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SCIENTIFIC INVESTIGATIONS

The treatment of mild OSA with CPAP or mandibular advancement device and the effect on blood pressure and endothelial function after one year of treatment

Thais Moura Guimarães, DDS, MSci[1]; Dalva Poyares, MD, PhD[1]; Luciana Oliveira e Silva, PT, PhD[1]; Gabriela Luz, PT, PhD[2]; Glaury Coelho, MSci[1]; Cibele Dal Fabbro, DDS, PhD[1]; Sergio Tufik, MD, PhD[1]; Lia Bittencourt, MD, PhD[1]

[1]Departamento de Psicobiologia, Universidade Federal de Sao Paulo, São Paulo, Brasil; [2]Departamento de Pneumologia, Universidade Federal de Sao Paulo, São Paulo, Brasil

Study Objectives: To evaluate and compare the effects of continuous positive airway pressure (CPAP), use of a mandibular advancement device (MAD), and no treatment on 24-hour ambulatory blood pressure monitoring and peripheral arterial tonometry at 6 and 12 months follow-up in individuals with mild obstructive sleep apnea (OSA), and in a subgroup who had an apnea-hypopnea index of < 5 events/h and adherence of ≥ 4 hours per night (effective-treatment subgroups).
Methods: The inclusion criteria were individuals with mild obstructive sleep apnea, any sex, age between 18 and 65 years, and a body mass index of ≤ 35 kg/m^2. Patients were randomized into CPAP, MAD, and no-treatment groups. The evaluations included physical examination, full polysomnography, 24-hour ambulatory blood pressure monitoring, and peripheral arterial tonometry at baseline and after 6 and 12 months. A generalized linear mixed model was used for comparisons.
Results: The CPAP and MAD groups had lower apnea-hypopnea indexes than the control group at 6 and 12 months, and the CPAP group had higher blood oxygen levels (SpO_2) than the MAD group. The MAD group had more hours of treatment per night and better adaptation to treatment than the CPAP group (MAD: 5.7 ± 2.7 h/night; CPAP: 3.8 ± 3.4 h/night; MAD: 16% did not adapt; CPAP: 42% did not adapt). No differences were found in the total sample and effective treatment in relation to peripheral arterial tonometry or 24-hour ambulatory blood pressure monitoring outcomes.
Conclusions: Treatment of mild obstructive sleep apnea with CPAP or MAD did not improve blood pressure or endothelial function after 1 year, even in patients with effective treatment.
Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Continuous Positive Airway Pressure and Oral Appliances Treatments in Mild Obstructive Sleep Apnea; URL: https://clinicaltrials.gov/ct2/show/NCT01461486; Identifier: NCT01461486.
Keywords: obstructive sleep apnea, mandibular advancement device, CPAP
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BRIEF SUMMARY
Current Knowledge/Study Rationale: Although mild obstructive sleep apnea is prevalent, the effects of the most common treatments for this population—continuous positive airway pressure and mandibular advancement device—on cardiovascular outcomes are still unknown.
Study Impact: To the best of our knowledge, this is the first randomized clinical trial that included continuous positive airway pressure, mandibular advancement device, and a no-treatment in a group composed only of patients with mild obstructive sleep apnea. The effects of the treatments were followed up for 12 months to better establish a long-term picture from 24-hour ambulatory blood pressure monitoring and peripheral arterial tonometry.

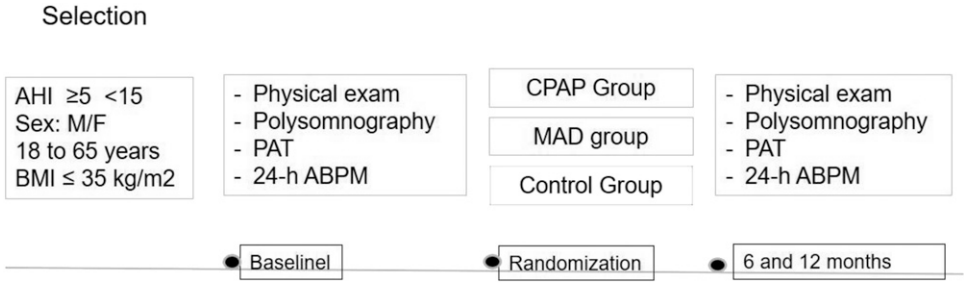
INTRODUCTION

Mild obstructive sleep apnea (OSA), defined as an hourly frequency of apneas or hypopneas of between 5 and 15 events per hour, is present in between 4% and 35% of the general population.[1] Estimates of the prevalence of mild OSA depend mainly on which of the diagnostic criteria of the American Academy of Sleep Medicine are used.[1] Most studies consider the apnea-hypopnea index (AHI) to be the main criterion for mild OSA.[1,2] In a systematic review, mild OSA was found not to be associated with cardiovascular outcomes such as hypertension, cardiac arrhythmias, cerebrovascular accidents, coronary artery disease, congestive heart failure, and mortality in transversal studies.[2] However, there is a lack of randomized clinical trials in respect of treatment for mild OSA,[2] and studies in high-risk populations that include individuals with conditions such as hypertension, nondipping pattern (the lack of a physiological mean blood pressure [BP] decline during sleep), and sleepiness are still needed.[2]

Continuous positive airway pressure (CPAP) is considered the gold standard treatment for OSA, but in respect of mild OSA, the use of a mandibular advancement device (MAD) has also been considered as a first-line treatment,[3] possibly due to its superior adherence.[4] In systematic reviews about OSA in general, CPAP and MAD have been shown to similarly reduce blood pressure,[4–6] and a few clinical trials have also reported that CPAP and MAD have similar positive effects on endothelial function.[7,8] However, it is unclear whether this is the case in respect of mild OSA.

Randomized clinical trials are still needed of CPAP and MAD in patients with mild OSA exclusively and including comorbidities. Previous studies evaluating the effects of mild

Figure 1—Study design.



