Sibutramine *versus* continuous positive airway pressure in obese obstructive sleep apnoea patients

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ABSTRACT: The aim of the present study was to compare the efficacy of 1 yr of sibutramine-induced weight loss *versus* continuous positive airway pressure (CPAP) treatment on sleep-disordered breathing, cardiac autonomic function and systemic blood pressure in obese patients with obstructive sleep apnoea.

Subjects with a body mass index of $\geq 30 \text{ kg}\cdot\text{m}^{-2}$ without previous treatment for obstructive sleep apnoea underwent either sibutramine ($n=22$) or CPAP ($n=18$) treatment for 1 yr.

Sibutramine induced a $5.4 \pm 1.4 \text{ kg}$ decrease in body weight compared to the CPAP group, in which no changes in anthropometric variables were observed. The CPAP treatment improved all sleep and respiratory variables, whereas sibutramine-induced weight loss improved only nocturnal arterial oxygen saturation profile. Only CPAP treatment improved night-time systolic and diastolic blood pressure and 24-h and daytime ambulatory diastolic blood pressure. Sibutramine-induced weight loss had no impact on indices of heart rate variability, whereas CPAP treatment increased daytime time domain indices.

CPAP treatment for 1 yr had beneficial impacts on nocturnal breathing disturbances, and improved nocturnal oxygenation, night-time systolic and diastolic blood pressure, and daytime cardiac parasympathetic modulation. Sibutramine did not improve sleep-disordered breathing, systemic blood pressure or heart rate variability. There were no adverse effects, such as increment in blood pressure or arrhythmias, associated with this treatment regimen.

KEYWORDS: Continuous positive airway pressure, obesity, sibutramine, sleep apnoea, weight loss

Being overweight or obese is strongly associated with a rise in the prevalence of obstructive sleep apnoea (OSA) [1]. Moreover, there is increasing evidence that OSA may be an independent factor that contributes to rising cardiovascular risk through periodic increases in sympathetic activity and blood pressure [2, 3]. Therefore, weight loss, regular physical activity and prevention of weight regain should be the first nonpharmacological recommendations for OSA patients in order to reduce the occurrence and severity of OSA, and its related morbidity [4–6].

A 10% weight loss is associated with a 50–60% decrease in the frequency of nocturnal breathing disorders and in the severity of nocturnal desaturation [5, 7]. More importantly, systemic hypertension and cardiac arrhythmias are highly prevalent in the OSA population, and may be reduced following weight loss intervention and normalisation of breathing with continuous positive airway pressure (CPAP) during sleep.

Sibutramine, which leads to an enhancement of satiety and thermogenesis by inhibiting serotonin and noradrenalin reuptake, has been shown to induce a dose-dependent weight loss ranging 2–10 kg, thus potentiating the effects of a low-calorie diet for up to 1 yr in obese patients [8, 9]. Although short-term administration of sibutramine does not seem to worsen OSA [10], its noradrenergic effects may trigger arrhythmias and slightly increase blood pressure [11]. However, evidence has shown that a moderate $\sim 10\%$ weight loss with sibutramine may improve OSA severity, without negative effects on blood pressure [12]. Thus there is an important need to compare the efficacy of this anti-obesity medication with the usual CPAP treatment on changes in sleep-related breathing disorders in obese patients.

MATERIALS AND METHODS

Study subjects

Eligible participants with untreated OSA syndrome were recruited through the sleep disorder

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outpatient clinic of Laval Hospital (Quebec, QC, Canada). Subjects were aged 18–65 yrs, with a body mass index (BMI) of $\geq 30 \text{ kg}\cdot\text{m}^{-2}$, or $\geq 27 \text{ kg}\cdot\text{m}^{-2}$ in the presence of other risk factors, such as controlled systemic hypertension, type 2 diabetes, dyslipidaemia and/or visceral obesity (as defined by a waist circumference of $\geq 102 \text{ cm}$ in males and $\geq 88 \text{ cm}$ in females). Exclusion criteria were uncontrolled systemic hypertension, defined as a blood pressure of $>145/90 \text{ mmHg}$, previous pharmacological or surgical treatment for weight loss, previous CPAP usage or the presence of severe diurnal hypersomnolence requiring immediate treatment. The main outcome measure in the present study was improvement in the apnoea/hypopnoea index (AHI). This protocol was approved by the Ethics Committee of Laval Hospital, and all patients provided written informed consent.

