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Chest 2007;131;740-749
DOI 10.1378/chest.06-0965

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The Effects of 1-Year Treatment With a Herbst Mandibular Advancement Splint on Obstructive Sleep Apnea, Oxidative Stress, and Endothelial Function*

Sarah Itzhaki, MSc; Hezi Dorchin, DDS; Glenn Clark, DDS; Lena Lavie, PhD; Peretz Lavie, PhD; and Giora Pillar, MD, PhD

Background: Obstructive sleep apnea (OSA) is associated with endothelial dysfunction. In the current study, we assessed the effect of long-term modified Herbst mandibular advancement splint (MAS) treatment on OSA, oxidative stress markers, and on endothelial function (EF).

Methods: A total of 16 subjects participated (11 men and 5 women; mean [± SD] age, 54.0 ± 8.3 years; mean body mass index, 28.0 ± 3.1 kg/m²), 12 of whom completed the 1-year evaluation. Apnea severity, levels of oxidative stress markers, and EF were assessed after 3 months and 1 year of receiving treatment. For comparison, 6 untreated patients underwent two evaluations 9 months apart, and 10 non-OSA individuals were assessed once as a reference group. The results are presented as the mean ± SD.

Results: The mean apnea-hypopnea index (AHI) decreased significantly from 29.7 ± 18.5 events/h before treatment to 17.7 ± 11.1 events/h after 3 months of treatment and 19.6 ± 11.5 events/h after 1 year of treatment (p < 0.005 for both). The mean Epworth sleepiness scale score decreased significantly from 12.4 ± 6.0 before treatment to 10.2 ± 6.6 after 3 months of treatment and 7.8 ± 3.8 after 1 year of treatment (p < 0.001 for both). The mean EF improved significantly from 1.77 ± 0.4 before treatment to 2.1 ± 0.4 after 3 months of treatment (p < 0.05) and 2.0 ± 0.3 after 1 year of treatment (p = 0.055), which were similar to the values of the reference group. Thiobarbituric acid-reactive substance (TBARS) levels decreased from 18.8 ± 6.2 nmol malondialdehyde (MDA)/mL before treatment to 15.8 ± 3.9 MDA/mL after 3 months of treatment (p = 0.09) and 15.5 ± 3.2 nmol MDA/mL after 1 year of treatment (p < 0.05). There was a correlation between the improvement in AHI and in EF or TBARS levels (r = 0.55; p = 0.05). The untreated control group remained unchanged.

Conclusions: The Herbst MAS may be a moderately effective long-term treatment for patients with OSA. EF improved to levels that were not significantly different than reference levels, even though apneic events were not completely eliminated. We think that these data are encouraging and that they justify the performance of larger randomized controlled studies.

(CHEST 2007; 131:740–749)

Key words: endothelial dysfunction; obstructive sleep apnea; oral appliance; oxidative stress

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; ED = endothelial dysfunction; EF = endothelial function; ESS = Epworth sleepiness scale; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAS = mandibular advancement splint; MDA = malondialdehyde; nCPAP = nasal continuous positive airway pressure; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; P = peroxide; RH-PAT = reactive hyperemia peripheral arterial tonometry; SDB = sleep-disordered breathing; TBARS = thiobarbituric acid-reactive substance; WP100 = Watch-PAT 100

Obstructive sleep apnea (OSA) is associated with increased cardiovascular morbidity and mortality.1–6 Some more recent studies have demonstrated that OSA patients who are free from cardiovascular comorbidity show early signs of atherosclerosis, as exhibited by endothelial dysfunction (ED), increased intima-media thickness, and decreased carotid diameter,7–14 as well as increased levels of biomarkers of...
oxidative stress and inflammation.15–20 The above-mentioned early signs of atherosclerosis (ie, oxidative stress and inflammation) were significantly correlated with determinants of OSA severity (eg, apnea-hypopnea index [AHI], and oxygen saturation).8,10,12–15,17,19 Currently, the most commonly used treatment for OSA is the nasal continuous positive airway pressure (nCPAP) device. Successful nCPAP treatment has reversed ED in OSA patients,8,10,21 reduced BP,22–24 ameliorated oxidative stress,15,18–20 and decreased cardiovascular morbidity and mortality in patients with severe OSA who were followed-up for 10 years.25 Compliance with nCPAP treatment, however, is problematic. nCPAP usage is initially declined by 5 to 50% of eligible patients, and 12 to 25% of the patients who start nCPAP treatment discontinue treatment within 3 years.26