OSA on cardiovascular outcomes were mainly retrospective,[9] had a small sample size,[10] included other OSA severity levels,[11–13] used other treatments as interventions,[14–17] or were population studies.[18] Considering the relative lack of clinical research on the use of CPAP or MAD in the treatment of mild OSA, associated or not with symptoms and comorbidities, we hypothesized that treatment with CPAP or MAD would improve blood pressure and endothelial function compared with no treatment after 1 year of follow-up. Therefore, the objective of this study was to evaluate and compare the effects of treatment with CPAP, MAD, and no treatment on mild OSA after 6 and 12 months, with 24-hour ambulatory blood pressure monitoring (ABPM) and peripheral arterial tonometry (PAT) (EndoPAT; Itamar Medical, Ltd., Caesarea, Israel) as the primary outcomes. We also sought to evaluate subgroups of patients according to the presence of sleepiness, hypertension, and nondipping pattern at baseline. We also assessed effective-treatment subgroups comprising patients who, at 6 or 12 months, had an AHI of < 5 events/h and adherence to treatment of more than 4 hours per night.

METHODS

Individuals with mild OSA (AHI ≥ 5 and < 15 events/h with symptoms) were selected from the sleep-disordered breathing ambulatory clinic of the Instituto do Sono (Sleep Institute), Sao Paulo, Brazil. This study was conducted in accordance with the amended Declaration of Helsinki, was approved by the Research Ethics Committee of UNIFESP (1300/11), and registered with ClinicalTrials.gov (NCT01461486). Results from the baseline cross-sectional analysis have already been reported.[19] All participants were instructed about the protocol, follow-up, and treatment before signing an informed consent form. At the end of the protocol, treatment was offered to all participants.

The inclusion criteria were: individuals of any sex, aged between 18 and 65 years with a body mass index of ≤ 35 kg/m^2. The exclusion criteria were: dental conditions unsatisfactory for use of MAD (active periodontal disease, caries, or insufficient teeth for appliance retention); nasal septum deviation grade III, and palatine tonsil hypertrophy grades III and IV; use of alcohol or psychoactive drugs; smoking; major neurological or psychiatric conditions; other sleep disorders, such as insomnia, restless legs syndrome (according to American Academy of Sleep Medicine, 2014),[20] central sleep apnea diagnosed by polysomnography (central AHI > 5 events/h); individuals doing shift work; and patients who had received previous OSA treatment.

This study was a randomized clinical trial. Participants received physical examination, polysomnography, PAT, and 24-hour ABPM, and completed the Epworth Sleepiness Scale. They were randomized into 3 groups: CPAP, MAD, and control (no-treatment). Simple randomization was used to allocate individuals to the groups. All participants were aware of the condition of the group into which they were randomized. After 6 months and 12 months, patient evaluations were repeated (**Figure 1**).

Groups

Volunteers in the CPAP group also received a second polysomnography for CPAP manual titration,[21] and the S8 Elite II ResMed (San Diego, CA) with humidifier was prescribed according to the optimal positive pressure found. Experienced respiratory therapists and sleep specialists monitored the CPAP patients at the first week, first month, third month, sixth month, and 12th month. Adherence to CPAP was systematically checked by data cards.

Volunteers in the MAD group received complete orthodontic documentation before treatment, and the Brazilian dental appliance (BRD) was used.[22] The MAD titration was made at 50% of maximal mandibular advancement, and progressive advancements of 1 mm per week were made until the maximum comfortable protrusion of mandibular advancement. The adherence to treatment was checked using a daily sleep diary in which the patient recorded the estimated number of hours of MAD use.

Volunteers from the control group attended a 15-minute presentation about OSA, sleep hygiene, food intake, and physical activity at a 3-month follow-up.

Measurements and definitions

The physical examination consisted of a calculation of body mass index [(weight (kg)/height^2 (m^2)] and neck and abdominal circumferences in centimeters.

The patients completed the Portuguese version of the Epworth Sleepiness Scale to evaluate their degree of subjective sleepiness,[23,24] and excessive sleepiness was considered if the Epworth Sleepiness Scale score was ≥ 10.

Full night polysomnography was performed using a digital polygraph (Embla N7000; Embla Systems, Inc., Broomfield, CO). The polysomnography recording included electroencephalogram (C3-A2, C4-A1, F3-A2, F4-A1, O2-A1, O1-A2), submental and tibialis electromyogram, bilateral electro-oculogram and electrocardiogram (modified derivative V1), nasal cannula and thermistor, plethysmography of chest and abdomen, pulse oximetry, position sensor placed over the region of the sternum bone, and a tracheal microphone to record snoring. For the scoring, the American Academy of Sleep Medicine guidelines were used, following the recommended rules for hypopnea (a drop higher or equal to 30% in nasal cannula associated with desaturation higher or equal to 4%).[25]

The 24-hour ABPM was performed using Dyna-MAPA equipment (Cardios Systems, São Paulo, Brazil). The equipment was installed on the nondominant arm, and all volunteers were instructed to keep a daily sleep and medication intake diary. Blood pressure was measured every 15 minutes during the day and every 30 minutes after 10 PM. The editing criteria used were those described by Casadei et al (1988),[26] which are reproducible editing criteria.[27] Arterial hypertension was defined as a mean 24-hour systolic blood pressure ≥ 130 mmHg and/or a mean 24-hour diastolic blood pressure ≥ 80 mmHg[28,29] and/or use of antihypertensive medication. Nondipping was classified as a mean nocturnal BP fall (systolic or diastolic) of < 10%, and dipping was defined as a fall of ≥ 10%.

