than ambulatory blood pressure, may lead to white-coat hypertension and precludes the assessment of day/night patterns of blood pressure, which may bias the results taking into account that the impact of CPAP on blood pressure in OSA patients is more pronounced during sleep than during wakefulness [24]. Nevertheless, office blood pressure measurements have been associated with many cardiovascular outcomes in large epidemiological and intervention studies, and in daily clinical practice it is more easily available than ambulatory blood pressure. Fourth, comorbid insomnia with short sleep duration is a common finding in women and may exert additive effects on blood pressure in OSA patients. Unfortunately, we did not assess this item in our study. Nevertheless, since this is a randomised trial, it should be expected that any effect of insomnia would have been balanced in both groups.

In conclusion, this study assessed, for the first time, the effect of CPAP therapy on several cardiometabolic variables in unselected women with moderate-to-severe OSA. We found that 12 weeks of CPAP therapy improves diastolic blood pressure measurements compared with conservative treatment. The magnitude of this improvement is similar to that found in many male samples. Some subgroups of patients, such as those with high blood pressure values, severe OSA and subjective excessive daytime sleepiness, may achieve larger reductions in blood pressure levels. Furthermore, 12 weeks of CPAP did not change the glucose or lipid profile of women with moderate-to-severe OSA. Given that OSA differs in men and women, and that a different cardiovascular risk profile cannot be ruled out, more research is needed to clarify the role of treatment in OSA-related cardiovascular risk in women.

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