Study design

After having cautiously discussed their clinical condition and the different treatment strategies with one of the investigator (F. Sériès), patients chose their treatment preference (sibutramine (combination of sibutramine and calorie- and fat-restricted weight-loss diet and physical activity recommendation) or CPAP (conventional CPAP treatment and lifestyle recommendations)). This study design was chosen because it was considered that letting the patient choose their own OSA treatment would enhance their compliance with the medical treatment. It was also considered that a study design based on randomised treatment allocation would alter the evaluation of the response expected from a given treatment strategy, and would not represent the clinical situation that clinicians and patients face in a clinical setting (*i.e.* OSA patients who refuse CPAP as a primary treatment are encouraged to loose weight, and patients who are not convinced of the benefits/feasibility of weight loss are not the targeted population for a weight-loss programme). The first group received 10 mg sibutramine for the first 4 weeks, at which time increasing the dosage to 15 mg was evaluated in the case of insufficient weight loss ($<1.8 \text{ kg}$) over the first month of treatment. Fasting blood samples were obtained at baseline and at 6 and 12 months for measurements of plasma glucose concentration, glycated haemoglobin (HbA_{1c}) level and lipid profile.

Polysomnography

Subjects underwent a conventional laboratory-based polysomnographic study at baseline and after 6 and 12 months of treatment. The measures consisted of continuous acquisition of the electroencephalogram, electro-oculogram, submental electromyogram, arterial oxyhaemoglobin saturation from transcutaneous sensing (SaO_2), nasal pressure with nasal prongs connected to a pressure transducer [13], oral airflow with a thermistor, chest and abdominal movements by inductive plethysmography (Respirtrace; Ambulatory Monitoring, Inc., Ardsley, NY, USA), and electrocardiogram. All variables were digitally recorded (Sandman EliteTM system; Mallinckrodt, Kenilworth, NJ, USA). Sleep–wake state and arousals were scored according to standardised criteria [14]. Subjects were asked to complete the 32-question Quebec Sleep Questionnaire (QSQ) [15], and the Epworth sleepiness scale (ESS) score was obtained [16].

CPAP treatment

CPAP treatment was initiated using manual titration of one overnight laboratory-based sleep recording. The effective pressure level chosen is the pressure level that abolishes all obstructive events (apnoea, hypopnoea, flow limitation and snoring) in every sleep stage and body position. Patients were referred to a healthcare company for choice of their CPAP devices and masks. The patient was contacted after 2 weeks in order to check subjective compliance and identify problems encountered with CPAP use. Compliance was determined using the downloadable data from the patient's CPAP device.

Heart rate variability

A 24-h Holter monitoring was performed before treatment (baseline) and during the course of therapies (Marquette Electronics, Inc., Milwaukee, WI, USA). Heart rate variability (HRV) was established through numerous indices [17], and the recording was scheduled to include the sleep recording period in order to identify apnoea-related disorders. Parameters from the spectral domain and time domain were calculated from the Holter recordings. Sub-analysis of daytime and night-time recordings was performed, as well as analysis for the full recording period [17]. In the spectral domain, power of low frequency (LF; 0.04–0.15 Hz, which is considered an index of both sympathetic and parasympathetic activity) and high frequency (HF; 0.15–0.4 Hz, which represents most efferent vagal parasympathetic activity to the sinus node) were assessed. The LF/HF ratio, representing the sympathovagal balance, was also calculated [18]. Using time domains, normal-to-normal R–R interval, SD of normal-to-normal R–R interval (SDNN), SD of the average normal-to-normal R–R interval calculated over a 5-min period (SDANN), square root of mean squared difference of successive normal-to-normal R–R intervals (rMSSD), number of adjacent normal-to-normal R–R intervals differing by $>50 \text{ ms}$ (NN50) and NN50 divided by total number of normal-to-normal R–R intervals expressed as a percentage (pNN50) were analysed. rMSSD and pNN50 are associated with HF and hence parasympathetic activity [17].