Peripheral arterial tonometry captures the plethysmographic record of the arterial pulse with pneumatic "probes" installed on the index fingers.[30] Tests were performed in the morning following the system rules, and included 3 recordings of 5 minutes before, during, and after arm occlusion. During the occlusion period, the cuff was inflated to a suprasystolic pressure of 60 mmHg and/or above 200 mmHg for 5 minutes for a complete cessation of blood flow to the hand, verified by the absence of the PAT signal from the occluded arm. The software used an algorithm to produce the reactive hyperemia index, calculated as a ratio of the post- to pre-occlusion PAT amplitude of the tested arm divided by the post- to pre-occlusion ratio obtained in the control arm.[30] A reactive hyperemia index lower than 1.67 is considered indicative of endothelial dysfunction and has been associated with cardiovascular events.[31] The augmentation index (AIx) is an estimate of the peripheral wave reflections derived from the 2 systolic peaks of the baseline PAT waveform.[32] Negative values are obtained when the wave reflections occur before the systolic peak, and positive values when they occur after the systolic peak.[33] Populational studies have found a significant association between higher AIx PAT values and coronary artery disease, hypertension, and atherosclerosis.[34–36] EndoPAT is considered valid method to assess peripheral vascular endothelial function[30] and has good reproducibility.[37]

Mild OSA subgroups

The subgroups included individuals with the presence of a comorbidity at baseline (daytime sleepiness, nondipping pattern, or hypertension) or those who presented success in relation to AHI reduction associated with good adherence at follow-up. The daytime sleepiness subgroup comprised participants with Epworth Sleepiness Scale scores higher or equal to 10 at baseline. The hypertensive subgroup comprised participants using antihypertensive medication and/or having a mean 24-hour systolic blood pressure ≥ 130 mmHg and/or a mean 24-hour diastolic blood a pressure ≥ 80 mmHg at baseline. The nondipping pattern subgroup comprised participants with a mean nocturnal BP fall (systolic or diastolic) lower than 10% at baseline. The effectiveness therapy group comprised participants with adherence higher or equal to 4 hours per night on average, and an AHI lower than 5 events/h at 6 or 12 months.

Statistical analysis

The statistical analysis was performed using the SPSS program (version 18.0 for Windows). The descriptive analyses are shown with mean and standard deviation. A generalized linear mixed model was used for interaction analyses, using the participant as random effects. In the subanalyses, the participant was used as a random effect for the sleepiness group, and participant and age as random effects for the hypertension group and effective therapy group. For the other subanalyses, participant and age were used as random effects, and sex was used as a fixed effect for the nondipping group. An unstructured matrix of covariance was used for the total sample. The matrices of covariance of the subanalyses were chosen individually for each variable depending on the Akaike information criterion (unstructured, diagonal, or AR1). The Tukey test was used as the post-hoc test. The analyses of the subgroups included only those included in the 6- and 12-month follow-ups. The generalized linear mixed model was used for the intention-to-treat analyses.

RESULTS

Seventy-nine patients met the inclusion criteria, 31 were allocated to the CPAP group, 25 to the MAD group, and 23 to the control group.

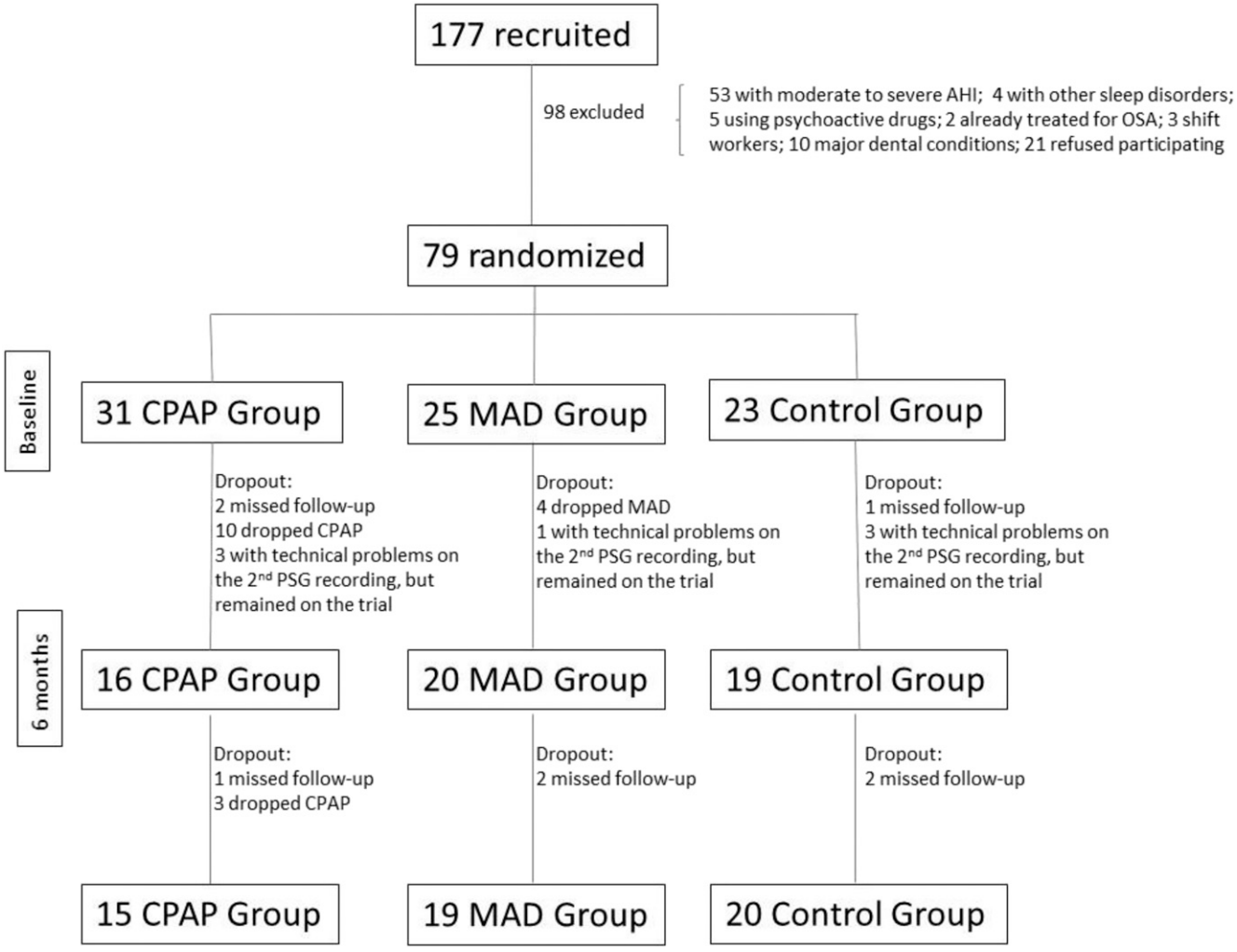
This study was a part of a larger study on mild OSA in which the wakefulness maintenance test was also administered to patients. This was a common reason given for dropping out as some participants were not able to spend an extra day in the sleep lab. Missing data at 6 months was due to the unavailability of the polysomnography laboratory; the patients continued in the protocol and were followed up again at 12 months. Finally, the level of treatment dropout due to the inability to adapt to treatment was also computed. The study flowchart is presented in **Figure 2**. Patients who discontinued MAD complained of hypersalivation and general discomfort. CPAP dropout patients complained of claustrophobia and discomfort.

