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SCIENTIFIC INVESTIGATIONS

The effect of gradually increased mandibular advancement on the efficacy of an oral appliance in the treatment of obstructive sleep apnea

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Study Objectives: To analyze the effect of gradual increments of mandibular advancement on the treatment efficacy of mandibular advancement devices and identify determinants of effective and target protrusion for OSA.

Methods: Patients were prospectively recruited. The mandible was titrated from 0 mm with a stepwise increment of 0.5 mm until the AHI was reduced to the lowest level. Rhinospirometry, rhinomanometry, and magnetic resonance imaging were used to observe the change of respiratory function and upper airway morphology.

Results: Forty-two patients aged 41.5 ± 9.0 years participated. There was a dose-dependent relationship between mandibular protrusion and the AHI improvement rate, the success rate, and the normalization rate; the changing curves plateaued after approximately 70% of maximal mandibular protrusion was achieved. The correlation between AHI and mandibular protrusion became stronger as the severity of OSA increased. The target protrusion for patients with mild, moderate, and severe OSA was 3.5 ± 1.8 mm (38.6 ± 19.4% maximal mandibular protrusion), 5.8 ± 1.9 mm (62.9 ± 18.8% maximal mandibular protrusion), and 5.9 ± 2.2 mm (68.8 ± 15.6% maximal mandibular protrusion), respectively. Regression analysis revealed that the factors influencing effective and target protrusion included change of maximal lateral dimension of the total upper airway with mandibular advancement devices, mean lateral dimension of the oropharynx, and soft palate length. Further protrusion brought more lateral expansion of the velopharynx, whereas the change in nasal ventilation was not significant.

Conclusions: The dose-dependent effect of mandibular protrusion on reduction of AHI by mandibular advancement devices was nonlinear and became more pronounced with increased severity of OSA. The mandibular protrusion should be more personalized to each patient.

Clinical Trial Registration: Registry: Chinese Clinical Trial Registry; Name: Study of the Onset Point of Oral Appliance Treatment in Obstructive Sleep Apnea and Hypopnea Syndrome; URL: http://www.chictr.org.cn/showproj.aspx?proj=22291; Identifier: ChiCTR-IND-17013232

Keywords: mandibular advancement, OSA, oral appliance

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The amount of mandibular protrusion is an important factor influencing the treatment response to oral appliances for patients with OSA. However, there is currently no gold-standard method to fine-tune the amount of mandibular advancement.

Study Impact: This study thoroughly analyzed the relationship between the treatment efficacy of oral appliances and mandibular advancement amounts. The findings of this study help explain the controversies regarding the difference between various mandibular advancement amounts and help clinicians determine a more personalized and effective mandibular position.

INTRODUCTION

OSA, a sleep disorder associated with recurrent upper airway collapse,[1] can be effectively treated by widening the upper airway through mandible protrusion, which is the main mechanism of mandibular advancement devices (MADs) and orthognathic surgery.[2,3] However, how much the mandible should protrude is usually determined according to the clinician's experience.[4–6] In the literature, 50%–75% of maximal mandibular protrusion (MMP) has generally been chosen, and sometimes the advancement amount can exceed 80% of the maximum protrusion.[7] Insufficient protrusion weakens the treatment effect, and excessive protrusion causes more adverse effects related to maxillofacial structure and function.[8,9]

The adjustable MAD is a suitable tool to observe the effect of mandible protrusion. Titration is a difficult but delicate process. There are 2 main issues that have arisen during previous titration studies. One is that most studies used image analysis instead of real changes in the AHI.[10,11] The other is that the stepwise increment was relatively large or the initial amount of protrusion was extensive.[12–15] In recent years, remotely controlled mandibular titration under single-night polysomnography has been studied; the monitoring time at a certain mandibular position is too short to span more than 1 sleep cycle, and the vertical opening of the device is relatively large.[16–19]

Previous titration studies have revealed some interesting findings. Some studies suggested that mandibular protrusion brought a dose-dependent response—that is, more protrusion

yielded a larger improvement in OSA.[12,13,15,20] It was also reported that 50% and 75% of maximum protrusion were equally effective in patients with mild to moderate OSA.[21] A meta-regression analysis found that mandibular advancement amounts did not significantly influence the success rate,[22] which was in contrast with the generally accepted opinion that increased mandibular advancement was accompanied by improvement in AHI.[23] Cephalometric and magnetic resonance imaging (MRI) studies on different amounts of mandibular protrusion also suggested a dose-dependent change, but the changing curve was not a straight line.[10,11] Considering the existing contradictions, it is important to know how mandibular protrusion influences treatment efficacy and where the effective protrusion position begins.

