

## SCIENTIFIC INVESTIGATIONS

# Mandibular Advancement Device as a Comparable Treatment to Nasal Continuous Positive Airway Pressure for Positional Obstructive Sleep Apnea

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**Study Objectives:** Positional obstructive sleep apnea (P-OSA) is a clinically common phenotype of OSA, which can be treated effectively with mandibular advancement devices (MADs). We hypothesized that the efficacy of an MAD is comparable to that of nasal continuous positive airway pressure (nCPAP) in P-OSA patients.

**Methods:** Among patients diagnosed with OSA at a single sleep center from January 2008 to May 2014, male subjects with moderate OSA were recruited and stringently categorized as having P-OSA when the ratio of their lateral apnea-hypopnea index (AHI) to supine AHI was  $\leq 0.5$ , their lateral sleep time was  $> 60$  minutes, and their lateral REM sleep time was longer than 10 minutes. Treatment efficacy was compared between P-OSA subjects with an MAD ( $n = 34$ ) and those with nCPAP ( $n = 34$ ) after matching for age, body-mass index, and baseline AHI.

**Results:** There were no significant differences in baseline AHI (MAD: nCPAP =  $20.6 \pm 3.9/h$ :  $21.3 \pm 1.7/h$ ,  $p = 0.35$ ) or in follow-up AHI (MAD: nCPAP =  $4.7 \pm 3.5/h$ :  $3.4 \pm 3.7/h$ ,  $p = 0.12$ ) between the 2 treatment groups, and hence MADs lowered the AHI to the same extent as nCPAP.

**Conclusions:** These findings suggest that an MAD is as efficacious as nCPAP for P-OSA patients. MAD treatment for this specific phenotype may be a promising patient-tailored and first-line approach to OSA.

**Commentary:** A commentary on this article appears in this issue on page 1079.

**Keywords:** positional obstructive sleep apnea, mandibular advancement device, oral appliance, nasal continuous positive airway pressure

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## INTRODUCTION

Mandibular advancement devices (MADs) have increasingly been recognized and prescribed for patients with moderate as well as mild obstructive sleep apnea (OSA).<sup>1–4</sup> However, every sleep dentist and physician is required to make a difficult decision regarding the selection of either an MAD or nasal continuous positive airway pressure (nCPAP) for each OSA patient, based predominantly upon efficacy, compliance, patient preference, cost-effectiveness, and short-term/long-term adverse effects.<sup>5</sup> Moreover, this decision is usually required immediately after a patient is diagnosed as having OSA.<sup>6</sup> Considering the generally lower efficacy of MADs than nCPAP, it is crucial to identify patients who will benefit from an MAD prior to device prescription, because suboptimal treatment outcomes of MADs may lead to cardiovascular consequences<sup>7</sup> and a deterioration in the patient's quality of life.<sup>8</sup>

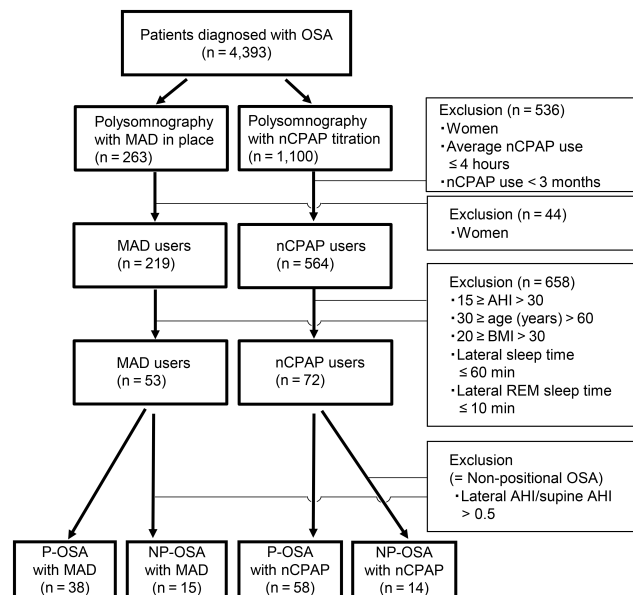
In clinical settings, many patients experience more severe OSA while asleep in the supine position than in the lateral position.<sup>9,10</sup> Individuals are defined as positional OSA (P-OSA) if their overall apnea-hypopnea index (AHI) is higher than 5 events/h, and the ratio of their lateral AHI to supine AHI is 0.5 or less. A substantial number of studies demonstrated

## BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Positional obstructive sleep apnea (P-OSA) is a clinically common phenotype of OSA, which can be treated effectively with mandibular advancement devices (MADs). Therefore, the authors hypothesized that the efficacy of a MAD is comparable to that of nasal continuous positive airway pressure (nCPAP) in P-OSA patients.