Total sample

There were no significant differences in relation to the anthropometric measurements or medication intake among the groups. The MAD group had higher adherence in terms of the average hours of use per day and the number of patients who adhered to treatment compared to the CPAP group (**Table 1**).

CPAP decreased the arousal index from baseline to 6 months, but an increase was observed between 6 months and 12 months. At baseline, the CPAP group had a higher arousal index compared with the control; at 6 months, the CPAP group had a lower arousal index compared with control. The AHI of the MAD and CPAP groups decreased from baseline to 6 months, and from baseline to 12 months. The control group continued to

Figure 2—Flow chart of study participants.



have a higher AHI compared to the CPAP and MAD groups at 6 and 12 months (Table 1).

CPAP increased mean blood oxygen level (SpO_2) from baseline to 12 months; at 12 months, the CPAP group had a higher medium SpO_2 than the MAD and control groups. CPAP increased the minimum SpO_2 between baseline and 6 months, and baseline and 12 months. At 6 and 12 months the CPAP group had higher minimum SpO_2 than the control and MAD groups (Table 1).

There were no differences in cardiovascular outcomes between the protocols (Table 2) and in the intention-to-treat analyses (Table 3).

When analyzing the excessive sleepiness sample, the hypertensive sample, and the nondipping sample, there were no differences in 24-hour ABPM and PAT parameters between the groups throughout the entire protocol, but these subanalyses had lower power (**Table S1** and **Table S2** in the supplemental material).

Effective sample results

In relation to the effective-treatment subgroups, there was a difference in age among the groups, so age was also used as random effect. The CPAP group had decreased diastolic blood pressure, dipping between 6 months and 12 months (Cohen D: 0.49), and AIx adjusted to 75 beats per minute decreased from baseline to 12 months in both the MAD and CPAP effectiveness treatment groups, but this was not statistically significant in the Tukey post-hoc test and had a low effect size (Cohen D = 0.38) (Table 4).

DISCUSSION

CPAP or MAD treatment for individuals with mild OSA did not improve BP parameters and overall PAT variables after 6 months and 1 year in the total sample. However, AIx adjusted to 75 beats per minute presented a significant trend toward improvement, decreasing in both entire effective-treatment groups, with a low effect size; diastolic BP dipping decreased between 6 months and 12 months in the effective-treatment CPAP group but also with a low effect size.

CPAP and MAD were more effective than control, and CPAP was more effective than MAD for most polysomnographic parameters. In the control group, there was no increase in OSA after 12 months in terms of polysomnographic results.

Table 1—Total sample analyses.

Total Sample	Control			MAD			CPAP			*P*
	Baseline (n = 23)	6 Months (n = 19)	12 Months (n = 20)	Baseline (n = 25)	6 Months (n = 20)	12 Months (n = 19)	Baseline (n = 31)	6 Months (n = 16)	12 Months (n = 15)	
Sex (male)#	11(47.8%)	—	—	15 (60.0%)	—	—	17 (54.8%)	—	—	.69
Age (years)	46 ± 16	46 ± 16	47 ± 16	45 ± 15	44 ± 15	46 ± 15	49 ± 14	50 ± 14	50 ± 14	.24
BMI (kg/m^2)	28.0 ± 7.6	29.0 ± 7.7	28.1 ± 7.8	28.2 ± 7.2	28.2 ± 7.5	28.1 ± 7.6	28.7 ± 6.5	29.2 ± 7.2	29.3 ± 7.3	.20
NC (cm)	39.1 ± 5.1	39.0 ± 5.4	38.9 ± 6.6	39.7 ± 5.1	39.3 ± 5.4	39.6 ± 6.7	39 ± 5.3	40.0 ± 5.8	40.2 ± 7.1	.26
WC (cm)	95.2 ± 18.1	97.9 ± 18.4	95.2 ± 18.5	99.4 ± 18.1	99.4 ± 18.3	98.5 ± 18.7	100.1 ± 19.1	101.4 ± 19.5	102.1 ± 20.1	.54
ESS	12 ± 9	11 ± 10	11 ± 11	11 ± 9	10 ± 10	10 ± 11	10 ± 8	7 ± 11	7 ± 12	.46
Cholesterol MI#	3	1	1	4	2	3	4	3	4	.70
Hypertension MI#	8	6	7	5	6	6	11	8	6	.88
Diabetes MI#	1	1	1	1	2	2	3	2	4	.81
Adherence (h/d)	—	—	—	—	5.8 ± 2.8	5.7 ± 2.7	—	3.8 ± 3.0$^{\&}$	3.8 ± 3.4$^{\&}$	< .01
Nonadherence#	—	—	—	—	4.0	0.0	—	10.0$^{\&}$	3.0$^{\&}$	.02
SE (%)	83.4 ± 20.4	84.0 ± 14.7	88.5 ± 16.1	81.7 ± 19.6	84.7 ± 14.2	82.4 ± 16.3	79.4 ± 17.6	85.8 ± 15.1	85.2 ± 17.7	.06
N3 stage (%)	22.8 ± 15.4	21.6 ± 25.4	25.5 ± 39.6	21.1 ± 17.8	25.7 ± 24.7	31.6 ± 40.5	22.2 ± 13.3	25.0 ± 27.3	22.0 ± 45.3	.32
REM (%)	21.3 ± 11.9	22.2 ± 20.2	22.4 ± 21.5	21.5 ± 11.6	25.9 ± 19.7	27.4 ± 22.1	19.4 ± 10.3	24.5 ± 21.6	20.0 ± 24.8	.39
AI (events/h)	13.8 ± 13.9	15.8 ± 10.9	16.9 ± 13.0	15.4 ± 13.3	12.8 ± 10.6	12.5 ± 13.2	19.0 ± 12.0 $^{\alpha}$	9.7 ± 11.3*$^{\alpha}$	15.9 ± 14.6**	<.01
AHI (events/h)	9.3 ± 5.3	9.5 ± 9.3	11.6 ± 12.3	9.3 ± 5.2	4.2 ± 9.1*$^{\alpha}$	3.8 ± 12.6*$^{\alpha}$	10.0 ± 4.6	1.2 ± 9.9*$^{\alpha}$	1.7 ± 14.2*$^{\alpha}$	<.01
SpO_2 baseline (%)	95.4 ± 2.6	95.5 ± 2.7	95.2 ± 2.5	95.0 ± 2.5	95.1 ± 2.7	95.1 ± 2.6	95.6 ± 2.3	96.1 ± 2.9	96.3 ± 2.8	.54
SpO_2 mean (%)	94.7 ± 2.9	94.1 ± 5.3	94.6 ± 2.4	94.6 ± 2.8	94.5 ± 5.1	94.4 ± 2.4	94.4 ± 2.5	95.6 ± 5.5	95.9 ± 2.6*$^{\alpha\&}$	<.01
SpO_2 minimum (%)	84.6 ± 7.6	84.8 ± 8.6	83.5 ± 8.9	84.2 ± 7.3	86.4 ± 8.6	85.5 ± 9.0	85.3 ± 6.6	91.5 ± 9.0*$^{\alpha\&}$	90.8 ± 9.6*$^{\alpha\&}$	<.01
Time below 90% (min)	4.6 ± 20.6	10.4 ± 29.9	9.1 ± 20.1	4.6 ± 19.8	3.2 ± 30.2	2.2 ± 20.4	5.2 ± 17.8	0 ± 32.0	0.1 ± 21.5	.14