We hypothesize that the treatment efficacy of MADs is not proportional to the increase of mandibular protrusion and that the changing curve is nonlinear. This study aims to verify the hypothesis and identify the determinants of effective protrusion amounts. Meanwhile, the changes in nasal respiratory function and upper airway structure caused by different mandibular protrusion amounts is investigated.

METHODS

This prospective study was registered in the Chinese Clinical Trial Registry (Identifier: ChiCTR-IND-17013232). It was approved by the medical ethics committee of the Peking University School and Hospital of Stomatology (PKUSSIRB—201418117). Written informed consent was obtained from all participants in the study.

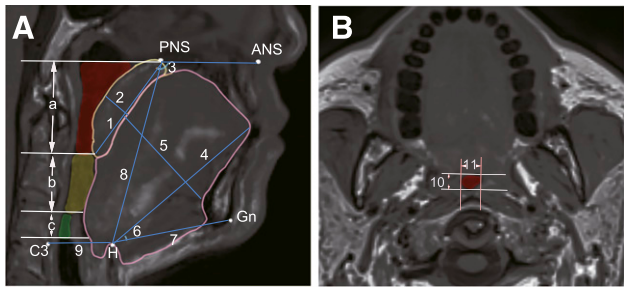
Participants

Patients with OSA were consecutively recruited from November 2017 to July 2018, from the Sleep Disorders Clinic of the Orthodontics Department at the Peking University School of Stomatology. Inclusion criteria were age older than 18 years, diagnosis made by whole-night laboratory polysomnography with AHI >5 events/h, no history of uvulopalatopharyngoplasty, and no severe nasal obstructive disease. Patients were excluded if they had an insufficient number of teeth to anchor the appliance, had a metal prosthesis, or had temporomandibular joint pain or limitation of mouth opening. The sample size was calculated according to the following formula: $n = [(Z_{\alpha/2}+Z_{\beta})S/\delta]$.[2] With $\alpha = 0.05$ and $\beta = 0.10$, 42 patients were needed. Considering possible dropout, an initial 44 patients were included.

MAD treatment

Plaster models of upper and lower teeth were obtained, and a custom-made MAD with standard adjustable Hyrax screws on both sides was fabricated. After 1 week's adaptation of MADs, patients were instructed to start to adjust the appliance. They were asked to titrate the mandible forward in 0.5 mm increments from 0 mm daily. To monitor the change of AHI, a portable monitor (ApneaLink Air, ResMed, San Diego, CA) that could continuously record for 48 hours was used. The monitor consisted of a nasal flow sensor, a respiratory effort belt, and a pulse oximeter and was classified as type III home sleep testing.[24] Baseline data were obtained with the portable monitor. The data were analyzed by the supporting software and checked manually.

Figure 1—Measurements of the upper airway and surrounding structures.



(A) Segments of upper airway and cephalometric landmarks on midsagittal MRI: a, velopharynx; b, oropharynx; c, hypopharynx; The soft palate, tongue, and hyoid measurements were as follows. 1, Length of soft palate (maximum length of soft palate). 2, Height of te soft palate (perpendicular to length). 3, Angle of soft palate (angle between length of soft palate and PNS-ANS). 4, Length of tongue (tongue tip to anterior-superior point of hyoid). 5, Height of tongue (linear distance from superior mental spine to tongue surface perpendicular to length). 6, Angle of tongue (angle between length of tongue and H-Gn). 7, Distance between hyoid and gnathion. 8, Distance between hyoid and posterior nasal spine. 9, Distance between hyoid and C3 vertebra. **(B)** Measurements of upper airway on axial slice: 10, Anteroposterior diameters. 11, Lateral diameters. ANS = anterior nasal spine, C3 = C3 vertebra, H = hyoid, Gn = gnathion, PNS = posterior nasal spine.