A mandibular advancement splint (MAS) is an alternative treatment for patients with mild or moderate OSA. Although somewhat less effective (with residual OSA of 20 to 50%), these devices are more tolerable than nCPAP.27–30 By protruding the mandible forward, the tongue and soft palate are anteriorly shifted, with consequent opening of the oropharyngeal airway space. This reduces the pharyngeal collapsibility, resulting in reduced OSA severity.28–32 To date, most studies have evaluated the effects of MAS on sleep apnea severity. Only two studies33,34 have reported a reduction in BP in patients with OSA who were treated with MAS. There are no data regarding the effects of MAS on cardiovascular risk factors such as endothelial function (EF) and/or levels of oxidative stress biomarkers. Therefore, we planned this study to prospectively follow-up symptomatic OSA patients who had been treated with a Herbst MAS for 1 year, to assess their OSA indexes as well as changes in cardiovascular risk factors. We aimed to assess whether MAS treatment reduces sleep-disordered breathing (SDB), ED, and levels of oxidative stress markers, and thus can offer an alternative treatment for otherwise untreated OSA patients.

**Materials and Methods**

**Subjects**

Patients were screened into the study from a pool of patients in whom OSA had been diagnosed by polysomnography and who had declined the use of nCPAP for lack of adjustment (the main stated reasons for refusal were claustrophobia, inconvenience, cost, nasal discomfort, and unappealing nature). Other inclusion criteria were an AHI of ≥ 10 and complaints of subjective sleepiness, forward jaw protrusion ability of at least 7 mm, and healthy teeth without dentures or movement. Exclusion criteria consisted of abnormal dentition, temporomandibular joint disease, alcohol abuse, and use of narcotic or psychiatric drugs. Twenty-five patients with OSA were screened for the study, but 6 patients did not participate. Thus, 19 patients (who had declined nCPAP) were enrolled into the study. None of the patients had substantial periodontal disease, more than two missing teeth per quadrant, or evidence of a substantial temporomandibular disorder. A medical history was taken, dental status was determined, and a physical examination was conducted at the baseline visit. Six other patients served as untreated control subjects and were measured twice 9 months apart. Three patients were dropouts from the current study, and three patients were recruited as control subjects from a different project. These untreated individuals served as control subjects for the follow-up on MAS treatment. In addition, another 10 individuals with an AHI of < 10, who were matched for age, gender, BMI, and comorbidities, served as a reference group. This was an opportunistic control group that was composed of seven control subjects who were recruited for a different study, and three patients who had been studied in the sleep laboratory for complaints of snoring, but in whom OSA had been excluded based on an AHI of < 10 and the absence of daytime sleepiness. They were assessed only once, to compare the 1-year values of the study group with those of non-OSA individuals. The study protocol was approved by the ethics committee of Rambam Medical Center, and all participants gave their written informed consent prior to participation.

**Procedure**

**Study Group:** Patients were initially screened for dental status as per the inclusion criteria (Fig 1). Enrolled patients underwent a baseline evaluation to screen for eligibility and to obtain informed consent. The participants were then assessed by polysomnography (Watch-PAT 100 [WP100]; Itamar-Medical Ltd; Caesarea, Israel) and Epworth sleepiness scale (ESS). Blood samples were taken and reactive hyperemia peripheral arterial tonometry (RH-PAT) were assessed in the morning after polysomnography. A cast model was made, and the MAS was fabricated and adjusted until the maximum allowable protrusion was obtained (75% of maximum). After each fitting, an ambulatory sleep study was performed (WP100) to assess efficacy, which was determined as a change in AHI, 4% oxygen desaturation index (ODI), and subjective reports of snoring. If no improvement (ie, a reduction of at least 20% in AHI and/or subjective...
improvement in vigilance) was reached, the patient was withdrawn from the study by mutual consent. In order to document the short-term effect of treatment for each patient after adjusting to sleeping with the device, an ambulatory sleep study (using the WP100) was conducted, blood samples were taken, and ESS was evaluated after 2 weeks of use. Success was defined as subjective satisfaction and OSA/snoring reduction. No further adjustments were performed after these procedures. The 3-month reevaluation included simultaneous polysomnography and WP100 studies (in the sleep laboratory), a physical examination, obtaining of blood samples, ESS score determination, and RH-PAT (EF) testing. The long-term effect of treatment was evaluated at the