Values are mean and standard deviation, except as noted. #Absolute frequency. $^{\&}P \leq .05$ compared to MAD at same time. $^{\alpha}P \leq .05$ compared to control at same time. *$P \leq .05$ compared to baseline in each group. **$P \leq 0.05$ compared to 6 months in each group. AHI = apnea-hypopnea index, AI = arousal index, BMI = body mass index, ESS = Epworth Sleepiness Scale, MI = medication intake, NC = neck circumference, RDI = respiratory disturbance index, SE = sleep efficiency, WC = waist circumference.

MAD had higher adherence than CPAP in terms of the average hours of use of treatment per day, as well as in respect to the number of patients who adhered to the treatment compared to CPAP. Our results are similar to the previous literature in regard to OSA in general. In a meta-analysis, CPAP was shown to be superior to MAD in improving AHI and minimum SpO_2 in OSA patients, regardless of severity level.[4,38] However, in respect to adherence, MAD showed better results, as in our results.[4] In the mild OSA group, an estimated 10% to 17% of the individuals accepted CPAP use,[39,40] with a dropout rate of 61%.[39,40] Studies have shown use of CPAP of 4.1–4.9 hours/night in a mild OSA sample, with 55% of subjects using it for over 6 hours/night.[39,40] Higher dropout rates in trials of CPAP in cases of mild OSA are expected, as we found in our study, although it was a little lower than in some of the studies cited. It is worth mentioning that no study, to our knowledge, has investigated the use of MAD in an exclusive sample of mild OSA patients. Due to the mild character of the disorder, lower rates of adherence were expected, but adherence to treatment is critical when evaluating cardiovascular outcomes.

In our sample of patients with mild OSA, 24-hour AMBP parameters did not change between pre- and post-treatment, compared to controls or between the CPAP and MAD groups. Systematic reviews about OSA in general have shown improvements in blood pressure in both CPAP and MAD treatments when they did pre- and post-treatment comparisons.[4,5,41] Reviews including studies comparing MAD with a control group have shown conflicting results; one study showed an improvement compared to control, but the other did not.[5,6] Regarding CPAP, all studies about OSA showed better results in terms of BP outcomes compared with controls,[5,6,42] and similar effects when compared with MAD.[4–6] Th present study is, to the best of our knowledge, the first to compare CPAP and MAD with a control using 24-hour AMBP in a sample of exclusively mild OSA patients.

In the CPAP effective-treatment group, we found a significant decrease in diastolic BP, dipping between 6 and 12 months (18.5% to 12.7%) but with a low effect size. These findings may have no clinical relevance because the percentage values of diastolic BP dipping remained normal, ie, higher than 10% throughout the protocol, and because of its low effect size.

In respect of endothelial function assessed by PAT, we found a trend toward improvement in the augmentation index between baseline and 12 months for the entire effective-treatment subgroups but with low clinical relevance (low effect size). The result for AIx adjusted to 75 beats per minute was intriguing, since the generalized linear mixed model showed significance in respect of the augmentation index adjusted to

Table 2—Total sample comparisons.