**Study Impact:** This is the first demonstration that a MAD is as efficacious as nCPAP for P-OSA patients. MAD treatment for this specific phenotype may be a promising patient-tailored and first-line approach to OSA.

that P-OSA is present in 50% to 60% of patients who undergo polysomnography.<sup>9,10</sup> Furthermore, a few reports suggested that P-OSA patients responded better to MAD than patients with non-positional OSA (NP-OSA).<sup>11–13</sup> Since P-OSA is likely to be a common OSA phenotype that can be detected by diagnostic polysomnography, MAD treatment for P-OSA patients may result in increased treatment efficacy and offer a patient-tailored and cost-effective approach to OSA.<sup>14</sup> Accordingly, in the present study, we aimed to test the hypothesis that the efficacy of MAD is comparable to that of nCPAP when used in patients with P-OSA.

**Figure 1**—Flowchart of patient recruitment.

At the end of the screening, 38 and 15 MAD users and 58 and 14 nCPAP users had met the criteria for P-OSA and NP-OSA, respectively. AHI, apnea-hypopnea index, BMI, body-mass index; MAD, mandibular advancement device; nCPAP, nasal continuous positive airway pressure; NP-OSA, non-positional obstructive sleep apnea; P-OSA, positional obstructive sleep apnea.

## METHODS

### Study Subjects

The present study was conducted in accordance with the amended Declaration of Helsinki. On their first visit to the outpatient clinic of the Yoyogi Sleep Disorder Center, every patient was asked whether they agreed to the anonymous use of their polysomnography data for research purposes. From January 2008 to May 2014, a total of 4,393 patients who had been diagnosed with OSA by polysomnography provided their written informed consent for the use of their above data, and were considered eligible for inclusion in the study.<sup>15</sup> The protocol of this study was approved by the Ethics Committee of the Foundation of Sleep and Health Sciences, Japan.

**Figure 1** shows a flowchart of patient recruitment. Inclusion/exclusion criteria were as follows: Those who completed nCPAP titration to determine the manually titrated optimal pressure of nCPAP and who had been using nCPAP for  $\geq 3$  months with an average compliance  $> 4$  h/night ( $n = 1,100$ ), and those who had been their follow-up polysomnography with a MAD in place ( $n = 263$ ) were included.<sup>5,7,16</sup> In addition, only male patients were recruited. Because it was reported that the severity of OSA in MAD patients tended to be less than that of nCPAP users,<sup>1</sup> patients were screened for the following inclusion criteria to match the AHI at baseline as much as possible between the 2 treatment groups: body-mass index ([BMI];  $20 < \text{BMI} \leq 30 \text{ kg/m}^2$ ), age ( $30 < \text{age} \leq 60$  years), and AHI at baseline ( $15 \leq \text{AHI} < 30$  events/h; moderate OSA). Moreover, we only considered subjects to be eligible

for inclusion in this study if their lateral sleep times were longer than 60 minutes and their lateral REM sleep times were longer than 10 minutes, for more robust interpretation of the results.<sup>17</sup>

Consequently, each treatment group was divided into 2 groups, namely, P-OSA and NP-OSA. P-OSA in this study was defined as OSA patients in whom the ratio of lateral AHI to supine AHI was  $\leq 0.5$ .<sup>9,10</sup> On the other hand, NP-OSA was defined as OSA patients in whom the above ratio was  $> 0.5$ . Finally, 38 and 15 MAD users met the criteria for P-OSA and NP-OSA, respectively, and 58 and 14 nCPAP users met the criteria for P-OSA and NP-OSA, respectively.

### Polysomnographic Evaluation

All patients were diagnosed with OSA based on initial diagnostic polysomnography following standard procedures.<sup>15,18</sup> Episodes of hypopnea were determined based on the American Academy of Sleep Medicine criteria of a reduction in airflow amplitude  $\geq 50\%$  from baseline persisting for  $\geq 10$  s, or some degree of reduction in airflow amplitude persisting for  $\geq 10$  s with the presence of respiratory-associated arousal or oxygen desaturation  $\geq 3\%$  (i.e., Chicago criteria).<sup>15</sup> The severity of OSA was assessed in terms of AHI (mild [ $\text{AHI} \geq 5$  to  $< 15$  events/h], moderate [ $\text{AHI} \geq 15$  to  $< 30$  events/h], severe [ $\text{AHI} \geq 30$  events/h]). In patients for whom nCPAP therapy was selected, a second polysomnography to determine the optimal nCPAP was performed within 2 weeks of the initial polysomnography. The optimal nCPAP was manually determined by registered polysomnographic technologists and was targeted to abolish respiratory events, such as apnea, hypopnea, flow limitation, and snoring.<sup>5,19</sup> The AHI after treatment was defined based solely on the optimal AHI obtained from the nCPAP titration study.