24-h ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed over a 24-h period in all subjects at baseline and at 1 yr (model 90 212; Spacelabs Healthcare, Issaquah, WA, USA) [19] in accordance with current recommendations [20, 21]. During the 24-h recording, measurements of systolic, diastolic and mean arterial blood pressure were determined using an oscillometric method, with one measurement every 15 min during the daytime period (06:00–22:00 h) and every 20 min during the night (22:00–06:00 h). Normal daytime and night-time blood pressure and the nondipping pattern were defined according to American Heart Association recommendations for blood pressure measurements [21].

Statistical analysis

The present study was designed to have 80% power in detecting a difference in AHI of $\geq 15 \text{ events}\cdot\text{h}^{-1}$ between the sibutramine and CPAP groups in 60% of subjects, given that 100% of subjects in the CPAP group would show an improved AHI [22], with a two-sided unpaired t-test and type I error of 5%. Thus, 20 subjects are required in the Sibutramine group in order to permit comparison with the reference group (CPAP).

Given a 10% drop-out rate, 22 patients would need to be included in the sibutramine group. Data are presented as means $\pm$ SD or percentages unless specified otherwise. Analysis of categorical data was carried out using the Chi-squared test or Fisher's exact test, as appropriate. Pearson's correlation coefficient was used for the analysis of associations between variables. For each outcome variable, a mixed model was performed to analyse the effects of two experimental factors, one associated with the comparison between treatments, and one linked to time (corresponding to baseline, 1 and/or 6 months and 1 yr) and analysed as a repeated-measure factor. Variables were logarithmically transformed where necessary to obtain a normal distribution. A p-value of <0.05 was considered significant. The data were analysed using the statistical package program SAS v9.1.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

OSA patients (n=42) participated in the present study. A total of 40 (95.2%) patients completed the 1-yr treatment. Two patients in the sibutramine group withdrew because of loss to follow-up and adverse events. Thus 22 patients with a baseline weight of 111 ± 14 kg and BMI of 36.7 ± 4.2 kg·m⁻² were included in the sibutramine group (table 1), and 18 patients received CPAP treatment and were analysed as the standard

reference group. Baseline characteristics were similar between the sibutramine and CPAP groups. The weight loss after 1-yr of sibutramine treatment was, on average, 5 kg ($p<0.001$), which corresponds to a relative reduction of 5% of initial weight concomitant with a 7% reduction in waist circumference ($p<0.001$), and a mean decrement in BMI of 2 kg·m⁻² ($p=0.0005$). The CPAP group experienced a 1.6 kg weight loss after 1 month of treatment ($p<0.002$), which was similar to that in the sibutramine group (1.6 kg). However, dietary changes were not maintained throughout the year in the CPAP group, and body weight had returned to baseline level at 6 months.

The mean AHIs of 54 and 52 events·h⁻¹ at baseline in the sibutramine and CPAP groups, respectively, indicated severe sleep apnoea. At 1 yr, the patients assigned to CPAP showed a greater (92%) reduction in AHI than did those in the sibutramine group (reduction of 40 ± 30 versus 3 ± 6 events·h⁻¹; $p<0.0001$) (fig. 1). It is of note that changes in AHI between baseline and 1 yr in the sibutramine group correlated with changes in body weight ($r=0.57$; $p=0.006$). Interestingly, sibutramine induced a significant increase in mean nocturnal SaO₂ (4.8 ± 1.7 versus $2.2 \pm 2.5\%$ for the sibutramine and CPAP groups, respectively; $p=0.007$), whereas CPAP induced the greater increase in minimum SaO₂ (9.8 ± 4.8 versus $3.8 \pm 6.3\%$ for the CPAP and sibutramine groups, respectively; $p=0.0001$). CPAP significantly decreased the percentage of time spent

TABLE 1 Subject characteristics at baseline and 1 yr in the sibutramine and continuous positive airway pressure (CPAP) groups