Total Sample	Control			MAD			CPAP			*P*
	Baseline (n = 23)	6 Months (n = 19)	12 Months (n = 20)	Baseline (n = 25)	6 Months (n = 20)	12 Months (n = 19)	Baseline (n = 31)	6 Months (n = 16)	12 Months (n = 15)	
RHI	1.9 ± 1.0	2.0 ± 1.1	1.9 ± 1.2	2.04 ± 1.0	2.0 ± 1.1	2.2 ± 1.3	2.1 ± 0.9	2.1 ± 1.2	1.9 ± 1.4	.49
Heart rate (bpm)	68.2 ± 18.0	69.8 ± 19.0	69.6 ± 19.3	68.0 ± 7.3	68.3 ± 18.5	69.4 ± 19.7	67.3 ± 15.5	68.2 ± 19.2	69.6 ± 20.6	.98
AIx (%)	9.7 ± 33.3	8.1 ± 32.1	10.0 ± 29.2	8.4 ± 32.0	7.8 ± 31.3	4.5 ± 29.6	12.4 ± 28.7	10.8 ± 31.9	4.1 ± 30.4	.26
AIx_75 (%)	5.5 ± 32.4	5.0 ± 31.6	6.4 ± 28.3	4.0 ± 31.1	3.6 ± 30.8	0.8 ± 28.3	7.6 ± 27.9	6.7 ± 31.0	0.8 ± 28.3	.23
Total SBP (mm Hg)	122.2 ± 21.9	123.6 ± 25.0	122.3 ± 23.8	121.4 ± 21.0	122.5 ± 24.4	121.2 ± 23.8	118.5 ± 18.8	120.2 ± 25.0	120.2 ± 23.7	.97
Total DBP (mm Hg)	75.4 ± 15.6	75.7 ± 17.0	75.0 ± 17.0	74.3 ± 14.9	74.4 ± 16.5	74.3 ± 16.9	72.1 ± 13.4	73.8 ± 16.6	72.3 ± 16.7	.92
Awake SBP (mm Hg)	126.6 ± 22.0	128.0 ± 26.4	126.1 ± 24.8	125.8 ± 21.1	126.6 ± 25.7	125.2 ± 24.9	122.2 ± 18.9	124.0 ± 26.6	123.1 ± 25.0	.99
Awake DBP (mmHg)	78.3 ± 15.7	78.8 ± 17.6	77.5 ± 17.6	77.3 ± 15.1	77.0 ± 17.1	76.7 ± 17.7	74.5 ± 13.5	76.7 ± 17.4	74.6 ± 17.6	.84
Sleep SBP (mm Hg)	108.7 ± 25.9	111.0 ± 23.7	111.3 ± 25.3	110.8 ± 25.3	111.7 ± 23.2	111.2 ± 25.7	107.1 ± 22.3	108.1 ± 23.7	110.0 ± 25.6	.92
Sleep DBP (mm Hg)	65.8 ± 17.1	66.9 ± 16.0	67.7 ± 17.4	66.8 ± 16.8	66.9 ± 15.8	67.9 ± 17.6	64.9 ± 14.8	64.9 ± 15.9	64.9 ± 17.4	.92
SBP dipping (mmHg)	14.2 ± 13.3	13.4 ± 13.2	11.6 ± 14.1	12.7 ± 13.0	12.4 ± 12.9	12.0 ± 14.7	12.3 ± 11.4	12.2 ± 13.7	10.1 ± 15.5	.94
DBP dipping (mmHg)	15.7 ± 15.6	15.1 ± 15.1	12.4 ± 15.8	14.2 ± 15.2	13.7 ± 14.8	12.2 ± 16.4	13.1 ± 13.4	14.6 ± 15.8	12.0 ± 17.5	.88
Nondipping#	7	6	9	8	9	9	12	6	9	.96

Values are mean and standard deviation, except as noted. The effect size for AIx_75 in MAD and CPAP pre- and post-treat were 0.14 and 0.26, respectively. #Absolute frequency. $P \leq .05$ interaction (time*group). AIx = augmentation index, AIx_75 = AIx adjusted to 75 bpm, DBP = diastolic blood pressure, GLMM = generalized linear mixed model, RHI = reactive hyperemia index, SBP = systolic blood pressure.

Table 3—Intention-to-treat analyses.

Intention to Treat	Control			MAD			CPAP			*P*
	Baseline (n = 23)	6 Months (n = 23)	12 Months (n = 23)	Baseline (n = 25)	6 Months (n = 25)	12 Months (n = 25)	Baseline (n = 31)	6 Months (n = 31)	12 Months (n = 31)	
Sex (male)#	11	—	—	15	—	—	17	—	—	.35
Age (years)	47.4 ± 12.9	—	—	46.1 ± 12.4	—	—	48.1 ± 11.1	—	—	.07
BMI (kg/m^2)	28.0 ± 6.9	27.8 ± 6.7	28.3 ± 7.2	28.2 ± 6.6	28.6 ± 6.4	28.4 ± 6.9	28.7 ± 5.9	29.1 ± 5.7	29.3 ± 6.2	.85
Cholesterol MI#	3	2	1	4	3	4	4	7	7	.18
Hypertension MI#	8	8	7	5	9	7	11	16	11	.29
Diabetes MI#	1	1	1	1	2	2	3	7	8	.14
RHI	1.9 ± 1.0	1.9 ± 0.9	1.9 ± 1.2	2.0 ± 1.0	2.0 ± 0.9	2.3 ± 1.2	2.1 ± 0.9	2.0 ± 0.8	1.8 ± 1.0	.23
Heart rate (bpm)	68.2 ± 18.0	68.9 ± 14.8	70.4 ± 14.8	68 ±.17.3	69.2 ± 14.2	69.3 ± 14.2	67.3 ± 15.5	68.5 ± 12.8	69.9 ± 12.8	.97
AIx (%)	9.7 ± 33.3	10.2 ± 26.6	11.5 ± 23.9	8.4 ± 32.0	9.2 ± 25.5	7.4 ± 22.9	12.4 ± 28.7	10.6 ± 22.9	4.6 ± 20.6	.12
AIx_75 (%)	5.5 ± 32.4	6.5 ± 26.7	8.5 ± 23.0	4.0 ± 31.1	6.0 ± 25.6	2.6 ± 22.1	7.6 ± 27.9	6.1 ± 23.0	1.2 ± 19.8	.08
Total SBP (mm Hg)	122.2 ± 21.9	122.9 ± 19.4	123.3 ± 18.9	121.4 ± 21.0	124.1 ± 18.6	121.9 ± 18.1	118.5 ± 18.8	120.5 ± 16.7	121.5 ± 16.3	.65
Total DBP (mm Hg)	75.4 ± 15.6	75.8 ± 13.8	75.5 ± 14.1	74.3 ± 14.9	76.0 ± 13.2	74.5 ± 13.5	72.1 ± 13.4	74.1 ± 11.9	72.2 ± 12.1	.90
Awake SBP (mm Hg)	126.6 ± 22.0	127.9 ± 20.5	126.8 ± 20.2	125.8 ± 21.1	128.2 ± 19.6	125.3 ± 19.4	122.2 ± 18.9	124.2 ± 17.6	123.8 ± 17.4	.89
Awake DBP (mm Hg)	78.3 ± 15.7	79.5 ± 14.3	78.3 ± 14.8	77.3 ± 15.1	78.0 ± 13.7	76.7 ± 14.2	74.5 ± 13.5	76.5 ± 12.3	74.8 ± 12.8	.98
Sleep SBP (mm Hg)	108.7 ± 25.7	110.5 ± 19.1	112.5 ± 20.0	110.7 ± 24.6	112.7 ± 18.4	111.5 ± 19.1	107.1 ± 22.1	109.6 ± 16.5	111 ± 17.2	.76
Sleep DBP (mm Hg)	65.8 ± 17.0	66.9 ± 13.0	67.8 ± 14.7	66.6 ± 16.3	67.6 ± 12.5	67.2 ± 14.1	64.9 ± 14.7	65.9 ± 11.2	65.1 ± 12.7	.81
SBP dipping (mm Hg)	14.2 ± 13.2	13.8 ± 10.5	11.2 ± 11.2	12.6 ± 12.7	12.0 ± 10.1	11.5 ± 10.7	12.3 ± 11.4	12.2 ± 9.1	10.7 ± 9.6	.88
DBP dipping (mm Hg)	15.7 ± 15.5	15.3 ± 12.2	12.2 ± 12.7	14.3 ± 14.8	13.9 ± 11.7	12.0 ± 12.2	13.1 ± 13.3	13.9 ± 10.5	11.6 ± 11.0	.91
Nondipping#	7	9	12	9	13	14	12	8	16	.46