Effective protrusion referred to the mandibular position where AHI was reduced by 50%. Target protrusion referred to the mandibular position where AHI was reduced to the lowest level (the titration was ceased if AHI was reduced to less than 5 events/h or if significant joint discomfort occurred).

Apnea was defined as a ≥90% reduction of airflow for more than 10 seconds and hypopnea was defined as at least a 30% reduction of airflow for more than 10 seconds, combined with a ≥4% oxygen desaturation from the pre-event baseline.[25] The severity was classified as mild ($5 \le AHI < 15$ events/h), moderate ($15 \le AHI < 30$ events/h), and severe ($AHI \ge 30$ events/h). The AHI improvement rate was calculated by the following formula: $\Delta AHI\ (\%) = (1-AHI_{post}/AHI_{pre})*100$. The success rate was defined as the percentage of patients who achieved at least a 50% reduction in AHI, and the normalization rate was the percentage of patients with posttreatment AHI <5 events/h.

Nasal respiratory function

Nasal breathing may be altered because of changes in the velopharyngeal airway. To measure the change of nasal respiratory function, rhinospirometry and rhinomanometry tests were conducted with no protrusion, effective protrusion, and target protrusion. An NV1 rhinospirometer (GM Instruments Ltd, Kilwinning, UK) was used to measure nasal inspiratory and expiratory capacity. An NR6 rhinomanometer (GM Instruments Ltd) was used to measure nasal inspiratory and expiratory resistance. All the measurements were repeated 3 times by the same researcher.

MRI

MRI of the upper airway was performed using an MRI scanner (MAGNETOM Aera 1.5 T, Siemens, Erlangen, Germany). The patients were placed supine and positioned with the Frankfort plane perpendicular to the horizontal plane during wakefulness. Foam pads were placed next to the ears, and silicon was placed between the head-neck coil frame and forehead to make sure the head position remained unchanged. Patients were asked to keep their mouth closed and tongue relaxed, breathe through their nose, and refrain from swallowing. Scans were carried out sequentially with no protrusion, effective protrusion, and target protrusion, with head position unchanged during 3 scans.

T1-weighted spin-echo 3-dimensional scans were acquired through the long axis of the airway (repetition time 600 ms, echo time 7.2 ms, field of view 250 mm, 256 × 256 matrix, thickness 1 mm) from above the level of the sella to below the level of the C5 vertebra. Magnetic resonance images were analyzed with Dolphin software (Dolphin Imaging & Management Solutions, Chatsworth, CA) and OsiriX (Mac OS X, Pixmeo SARL, Bernex, Switzerland). Upper airway regions were defined as follows: velopharynx (hard palate to tip of uvula), oropharynx (tip of uvula to tip of epiglottis), and hypopharynx (tip of epiglottis to vocal cords).

The measurements of soft palate, tongue, and hyoid were completed on midsagittal images and are illustrated in **Figure 1A.** Anteroposterior and lateral dimensions and the cross-sectional area of the upper airway were obtained from the axial slice and are shown in **Figure 1B.**

Statistical analysis

All statistical analyses were conducted with statistical software package SPSS (version 24.0 for Mac, IBM, New York, NY). Normally distributed variables were expressed as means ± standard deviation, and skewed distributed variables were expressed as median and interquartile range. The changes of nasal ventilation function and upper airway dimensions at 3 different positions were compared using a repeated-measures 1-way analysis of variance. The Greenhouse-Geisser correction would be applied if the Mauchly test of sphericity was violated. Subsequently, the Bonferroni-Holm method was used to correct multiple comparisons. Values of P were considered statistically significant when $<.05$.

To evaluate the influence of each independent variable (age, body mass index, baseline AHI, MMP, baseline and change of nasal ventilation and imaging parameters) on effective protrusion and target protrusion, single-factor linear regression analysis was conducted first to screen variables (included if $P < .1$). Then stepwise multiple linear regression analyses were performed to find the main predictors of the required mandibular protrusion.

RESULTS

A total of 44 patients participated in the study; 2 patients dropped out because they were unable to finish the home sleep testing. Thus, 42 patients aged 41.5 ± 9.0 years completed

Table 1—Clinical characteristics of patients at baseline (n = 42).