A custom-made monobloc (i.e., single jaw position) MAD made from polyolefin (ASO International Inc., Tokyo, Japan) was provided for each patient who was selected to use the device. The MADs were fabricated on plaster working casts of maxillary and mandibular dental arches and a bite registration. The absolute range of maximal mandibular protrusion was measured (in mm) with the use of the George Gauge (Great Lakes Orthodontics, Ltd., New York, USA). Subsequently, the construction bite was registered at 50% of the maximum mandibular protruded position using the bite fork of the George Gauge and vinyl polysiloxane dental impression material (Exafine, GC, Tokyo, Japan). After MAD insertion, patients were advised to stop using the oral appliance until the next visit if discomfort occurred in the temporomandibular joint or jaw muscle. If no such significant problems occurred during the acclimatization period (approximately 4 weeks), the lower part of the appliance was ventrally advanced according to the following process. A new construction bite was registered using the George Gauge at a more advanced mandibular position than the initial position. The upper and lower parts of the appliance were separated and thereafter reattached with the use of the plaster casts and the new bite registration. This step was repeated several times as necessary until the maximum comfortable limit of mandibular advancement was reached, which took 2–5 months. In addition, we also considered the

**Table 1**—Baseline characteristics of the 4 groups of patients with OSA.

	P-OSA with an MAD <sup>(a)</sup> (n = 38)	NP-OSA with an MAD <sup>(b)</sup> (n = 15)	P-OSA with nCPAP <sup>(c)</sup> (n = 58)	NP-OSA with nCPAP <sup>(d)</sup> (n = 14)	Post hoc analysis
Age (years)	48.2 ± 7.5	44.0 ± 6.4	48.1 ± 7.3	46.7 ± 7.0	n.s.
BMI (kg/m <sup>2</sup> )	24.1 ± 2.7	24.4 ± 2.4	25.2 ± 2.1	25.8 ± 2.4	n.s.
At baseline					
Total AHI (events/h)	20.1 ± 4.0	20.4 ± 4.0	23.3 ± 3.0	24.5 ± 3.1	c > a, b d > a, b
Supine AHI (events/h)	32.9 ± 10.2	22.1 ± 6.6	38.3 ± 11.1	26.3 ± 11.4	a > b, d c > b, d
Lateral AHI (events/h)	4.8 ± 3.9	17.8 ± 4.1	7.1 ± 4.6	19.3 ± 4.1	b > a, c d > a, c
Nadir SpO <sub>2</sub> (%)	82.7 ± 7.5	81.7 ± 8.2	81.5 ± 6.3	72.0 ± 13.1	a, b, c > d
ESS (points)	13.3 ± 5.4	12.3 ± 6.0	11.1 ± 5.1	12.9 ± 5.3	n.s.
After treatment					
Total AHI (events/h)	4.8 ± 3.5	8.4 ± 6.0	3.6 ± 3.4	4.5 ± 4.2	b > a, c, d
Supine AHI (events/h)	6.2 ± 4.6	10.4 ± 7.1	4.0 ± 3.6	5.2 ± 5.4	b > a, c, d
Lateral AHI (events/h)	1.5 ± 1.8	4.0 ± 4.1	2.7 ± 5.5	3.1 ± 4.4	n.s.
Nadir SpO <sub>2</sub> (%)	90.4 ± 3.9	88.1 ± 4.7	92.4 ± 3.2	90.1 ± 4.2	c > a c > b
ESS (points)	10.2 ± 5.8	8.7 ± 5.0	11.0 ± 5.1	12.9 ± 5.4	n.s.

One-way ANOVA and the Bonferroni test were used to compare the 4 groups. AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; SpO<sub>2</sub>, percutaneous oxygen desaturation; n.s., not significant.

mandibular position to be titrated when the patient or bed partner reported a cessation of snoring and resolution of OSA symptoms, leading to no further advancement of the device (i.e., endpoint of MAD titration). A second polysomnogram was undertaken with the adjusted MAD in place after confirming that the patient felt the final mandibular position to be comfortable.

### Statistical Analysis

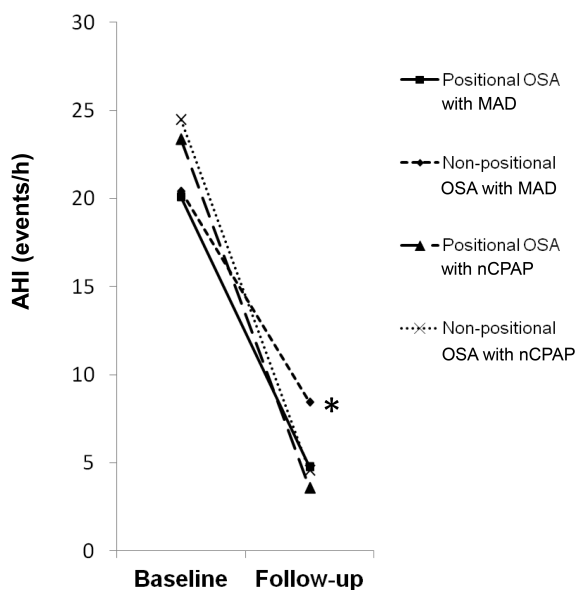
One-way analysis of variance, followed by the Bonferroni-Dunn test was performed to compare descriptive variables among the 4 groups. Differences among the 4 groups in changes in AHI and nadir percutaneous oxygen saturation (SpO<sub>2</sub>) from baseline to after treatment were tested using one-way analysis of covariance (ANCOVA) while controlling for the effect on AHI at baseline and SpO<sub>2</sub> at baseline, respectively. The Bonferroni test was performed as a post hoc analysis. Moreover, a subgroup comparison between the P-OSA with MAD group and the P-OSA with nCPAP group was performed by the unpaired *t*-test after matching for the baseline mean values of age, AHI, and BMI. Additionally, we prepared 4×2 and 2×2 cross tables for the  $\chi^2$  test with the Yates correction where appropriate to investigate the effects of positional dependency and type of treatment on the rate of patients achieving AHI < 5. All statistical analyses were performed using SPSS version 11.5.1J software for Windows (SPSS Inc., Tokyo, Japan). A *p* value < 0.05 was considered to indicate a statistically significant difference between groups.

