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Title page:

Sibutramine vs. CPAP in the treatment of obese patients with obstructive sleep apnoea

A. Ferland[1], P. Poirier[1,2] and F. Sériès[1,3]

Affiliations:

1) Centre de recherche de l'Hôpital Laval, Institut universitaire de cardiologie et de pneumologie, Université Laval, Québec (Québec), Canada ;

2) Faculty of pharmacy, Laval University, Québec (Québec), Canada;

3) Faculty of medicine, Laval University, Québec (Québec), Canada.

Correspondence:

Frédéric Sériès, MD

Institut universitaire de cardiologie et de pneumologie, Hôpital Laval

2725 Chemin Sainte-Foy, Québec (Québec), Canada, G1V 4G5.

Tel: +1 (418) 656-8711

Fax: +1(418) 656-4918

E-mail: Frederic.Series@crhl.ulaval.ca

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ABSTRACT: We compared the efficacy of 1-yr sibutramine-induced weight loss vs. continuous positive airway pressure (CPAP) treatment on sleep disordered

breathing, cardiac autonomic function and systemic blood pressure in obese patients with obstructive sleep apneoa (OSA).

Subjects with a body mass index (BMI) $\geq$ 30 kg/m^2 without previous treatment for OSA underwent either sibutramine (n=22) or CPAP (n=18) treatment for a 1-yr duration.

Sibutramine induced a 5.4±1.4 kg decrease in body weight compared to the CPAP group, where no changes in anthropometric variables were observed. The CPAP treatment improved all sleep and respiratory variables, whereas sibutramine-induced weight loss improved nocturnal SaO_2 profile only. Only CPAP treatment improved night time systolic and diastolic blood pressure, 24-hour 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.

One-year of CPAP treatment had beneficial impacts on nocturnal breathing disturbances, improves nocturnal oxygenation, night time systolic and diastolic blood pressure, and daytime cardiac parasympathetic modulation. Sibutramine did not improve sleep disordered breathing, systemic blood pressure and 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 apneoa, Weight loss.

Body of paper:

Introduction

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

A 10% weight loss is associated with a 50 to 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 normalization of breathing with continuous positive airway pressure (CPAP) during sleep. Sibutramine, which leads to an enhancement of satiety and thermogenesis by inhibiting serotonin and norepinephrine reuptake, has been shown to induce a dose-dependent weight loss ranging from 2 to 10 kg, thus potentiating the effects of a low-calorie diet for up to a year 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, evidences have shown that a moderate ~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 to the usual CPAP treatment on changes in sleep-related breathing disorders in obese patients.

MATERIALS AND METHODS

Study subjects: Eligible participants with non-treated OSA syndrome were recruited through the sleep disorder outpatient clinic of Laval Hospital. Subjects were aged between 18 to 65

years, with a body-mass index (BMI) $\geq$ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors such as controlled systemic hypertension, type 2 diabetes, dyslipidemia and/or visceral obesity (as defined by a waist circumference ≥ 102 cm in men and ≥ 88 cm in women). Exclusion criteria were uncontrolled systemic hypertension defined as blood pressure > 145/90 mm Hg, previous pharmacological or surgical treatment for weight loss, previous CPAP usage or presence of severe diurnal hypersomnolence requiring immediate treatment. The main outcome measure in this study was the improvement in 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 (FS), patients chose their treatment preference (treatment preference-sibutramine [combination of sibutramine with calorie- and fat-restricted weight loss diet and physical activity recommendation] or treatment preference-CPAP [conventional CPAP treatment and lifestyle recommendations]). We chose this study design because we considered that letting the patient choose their OSA treatment would enhance their compliance to the medical treatment. We also considered that a study design based on randomized treatment allocation would alter the evaluation of the response expected from a given treatment strategy, and would not represent the real clinical situation clinicians and patients are faced 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 program). The first group received sibutramine 10 mg for the first 4 weeks, at which time consideration of increasing dosage to 15 mg was re-evaluated in the case of insufficient weight loss ($<$ 1.8 kg) over the first month of treatment. Fasting blood samples were obtained at baseline, 6 and 12 months for measurements of plasma glucose concentration, glycated haemoglobin (HbA1c) and lipid profile.