Patient Characteristics	Mean ± SD	Minimum – Maximum
Age (y)	41.5 ± 9.0	25–62
BMI (kg/m^2)	24.9 ± 2.5	21–31.7
Neck circumference (cm)	40.6 ± 1.3	39–42
MMP (mm)	8.9 ± 1.5	5–13
ESS score	5.4 ± 3.4	0–18
AHI (events/h)	23.4 ± 11.5	6.6–56.5
AI (/h)	14.2 ± 9.5	1.3–39.6
HI (/h)	9.3 ± 8.7	0.2–42
Supine AHI (/h)	31.1 ± 19.7	0–81.2
Nonsupine AHI (/h)	17.6 ± 12.7	0–47.6
NREM AHI (/h)	23.9 ± 18	0–60.5
REM AHI (/h)	28.7 ± 15.5	2.7–63
ODI (/h)	17.1 ± 12.1	1.2–55.3
Average SpO_2 (%)	94.6 ± 2.4	86–98.1
Minimum SpO_2 (%)	81.1 ± 6.7	60–91
Time spent SpO_2 < 90% (%)	3.9 ± 8.1	0–44.3
Systolic blood pressure before sleep (mm Hg)	119.2 ± 12.3	96–160
Diastolic blood pressure before sleep (mm Hg)	76.9 ± 8.4	51–90
Systolic blood pressure after awakening (mm Hg)	122 ± 14.6	100–150
Diastolic blood pressure after awakening (mm Hg)	82.1 ± 12.3	60–100

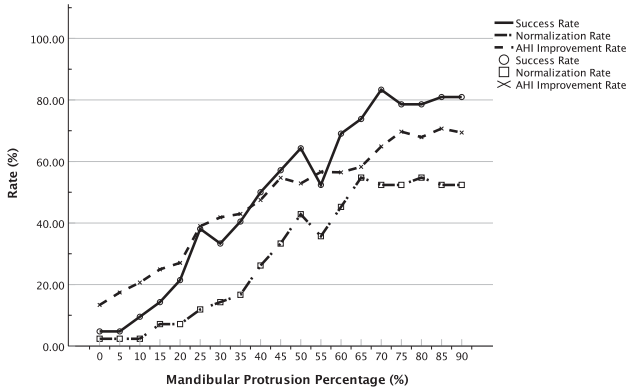
AI = apnea index, BMI = body mass index, ESS = Epworth Sleepiness Score, HI = hypopnea index, MMP = maximal mandibular protrusion, NREM = nonrapid eye movement, ODI = oxygen desaturation index, SD = standard deviation; SpO_2 = pulse oxygen saturation.

Table 2—Treatment effects of MADs and required mandibular protrusion amounts.

	Total (n = 42)	Mild (n = 19)	Moderate (n = 12)	Severe (n = 11)
Pretreatment AHI (events/h)	16.8 (9.8–30.7)[a]	11.0 ± 5.5	21.8 ± 4.2	39.3 ± 12.4
Posttreatment AHI (events/h)	4.3 (2.7–7.3)[a]	4.0 ± 3.6	5.1 ± 3.0	7.4 ± 3.0
Success rate (>50% reduction in AHI)	40/42 (95.2%)	18/19 (94.7%)	12/12 (100.0%)	10/11 (90.9%)
Normalization rate (AHI <5 events/h)	26/42 (61.9%)	17/19 (89.5%)	7/12 (58.3%)	2/11 (18.2%)
Effective protrusion				
Absolute value (mm)	3.2 ± 1.9	3.1 ± 1.7	3.0 ± 2.2	3.5 ± 2.1
Percentage of MMP (%)	35.7 ± 19.5	34.5 ± 16.9	33.2 ± 23.8	40.6 ± 19.8
Target protrusion				
Absolute value (mm)	4.8 ± 2.3	3.5 ± 1.8	5.8 ± 1.9	5.9 ± 2.2
Percentage of MMP (%)	53.5 ± 22.6	38.6 ± 19.4	62.9 ± 18.8	68.8 ± 15.6