Figure 1. A schematic description of the study design and procedures, along with the number of participants in each stage. Initially, 25 patients were screened for the study. Nineteen patients (all declined treatment with continuous positive airway pressure) passed the screening and were enrolled in the study. In three patients, no improvement (ie, reduction of at least 20% in AHI and/or subjective improvement in vigilance) was reached during the MAS adjustment phase, and they were withdrawn from the study by mutual consent. All of the remaining 16 patients were treated for 3 months and completed the reevaluation tests. Twelve patients also completed the 1-year assessment (only the in-home study, with and without the MAS, 5 days apart). PSG = polysomnography; endoPAT = measuring equipment.
1-year follow-up, when two WP100 studies were performed at the patients' homes 5 nights apart, one without the MAS and one with the MAS. In addition, a physical examination was conducted, blood samples were obtained, ESS score was determined, and RH-PAT test was assessed.

**Control Groups**

*Follow-up Control Group:* Patients in this group were similar to study group patients (all were noncompliant with nCPAP). Those patients were evaluated twice with a mean time gap of 9 months between evaluations, and they were not treated during this period (by their own choice; this was not enforced by the study protocol). Evaluation consisted of an in-laboratory sleep study, morning blood sample collections, and RH-PAT evaluations.

*Reference Group:* Ten subjects, 7 of whom were control subjects and 3 of whom had been referred to the sleep laboratory with snoring underwent polysomnography, which revealed no OSA. In all subjects, the AHI was < 10 events/h and assessments were performed once. These assessments consisted of the same measurements as those conducted in the study group. The 10 subjects were chosen to match the study group in terms of gender, age, body mass index (BMI), and comorbidities, thus serving as a reference group for monitoring the magnitude of the treatment effect.

**The Herbst MAS**

An impression of the teeth was taken, and a dental cast was fabricated for construction of the custom made MAS (Smile Foundation Laboratory; Chatsworth, CA). Upper (maxillary) and lower (mandibular) acrylic appliances were constructed that could be clipped onto the two dental arches. Those arches were connected, and the protrusive position was set and adjusted by alteration of the Herbst attachments (rod and sleeve) on each side of the jaw. The two portions of the appliance were held together with elastic bands. The appliance allowed for opening, protrusion and some side-to-side movement. The original manufacturers of the oral appliance (WP100) and the measuring equipment (Endo-PAT) had no access to or control over the patients being studied, had no effect on or control of the data, the results of the study, or the decision to publish it.

**Sleep Assessment**

Standard full-night, in-laboratory polysomnography (throughout referred to as polysomnography) was performed using a computerized recording system (Embla; Flaga Medical; Reykjavik, Iceland) with the following channels: EEG; electrooculogram; chin electromyogram; arterial oxygen saturation (finger oximeter); nasal/oral airflow (pressure cannula); ECG; chest and abdominal wall motion (piezo electrodes); bilateral tibialis electromyogram; and body position. The polysomnography recordings were scored manually for sleep stages and for respiratory disturbance indexes.

Ambulatory sleep studies utilized the WP100 system, which has been previously described in detail. It records pulse oximetry, PAT, actigraphy, and pulse rate. This method has been previously shown to accurately quantify sleep/wake states and respiratory disturbance indexes.