Polysomnography: Subjects underwent a conventional in-lab polysomnographic study at baseline and after 6 and 12 months of treatment. The measures consisted of continuous acquisitions of the electroencephalogram, the electrooculogram, the submental electromyogram, the arterial oxyhemoglobin saturation from transcutaneous sensing (SaO_2), the nasal pressure with nasal prongs connected to a pressure transducer [13] the oral airflow with thermistor, the chest and abdominal movements by inductive plethysmography (Respitrace, Ambulatory Monitoring Inc, Ardsley, NY), and the electrocardiogram. All variables were digitally recorded (Sandman Elite™ system, Mallinckrodt, Kenilworth, NJ). Sleep-wake state and arousals were scored according to standardized criteria [14]. Subjects were asked to complete the 32-question Québec sleep apneoa questionnaire (QSQ) [15], and the Epworth sleepiness score (ESS) was obtained [16].

CPAP treatment: CPAP treatment was initiated with manual titration under one overnight in-lab sleep recording. The effective pressure level chosen is the pressure level that abolished all obstructive events (apneoal, hypopnoea, flow limitation, snoring) in every sleep stage and body position. Patients were referred to an health care company for choosing their CPAP devices and masks. The patient was contacted after 2 weeks to check subjective compliance and to identify problems encountered with CPAP use. Compliance was determined using the downloadable data from the patient's CPAP device.

Heart Rate Variability: A 24-hour Holter monitoring was performed before treatment (baseline) and during the course of therapies (Marquette Electronics Inc., Milwaukee, WI). Heart rate variability (HRV) was established throughout numerous indices [17] and the recording was scheduled to include the sleep recording period in order to identify apneoa-related disorders. Parameters from the spectral domain and the 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, low-

frequency power (LF; 0.04-0.15Hz, which is considered an index of both sympathetic and parasympathetic activity) and HF (0.15-0.4 Hz, which represents the 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, R-R interval, and standard deviation of R-R interval (SDNN), standard deviation of the mean R-R calculated over a 5-minute period (SDANN), square root of the mean squared difference of successive R-R intervals (rMSSD), number of adjacent N-N differing by more than 50 milliseconds (NN50), and NN50 divided by total number of N-N intervals (pNN50) were analysed. The rMSSD and pNN50 indices are associated with HF and hence parasympathetic activity [17].

24-hr Ambulatory Blood Pressure Monitoring: Ambulatory blood pressure monitoring (ABPM) was performed over a 24-hour period in all subjects at baseline, and 1-year of the study (model 90 212, Space-lab, Canada) [19] in accordance with current recommendations [20, 21]. During the 24-hour recording, measurements of systolic, diastolic, and mean arterial blood pressure values were determined by oscillometric method with one measurement every 15 min during daytime period (6:00 AM to 10:00 PM), and every 20 min during night time (10:00 PM to 6:00 AM). Normal daytime, night time blood pressure and the nondipping pattern were defined according to the AHA Recommendation for Blood Pressure Measurements [21].

Statistical Analysis: The study was designed to have 80 percent power to detect a difference in AHI of ≥ 15 events/hours between the sibutramine and CPAP groups in 60 percent of subjects, considering that 100 percent of subjects of the CPAP group will improve their AHI [22], with a two-sided Student's t test and a type I error of 5 percent. Thus, 20 subjects are needed in the Sibutramine group to allow the comparison with the reference group (CPAP). Considering a 10 percent dropout rate, 22 patients are needed to be included in the sibutramine. Data are expressed as means ± SD or as percentages unless specified otherwise. Analysis of categorical data was carried out with the χ^2 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 the time levels (corresponding to baseline, 1-month and/or 6-month and 1-year) and analysed as a repeated-measure factor. Variables were log-transformed when necessary to obtain a normal distribution. A *p*-value <0.05 was considered statistically significant. The data were analyzed using the statistical package program SAS v9.1.2 (SAS Institute Inc., Cary, NC).