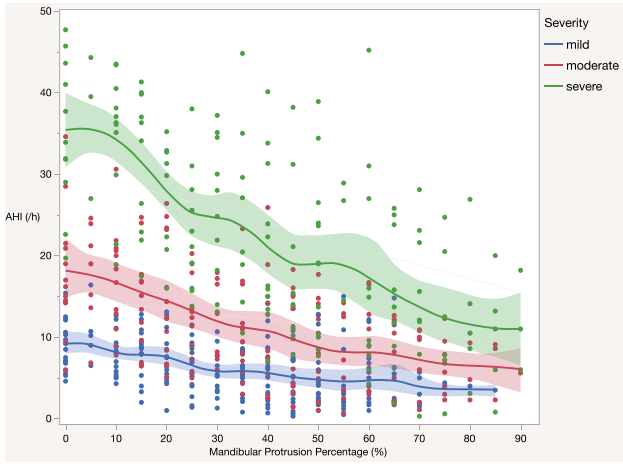
[a]Median and interquartile range. MAD = mandibular advancement device, MMP = maximal mandibular protrusion.

Figure 2—Changing curves of average AHI improvement rate, success rate, and normalization rate along with mandible protrusion (presented as percentage of MMP).



AHI improvement rate: $\Delta AHI\,(\%) = (1-AHI_{post}/AHI_{pre})*100$; success rate is the percentage of patients with a more than 50% AHI reduction; normalization rate is the percentage of patients with AHI reduced to less than 5 events/h. MMP = maximal mandibular protrusion.

Figure 3—Changing curves of AHI along with mandible protrusion (presented as percentage of MMP) in mild, moderate, and severe OSA groups.



Lines represent smoothing spline fitting and the shaded areas represent confidence interval. MMP = maximal mandibular protrusion.

the study. Clinical characteristics at baseline values are presented in **Table 1.**

Treatment outcome

The MADs brought obvious improvement in 40 of 42 patients. The treatment effects and required mandibular protrusion amounts are shown in **Table 2.** The AHI decreased from 16.8 (9.8–30.7) events/h to 4.3 (2.7–7.3) events/h ($P < .001$). The success rates (>50% AHI reduction) in groups with mild to severe OSA were both >90%, whereas the normalization rate (AHI <5 events/h) decreased as the severity increased. The required protrusion varied greatly among individuals, with a mean effective protrusion of 3.2 ± 1.9 mm (35.7 ± 19.5% of MMP) and a target protrusion of 4.8 ± 2.3 mm (53.5 ± 22.6% of MMP). In groups with moderate and severe OSA the mean effective protrusions were 33% and 41% of MMP or 3–3.5 mm, and the mean target protrusions were 63% and 69% of MMP or 5.8–5.9 mm. The target protrusion was larger than the effective protrusion in 22 patients.

Dose-dependent effects

The change in the average AHI improvement rate, success rate, and normalization rate along with mandibular protrusion (presented as the percentage of MMP) are shown in **Figure 2.** The changing curves were steeper within smaller protrusions, and the increase slowed down after a certain degree. The success rate curve flattened after 70% MMP, and the normalization rate curve flattened after 65% MMP. The AHI improvement rate curve flattened after 75% MMP. The dose-dependent relationship was more pronounced at smaller protrusions and was weakened at larger protrusions.

The decrease of AHI along with mandible protrusion (presented as the percentage of MMP) in the mild, moderate, and severe OSA groups are displayed in **Figure 3.** For mild OSA, the correlation between AHI and mandibular protrusion was relatively weak. The dose-dependent relationship between AHI and mandibular protrusion was more obvious with the increase in severity, especially in patients with severe OSA.

Nasal respiratory function and MRI

The rhinospirometry, rhinomanometry, and MRI measurements with no protrusion, effective protrusion, and target protrusion are shown in **Table 3.** The nasal inspiratory capacity increased significantly with effective protrusion but was not significant with target protrusion. The nasal resistance showed no significant change. **Figure 4** shows that the tongue became more upright and compressed, the soft palate became more straightened because of palatal stiffening, and the upper airway enlarged, particularly because of enlargement of the velopharynx.

Regression analysis

Single-factor linear regression showed that age, body mass index, baseline AHI, and nasal ventilation were parameters not significantly associated with effective and target protrusion. **Table 4** shows the results of multiple linear regression analysis of the factors affecting effective protrusion and target protrusion. The model showe that the main determinants of effective protrusion were the change of the maximal lateral dimension of the total upper airway and the mean lateral dimension of the oropharynx (R^2 = .409; P = .000). The main determinants of target protrusion were the soft palate length and the change of the maximal lateral dimension of the total upper airway (R^2 = .618; P = .002).