**RH-PAT Test**

The finger plethysmographic methodology, which was used to measure the response to hyperemia of the peripheral arterial tone induced by brachial artery occlusion as an index of endothelial functioning, has been described in detail previously. Briefly, the Endo-PAT (Itamar Medical Ltd) device consists of two finger-mounted probes that measure the pulse wave amplitude in the test and control fingers. The test consists of the following three stages: 5-min baseline stage; 5-min occlusion stage; and 5-min postocclusion recording stage. The RH-PAT index is a ratio that is calculated as the average amplitude of the PAT signal after occlusion divided by the average amplitude before occlusion, normalized to the concurrent signal from the nonischemic hand.

In order to adjust for the effect of time of day on PAT, all tests were performed between 10:00 and 10:30 AM. Subjects were instructed to avoid using vasoactive drugs for 24 h before the assessment, to fast, and to refrain from smoking for a minimum of 4 h before the examination.

**Lipid Peroxidation Assays**

Lipid peroxidation for thiobarbituric acid-reactive substance (TBARS) levels and peroxide (PD) assays has been described in detail previously. For TBARS levels, data are expressed in nanomoles of malondialdehyde (MDA) per milliliter of plasma. For PD, data are expressed in nanomoles of PD per milliliter of plasma. The methodology of paraoxonase 1-arylesterase assay has also been previously described in detail, and the data are presented in units of activity per minute per milliliter of serum.

**Statistical Analysis**

Since the results of the polysomnography and WP100 testing were in very good agreement (presented separately in Table 1), when performed both in the laboratory and at home (ie, at baseline and at the 3-month follow-up), the AHI was considered as the average between the two tests for correlation analyses. At the 1-year evaluation (with and without the MAS), the AHI was derived from the values of the in-home study. The data are expressed as the mean ± SD. Two-tailed paired t tests and analysis of variance were performed to compare the assessments using a statistical software package (Sigmastat; SPSS; Chicago, IL). The treatment effect at the 1-year evaluation relative to baseline was measured only for the 12 patients who completed the 1-year evaluation.

The calculation of the treatment effect was performed with the following equation:

$$\Delta \text{parameter}\% = (\text{parameter}\text{[baseline]} - \text{parameter}\text{[1 year]}) / \text{parameter}\text{[baseline]} \times 100,$$

where parameters = AHI, TBARS, RH-PAT (result multiplied by [−1]). For comparisons with control groups, the unpaired t test was utilized. A p value of < 0.05 was considered to be statistically significant.

**RESULTS**

Of the 19 patients initially enrolled in the study, 3 dropped out due to ineffective treatment (ie, unchanged SDB despite maximum allowable jaw protrusion), and 16 continued in the study for 3 months. Two patients stopped using the MAS at 3 months, and of the 14 who continued using it with good
Table 1—Characteristics of the Patient Group, the Control Group, and the Reference Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Group</th>
<th>Untreated Control Group</th>
<th>Reference Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 mo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Age, yr</td>
<td>54 ± 8.3</td>
<td>54 ± 8.3</td>
<td>55 ± 7.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.0 ± 3.1</td>
<td>28.3 ± 3.2</td>
<td>28.0 ± 3.1</td>
</tr>
<tr>
<td>Waist-to-hip ratio, cm</td>
<td>0.91 ± 0.1</td>
<td>0.92 ± 0.08</td>
<td>0.92 ± 0.09</td>
</tr>
<tr>
<td>Cardiovascular dysfunction (%)</td>
<td>6.3 (7.5)</td>
<td>6.3 (7.5)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 (25)</td>
<td>4 (25)</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130.5 ± 27.6</td>
<td>125 ± 16.5</td>
<td>125.4 ± 18.5</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80.5 ± 12.7</td>
<td>77.8 ± 8.6</td>
<td>77.9 ± 10.1</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>29.5 ± 14.7</td>
<td>15.4 ± 12.0</td>
<td>16.0 ± 11.5</td>
</tr>
<tr>
<td>WPT-100</td>
<td>30.1 ± 26.6</td>
<td>20.0 ± 12.7</td>
<td>19.6 ± 11.5</td>
</tr>
<tr>
<td>ODI, events/h</td>
<td>14.9 ± 17.7</td>
<td>6.6 ± 7.6</td>
<td>5.9 ± 9.9</td>
</tr>
<tr>
<td>Minimum O₂₉, %</td>
<td>85.0 ± 6.9</td>
<td>85.4 ± 6.6</td>
<td>87.3 ± 5.6</td>
</tr>
<tr>
<td>Respiratory index, RHI-PAT</td>
<td>1.7 ± 0.4</td>
<td>2.1 ± 0.4</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>ESS score</td>
<td>12.4 ± 6.0</td>
<td>10.2 ± 6.6</td>
<td>7.8 ± 3.8</td>
</tr>
</tbody>
</table>