Values are mean and standard deviation, except as noted. #Absolute frequency. *$P \leq .05$ interaction (time*group). The effect size for AIx_75 in MAD and CPAP pre and post treat were 0.07 and 0.26, respectively. AIx = augmentation index, AIx_75 = AIx adjusted to 75 bpm, BMI = body mass index, DBP = diastolic blood pressure, GLMM = generalized linear mixed model, MI = medication intake, RHI = reactive hyperemia index, SBP = systolic blood pressure.

75 beats per minute, but Tukey's post-hoc did not. The low effect size reinforced the negative interpretation of this result, showing low clinical relevance. In systematic reviews, CPAP has been shown to be effective in improving arterial stiffness and flow-mediated dilatation but not pulse wave velocity in OSA patients with any level of OSA severity.[43–46] MAD showed

Table 4—Analyses of effective sample.

Effective Sample	MAD			CPAP			Time	Interaction
	Baseline (n = 13)	6 Month (n = 12)	12 Months (n = 11)	Baseline (n = 10)	6 Months (n = 9)	12 Months (n = 10)		
Sex (male)#	9	—	—	8	—	—	—	0.33
Age (years)	44.1 ± 9.9	—	—	49.0 ± 11.3	—	—	—	0.01
BMI (kg/m^2)	27.5 ± 4.9	27.4 ± 5.7	26.9 ± 6.2	28.7 ± 5.6	29.5 ± 6.6	29.2 ± 6.5	0.95	0.90
Cholesterol MI#	2	1	2	1	1	1	ISS	
Hypertension MI#	3	4	4	4	4	4	0.69	0.69
Diabetes MI#	0	1	1	0	0	1	ISS	
RHI	2.0 ± 0.8	2.0 ± 0.8	2.1 ± 0.6	2.1 ± 0.9	1.9 ± 1.0	1.8 ± 0.6	0.75	0.35
Heart rate (bpm)	69.8 ± 13.1	70.1 ± 13.3	70.0 ± 13.6	68.4 ± 15.9	67 ± 16.3	70.4 ± 16	0.65	0.63
AIx (%)	4.6 ± 25.2	3.0 ± 19.1	0.2 ± 22.1	6.9 ± 30.6	3.0 ± 24.0	–2.7 ± 26.4)	0.07	0.70
AIx_75 (%)	3.0 ± 15.1	6.3 ± 14.4	–3.0 ± 15.1)*	3.3 ± 8.4	(–6.3 ± 14.4)	(–3.3 ± 8.4)*	0.05	0.66
SBP total (mm Hg)	116.5 ± 14.2	118.4 ± 14.5	115.9 ± 14.6	116.9 ± 17.7	119.9 ± 18.0	116.9 ± 17.7	0.38	0.68
DBP total (mm Hg)	71.3 ± 9.5	71.6 ± 9.7	70.3 ± 9.8	71.5 ± 11.7	73.9 ± 11.9	71.5 ± 11.7	0.35	0.70
SBP awake (mm Hg)	120.7 ± 14.5	123.1 ± 14.9	121.0 ± 15.0	120.5 ± 17.9	124.4 ± 18.3	120.0 ± 17.9	0.29	0.88
DBP awake (mm Hg)	74.2 ± 9.3	74.4 ± 9.6	73.3 ± 9.7	74.0 ± 11.5	77.2 ± 11.7	73.9 ± 11.5	0.33	0.60
SBP sleep (mm Hg)	104.7 ± 16.4	106.6 ± 16.7	103.9 ± 17.1	105.1 ± 20.3	105.0 ± 20.7	106.2 ± 20.3	0.91	0.67
DBP sleep (mm Hg)	62.5 ± 11.4	64.0 ± 11.3	62.5 ± 11.9	64.1 ± 14.2	62.9 ± 14.3	64 ± 14.2	0.99	0.57
SBP dipping (%)	12.8 ± 8.9	13.1 ± 6.7	13.7 ± 10.6	12.9 ± 10.5	15.3 ± 8.1	11.1 ± 11.5	0.42	0.31
DBP dipping (%)	15.3 ± 12.5	14.2 ± 8.5	14.4 ± 11.3	13.3 ± 15.0	18.5 ± 10.6	12.7 ± 13.1**	0.07	0.03
Nondipping#	5	6	5	3	2	6	0.24	0.19