## RESULTS

The characteristics of the patients are shown in **Table 1**. There was a significant difference in the total AHI at baseline among the 4 groups ( $F_{3,121} = 10.1$ , *p* < 0.01). The Bonferroni-Dunn post hoc test showed that the total AHI values at baseline in the P-OSA with nCPAP group and the NP-OSA with nCPAP group were significantly higher than those in the P-OSA with MAD group (*p* < 0.01 for both) and in the NP-OSA with MAD group (*p* < 0.05 for both). Similarly, there was a significant difference in the supine AHI at baseline among the 4 groups ( $F_{3,121} = 13.5$ , *p* < 0.01). The supine AHI values at baseline in the P-OSA with MAD group and the P-OSA with nCPAP group were significantly higher than those in the NP-OSA with MAD group (*p* < 0.01 for both) and the NP-OSA with nCPAP group (*p* < 0.01 for both). In addition, there was also a significant difference in the lateral AHI at baseline among the 4 groups ( $F_{3,121} = 64.6$ , *p* < 0.01). The Bonferroni-Dunn post hoc test showed that the lateral AHI values at baseline in the NP-OSA with MAD group and the NP-OSA with nCPAP group were significantly higher than those in the P-OSA with MAD group (*p* < 0.01 for both) and the P-OSA with nCPAP group (*p* < 0.01 for both).

There was a significant difference in the nadir SpO<sub>2</sub> at baseline among the 4 groups ( $F_{3,121} = 6.8$ , *p* < 0.01). The Bonferroni-Dunn post hoc test showed that SpO<sub>2</sub> at baseline of the NP-OSA with nCPAP group was significantly lower than those of the P-OSA with MAD group (*p* < 0.01), NP-OSA with MAD

**Figure 2**—Comparison of changes in the AHI from baseline to after treatment among the 4 groups.



There were significant differences in changes in the total AHI from baseline to after treatment within each group (one-way ANCOVA). Changes in the total AHI from baseline to after treatment in the NP-OSA with MAD group ( $12.0 \pm 6.2/h$ ) were lower (\*:  $p < 0.05$ ) than those in the P-OSA with MAD group ( $15.3 \pm 5.0$ ), the P-OSA with nCPAP group ( $19.8 \pm 4.5$ ), and the NP-OSA with nCPAP group ( $19.9 \pm 5.8$ ). No significant differences in changes in the AHI from baseline to after treatment were found among the 3 other groups. AHI, apnea-hypopnea index, MAD, mandibular advancement device; nCPAP, nasal continuous positive airway pressure; NP-OSA, non-positional obstructive sleep apnea; P-OSA, positional obstructive sleep apnea.

group ( $p < 0.01$ ), and the P-OSA with nCPAP group ( $p < 0.01$ ). Similarly, there was a significant difference in the nadir SpO<sub>2</sub> after treatment among the 4 groups ( $F_{3,121} = 6.1, p < 0.01$ ). The Bonferroni-Dunn post hoc test showed that SpO<sub>2</sub> after treatment in the NP-OSA with MAD group was significantly lower than that in the P-OSA with nCPAP group ( $p < 0.01$ ). No significant differences in age, BMI, Epworth Sleepiness Scale (ESS) at baseline, and ESS were found after the treatment among the 4 groups.

After treatment, there were significant differences both in the total AHI ( $F_{3,121} = 6.2, p < 0.01$ ) and supine AHI ( $F_{3,121} = 7.8, p < 0.01$ ) among the 4 groups. However, no significant differences were found in the lateral AHI ( $F_{3,121} = 1.4, p = 0.08$ ) after treatment among the 4 groups. The Bonferroni-Dunn post hoc test showed that the total AHI and supine AHI after treatment in the NP-OSA with MAD group were both significantly higher than those of the P-OSA with MAD group ( $p < 0.05$  for both), the P-OSA with CPAP group ( $p < 0.01$  for both), and the NP-OSA with CPAP group ( $p < 0.05$  for both).