*Values are given as No. (%), or mean ± SD, unless otherwise indicated. FSG = polysomnography; ND = not done; NS = not significant; NA = not applicable.
†Mean duration, 9 months.
‡Statistical difference between the baseline and 1-year evaluation characteristics of the 12 subjects who completed the 1-year evaluations or the 6 subjects in the control group or baseline levels relative to 3-month evaluation for the FSG evaluation in the study group.
§Statistical difference between the reference group and the 1-year evaluation of the study group.
¶Cardiovascular dysfunction comprises hyperlipidemia, diabetes mellitus, and hypertension.
||One-year evaluation of sleeping with the MAS relative to sleeping without it.

Compliance based on the results of their questionnaires, 12 underwent full assessment at 1 year and 2 refused to be restudied. Table 1 presents the demographic, clinical, and biochemical data of the study group, the control group, and the reference group. The three groups were matched for gender, BMI, comorbidities, and smoking. The control group matched the study group in AHI and ODI values, while the reference group had significantly lower AHI and ODI values.

Indexes of OSA Severity

Assessment of the AHI at baseline and at 3 months by polysomnography and WPT100 correlated significantly (baseline: r = 0.88; p < 0.001; at 3 months: r = 0.69; p < 0.01) with the line equation y = 0.95x. Table 1 presents the data separately for the methods at baseline and 3 months; these methods did not differ significantly from each other (baseline, p = 0.91; 3 months, p = 0.26). Given the good comparability between both methods, and, as sleep studies were performed in the laboratory (until the 3-month evaluations) and at home at the 1-year assessment, both measurements were averaged in order to simplify analysis. The mean AHI of the study group had decreased significantly with treatment from 29.7 ± 18.5 events/h at baseline to a mean level of 19.6 ± 11.5 events/h at the 1-year evaluation. This reduced level was still significantly higher than that of the reference group (p = 0.0038). The follow-up of the control group exhibited no significant change in AHI (Table 1).

Figure 2 illustrates the mean AHI levels at different time points along the study. The baseline AHI of the 16 patients investigated at 3 months was not statistically different from the baseline AHI of the 12 patients who completed the 1-year evaluation (28.8 ± 12.5 events/h; p = 0.9).
Using the MAS resulted in a significant decrease in AHI at the 2-week (p < 0.05), 3-month (p < 0.02), and 1-year (p < 0.005) evaluations of the 12 patients without the MAS. Mean AHI decreased significantly relative to baseline levels at the 2-week (p < 0.05), 3-month (p < 0.02), and 1-year (p < 0.005) evaluations. BL-0 = baseline untreated; 2 Wks = 2 weeks; 3 Mon = 3 months; 1 YR-BL = sleeping without the MAS at 1 year; 1 YR-MAS = sleeping with MAS at 1 year; error bars = SE.

Table 2 presents the differences between SDB indexes (absolute and percentage) with and without use of the MAS at the 1-year evaluation. The mean decreases in AHI and ODI were 32.8 ± 23.9% and 45.3 ± 37.4%, respectively (p < 0.05 for both). ESS (Fig 3) decreased significantly with treatment from the baseline level of 12.4 ± 6 to 7.8 ± 3.8 at the 1-year evaluation (p < 0.002). In the control group, ESS did not change over time (Table 1).