Values are mean and standard deviation, except as noted. #Absolute frequency. *$P \leq .05$ compared to baseline in both groups associated; **$P \leq .05$ compared to 6 months in each group. AIx = augmentation index, AIx_75 = AIx adjusted to 75 bpm, DBP = diastolic blood pressure, GLMM = generalized linear mixed model, ISS = insufficient sample for statistics, SBP = systolic blood pressure, RHI = reactive hyperemia index.

the same endothelial function improvement as CPAP in clinical trials when compared to controls in studies including patients with an AHI > 15 events/h.[7,8,47] A meta-analysis of MAD and endothelial function was inconclusive because of the paucity of studies about MAD.[5] Studies about treatment with CPAP or MAD and the effects on blood pressure or studies utilizing PAT have included a range of OSA severity, and no study, to the best of our knowledge, has analyzed PAT and BP in a group of patients with mild OSA. This current study is also the first study to use PAT to investigate endothelial function in mild OSA. Endothelial function is one of the first cardiovascular alterations in OSA, and its evaluation is therefore important in mild OSA.

We analyzed 3 subgroups with comorbid conditions at baseline: sleepiness, hypertension, and nondipping pattern. The subanalyses that have low power are shown in the **supplemental material**. This lack of power is a limitation of the results, but the results still may have implications for future studies. We examined sleepiness because when associated with OSA it may be related to cardiovascular outcomes.[48] We acknowledge that the subsamples of hypertensive and nondipping BP are patients perhaps more prone to respond to treatment, as they had already presented cardiovascular alterations. Indeed, in hypertension and resistant hypertension associated with OSA, CPAP has been more effective in reducing blood pressure in moderate to severe OSA than OSA with normal BP.[49,50] Similarly, CPAP has also been associated with an improvement in nocturnal BP dipping in moderate to severe OSA.[51–53] However, in this subgroup of comorbid mild OSA patients, we failed to show any significant improvement in BP and endothelial functions. The analyses of the effective-treatment groups in the sample were carried out because in our mild OSA study 42% of CPAP users did not adapt to treatment, and those who did used it on average for less than 4 hours per night, and because some of the patients in the MAD group did not reach an AHI of < 5 events/h. Bratton et al (2015) showed that increased CPAP of 1 hour per night was associated with an additional reduction in diastolic BP and systolic BP in a systematic review of studies of all degrees of OSA.[6] Another study showed improvement in flow-mediated dilation only in a MAD success group (AHI of < 5 events/h or a reduction in AHI if 50% or more) after 2 months in severe OSA patients.[54]

In a study in which the sample was exclusively of mild OSA patients, Duchna et al (2006) showed an improvement in bradykinin vasodilatation after 3 months of CPAP in 7 individuals with good adherence (mean of 5.8 ± 1.3 hours per night).[10] However, 30% of the patients in the study dropped out of CPAP treatment.[10] Jaimchariyatam, Rodriguez, and Budur (2010) showed a decrease in clinical blood pressure compared to a control group in a retrospective study in mild OSA associated with sleepiness after 2.8 years with good adherence to CPAP (more than 4 h/d and > 5 d/wk).[9] In our study, independently of the groups, the effective-treatment group showed a trend to an improved augmentation index adjusted for 75 beats per minute,

but with low clinical relevance because of the small effect size. There is a paucity of studies reporting the effect of OSA treatment on AIx, and no threshold values have been described. We highlight the importance of AIx, since population studies show that high AIx is associated with a higher frequency of coronary artery disease.[36] A previous study by our group found an association between AIx and dipping patterns, but not with AHIs, in a cross-sectional controlled study including the same baseline mild OSA sample.[19]

Another study about the treatment of mild OSA used a low-calorie diet as an intervention and showed an improvement in flow-mediated dilatation, but it was not statistically different compared to the control,[14] and there was no difference in blood pressure.[13–15,17] A study using upper airway surgery in a sample of patients with hypertension associated with mild OSA showed improvement in mean 24-hour systolic BP, daytime diastolic blood pressure, nocturnal systolic blood pressure, and dipping pattern compared to their pretreatment condition.[16] A prospective observational cohort study, which did a subanalysis with a mild OSA subgroup, found no differences between patients using CPAP and those who declined CPAP or did not adhere to treatment in relation to incidence of hypertension.[18]

There has been some discussion of whether mild OSA should be treated. In this respect, our study failed to show any relevant blood pressure or endothelial function impairments in this population, or any significant effect of CPAP or MAD at the 1-year follow-up. In addition, the control group did not get worse compared with baseline. More studies about mild OSA with larger samples are required to confirm these results.

The strong points of this study are that it was a randomized clinical trial, which enabled us to confirm the finding using a control group. It used 2 of the most common treatments for mild OSA (CPAP and MAD) and will therefore be of wide interest. The sample comprised only patients with mild OSA, meaning that, unlike in many other studies which included all types of OSA, we were able to focus on this particular and common type of OSA. The effects of the treatments were followed up for 12 months so that a better picture of longer-term effects could be established. In addition, we used 24-hour ABPM, the gold standard to measure blood pressure, and PAT, a noninvasive method of assessing of endothelial function. The limitations of this study are: the relatively low number of subjects in the hypertensive and nondipping pattern subgroups, the lack of assessment of inflammation markers, and the absence of groups in the sample with resistant hypertension or other cardiovascular diseases.

CONCLUSIONS

In conclusion, the treatment of mild OSA with CPAP or MAD did not improve blood pressure or endothelial function after 6 months or 1 year, even when treatment effectiveness was analyzed.

ABBREVIATIONS

ABPM, ambulatory blood pressure monitoring
AHI, apnea-hypopnea index
AIx, augmentation index
BP, blood pressure
CPAP, continuous positive airway pressure
MAD, mandibular advancement device
OSA, mild obstructive sleep apnea
PAT, peripheral arterial tonometry
SpO_2, blood oxygen level

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Address correspondence to: Dalva Poyares, MD, PhD, Departamento de Psicobiologia, Universidade Federal de Sao Paulo, Rua Napoleao de Barros, 925, Vila Clementino, CEP 04021-002, São Paulo, Brasil; Email: poyares@unifesp.br

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