RESULTS

Forty-two OSA patients participated in the study. A total of 40 patients (95.2%) completed the 1-year treatment. Two patients withdrew in the sibutramine group because of lost to follow-up and adverse events. Thus, 22 patients with a baseline weight of 111±14 kg and a BMI of 36.7±4.2 kg/m^2 were included in the sibutramine group (Table 1). Eighteen patients received CPAP as treatment and were analyzed as the standard reference group. Baseline characteristics were similar between the sibutramine and the CPAP groups. Weight loss after 1-year of sibutramine treatment was on average 5 kg (p<0.001), which correspond to a relative reduction of 5% of initial weight concomitantly to a 7% reduction in waist circumference (p<0.001), corresponding to an average decrement of 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 the sibutramine group (-1.6 kg). However, dietary changes were not maintained throughout the year in the CPAP group, and body weight returned to baseline level at 6 months.

The mean AHI of 54 and 52 per hour at baseline for the sibutramine and the CPAP groups respectively indicated severe sleep apneoa. At one year, the patients assigned to CPAP had a greater (92%) reduction in the AHI than those in the sibutramine group (-40±30 vs. -3±6 per hours, p<0.0001) (Figure 1). Of note, changes in the AHI between baseline and 1-year in

the sibutramine group were correlated with changes in body weight (r=0.57; p=0.006). Interestingly, sibutramine induced a significant increase in mean nocturnal oxygen saturation (4.8±1.7 vs. 2.2±2.5% for the sibutramine and the CPAP groups respectively, p=0.007), whereas CPAP induced the greater increase in minimum oxygen saturation (9.8±4.8 vs. 3.8±6.3% for the CPAP and the sibutramine group respectively, p=0.0001). CPAP significantly decreased the percent time spent below 90% saturation (12.4±22.7 to 2.6±8.8% after 1 year, p=0.02), whereas no changes was observed after Sibutramine treatment (8.4±18.8% to. 2.1±4.2% after 1 year, p=0.08). The two treatments decreased the percent of sleep in stage 1 and 2 (p<0.05) and increased the percent of sleep in stage REM *(*p<0.001). However, after one year of treatment, a better 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 to sibutramine-induced weight loss (Table 2). At 12-month, subjects used CPAP for a mean 6.6±1.6 hours per day, and 89.4% used CPAP for the minimum treatment time of 4 hours per day. No difference was found in subjective daytime sleepiness before and after 1 year of sibutramine treatment, whereas CPAP improved this parameter (p<0.0001), as assessed by 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 both groups compared to 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 vs.1-month of treatment), and pNN50 parameters (p=0.03; 1-year vs. baseline). The 24-hours rMSSD and pNN50 parameters of HRV were higher after 1-year of CPAP compared to 1-year of sibutramine. Table 4 shows spectral domain indices of the Holter monitoring. Sibutramine induced no changes in low- and high-frequency power or in the LF/HF ratios. The CPAP treatment increased significantly the 24-hour and the nighttime LF power data compared to the 1-month value (all p<0.01). Moreover, daytime HF was higher

after 1-year of CPAP compared to 1-year treatment with sibutramine. There were no changes in arrhythmias in both groups.

At baseline, a non-dipping 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-hour, day, and night ambulatory SBP and DPB were near normal at baseline and were comparable between groups. Sibutramine induced no changes in mean 24-hour SBP and DBP over the year (129±8 vs. 130±10 mmHg for SBP and 80±6 vs. 82±8 mm Hg for DPB pre vs. post sibutramine treatment). Also, no significant differences were observed in daytime and night time mean SBP and DBP. One-year of CPAP treatment improved night time SBP and DBP (117±7 vs. 109±13 mm Hg for SBP and 72±8 vs. 68±8 mmHg for DBP pre vs. post CPAP treatment; all $p<0.01$). A significant decrease was also observed in the 24-hour and daytime ambulatory DBP (all $p=0.04$). More so, after 1-year of treatment, the 24-hour and daytime DBP were lower in the CPAP group compared to the sibutramine group (all $p<0.01$).

