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Original Article

ORIGINAL ARTICLE

Influence of mandibular advancement on tongue dilatory movement during wakefulness and how this is related to oral appliance therapy outcome for obstructive sleep apnea

Lauriane Jugé[1,2], Jade Yeung[1], Fiona L. Knapman[1,2], Peter G.R. Burke[1,2,3], Aimee B. Lowth[4,5], Ken Z.C. Gan[1,2], Elizabeth C. Brown[1,6], Jane E. Butler[1,2], Danny J. Eckert[1,2,7], Joachim Ngiam[4], Kate Sutherland[4,5], Peter A. Cistulli[4,5] and Lynne E. Bilston[1,2,*]

[1]Neuroscience Research Australia, Sydney, New South Wales, Australia, [2]Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia, [3]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia, [4]Respiratory and Sleep Medicine Department, Royal North Shore Hospital, Sydney, New South Wales, Australia, [5]Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia, [6]Respiratory and Sleep Medicine Department, Prince of Wales Hospital, Sydney, New South Wales, Australia, [7]Adelaide Institute for Sleep Health, Flinders University, Adelaide, South Australia, Australia

*Corresponding author. Lynne Bilston, Neuroscience Research Australia, Margarete Ainsworth Building, Barker Street, PO Box 1165, Randwick, Sydney, NSW 2031, Australia. Email: l.bilston@neura.edu.au.

Abstract

Study Objectives: To characterize how mandibular advancement splint (MAS) alters inspiratory tongue movement in people with obstructive sleep apnea (OSA) during wakefulness and whether this is associated with MAS treatment outcome.

Methods: A total of 87 untreated OSA participants (20 women, apnea–hypopnea index (AHI) 7–102 events/h, aged 19–76 years) underwent a 3T MRI with a MAS in situ. Mid-sagittal tagged images quantified inspiratory tongue movement with the mandible in a neutral position and advanced to 70% of the maximum. Movement was quantified with harmonic phase methods. Treatment outcome was determined after at least 9 weeks of therapy.

Results: A total of 72 participants completed the study: 34 were responders (AHI < 5 or AHI ≤ 10events/h with >50% reduction in AHI), 9 were partial responders (>50% reduction in AHI but AHI > 10 events/h), and 29 nonresponders (change in AHI <50% and AHI ≥ 10 events/h). About 62% (45/72) of participants had minimal inspiratory tongue movement (<1 mm) in the neutral position, and this increased to 72% (52/72) after advancing the mandible. Mandibular advancement altered inspiratory tongue movement pattern for 40% (29/72) of participants. When tongue dilatory patterns altered with advancement, 80% (4/5) of those who changed to a counterproductive movement pattern (posterior movement >1 mm) were nonresponders and 71% (5/7) of those who changed to beneficial (anterior movement >1 mm) were partial or complete responders.

Conclusions: The mandibular advancement action on upper airway dilator muscles differs between individuals. When mandibular advancement alters inspiratory tongue movement, therapeutic response to MAS therapy was more common among those who convert to a beneficial movement pattern.

Statement of Significance

Prediction of mandibular advancement splint (MAS) treatment outcome for obstructive sleep apnea (OSA) patients is currently unreliable. This study investigated whether the effect of mandibular advancement on inspiratory tongue dilatory movement during wakefulness in people with OSA is related to MAS treatment outcome. The results show that mandibular advancement alters inspiratory tongue movement pattern in 40% of individuals, likely reflecting an interaction between airway enlargement with mandibular advancement and dilator muscle function. When mandibular advancement changes how the tongue moves during inspiration, therapeutic response to MAS was more common among those who convert to a beneficial pattern (anterior movement >1 mm) during inspiration.

Key words: mandibular advancement splint; obstructive sleep apnea; magnetic resonance imaging; tagged MRI; upper airway mechanics

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Introduction

Obstructive sleep apnea (OSA) is an increasingly common sleep disorder [1, 2], where collapse of the airway occurs multiple times per night, resulting in oxygen desaturation, arousal, and sleep fragmentation [3]. As well as daytime sleepiness and reduced quality of life [4], OSA is linked to cardiac [5], metabolic [6], and neurocognitive [7] disorders. OSA is a multifactorial disease. While all patients have a degree of impaired upper airway anatomy (e.g. a narrow or collapsible airway), heterogeneous combinations of nonanatomical traits, such as impaired muscle responsiveness, low arousal threshold, and unstable ventilatory control also contribute to disease severity [8, 9].