	Sibutramine		CPAP	
	Baseline	1 yr	Baseline	1 yr
Females/males n		3/19		2/16
Age yrs		49 $\pm$ 9		49 $\pm$ 9
Weight kg	110.9 $\pm$ 14.3	105.5 $\pm$ 17.4***	109.2 $\pm$ 12.2	109.8 $\pm$ 14.7
BMI kg·m⁻²	36.8 $\pm$ 4.2	35.0 $\pm$ 5.3***	36.4 $\pm$ 4.2	36.4 $\pm$ 4.1
Glucose mM	5.7 $\pm$ 1.1	6.1 $\pm$ 1.4	5.9 $\pm$ 0.7	6.1 $\pm$ 1.2
Blood pressure				
SBP mmHg	133 $\pm$ 8	132 $\pm$ 10	128 $\pm$ 11	125 $\pm$ 14 [#]
DBP mmHg	82 $\pm$ 6	84 $\pm$ 8	77 $\pm$ 7 [#]	81 $\pm$ 9
Dippers %	71.4	60.0	50.0	61.5
Nondippers %	28.6	40.0	50.0	38.5
Heart rate beats·min⁻¹				
Minimal	49 $\pm$ 9	49 $\pm$ 8	47 $\pm$ 8	46 $\pm$ 6
Maximal	131 $\pm$ 18	125 $\pm$ 19	130 $\pm$ 14	126 $\pm$ 9
Mean	80 $\pm$ 12	79 $\pm$ 11	80 $\pm$ 7	74 $\pm$ 7*** [#]
Lipid profile mM				
Total cholesterol	4.64 $\pm$ 0.87	4.87 $\pm$ 0.72	4.84 $\pm$ 0.83	4.57 $\pm$ 0.95
Triglycerides	1.74 $\pm$ 1.06	1.52 $\pm$ 0.68	1.76 $\pm$ 0.71	1.89 $\pm$ 0.52
HDL-C	1.10 $\pm$ 0.27	1.27 $\pm$ 0.33***	1.15 $\pm$ 0.23	1.14 $\pm$ 0.24
LDL-C	2.80 $\pm$ 0.73	2.94 $\pm$ 0.66	2.88 $\pm$ 0.80	2.55 $\pm$ 0.82*
Total cholesterol/HDL-C	4.37 $\pm$ 0.92	4.07 $\pm$ 0.97	4.31 $\pm$ 0.92	4.09 $\pm$ 0.80
Medication n (%)				
Antihypertensive agents		5 (23)		6 (33)
Antidiabetic agents		1 (5)		2 (11)
Cholesterol-lowering agents		2 (9)		4 (22)

Data are presented as mean $\pm$ SD unless otherwise indicated. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol. *: $p<0.05$; ***: $p<0.001$ versus baseline; #: $p<0.05$ between groups.

FIGURE 1. Effect of 1 yr of continuous positive airway pressure (○) and sibutramine (●) treatment on: a) apnoea/hypopnoea index (AHI); b) mean arterial oxygen saturation (SaO₂); and c) minimum SaO₂. Data are presented as mean ± SD. ***: $p < 0.001$ between groups; ###: $p < 0.001$ versus baseline.

below an SaO₂ of 90% (12.4 ± 22.7 to $2.6 \pm 8.8\%$ after 1 yr; $p = 0.02$), whereas no change was observed following sibutramine treatment ($8.4 \pm 18.8\%$ to $2.1 \pm 4.2\%$ after 1 yr; $p = 0.08$). The two treatments decreased the percentage of sleep in stages 1 and 2 ($p < 0.05$) and increased the percentage of rapid eye movement stage sleep ($p < 0.001$). However, after 1 yr of treatment, a greater improvement in sleep architecture was observed in the CPAP group ($p < 0.001$). Thus the CPAP treatment improved all sleep and respiratory variables ($p < 0.01$) compared with sibutramine-induced weight loss

(table 2). At 12 months, subjects used CPAP for a mean of 6.6 ± 1.6 h·day⁻¹, and 89.4% used CPAP for the minimum treatment time of 4 h·day⁻¹. No difference was found in subjective daytime sleepiness before and after 1 yr of sibutramine treatment, whereas CPAP improved this parameter ($p < 0.0001$), as assessed using the ESS.