HDL cholesterol levels increased by 15% in the sibutramine group ($p<0.0001$) and LDL cholesterol levels were reduced by 11% in the CPAP group ($p=0.02$). Moreover, glycated haemoglobin 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 after treatment.

DISCUSSION

Our results show that CPAP treatment improved numerous sleep and respiratory variables compared to sibutramine-induced weight loss. Indeed, despite significant weight loss, this study documents a lack of efficacy of sibutramine in improving symptoms of sleep apneoa 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 utilization was not associated with worsening of sleep breathing patterns, arrhythmias and blood pressure among these patients [12, 23, 24]. This was corroborated in our 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% to 60%) in nocturnal breathing disorders and in severity of nocturnal desaturation have been observed with relatively small amount of weight loss (< 10kg) in other studies [5, 7]. At present, the literature is sparse regarding the use of anti-obesity medication in patients with OSA. Even if the efficacy of orlistat in reducing body weight in obese patients has been demonstrated in large, multicenter, randomized, double-blind, 2-year study [28], this medication have not yet been studied in patients with OSA. Thus, we choose to use sibutramine over all other pharmacological agents since some prospective study 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 presence of OSA.

A study of Martinez *et al*. [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 the 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 in 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 has to be underlined that the long-term efficiency of these

pharmaceutical treatments for weight loss in OSA patients were until this time unknown, the follow-up duration of the above-mentioned studies ranging from 1 to 6 months.

Although the majority of sleep and respiratory variables was not significantly improved in our study after a 1-year treatment with sibutramine, the 5% weight loss had positive impacts on nocturnal mean oxygen saturation values and in AHI. In fact, the improvement in AHI is associated with the importance of weight loss induced with Sibutramine. These findings are consistent with findings of Yee *et al*. [12] in which the magnitude of improvement in OSA was associated with the degree of weight loss. It should be noted that subjects in our study achieved only a modest amount of weight loss with sibutramine, but had severe sleep apneoa at baseline, which probably limited the overall improvement in OSA. Thus, the CPAP treatment improved all other sleep and respiratory variables compared to weight loss. The changes observed in the lipid profile following CPAP and sibutramine therapies might be related to weight loss or CPAP *per se*. Accordingly, a decline in triglyceride and an increase in HDL-cholesterol are commonly observed following weight loss [26]. A study from Wirth *et al*. [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 study also observed a decrease in LDL-cholesterol values in both the sibutramine and placebo groups, and a substantial decline in triglyceride levels in both groups [23]. In contrast, patients with moderate-to-severe obstructive sleep apneoa, compliant to CPAP usage may improve their insulin secretion capacity, reduce their total cholesterol and low-density lipoprotein levels [32].

Previous studies have shown sibutramine to have variable effects on blood pressure and heart rate. In our study, mean, daytime and nighttime ABPM in the sibutramine group did not change through the year even in the presence of significant weight loss. This stability may be due to sibutramine since this medication may have 2 opposing effects: 1) weight loss induces a decrease in blood pressure while, 2) this decrease may be offset by the sympathomimetic

effect of sibutramine, causing an increase in blood pressure. Thus, the absence of change in blood pressure with Sibutramine could result from these opposite effects [33]. Our results show that CPAP therapy improves night time SBP and DBP, and decreases the 24-hour and daytime ambulatory DBP. Accordingly, a meta-analysis from Bazzano *et al*. [34] provides evidence that CPAP treatment reduces blood pressure levels in individuals with OSA, with a mean net change of -2.46 mm Hg in SBP and -1.83 mm Hg in DBP among those using CPAP therapy compared to those in the control groups. No changes in autonomic cardiac modulation were observed after 1-year of sibutramine treatment, even if sibutramine 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 accordance, Birkenfeld *et al*. [11] reported that a few days with sibutramine regimen profoundly attenuates the pressor 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 was accompanied with a significant decrease in mean heart rate.