DISCUSSION

In this study, the success rate was relatively higher compared with previous studies.[26,27] One reason is that the average body mass index of the participants was relatively low, and another reason is that the monitoring by home sleep testing facilitated the titration. MADs are currently titrated mainly based on self-reported evaluation, but self-reported evaluation alone may not be accurate. It is necessary to titrate MADs with objective measurements. The complexity and cost of repeated polysomnography are impediments to MAD titration studies. Therefore, home sleep testing is recommended to monitor the

Table 3—Comparison of nasal respiratory function and upper airway dimensions at 3 different positions (n = 22).

	No protrusion	Effective protrusion	Target protrusion	F	*P*
Inspiratory capacity (cm^3)	2.03 ± 1.17	2.62 ± 1.36[b]	2.34 ± 1.21	5.422	.008[a]
Expiratory capacity (cm^3)	2.48 ± 1.33	2.51 ± 1.14	2.64 ± 1.37	0.418	.661
Inspiratory resistance ($Pa/cm^3/s$)	0.19 ± 0.09	0.17 ± 0.09	0.22 ± 0.19	1.414	.250
Expiratory resistance ($Pa/cm^3/s$)	0.19 ± 0.09	0.19 ± 0.10	0.19 ± 0.09	0.353	.704
Velopharynx mean L (cm)	1.42 ± 0.31	1.65 ± 0.49[b]	1.71 ± 0.48[c]	13.134	.000[a]
Velopharynx mean AP (cm)	0.96 ± 1.6	1.03 ± 0.14	1.05 ± 0.17[c]	5.154	.017[a]
Velopharynx mean CSA (cm^2)	1.18 ± 0.45	1.47 ± 0.54[b]	1.53 ± 0.58[c]	13.783	.000[a]
Velopharynx volume (cm^3)	4.29 ± 1.76	5.36 ± 2.07[b]	5.63 ± 2.27[c]	16.960	.000[a]
Total upper airway minimum L (cm)	0.87 ± 0.35	0.98 ± 0.37	1.08 ± 0.41[c,d]	7.379	.006[a]
Total upper airway mean L (cm)	1.89 ± 0.31	2.05 ± 0.35[b]	2.06 ± 0.40	6.399	.010[a]
Total upper airway maximum L (cm)	31.6 ± 4.1	31.8 ± 3.7	32.2 ± 5.1	0.286	.686
Total upper airway mean AP (cm)	1.18 ± 0.18	1.18 ± 0.15	1.19 ± 0.18	0.014	.986
Total upper airway minimum CSA (cm^2)	0.42 ± 0.24	0.40 ± 0.17	0.46 ± 0.21	2.132	.131
Total upper airway mean CSA (cm^2)	1.87 ± 0.42	2.01 ± 0.41[b]	2.02 ± 0.47	4.006	.026[a]
Total upper airway volume (cm^3)	16.53 ± 4.26	18.05 ± 4.43[b]	18.02 ± 4.80	4.529	.017[a]
Soft palate area (cm^2)	3.9 ± 0.4	3.6 ± 0.5	3.8 ± 0.5	1.970	.152
Soft palate angle (°)	119.0 ± 7.1	122.5 ± 5.6[b]	121.0 ± 7.2	4.261	.021[a]
Soft palate length (cm)	4.1 ± 0.3	4.0 ± 0.4	4.0 ± 0.4	0.710	.498
Soft palate height (cm)	1.1 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	3.220	.050
Tongue area (cm^2)	31.8 ± 3.5	30.4 ± 4.1	30.9 ± 3.7	4.074	.024[a]
Tongue angle (°)	33.2 ± 5.3	43.7 ± 5.7[b]	44.9 ± 8.0[c]	80.433	.000[a]
Tongue length (cm)	6.9 ± 0.9	6.5 ± 1.0[b]	6.5 ± 0.9[c]	5.576	.007[a]
Tongue eight (cm)	4.9 ± 0.4	5.2 ± 0.6[b]	5.3 ± 0.6[c]	14.544	.000[a]
H-Gn (cm)	4.4 ± 0.6	4.3 ± 0.7	4.3 ± 0.7	0.338	.715
H-PNS (cm)	7.5 ± 0.7	7.6 ± 0.8	7.5 ± 0.8	0.659	.523
H-C3 (cm)	3.6 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	0.245	.784