The second line treatment for OSA, after continuous positive airway pressure (CPAP), is mandibular advancement splint (MAS) therapy [10]. CPAP is the most efficacious treatment [11]. However, while MAS is less efficacious, it is better tolerated by patients resulting in higher compliance [12] and similar real world effectiveness [13]. MAS is completely efficacious for less than 50% of OSA patients [14]. Currently, it is not possible to accurately predict who will benefit [15]. The mechanisms of action of MAS are thought to be largely anatomical, since holding the mandible forward during sleep widens the upper airway [16] and decreases airway collapsibility [17, 18]. However, previous studies have suggested that MAS may also affect nonanatomical factors such as upper airway muscle activity [19–21]. Patients with unstable ventilatory control are also less likely to respond to MAS treatment [22]. Better understanding of the precise mechanisms of MAS action will help predict treatment response for individual patients.

Active dilation of the upper airway muscles is a major contributor to maintaining airway patency to counter collapsing forces on the airway (e.g. negative inspiratory pressure, gravity when supine) [23]. Of particular interest is the genioglossus muscle in the tongue, as it is the largest pharyngeal dilator. Using tagged magnetic resonance imaging (tMRI), a spatial modulation of magnetization technique which allows dynamic tissue movements to be quantified [24], it has been reported that typically the posterior genioglossus moves anteriorly to widen the airway during inspiration, while relaxing posteriorly during expiration, with more movement likely to occur in the oropharyngeal region of the tongue [25, 26]. A narrower upper airway has previously been associated with greater dilatory movement of the genioglossus during inspiration in obese people without OSA [27]. Additionally, dilatory pattern was related to OSA severity with minimal movement observed in people with very severe OSA and larger anterior movement in matched controls without OSA [28]. The airway enlargement and OSA improvement with MAS therapy could therefore alter inspiratory tongue movements. However, to date, no study has examined the interactions between mandibular advancement, airway enlargement and dilator muscle function in people with OSA recommended for MAS therapy.

In this study, tMRI was used to examine how MAS alters inspiratory tongue movement in awake OSA patients during quiet breathing. The aims were (1) to compare the anterior and posterior movement of the tongue with the mandible in neutral and advanced position to investigate the impact of oral appliance on inspiratory dilatory function and (2) to investigate whether alterations in these movements with mandibular advancement relate to MAS treatment outcome. We hypothesized that (1) enlargement of the airway with mandibular advancement will result in reduced inspiratory tongue movement and (2) larger anterior tongue movement in people with OSA will be associated with better treatment outcomes when the mandible is advanced.

Methods

Participants

The protocol was approved by the local human research ethics committee (South Eastern Sydney Local Health District, ref 14/305 [HREC/14/POWH/699]). It adheres to the Declaration of Helsinki (2013) with the exception of registration in a publicly accessible database (clause 35) because this is not a clinical trial. This was a prospective study and none of the data presented has been previously reported. Written informed consent was obtained from all participants. A total of 105 participants (26 females) with untreated OSA who were recommended for MAS treatment by their sleep physician were recruited from local sleep clinics for this study. Exclusion criteria included an apnea–hypopnea index (AHI) below 5 events/h, any contraindications to standard MRI safety criteria, prior upper airway surgery or OSA treatment, and medications which could affect sleep or respiratory muscle function. Baseline AHI was determined with a diagnostic polysomnography (PSG) conducted within 15 months prior to recruitment. All PSGs were conducted with standard equipment, and recordings included electroencephalography, chin electromyography, electrocardiogram, airflow, respiratory effort, and oximetry. PSGs were scored following the American Academy of Sleep Medicine manual (v2.4) [29] across 3 separate sites (i.e. independent private scorer, Neuroscience Research Australia [NeuRA], and Royal North Shore Hospital [RNSH]). Either good or excellent concordance were observed between scorers (see Supplementary File). Participants were grouped according to untreated OSA severity, where $10 < \text{AHI} \leq 15$ events/h was considered mild OSA, $15 < \text{AHI} \leq 30$ events/h was moderate OSA, and an AHI > 30 events/h was considered severe.