Even if our participating subjects chose between the weight loss program and conventional CPAP treatment, the sibutramine and the CPAP groups were remarkably similar at baseline. We felt that this study design would best reflect usual clinical practice, and is a key issue for this study to be considered as clinically valuable. After confirmation of the diagnosis of OSA, patients were presented the different treatment management strategies that included weight loss and CPAP. CPAP might not have been 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 dietary and exercise requirements needed for significant weight loss. Of interest, the PREFER study was a randomized 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 patients' treatment choice a very important issue in establishing treatment plan as it should be in clinical practice. This is firmly supported by the very high compliance to treatment that was observed in each treatment arm (91.7% and 100.0% after 1 year for the sibutramine and the CPAP treatment, respectively). Although entirely speculative, our results suggest that sibutramine combined with a conventional CPAP therapy is probably safe in order to optimize weight loss in the management and treatment of OSA in obese patients, since there were no changes in blood pressure and arrhythmias associated with this treatment regimen. This underlines the need for randomized controlled trials comparing sibutramine in addition to CPAP to CPAP alone in patients with severe sleep apneoa. On the other hand, in patients with mild to moderate sleep apneoa, weight loss therapy could be more effective in reducing AHI. Therefore, in strongly motivated subjects free of clinically significant co-morbidities 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 by adequately designed clinical trials.

In conclusion, our results show that 1-year of CPAP treatment has a beneficial impact of OSA in improving nocturnal oxygenation, night time SBP and DBP, and daytime indices of HRV. On the other hand, despite a significant weight loss, sibutramine did not modify OSA, HRV or blood pressure. Nevertheless, our results suggest that sibutramine is safe in order to optimise weight loss in the management and treatment of OSA in obese patients, since there was no change in blood pressure or arrhythmias associated with this treatment regimen.

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Table 1 - Subject characteristics at baseline and 1-yr, on the sibutramine group, and on the CPAP group

Characteristics	Sibutramine		CPAP	
	Baseline	1-yr	Baseline	1-yr
N (women/men)	22 (3/19)		18 (2/16)	
Age (years)	49±9		49±9	
Weight (kg)	110.9 ± 14.3	105.5 ± 17.4 ∗	109.2 ± 12.2	109.8 ± 14.7
BMI (kg/m^2)	36.8 ± 4.2	35.0 ± 5.3 ∗	36.4 ± 4.2	36.4 ± 4.1
Glucose (mmol/L)	5.7 ± 1.1	6.1 ± 1.4	5.9 ± 0.7	6.1 ± 1.2
Blood pressure and Heart rate				
SBP (mm Hg)	133 ± 8	132 ± 10	128 ± 11	125 ± 14 §
DPB (mm/Hg)	82 ± 6	84 ± 8	77 ± 7 §	81 ± 9
Dippers (%)	71.4	60.0	50.0	61.5
Non-dippers (%)	28.6	40.0	50.0	38.5
Heart rate (beats/min)				
Minimal	49 ±9	49 ± 8	47 ± 8	46 ± 6
Maximal	131 ± 18	125 ± 19	130 ± 14	126 ± 9
Mean	80 ± 12	79 ± 11	80 ± 7	74 ± 7 ∗ §
Lipid profile (mmol/L)				
Total Cholesterol	4.64 ± 0.87	4.87 ± 0.72	4.84 ± 0.83	4.57 ± 0.95
Triglycerides	1.74 ± 1.06	1.52 ± 0.68	1.76 ± 0.71	1.89 ± 0.52
HDL-C	1.10 ± 0.27	1.27 ± 0.33 ∗	1.15 ± 0.23	1.14 ± 0.24
LDL-C	2.80 ± 0.73	2.94 ± 0.66	2.88 ± 0.80	2.55 ± 0.82 ∗∗
Total-C/HDL-C	4.37 ± 0.92	4.07 ± 0.97	4.31 ± 0.92	4.09 ± 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 mean ± SD. ∗ p<0.001 vs. baseline; ∗∗ p<0.05 vs. baseline; § p<0.05 between groups.

CPAP, continuous positive airway pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Body-mass index (BMI) is defined as the weight in kilograms divided by the square of the height in meters.