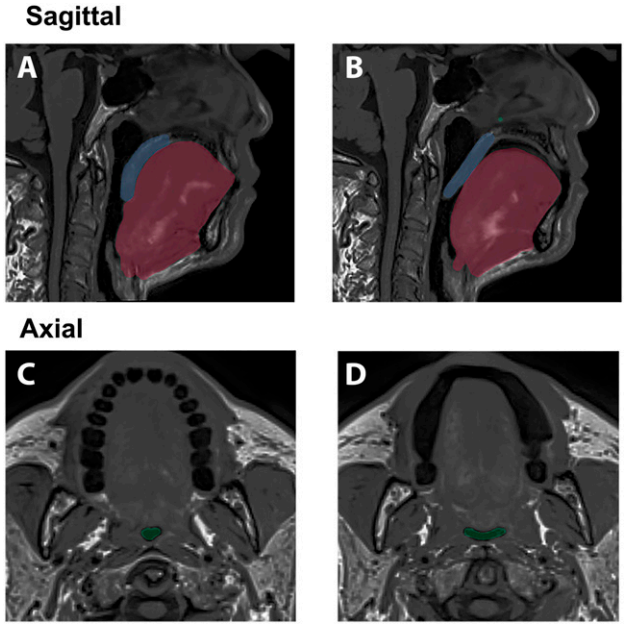
[a]After Bonferroni–Holm correction, within 3 groups, P < .05. [b]No protrusion compared with effective protrusion, P < .05. [c]No protrusion compared with target protrusion, P < .05. [d]Effective protrusion compared with target protrusion, P < .05. AP = anteroposterior dimension, C3 = C3 vertebra, CSA = cross-sectional area, H = hyoid, Gn = gnathion, L = lateral dimension, Pa = pascal, PNS = posterior nasal spine.

treatment response of MADs after a baseline diagnostic polysomnography has been performed.[28] Fleury et al[29] reported that the effectiveness of oral appliances could be improved by combining clinical and oximetric parameters.

The dose-dependent effect associated with mandibular protrusion has been proposed but not thoroughly investigated. We found that the dose-dependent relationship between AHI reduction and mandibular protrusion was nonlinear, and the overall success and normalization rate entered a relative plateau stage after approximately 70% MMP. In addition, the dose-dependent effect on AHI reduction brought by gradual mandibular protrusion became more pronounced as the severity of OSA increased. In the literature, 50%–75% MMP has been widely reported, consistent with the mean target protrusion of patients with moderate and severe OSA (63% and 69% MMP or 5.8 or 5.9 mm, respectively) but more than that of patients with mild OSA (39% MMP or 3.5 mm) in our study.[4,5,20,30–32] The meta-analysis showed that 75% MMP did not significantly increase the success and normalization rates or the AHI improvement rate compared with 50% MMP.[22,33] A randomized controlled trial by Tegelberg et al[21] compared MAD at 50% and 75% of MMP in the treatment of patients with mild to moderate OSA and found no significant difference in the 2 groups. Another randomized controlled trial conducted in patients with severe OSA reported that the normalization rate with 75% MMP was significantly higher than that with 50% MMP.[20] The changing curves displayed in our study showed that there was some difference between 50% MMP and 75% MMP, but the difference was small especially in patients with nonsevere OSA. In patients with moderate and severe OSA, 75% MMP may be better than 50% MMP. However, in a group with mild OSA, AHI reduction is more easily obtained at smaller protrusion degrees, so the widely used 75% MMP may overprotrude the mandible in patients with mild OSA. Anitua et al[34] reported that to achieve a 50% reduction of AHI, the mean mandibular advancement was 1.7 ± 1.5 mm in 72% of the patients in their study, which was even smaller than the mean effective protrusion of 3.2 ± 1.9 mm (35.7 ± 19.5% MMP) in our study. Forces created by progressive mandibular advancement with oral appliances were determined to reach 1.18 N per millimeter of advancement.[35] Thus, unnecessary overprotrusion may cause heavier forces to be applied to the oral and maxillofacial system and consequently may cause more adverse effects, such as temporomandibular joint pain and dental changes, that may interrupt long-term therapy with MADs.[36–38]

How to determine a personalized effective protrusion is a critical issue in clinical practice. In addition to the changing curves and general rule previously discussed, other factors should also be considered in patient-specific mandibular

Figure 4—Change of upper airway and surrounding soft tissues caused by MAD.