One-way ANCOVA while controlling the effect of AHI at baseline demonstrated that there were significant differences in changes in the total AHI from baseline to after treatment within each group ( $F_{3,121} = 6.2, p < 0.01$ ) (Figure 2). Post hoc analysis using the Bonferroni test demonstrated that changes

**Table 2**—Comparison of treatment outcomes between the P-OSA with MAD group and the P-OSA with nCPAP group after matching the AHI at baseline.

	P-OSA with MAD (n = 34)	P-OSA with nCPAP (n = 34)	p value
Age (years)	47.6 ± 7.6	47.2 ± 6.8	0.81
BMI (kg/m <sup>2</sup> )	24.4 ± 2.7	25.4 ± 2.1	0.07
At baseline			
Total AHI (events/h)	20.6 ± 3.9	21.3 ± 1.7	0.35
Supine AHI (events/h)	32.5 ± 9.0	36.1 ± 10.9	0.14
Lateral AHI (events/h)	5.2 ± 4.0	6.5 ± 3.9	0.15
Nadir SpO <sub>2</sub> (%)	82.5 ± 7.9	81.0 ± 6.6	0.34
ESS	13.2 ± 5.9	10.9 ± 4.8	0.09
After treatment			
Total AHI (events/h)	4.7 ± 3.5	3.4 ± 3.7	0.12
Supine AHI (events/h)	6.1 ± 4.5	3.8 ± 3.8	0.03
Lateral AHI (events/h)	1.6 ± 1.9	2.7 ± 6.5	0.35
Nadir SpO <sub>2</sub> (%)	90.4 ± 4.0	92.0 ± 3.6	0.09
ESS	9.9 ± 6.0	10.8 ± 4.7	0.49

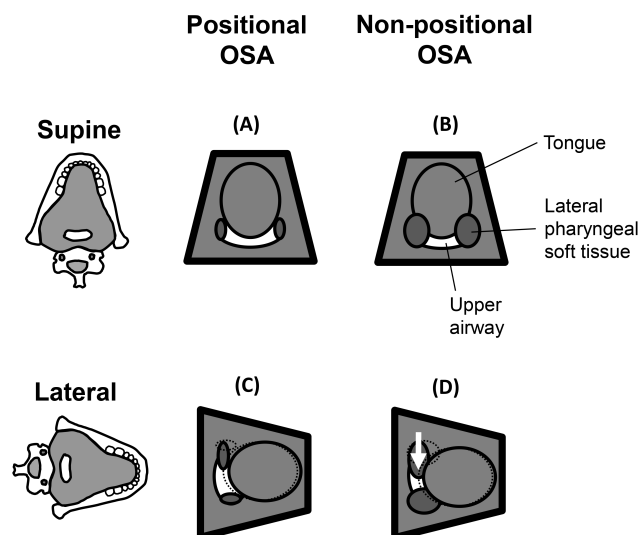
The Student *t*-test was used to compare the 2 treatment groups. AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; SpO<sub>2</sub>, percutaneous oxygen desaturation; n.s.: not significant.

in the total AHI from baseline to after treatment in the NP-OSA with MAD group ( $12.0 \pm 6.2/h$ ) were lower than those in the P-OSA with MAD group ( $15.3 \pm 5.0, p < 0.05$ ), the P-OSA with nCPAP group ( $19.8 \pm 4.5, p < 0.01$ ), and the NP-OSA with nCPAP group ( $19.9 \pm 5.8, p < 0.01$ ). However, no significant differences in changes in the AHI from baseline to after treatment were found among the 3 other groups ( $p = 0.99$ , respectively).

Similarly, one-way ANCOVA while controlling the effect of nadir SpO<sub>2</sub> at baseline demonstrated that there were significant differences in changes in the SpO<sub>2</sub> from baseline to after treatment within each group ( $F_{3,121} = 7.7, p < 0.01$ ). Post hoc analysis using the Bonferroni test demonstrated that changes in SpO<sub>2</sub> from baseline to after treatment in the P-OSA with CPAP group ( $11.0\% \pm 5.9\%$ ) were greater than those of the P-OSA with MAD group ( $7.7\% \pm 6.6\%, p < 0.05$ ) and the NP-OSA with MAD group ( $6.4\% \pm 6.0\%, p < 0.01$ ). In addition, changes in SpO<sub>2</sub> from baseline to after treatment in the NP-OSA with CPAP group ( $18.8\% \pm 14.2\%$ ) were greater than those of the NP-OSA with MAD group ( $6.4\% \pm 6.0\%, p < 0.05$ ). When age, BMI, and baseline AHI were matched between the P-OSA with MAD group ( $n = 34$ ) and the P-OSA with nCPAP group ( $n = 34$ ), there were no significant differences in baseline AHI (MAD: nCPAP =  $20.6 \pm 3.9/h$ :  $21.3 \pm 1.7/h, p = 0.35$ ) or follow-up AHI (MAD: nCPAP =  $4.7 \pm 3.5/h$ :  $3.4 \pm 3.7/h, p = 0.12$ ) between the 2 treatment groups (Table 2).