Table 2 - Polysomnographic recording at baseline and 1-yr, on the sibutramine group, and on the CPAP group

Parameters	Sibutramine		CPAP	
	Baseline	1-yr	Baseline	1-yr
Total sleep time	507 ± 31	495 ± 28	489 ± 20	518 ± 21 §
% Stage 1-2	76.4 ± 18.2	67.5 ± 11.5 ∗	67.4 ± 18.8	52.1 ±11.4 ∗ §
% Stage 3-4	13.1 ±12.7	16.5 ± 8.4	19.4 ±16.7	25.2 ±9.2 §
% Stage 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	24.9 ± 23.9	26.3 ± 26.4	49.7 ± 40.6	5.1 ± 6.9∗
Sleep efficiency (TST/SPT) %	73.5±15.3	76.7±15.1	68.4±21.2	77.0±21.0
Arousals from sleep (no./hr of sleep)	24 ± 25	23 ± 17	27 ± 24	2 ± 1∗
Total AHI	39.8±28.0	37.0±21.8	44.0±33.1	3.8±3.0 ∗ §
Obstructive AHI index	41.5±29.1	33.0±21.6	45.6±32.1	2.1±2.4 ∗ §
Obstructive AHI NREM	35.1±28.5	32.5±21.3	40.0±29.8	1.7±1.7 ∗ §
Obstructive AHI REM	36.9±26.5	40.1±19.8	50.5±30.6	8.7±6.9 ∗ §
SaO_2 awake	95.6±1.7	97.2±1.1 ∗	95.6±2.3	96.8±1.4 ∗
SaO_2 <90%	10.8±20.5	2.1±4.2	12.4±22.7	2.1±8.8 ∗∗
Epworth sleepiness score (ESS)	13 ± 5	11 ± 6	13 ±7	8 ± 5 ∗ §
Québec sleep apnea questionnaire (QSAQ)				
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	4.011.3	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 mean ± SD. ∗ p<0.001 vs. baseline; ∗∗ p<0.05 vs. baseline; § p<0.01 between groups.

TST, Total sleep time; SPT, Sleep period time; AHI, Apnea-hypopnea index; REM, Rapid eye movement; NREM, Non rapid eye movement; SaO_2, Arterial oxygen saturation.

Table 3 - Heart rate variability indices in the time domain in the sibutramine and the CPAP groups