Mean heart rate decreased only in the CPAP group ($p = 0.003$), whereas minimal and maximal heart rate did not change significantly in either group compared with baseline (table 1). Weight loss induced no changes in any measures of time domain assessed from the Holter recording (table 3). The CPAP treatment enhanced daytime SDNN, SDANN ($p = 0.02$; 1 year versus 1 month of treatment) and pNN50 ($p = 0.03$; 1 year versus baseline). The 24-h rMSSD and pNN50 parameters of HRV were higher after 1 yr of CPAP compared with 1 yr of sibutramine. Table 4 shows spectral domain indices of the Holter monitoring. Sibutramine induced no changes in LF and HF power or in LF/HF ratios. CPAP treatment significantly increased the 24-h and night-time LF power data compared to the 1-month values (all $p < 0.01$). Moreover, daytime HF was higher after 1 yr of CPAP compared with 1 yr of treatment with sibutramine. There were no changes in arrhythmias in either group.

At baseline, a nondipping pattern of blood pressure was observed in 28.6% of patients included in the sibutramine group, whereas this abnormality was present in 50.0% of CPAP patients (table 1). Mean 24-h, daytime and night-time ambulatory SBP and DBP were near normal at baseline and were comparable between groups. Sibutramine induced no changes in mean 24-h SBP and DBP over the year (129 ± 8 versus 130 ± 10 mmHg for SBP and 80 ± 6 versus 82 ± 8 mmHg for DBP before and after sibutramine treatment). In addition, no significant differences were observed in daytime and night-time mean SBP and DBP. CPAP treatment for 1 yr improved night-time SBP and DBP (117 ± 7 versus 109 ± 13 mmHg for SBP and 72 ± 8 versus 68 ± 8 mmHg for DBP before and after CPAP treatment; all $p < 0.01$). A significant decrease was also observed in the 24-h and daytime ambulatory DBP (all $p = 0.04$). Moreover, after 1 yr of treatment, the 24-h and daytime DBP were lower in the CPAP group compared with the sibutramine group (all $p < 0.01$).

High-density lipoprotein (HDL)-cholesterol levels increased by 15% in the sibutramine group ($p < 0.0001$), and low-density lipoprotein (LDL)-cholesterol levels were reduced by 11% in the CPAP group ($p = 0.02$). Moreover, the glycated haemoglobin level was increased by 5% in the CPAP group ($p = 0.04$), whereas no changes were observed in glucose concentrations. All other biochemical parameters did not change significantly following treatment.

DISCUSSION

The present results show that CPAP treatment improved numerous sleep and respiratory variables compared to sibutramine-induced weight loss. Indeed, despite significant weight loss, the present study documents a lack of efficacy of sibutramine in improving symptoms of sleep apnoea in obese subjects with OSA. However, even if the noradrenergic effects of sibutramine could potentially account for an increase in blood pressure and triggering of arrhythmias [11], its long-term

TABLE 2 Polysomnographic recording at baseline and 1 yr in the sibutramine and continuous positive airway pressure (CPAP) groups

	Sibutramine		CPAP	
	Baseline	1 yr	Baseline	1 yr
TST min	507±31	495±28	489±20	518±21 ^{##}
Sleep stage %				
1–2	76.4±18.2	67.5±11.5***	67.4±18.8	52.1±11.4***,##
3–4	13.1±12.7	16.5±8.4	19.4±16.7	25.2±9.2 ^{##}
REM	10.6±8.1	15.9±6.7***	13.2±4.9	20.8±3.4***,##
Supine sleep time %	41.3±27.3	38.0±21.3	45.5±32.4	47.4±33.1
AHI in supine position events·h⁻¹	24.9±23.9	26.3±26.4	49.7±40.6	5.1±6.9***
Sleep efficiency[#] %	73.5±15.3	76.7±15.1	68.4±21.2	77.0±21.0
Sleep arousals events·h⁻¹	24±25	23±17	27±24	2±1***
Total AHI events·h⁻¹	39.8±28.0	37.0±21.8	44.0±33.1	3.8±3.0***,##
Obstructive AHI events·h⁻¹	41.5±29.1	33.0±21.6	45.6±32.1	2.1±2.4***,##
Obstructive NREM AHI events·h⁻¹	35.1±28.5	32.5±21.3	40.0±29.8	1.7±1.7***,##
Obstructive REM AHI events·h⁻¹	36.9±26.5	40.1±19.8	50.5±30.6	8.7±6.9***,##
Sa_{o2} awake %	95.6±1.7	97.2±1.1***	95.6±2.3	96.8±1.4***
Sa_{o2} <90% % TST	10.8±20.5	2.1±4.2	12.4±22.7	2.1±8.8*
ESS score	13±5	11±6	13±7	8±5***,##
QSQ score				
Hypersomnolence	4.2±1.6	5.2±1.8***	4.4±1.3	6.0±1.2***
Diurnal symptoms	4.2±1.4	4.8±1.8	3.8±1.6	5.7±1.2***
Nocturnal symptoms	4.1±1.4	4.9±1.2	4.0±11.3	5.8±1.2***
Emotions	4.1±1.4	4.9±1.2*	4.0±1.3	5.8±1.2***
Social interactions	4.5±1.8	5.6±1.2***	5.0±1.2	6.4±1.0***,##