Finally, the rate of subjects achieving AHI < 5 events/h with treatment was determined (Table 3). There were no significant differences in the percent of patients achieving AHI < 5 among no baseline AHI matched 4 groups (Yates  $\chi^2 = 4.41, p = 0.220$ ) nor baseline AHI matched 2 groups (Yates  $\chi^2 = 3.15, p = 0.076$ ).

**Figure 3**—Schematic illustration of the configuration of the upper airway in patients with P-OSA or NP-OSA.



Part of this illustration was based on that of Isono et al.<sup>22</sup> The illustration shows the upper airway and its surrounding soft tissue in the horizontal plane at the mandibular level in both the supine and lateral positions. An originally wider upper airway in the lateral dimension in P-OSA (A) than in NP-OSA (B) is shown. The upper airway of patients with P-OSA (A) as well as those with NP-OSA (B) collapses easily owing to displacement of soft tissue by gravitational effects in the supine position. Soft tissue, which is more affected in the lateral position in NP-OSA (D) than in P-OSA (C) by gravitation owing to the smaller volume (i.e., being lighter in weight) of the pharyngeal soft tissue are emphasized (white arrow). NP-OSA, non-positional obstructive sleep apnea; P-OSA, positional obstructive sleep apnea.

## DISCUSSION

This is the first study to the best of our knowledge that directly compares the treatment efficacy between MAD and nCPAP in P-OSA patients. Our results demonstrated that MAD was as efficacious as nCPAP in reducing the AHI in P-OSA patients. In contrast, an MAD was not as efficacious as nCPAP for NP-OSA subjects, although nCPAP improved the AHI regardless of positional dependency.

The reason for the favorable effect of MAD treatment that was found in this study remains to be investigated. However, we speculate that modification of the upper airway configuration by mandibular protrusion is greatly affected by the amount of its change in response to body position alteration, which might be highly enhanced by gravitation (Figure 3). Saigusa et al.<sup>17</sup> reported that patients with P-OSA have a wider upper airway in the lateral dimension than patients with NP-OSA, and that the volume of the lateral pharyngeal wall soft tissue of P-OSA patients was smaller than that of patients with NP-OSA (Figure 3A and 3B). In the supine position, the upper airway of patients with P-OSA (Figure 3A) and those with NP-OSA (Figure 3B) can collapse easily owing to dorsal displacement of the tongue and the soft palate because of gravitation.<sup>9,20,21</sup> On the other hand, patients with P-OSA might be able to maintain their upper airway cross-sectional area when moving from

**Table 3**—Effects of positional dependency and type of treatment on total AHI after treatment.

	AHI < 5 events/h (%)	AHI ≥ 5 events/h (%)	Total n
No baseline AHI matched			
P-OSA with an MAD	21 (55)	17 (45)	38
NP-OSA with an MAD	6 (40)	9 (60)	15
P-OSA with nCPAP	41 (71)	17 (29)	58
NP-OSA with nCPAP	10 (71)	4 (29)	14
Total (n)	78	47	125
Baseline AHI matched			
P-OSA with an MAD	18 (53)	16 (47)	34
P-OSA with nCPAP	26 (76)	8 (24)	34
Total (n)	44	24	68

Note that there were neither significant differences in the percent of patients achieving AHI < 5 among no baseline AHI matched 4 groups nor baseline AHI matched 2 groups. AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; SpO<sub>2</sub>, percutaneous oxygen desaturation; n.s., not significant.

the supine position to the lateral position (Figure 3A–3C) to a greater extent than patients with NP-OSA (Figure 3B–3D). This was because of (1) an originally wider upper airway in the lateral dimension and (2) the reduced gravitational effects due to the smaller volume (i.e., being lighter in weight) of the pharyngeal soft tissue.<sup>17,22</sup> The fact that mandibular advancement reduced both supine and lateral AHI suggests that MADs enlarge the upper airway both in the dorsoventral and lateral dimensions. However, mandibular advancement is expected to affect upper airway cross-sectional area to a greater extent in the supine position than in the lateral position, because mandibular advancement not only repositions the dorsally collapsed tongue ventrally, but also counteracts the effect of gravitation in the supine position. Conversely, in comparison with the supine position, ventral advancement of the mandible using an MAD in the lateral position would neither counteract the effect of gravitation nor reposition the collapsed lateral pharyngeal wall.