(A and B) Tongue (red) and soft palate (blue) before and after mandibular advancement. **(C and D)** Minimum cross-sectional area (green) of upper airway before and after mandibular advancement. MAD = mandibular advancement device.

Table 4—Multiple linear regression analysis of effective protrusion and target protrusion.

Variables	Coefficient	Standardized Coefficient	95% CI	T	*P*
Predictors of effective protrusion[a]					
Constant	6.899		4.060–9.737	4.929	.000
Change of maximum L in total upper airway	0.237	0.521	0.119–0.356	4.060	.000
Oropharynx mean L	−0.183	−0.346	−0.321–−0.046	−2.700	.011
Multivariate ANOVA F-test: $P = .000$, $R^2 = .409$					
Predictors of the target protrusion[b]					
Constant	−6.565		−13.975–0.846	−1.914	.078
Soft palate length	2.872	0.579	1.015–4.728	3.342	.005
Change of maximum L in total upper airway	0.204	0.453	0.035–0.373	2.612	.022
Multivariate ANOVA F-test: $P = .002$, $R^2 = .618$					

[a]Effective protrusion was mandibular advancement amount when API was reduced by 50%. [b]Target protrusion was mandibular advancement amount when API was reduced to the least. ANOVA = analysis of variance, CI = confidence interval, L = lateral dimension.

reposition. The regression model showed that the change of the maximal lateral dimension of the total upper airway was an unfavorable factor for both effective protrusion and target protrusion, which means that more mandibular protrusion was needed if the maximal lateral dimension increased with MADs. The increase of the maximal lateral dimension would negatively affect the difference between the minimum and maximum cross-sectional area of the upper airway. In addition, the mean lateral dimension of the oropharynx was negatively associated with effective protrusion; that is, patients with a transversely narrow oropharynx would require more protrusion to achieve a 50% reduction in AHI. The soft palate length was also an unfavorable factor for the target protrusion. Patients with a long soft palate would require more protrusion to obtain the best reduction of AHI. Other potential factors such as sex and race still need further investigation to improve the prediction ability of the model.

Therapeutic mechanisms of mandibular protrusion are airway dilatation and airway resistance reduction. However, we found that the measurements of nasal resistance and nasal flow were not sensitive enough, and it was not feasible to use them as mandibular titration parameters alone as a previous study reported.[39] The morphologic changes of the velopharynx seen on MRI were more sensitive, mainly by lateral expansion, consistent with previous studies.[2,40] Midsagittal imaging studies showed that the hyoid was not raised as previously reported.[2] A gradual increase in tongue height and a decrease in tongue length were observed. The increased tongue angle indicated that the tip of the tongue may drop back as a result of tongue muscle relaxation induced by the increased oral cavity. This may explain the decreased expansion of the anterior-posterior dimensions of the oropharynx.[41,42] MADs combined with measures to prevent the tongue tip from dropping back may improve the enlargement of the oropharynx, thus improving the efficacy of MADs.

There were some limitations to this study. First, because of the long duration of titration and monitoring, it is difficult to recruit a large number of patients who can finish the entire test. Second, the portable monitors used in this study could not record sleep position,[43] so the influence of sleep posture could not be recognized. Third, MRI was performed when patients were supine and awake; thus, the structural changes of the upper airway may not be identical to those that occur during sleep, and the evaluation of the results was not blind. Fourth, the mean body mass index of the population in this study was relatively low. Therefore, caution is needed when generalizing the conclusion to all OSA populations.

In conclusion, the dose-dependent effect of mandibular protrusion on AHI reduction by MADs was nonlinear, and the success and normalization rates entered a relative plateau stage after approximately 70% MMP. The dose-dependent relationship became more pronounced as the severity of OSA increased. The determination of mandibular protrusion should be more personalized for each patient, taking into consideration not only the severity of OSA but also the change of the maximal lateral dimension of the total upper airway with MADs, mean lateral dimension of the oropharynx, and soft palate length.

ABBREVIATIONS

MAD, mandibular advancement device
MMP, maximal mandibular protrusion
MRI, magnetic resonance imaging

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