Data are presented as mean±sd. TST: total sleep time; REM: rapid eye movement; NREM: non-REM; AHI: apnoea/hypopnoea index; Sa_{o2}: arterial oxygen saturation; ESS: Epworth Sleepiness Scale; QSQ: Quebec Sleep Questionnaire. #: TST/sleep period time. *: p<0.05; ***: p<0.001 versus baseline; ##: p<0.01 between groups.

utilisation is not associated with worsening of sleep breathing patterns, arrhythmias and blood pressure among these patients [12, 23, 24]. This was corroborated in the present study.

Several studies have evaluated the effectiveness of weight loss for OSA treatment. Important weight loss following bariatric surgery has demonstrated the best efficiency, with improvements ranging to near-normal breathing during sleep as early as 1 month post-surgery [25–27]. Moreover, dramatic improvements (50–60%) in nocturnal breathing disorders and in severity of nocturnal desaturation have been observed with a relatively small amount of weight loss (<10 kg) in other studies [5, 7]. At present, the literature is sparse regarding the use of anti-obesity medication in patients with OSA. Although the efficacy of orlistat in reducing body weight in obese patients has been demonstrated in a large multicentric randomised double-blind 2-yr study [28], this medication has not yet been studied in patients with OSA. Thus it was decided to use sibutramine above other pharmacological agents since some prospective studies have shown that groups treated with sibutramine lost more weight [29]. Sibutramine appears to have a more positive effect on the reduction in central adiposity compared to orlistat [30], which is a common phenotypic feature in the presence of OSA.

A study of MARTINEZ and BASILE [10], which assessed the acute effects of sibutramine over a 1-month period without weight

loss, did not find any changes in sleep architecture or severity of sleep-disordered breathing. In contrast, a 6-month treatment with sibutramine in 87 obese subjects with symptomatic OSA resulted in a 10% weight loss and improvement in OSA severity without changes in blood pressure [12]. STROBEL *et al.* [31] found, in a pilot uncontrolled study conducted in 13 OSA patients, that a 6-month treatment with fenfluramine, leading to a 14-kg weight loss, was associated with a dramatic decrease in the frequency of obstructive breathing disorders. It should be underlined that the long-term efficiency of these pharmaceutical treatments for weight loss in OSA patients were unknown until now, the follow-up duration of the above-mentioned studies ranging 1–6 months.

Although the majority of sleep and respiratory variables were not significantly improved in the present study after a 1-yr treatment with sibutramine, the 5% weight loss had positive impacts on nocturnal mean Sa_{o2} and AHI. Indeed, the improvement in AHI is associated with the importance of weight loss induced with sibutramine. These findings are consistent those of YEE *et al.* [12], who found that the magnitude of improvement in OSA was associated with the degree of weight loss. It should be noted that subjects in the present study achieved only a modest amount of weight loss with sibutramine, but had severe sleep apnoea at baseline, which probably limited the overall improvement in OSA. CPAP treatment improved all other sleep and respiratory

TABLE 3 Heart rate variability indices in the time domain in the sibutramine and continuous positive airway pressure (CPAP) groups