Although an MAD lowered total AHI to a similar extent to nCPAP, nCPAP was more efficacious in reducing supine AHI (Table 2). These findings are understandable because the application of positive airway pressure using nCPAP increases the reduced functional residual capacity that results in the increased longitudinal tension of the upper airway, thus decreasing its collapsibility by stiffening the airway wall.<sup>23</sup> A MAD, which solely enlarges the constricted site of the upper airway, is unlikely to provide such effects on longitudinal upper airway dimension by tracheal traction.<sup>6,24</sup> Moreover, as the results of our study showed that nCPAP treatment had higher efficacy of improving nadir SpO<sub>2</sub> than MAD treatment (Table 1), it is possible that suboptimal treatment outcomes of MADs may lead to higher incidences of cardiovascular consequences and decreased quality of life.

In the present study, we were able to collect a relatively large number of patients in each of the four groups, even under the use of such a strict definition of P-OSA. Such stringent criteria

of P-OSA may be more clinically applicable, and should clarify whether it is appropriate to assume an OSA patient as P-OSA if the patient's lateral sleep time is only 10 minutes of total sleep time on polysomnography. In addition, the results of this study are thought to be reliable, as patients with OSA were diagnosed and treated using a MAD and nCPAP at a single institution. However, we acknowledge that both the present study as well as previous studies have several significant limitations.<sup>25</sup> First, this study was conducted retrospectively over a 6-year period. Although such a long sampling period is advantageous for increasing the total number of eligible subjects even under certain stringent P-OSA inclusion/exclusion criteria, risks of both patient and treatment biases simultaneously increase. For instance, detailed information on why some patients chose OSA treatment whereas others did not, and why a subject had selected either MAD or nCPAP was unclear from the remaining data. Thus, randomized, controlled, and ideally, crossover trials are required to reconfirm our retrospective findings. Second, this study was restricted to Japanese men, and therefore, the findings may not reflect female patients or patients of other races. As Oksenberg<sup>14</sup> recently reported, the effects of racial differences as well as sex should also be considered in future studies, although interestingly, P-OSA is predominantly observed in men. Third, the final number of subjects eligible for analyses was small ( $n = 125$ , 2.8%) considering the total number of subjects diagnosed with OSA ( $n = 4,393$ ). We speculate that the small number of subjects was partly because of the stringent definition of P-OSA that we used (i.e., lateral sleep time  $\leq 60$  min and lateral REM sleep time  $\leq 10$  min in addition to the ratio of lateral apnea-hypopnea index [AHI] to supine AHI  $\leq 0.5$ ), which significantly limited the number of patients who met the inclusion criteria. Furthermore, an adjustment of demographics was necessary to match the baseline conditions between the 2 treatment groups as much as possible (i.e.,  $20 < \text{BMI} \leq 30 \text{ kg/m}^2$ ,  $30 < \text{age} \leq 60$  years, and  $15 \leq \text{AHI} < 30$  events/h) (**Figure 1**). This adjustment, however, resulted in a reduced number of samples for analyses; eligible patients were consequently limited to relatively non-obese, middle-aged, and moderate OSA severity out of 4,393 subjects (**Table 1** and **Table 2**). Thus, it may be difficult to generalize our findings from a single sleep center to all OSA patients. Fourth, although we tried to match the baseline characteristics of the four groups with the use of the strict inclusion/exclusion criteria and the exclusion of confounding factors, it was difficult to completely adjust them, including AHI, because nCPAP is usually indicated for more severe OSA, whereas MAD is indicated for milder OSA in clinical settings.<sup>26</sup> Finally, although we think there may be anatomical differences between patients with P-OSA and those with NP-OSA, an unavoidable methodological limitation to this study and others is the inability to perform three-dimensional diagnostic imaging, including CT and MRI in the lateral position; sophisticated endoscopic techniques may be suitable alternative options to test this hypothesis.

The results from our study have some clinical and practical implications. Predictors of the treatment outcome of an MAD are important in selecting patients for this procedure in any clinical setting, owing to the generally lower efficacy of MADs than nCPAP, as noted earlier. Among the various

predictors of the responses to MADs that have been proposed by clinical and laboratory studies,<sup>5,6,27–29</sup> no studies have compared the predicted outcomes of MAD with those of nCPAP. The strength of our present study is that we demonstrated that MADs lowered the AHI to a similar extent to nCPAP, simply by focusing on a particular phenotype of OSA. The advantage of focusing on positional dependency is that it is easily detectable by initial diagnostic polysomnography.<sup>9,10,14</sup> In the present study, we chose to use non-adjustable MADs because this type of device is the most common type of MAD in Japan for which the costs are partially reimbursable (in Japan, patients usually pay 30% of the total medical care expenses for fabrication devices and treatment).<sup>5</sup> On the basis of a recent report by Quinzel et al.<sup>30</sup> demonstrating that non-adjustable MADs achieved clinically important improvements in mild to moderate OSA and were cost-effective, we speculate that MAD treatment in P-OSA will become a cost-effective therapy for OSA in Asian countries, in which P-OSA occurs frequently.<sup>9</sup>

In conclusion, an MAD can be as efficacious as nCPAP for patients with P-OSA. MAD treatment for this specific phenotype may be a promising patient-tailored and recommended approach to OSA. The information on positional dependency should also be useful for both patients with OSA as well as sleep physicians and dentists for determining the type of treatment to use immediately after diagnosis.