**RH-PAT**

Mean indexes of EF improved with use of the MAS from 1.77 ± 0.4 at baseline to 2.08 ± 0.5 at the 3-month evaluation and 2.0 ± 0.35 at the 1-year evaluation (p = 0.028 and 0.055, respectively) [Fig 4]. The level at the 1-year evaluation of the MAS group was not statistically different from that of the reference group. EF did not change significantly with time in the control group (Table 1). Of note, the threshold for cardiovascular risk is considered to be < 1.67, although this was assessed in subjects evaluated for potential ischemic heart disease.38,39 There was a trend toward an association between the change in EF relative to baseline at the 1-year evaluation and to the change in AHI (r = 0.49; Figure 4). Mean RH-PAT (RH-PAT-M) at main time points. The RH-PAT index is a ratio calculated as the average amplitude of the PAT signal postocclusion divided by the average amplitude preocclusion, normalized to the concurrent signal from the nonischemic hand. A score of > 1.67 is considered to be the threshold for normality. Baseline levels were not statistically different between the 16 patients who were treated for 3 months and completed the reevaluation tests and the 12 patients who also completed the 1-year assessment. Mean RH-PAT levels were increased at the 3-month and 1-year evaluations (p = 0.028 and 0.055, respectively). See Figure 2 for definition of terms not used in the text.
Index of Oxidative Stress

Figure 6 and Table 1 depict TBARS levels throughout the study. The mean baseline level was 18.8 ± 6.2 nmol MDA/mL (or 17.2 ± 3.4 for the 12 patients who were reevaluated at 1 year). This level tended to decrease to 16.3 ± 4.7 and 15.8 ± 3.9 nmol MDA/mL after 2 weeks (p = 0.1) and 3 months (p = 0.09) of treatment, respectively. One year of treatment resulted in a significant reduction to 15.5 ± 3.2 nmol MDA/mL (p < 0.05), which did not significantly differ from the mean level of 13.7 ± 4.6 nmol MDA/mL of the reference group (p = 0.18). The changes in TBARS concentrations at the 3-month and 1-year evaluations relative to baseline correlated positively with the corresponding changes in AHI (r = 0.59 and 0.51, respectively; p ≤ 0.05) [Fig 7, top, A, and bottom, B, respectively]. TBARS levels did not change in the control group between both measurements (Table 2).

Discussion

This is the first study to provide data on the long-term effects of MAS therapy on OSA and cardiovascular risk factors. The two major findings of our study are as follows: (1) treatment with the MAS may improve OSA both objectively and subjectively in patients with moderate and even severe OSA, and the MAS can thus be an alternative treatment when other treatment fails; and (2) the improvement in OSA severity tended to correlate with the improvement in cardiovascular pathophysiologic factors such as ED and some oxidative stress measures such as TBARS levels, suggesting the potential reversibility of these risk factors at least to some extent. Nevertheless, evaluation with the device in place revealed residual apnea with an AHI of 19 events/h and an ODI of 6 events/h, indicating that this option should not be considered as a first-line treatment and should be kept for use in certain circumstances only.

Since the basic pathophysiologic factor in OSA is compromised upper airway anatomy,44 it is not surprising that use of the MAS resulted in improvement, as has also been summarized in several reviews.28,29,32 Use of the MAS has been shown to reduce AHI and to improve subjective sleepiness in patients with OSA in a manner comparable to upper airway surgery,29 although it is less effective than nCPAP.27–30,34 However, given the high rate of nCPAP nonadherence, this alternative treatment is of substantial importance. The AHI in our study decreased with use of the MAS by some 40%, which is in agreement with the results of previous studies30,31,34 although some studies have reported better short-term improvements.27,45 Our study shows that the improvement in OSA parameters (ie, AHI, ODI, sleepiness, and satisfaction) remain for at least 1 year following use of the MAS appliance, and that compliance with treatment using the MAS is better in these patients than it was with nCPAP treatment. A treatment level of 63% (12 of 19 patients) or 74% (14 of 19 who were still using the device) of a population of patients who refuse to use nCPAP is a good alternative to minimizing the numbers of oth-
erwise untreated OSA patients. As ODI significantly improved, episodes of ischemia-reperfusion probably decreased, potentially reducing the well-established risk of cardiovascular complications that have been reported to develop in untreated patients.46–48 Improvement in subjective vigilance is also in accordance with the findings of previous reports.45,49

There is no consensus on the definition of successful treatment of sleep apnea. Although with nCPAP the AHI frequently decreases to <10 events/h, there is frequently residual sleepiness and residual AHI levels even as soon as 1 year following pressure adjustment.50 With oral appliances, successful treatment was traditionally defined as either improvement by 50% in OSA indexes or a reduction of AHI to <20 or 10 events/h.27–29 According to these definitions, only four to seven of our patients had successful treatment. Nevertheless, the fact that subjective sleepiness improved to near-normal levels, and important cardiovascular mechanistic pathologies (ie, EF and a measure of oxidative stress) improved to near-normal scores, questions these traditional definitions of success.