	Sibutramine [#]			CPAP [‡]		
	Baseline	1 month	1 yr	Baseline	1 month	1 yr
24-h						
SDNN ms	119±38	127±33	126±42	139±41	141±46	145±40
SDANN ms	107±33	115±30	111±42	124±39	128±41	131±40
rMSSD ms	26±10	24±11	25±10	30±9	32±20	31±11 ⁺
pNN50 %	7±6	6±6	6±7	9±6	11±12	11±9 ⁺
Daytime						
SDNN ms	83±29	78±24	83±30	85±25	88±37	99±30 [§]
SDANN ms	67±24	59±16	67±25	69±21	67±31	79±27 [§]
rMSSD ms	19±8	19±9	21±8	22±7	28±20	26±9
pNN50 %	3±5	3±5	4±5	4±5	8±12	7±7 [*]
Night-time						
SDNN ms	92±26	100±37	92±28	110±31	107±44	102±29
SDANN ms	60±17	64±27	62±19	67±17	65±21	66±24
rMSSD ms	30±14	33±15	32±15	40±16 ⁺	41±28	39±14
pNN50 %	11±11	12±12	11±12	18±13	17±18	18±14

SDNN: sd of normal-to-normal R-R interval; SDANN: sd of the average normal-to-normal R-R interval calculated over a 5-min period; rMSSD: square root of mean squared difference of successive normal-to-normal R-R intervals; pNN50: number of adjacent normal-to-normal R-R intervals differing by >50 ms divided by total number of normal-to-normal R-R intervals. [#]: n=22; [‡]: n=18. *: p<0.05 versus baseline; ⁺: p<0.05 between groups; [§]: p<0.05 versus 1 month.

variables compared to weight loss. The changes observed in the lipid profile following CPAP and sibutramine therapy might be related to weight loss or CPAP *per se*. Accordingly, a

decline in triglyceride and increase in HDL-cholesterol are commonly observed following weight loss [26]. A study of WIRTH and KRAUSE [24] reported that sibutramine, administered for 48 weeks to a typically obese population, resulted in clinically relevant weight loss associated with an increase in HDL-cholesterol compared to placebo. Other studies also observed a decrease in LDL-cholesterol levels in both sibutramine and placebo groups, and a substantial decline in triglyceride levels in both groups [23]. In contrast, patients with moderate-to-severe OSA compliant with CPAP usage may improve their insulin secretion capacity and reduce their total cholesterol and LDL levels [32].

Previous studies have shown sibutramine to have variable effects on blood pressure and heart rate. In the present study, mean, daytime and night-time ABPM did not change throughout the year in the sibutramine group, even in the presence of significant weight loss. This stability may be due to sibutramine since this medication may have two opposing effects: 1) weight loss, inducing a decrease in blood pressure; and 2) a sympathomimetic effect, causing an increase in blood pressure. Thus the absence of a change in blood pressure with sibutramine may result from these opposite effects [33]. The present results show that CPAP therapy improves night-time SBP and DBP, and decreases the 24-h and daytime ambulatory DBP. Accordingly, a meta-analysis of BAZZANO *et al.* [34] provided evidence that CPAP treatment reduces blood pressure in individuals with OSA, with a mean net change of -2.46 mmHg in SBP and -1.83 mmHg in DBP among those using CPAP therapy compared to those in the control groups. No changes in autonomic cardiac modulation were observed after 1 yr of sibutramine treatment, even if it induced a 5% weight loss. The impact of this medication on blood pressure and heart rate might have attenuated the beneficial impact of weight loss on HRV and ABPM variables. In agreement with this, BIRKENFELD *et al.* [11] reported that a few days on a sibutramine regimen profoundly attenuated the pressor

TABLE 4 Heart rate variability indices in the frequency domain

	Sibutramine [#]			CPAP [‡]		
	Baseline	1 month	1 yr	Baseline	1 month	1 yr
24-h						
Ln LF ms ²	5.83±0.90	5.93±1.01	5.88±0.80	6.05±0.97	5.66±1.22	6.21±0.67**
Ln HF ms ²	4.35±0.93	4.48±1.08	4.46±0.87	4.82±0.95	4.50±1.09	5.00±0.77
LF/HF	4.91±2.34	4.94±2.93	4.55±2.51	3.74±1.83	3.54±1.84	3.80±1.63
Daytime						
Ln LF ms ²	5.53±0.94	5.68±1.05	5.61±0.86	5.67±1.09	5.42±1.19	5.96±0.64
Ln HF ms ²	3.85±1.06	3.97±1.15	3.97±0.95	4.20±1.05	4.22±1.09	4.58±0.81 ^{##}
LF/HF	6.33±3.28	6.65±3.89	5.92±3.97	4.79±2.09	3.89±2.52	4.59±2.26
Night-time						
Ln LF ms ²	6.20±0.99	6.37±1.10	6.21±0.87	6.48±0.99	5.99±1.31	6.52±0.79**
Ln HF ms ²	4.91±1.14	5.23±1.11	5.09±0.97	5.45±0.98	4.90±1.11	5.46±0.84
LF/HF	4.32±2.61	3.79±2.42	3.50±1.90	3.32±2.45	3.27±1.57	3.31±1.77