## ABBREVIATIONS

- AHI, apnea-hypopnea index
- BMI, body mass index
- ESS, Epworth Sleepiness Scale
- MAD, mandibular advancement device
- nCPAP, nasal continuous positive airway pressure
- NP-OSA, non-positional obstructive sleep apnea
- OSA, obstructive sleep apnea
- P-OSA, positional obstructive sleep apnea

## REFERENCES

1. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006;29:240–3.
2. Randerath WJ, Verbraecken J, Andreas S, et al. European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011;37:1000–28.
3. Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. *Eur Respir J* 2012;39:1241–7.
4. Sharples L, Glover M, Clutterbuck-James A, et al. Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure. *Health Technol Assess* 2014;18:1–296.
5. Tsuki S, Kobayashi M, Namba K, et al. Optimal positive airway pressure predicts oral appliance response to sleep apnoea. *Eur Respir J* 2010;35:1098–105.
6. Tsuki S, Ito E, Isono S, et al. Oropharyngeal crowding and obesity as predictors of oral appliance treatment response to moderate obstructive sleep apnea. *Chest* 2013;144:558–63.

7. Fukuda T, Tsuiki S, Kobayashi M, Nakayama H, Inoue Y. Selection of response criteria affects the success rate of oral appliance treatment for obstructive sleep apnea. *Sleep Med* 2014;15:367–70.
8. Gupta MA, Simpson FC, Lyons DC. The effect of treating obstructive sleep apnea with positive airway pressure on depression and other subjective symptoms: a systematic review and meta-analysis. *Sleep Med Rev* 2015;28:51–64.
9. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med Rev* 2014;18:7–17.
10. Oksenberg A, Silverberg DS, Arons E, Radwan H. Are we missing a simple treatment for most adult sleep apnea patients? The avoidance of the supine sleep position. *J Sleep Res* 2014;23:204–10.
11. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest* 1998;114:1630–5.
12. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* 2004;125:1270–8.
13. Chung JW, Enciso R, Levendowski DJ, et al. Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;109:724–31.
14. Oksenberg AS. Positional therapy for sleep apnea: a promising behavioral therapeutic option still waiting for qualified studies. *Sleep Med Rev* 2014;18:3–5.
15. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
16. Smith DM, Stradling JR. Can mandibular advancement devices be a satisfactory substitute for short term use in patients on nasal continuous positive airway pressure? *Thorax* 2002;57:305–8.
17. Saigusa H, Suzuki M, Higurashi N, Kodera K. Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. *Anesthesiology* 2009;110:885–90.
18. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep* 1992;15:173–84.
19. Loreda JS, Berry C, Nelesen RA, Dimsdale JE. Prediction of continuous positive airway pressure in obstructive sleep apnea. *Sleep Breath* 2007;11:45–51.
20. Pevernagie DA, Stanson AW, Sheedy PF 2nd, et al. Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1995;152:179–85.
21. Tsuiki S, Almeida FR, Bhalla PS, A Lowe AA, Fleetham JA. Supine-dependent changes in upper airway size in awake obstructive sleep apnea patients. *Sleep Breath* 2003;7:43–50.
22. Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. *Anesthesiology* 2002;97:780–5.
23. Kuna ST, Remmers JE. Anatomy and physiology of upper airway obstruction. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*, 3rd ed. Philadelphia, PA: WB Saunders, 2000:840–58.
24. Kairaitis K, Stavrinou R, Parikh R, Wheatley JR, Amis TC. Mandibular advancement decreases pressures in the tissues surrounding the upper airway in rabbits. *J Appl Physiol* 2006;100:349–56.
25. Sutherland K, Takaya H, Qian J, et al. Oral appliance treatment response and polysomnographic phenotypes of obstructive sleep apnea. *J Clin Sleep Med* 2015;11:861–8.
26. Ferguson KA, Cartwright R, Rogers R, et al. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 2006;29:244–62.
27. Cistulli PA, Gotsopoulos H, Marklund M, Lowe AA. Treatment of snoring and obstructive sleep apnea with mandibular repositioning appliances. *Sleep Med Rev* 2004;8:443–57.
28. Remmers J, Charkhandeh S, Grosse J, et al. Remotely controlled mandibular protrusion during sleep predicts therapeutic success with oral appliances in patients with obstructive sleep apnea. *Sleep* 2013;36:1517–25.
29. Vroegop AV, Vanderveken OM, Dieltjens M, et al. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *J Sleep Res* 2013;22:348–55.
30. Quinnell TG, Bennett M, Jordan J, et al. A crossover randomised controlled trial of oral mandibular advancement devices for obstructive sleep apnoea-hypopnoea (TOMADO). *Thorax* 2014;69:938–45.

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