The increased baseline TBARS levels in the current study were reduced significantly with treatment as was previously shown with nCPAP, albeit to a lesser degree.15–19 The level of 15 nmol MDA/mL that we observed at 1 year compared to the mean level of 12.9 ± 3.5 nmol MDA/mL that we previously found in control subjects,15 or relative to the levels found in our reference group, is probably a result of the residual apnea that we observed. The correlation between the reduction in TBARS levels and the improvement in AHI with treatment supports a relationship between OSA and oxidative stress, and its partial reversibility with effective MAS treatment.

Our results demonstrated a significant improvement in EF with a trend toward correlation between the improvement in OSA severity and that in EF. This is in accordance with previous reports on nCPAP treatment.8,10,21 The present findings on ED in sleep apnea measured at approximately 10:00 AM complement our previous findings that were obtained immediately after patients awoke, suggesting that those findings reflected a stable state rather than overnight effects.12 ED, which is a documented subclinical condition that precedes atherosclerosis,51 improved to normal levels during the 1 year of treatment with MAS, and TBARS levels decreased to near-normal levels. Therefore, we speculate that, despite the substantial residual apnea, treatment with the MAS may have a positive protective effect from future cardiovascular complications, although this has to be further investigated. Only two studies3,33 so far have addressed the potential favorable effects of MAS treatment on cardiovascular risk factors, exhibiting a significant reduction in diastolic BP after treatment. Since cardiovascular complications tend to develop in untreated patients with OSA, even if the OSA does not worsen,47 we believe that the current results support offering treatment with the MAS to patients who do not respond to nCPAP treatment, with the hope that further cardiovascular damage will be reduced or slowed. This is supported by the similar RH-PAT findings of patients with MAS at 1 year and those of the reference group, although the remnant OSA had a bearing on TBARS levels, which had decreased significantly but did not reach the levels of the reference group. In the untreated control group, on the other hand, the initial EF of 1.9 ± 0.4 deteriorated to 1.7 ± 0.4.
following 9 month without treatment (Table 1). The
lipid levels (ie, low-density lipoprotein [LDL], high-
density lipoprotein [HDL], and triglycerides) were
significantly reduced in the study group at the 1-year
evaluation. This drop cannot be readily explained as
there were no changes in medical status or interven-
tions performed during this year, although we did
not monitor patient lifestyles, which could have
changed following MAS treatment. While lowering
lipid levels can potentially benefit EF, we believe
that this is less likely in the current study due to
several reasons. First, HDL levels decreased similar-
lly to LDL levels. Second, EF increased signifi-
cantly in the treatment group at the 3-month evalu-
ations, before the significant changes in lipid levels
occurred. Finally, the lipid levels in the reference
group were similar to the baseline levels of the
treatments performed during this year, although we did
not monitor patient lifestyles, which could have
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that this is less likely in the current study due to
several reasons. First, HDL levels decreased similar-
lly to LDL levels. Second, EF increased signifi-
cantly in the treatment group at the 3-month evalu-
ations, before the significant changes in lipid levels
occurred. Finally, the lipid levels in the reference
group were similar to the baseline levels of the
treatment group (total cholesterol level, \( p = 0.74; \)
triglycerides, \( p = 0.9 \)), yet their EF was higher.