CPAP: continuous positive airway pressure; LF: low frequency; HF: high frequency. [#]: n=22; [‡]: n=18. **: p<0.01 versus 1 month; ^{##}: p<0.01 between groups.

response to sympathetic stimuli through a clonidine-like sympatholytic effect. As reported elsewhere [35–37], the analysis of daily fluctuations in HRV in the CPAP group showed that improvements in indices in the time domain were accompanied by a significant decrease in mean heart rate.

Although the present participants chose between the weight loss programme and conventional CPAP treatment, the sibutramine and CPAP groups were remarkably similar at baseline. It was felt that this study design would best reflect usual clinical practice, and is a key issue in this study being considered clinically valuable. After confirmation of the diagnosis of OSA, patients were presented with the different treatment management strategies, which included weight loss and CPAP. CPAP might not be selected as a primary treatment in a significant number of patients. Similarly, although weight loss is always presented as an important component of the treatment strategy, some patients do not feel that they would be able to stick with the dietary and exercise requirements required for significant weight loss. It is of interest that the PREFER study was a randomised controlled clinical trial testing treatment preference in subjects assigned to one of two calorie- and fat-restricted diets [38]. They found that choosing treatment preference was probably the most influential factor in determining adherence to the diet treatment, and suggest that it would be important to use this concept with those who are willing to make significant changes in their lifestyle. Therefore, we feel that sleep apnoea treatment must be tailored according to the willingness of patients to comply with specific requirements, making the patient's treatment choice a very important issue in establishing a treatment plan, as it should be in clinical practice. This is firmly supported by the very high compliance with treatment that was observed in each treatment arm (91.7 and 100.0% after 1 yr for sibutramine and CPAP treatment, respectively). Although entirely speculative, the present results suggest that sibutramine combined with conventional CPAP therapy is probably safe for optimised weight loss in the management and treatment of OSA in obese patients, since there were no changes in blood pressure and arrhythmia associated with this treatment regimen. This underlines the need for randomised controlled trials comparing sibutramine in addition to CPAP to CPAP alone in patients with severe sleep apnoea. Conversely, in patients with mild-to-moderate sleep apnoea, weight loss therapy might be more effective in reducing the AHI. Therefore, in strongly motivated subjects free of clinically significant comorbid conditions and/or clinical symptoms (*i.e.* excessive daytime sleepiness), drug-induced weight loss could potentially represent a first-line treatment strategy, and this should be assessed in adequately designed clinical trials.

In conclusion, the present results show that 1 yr of CPAP treatment has a beneficial impact on OSA in improving nocturnal oxygenation, night time SBP and DBP, and daytime indices of HRV. Conversely, despite significant weight loss, sibutramine did not modify OSA, HRV or blood pressure. Nevertheless, these results suggest that sibutramine is safe for the optimisation of weight loss in the management and treatment of OSA in obese patients, since there was no change in blood pressure or arrhythmia associated with this treatment regimen.

CLINICAL TRIALS

This study is registered at ClinicalTrials.gov (trial number NCT00729963).

SUPPORT STATEMENT

A. Ferland is a Canadian Diabetes Association (Toronto, ON, Canada) postdoctoral fellow. P. Poirier is a clinician-scientist of the Fonds de la Recherche en Santé du Québec (FRSQ; Montreal, QC, Canada). F. Sériès is a national researcher of the FRSQ. The funding source played no role in the design, collection, analysis or interpretation of the data, or in the decision to submit the study for publication.

STATEMENT OF INTEREST

A statement of interest for this study can be found at www.ersjournals.com/misc/statements.dtl

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