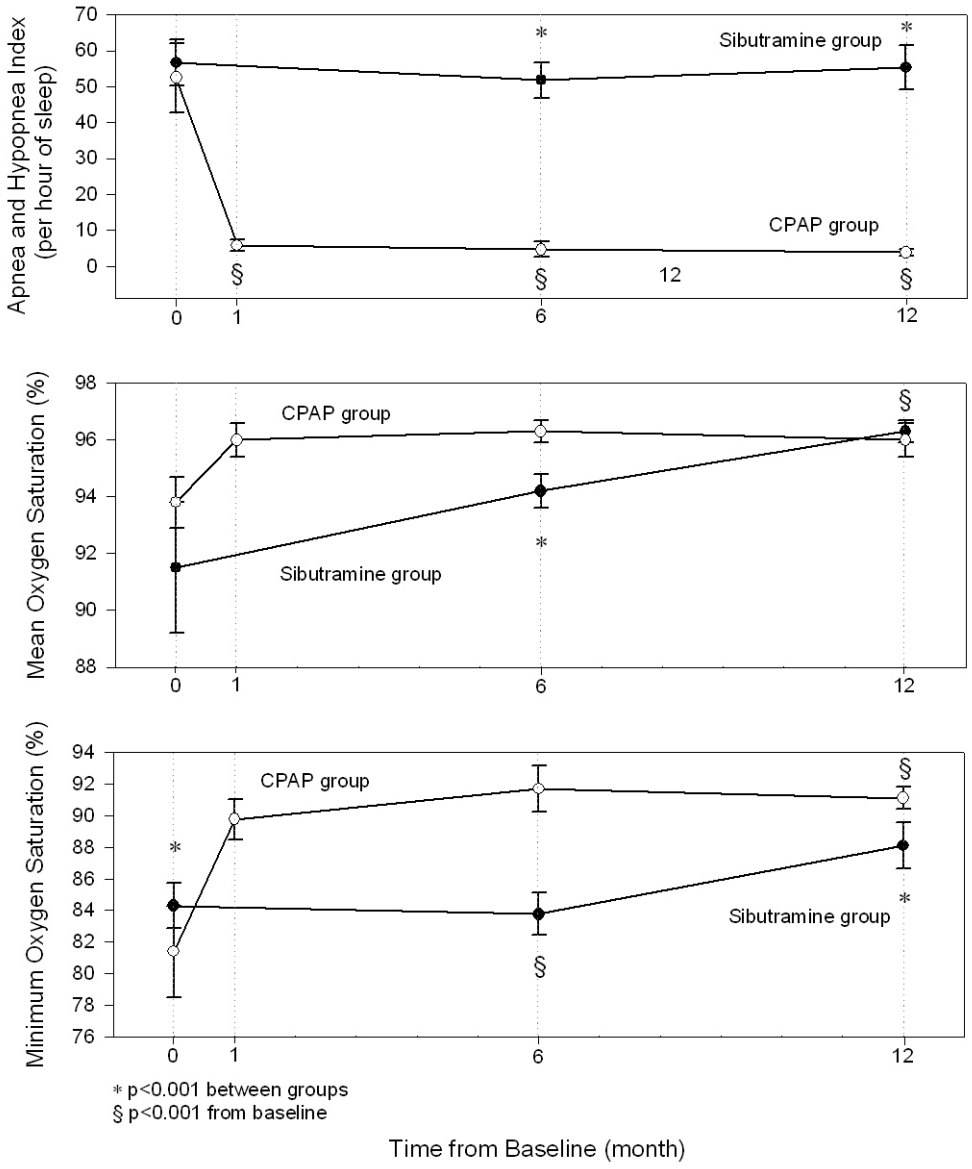
	Sibutramine (n=22)			CPAP (n=18)		
	Baseline	1-month	1-year	Baseline	1-month	1-year
24 h						
SDNN	119 ± 38	127 ± 33	126 ± 42	139 ± 41	141 ± 46	145 ± 40
SDANN	107 ± 33	115 ± 30	111 ± 42	124 ± 39	128 ± 41	131 ± 40
rMSSD	26 ± 10	24 ± 11	25 ± 10	30 ± 9	32 ± 20	31 ± 11 §
pNN50	7 ± 6	6 ±6	6 ± 7	9 ± 6	11 ± 12	11 ± 9 §
Daytime						
SDNN	83 ± 29	78 ± 24	83 ± 30	85 ±25	88 ± 37	99 ± 30 **
SDANN	67 ± 24	59 ± 16	67 ± 25	69 ± 21	67 ± 31	79 ± 27 **
rMSSD	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 *
Nighttime						
SDNN	92 ± 26	100 ± 37	92 ± 28	110 ± 31	107 ± 44	102 ± 29
SDANN	60 ± 17	64 ± 27	62 ± 19	67 ± 17	65 ± 21	66 ± 24
rMSSD	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

Table 4 - Heart rate variability indices in the frequency domain

	Sibutramine (n=22)			CPAP (n=18)		
	Baseline	1-month	1-year	Baseline	1-month	1-year
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
Nighttime						
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

Figure 1 - Effect of 1-year of CPAP and sibutramine treatment of the apnea and hypopnea index, mean, and minimal oxygen saturation

Figure 1.


Apnea and Hypopnea Index (per hour of sleep)
70
60
50
40
30
20
10
0
Sibutramine group
CPAP group
*
*
§
§
§
12
0
1
6
12
Mean Oxygen Saturation (%)
98
96
94
92
90
88
CPAP group
Sibutramine group
§
*
0
1
6
12
Minimum Oxygen Saturation (%)
94
92
90
88
86
84
82
80
78
76
CPAP group
Sibutramine group
*
*
§
§
0
1
6
12
* p<0.001 between groups
§ p<0.001 from baseline
Time from Baseline (month)