Our study has several limitations. First, it was
limited by its relatively small sample size. Thus,
larger scale studies are warranted to further establish
the beneficial effects of the MAS on oxidative stress
and EF. Second, we did not compare our results to
those with nCPAP or sham MAS treatment. In order
to compensate for this, we included two other groups
as references (an untreated control group that was
assessed twice, 9 months apart, and a reference
control group with an AHI of < 10 as an index of
non-OSA control subjects). It should be noted that
the reference group was composed of a small con-
venience group of simple snorers who had been
referred to the sleep laboratory with suspected OSA
(mean AHI, 7.1 events/h) and thus may not have
served as a healthy control group. This may have
bearing on the findings for the reference group,
which may differ from those of subjects with an AHI
of < 5 events/h. However, the reference group was
closely matched to the study group in terms of
gender, demographics, and comorbidities. We also
performed a sleep study without MAS treatment at
the 1-year evaluation of the study group, proving that
baseline OSA status was unchanged, with patients
acting as their own control subjects. It should also be
kept in mind that our participants had previously
refused nCPAP, so a nCPAP control group is less
relevant clinically. Thus, given the relatively small
sample size and the lack of sham MAS control
subjects, our results may be regarded as a pilot study,
which should be expanded with a larger number of
participants in whom findings can be analyzed by
intention-to-treat analysis, possibly for a shorter pe-
riod of time. Such a design may allow the use of a
sham MAS as a control group in a double-blind,
randomized, controlled trial.

In conclusion, despite these limitations, we believe
that our findings support the use of the MAS as an
alternative treatment for OSA patients when they do
not comply with nCPAP, and more importantly even
if the OSA is severe. MAS treatment resulted in a
moderate improvement of OSA, which was corre-
lated with an improvement in EF and in levels of
oxidative stress markers. Our patients also experi-
cenced improved diurnal alertness and reduced noc-
turnal snoring. Thus, we think that this device should
be offered to patients instead of leaving them un-
treated, although a reduction in future cardiovas-
cular complications still needs to be shown.

**REFERENCES**

1. Peppard PE, Young T, Palta M, et al. Prospective study of the
association between sleep disordered breathing and hyper-

events in patients with obstructive sleep apnea syndrome and
ischemic heart disease: effects of continuous positive air

3. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnea
syndrome as a risk factor for hypertension: population study.
BMJ 2000; 320:479–482

cardiovascular disease in middle-aged men with obstructive
sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med
2002; 166:159–165

5. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-
disordered breathing, sleep apnea, and hypertension in a
large community-based study: Sleep Heart Health Study.
JAMA 2000; 283:1829–1836

6. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep
apnea: implications for cardiac and vascular disease. JAMA
2003; 290:1906–1914

of endothelium dependent vasodilation of resistance vessels
in patients with obstructive sleep apnea. Circulation 2000;
102:2607–2610

8. Imadojemo VA, Gleeson K, Quatraishi SA, et al. Impaired
vasodilator responses in obstructive sleep apnea are improved
with continuous positive airway pressure therapy. Am J
Respir Crit Care Med 2002; 165:950–953

markers of vascular endothelial function in a large community
sample of older adults. Am J Respir Crit Care Med 2004;
169:354–360

10. Ip MSM, Tse HF, Lam B, et al. Endothelial function in
obstructive sleep apnea and response to treatment. Am J
Respir Crit Care Med 2004; 169:348–353

of vascular endothelial function and left ventricular filling;
association with the severity of apnea-induced hypoxemia

obstructive sleep apnea measured by peripheral arterial tone
response in the finger to reactive hyperemia. Sleep 2005;
28:594–600

atherosclerosis in obstructive sleep apnea. Am J Respir Crit
Care Med 2005; 172:613–618

intima-media thickness and serum inflammatory markers of

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Original Research

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19 Carpayano GE, Kharitonov SA, Resta O, et al. S-Isoprostanate, a marker of oxidative stress, is increased in exhaled breath condensate of patients with obstructive sleep apnea after night and is reduced by continuous positive airway pressure therapy. Chest 2003; 124:1386–1392
33 Gostopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnea: a randomized controlled trial. Sleep 2004; 27:934–941
51 Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004; 109(suppl);27–32
The Effects of 1-Year Treatment With a Herbst Mandibular Advancement Splint on Obstructive Sleep Apnea, Oxidative Stress, and Endothelial Function

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*CHEST* 2007;131;740-749
DOI 10.1378/chest.06-0965

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