Experimental protocol and MAS device

The protocol comprised several stages: (1) dental appointments for impressions and fitting of a MAS device, (2) MRI scan, and (3) an in-lab overnight PSG to determine treatment outcome. Once recruited, a custom made MAS device (SomnoDent Flex, SomnoMed Pty Ltd, Australia) [30, 31] was manufactured for each participant. This is a titratable device with two pieces fitted to the participant's upper and lower dental arches, and a screw mechanism to adjust the level of mandibular advancement. The MRI scan was performed approximately 2 weeks after enrollment, before starting MAS therapy. Participants were asked to wear the device nightly for at least 8 weeks and incrementally titrated over this timeframe, starting at 70% of maximum advancement to a comfortable maximum protrusion. Once the maximum protrusion was achieved and confirmed by the dentist, the MAS was worn for at least another week before a final in-lab overnight PSG was performed, with the participant wearing the MAS to determine treatment response. Treatment response to MAS was determined by the AHI in the follow-up PSG. Participants were grouped into responders (MAS AHI ≤ 5

events/h or MAS AHI ≤ 10 events/h with AHI reduction from before MAS therapy ≥50%), partial responders (MAS AHI > 10 events/h, but with AHI reduction ≥50%), and nonresponders (AHI reduction < 50%).

MR acquisition

Participants were scanned supine in a clinical 3T MRI scanner (Achieva TX, Philips Medical Systems, Best, The Netherlands). As the SomnoMed MAS has a metal component for titration, a temporary MRI compatible device was worn for the entire scan (Apneagard, BMedical Pty Ltd, Australia), and imaging was obtained in two jaw positions—an "advanced" position which was set at 70% of the participant's maximum advancement and a "neutral" position, which was a comfortable normal jaw position (no advancement). 70% of the maximal protrusion was used to assess the effect of mandibular advancement in all participants, as it is commonly used at the start of the treatment by dentists.

T2-weighted anatomical scans were obtained in the sagittal and axial planes in both mandible positions, for anatomical and volumetric measurements. tMRI scans were obtained in the sagittal plane to characterize inspiratory tongue movement. Detailed imaging parameters and MRI methods are presented in Supplementary File.

MR analysis

All data were analyzed blinded to OSA severity and treatment outcome.

tMRI scans

Inspiratory tongue movement from tMRI images was analyzed using a previously validated technique with excellent reproducibility [32] (see Supplementary File for more details). The antero-posterior movement of each point was quantified by tracking the displacement from the start of inspiration to the start of expiration. The antero-posterior direction was defined as perpendicular to the participant's posterior pharynx wall. As tongue movement was similar across the three breaths for the nasopharyngeal and oropharyngeal posterior of the tongue in both mandible positions (intraclass correlation coefficient two-way mixed model ICC > 0.85, $p < 0.001$ for all tests, $n = 87$), the movements for each point were averaged across the three breaths. Data were then grouped into the nasopharyngeal region (points above the inferior tip of the soft palate) or oropharyngeal region (Figure 1, A), and averaged to obtain representative nasopharynx and oropharynx movements. Positive displacements represent posterior movement (which would narrow the airway) and negative displacements represent anterior movements (which would cause dilation).

For each mandible position, inspiratory tongue movement was defined as "beneficial," "minimal," or "counterproductive". Beneficial movement patterns encompassed those where the nasopharyngeal and/or oropharyngeal regions moved anteriorly >1 mm (widening the upper airway). Movement <1 mm in both regions was classified as minimal. Counterproductive patterns included those where one or both regions moved posteriorly >1 mm (narrowing the upper airway). Inspiratory dilatory patterns were defined before the study initiation. They are based on previous studies [28, 33], where the threshold of 1 mm was used to separate the minimal pattern group from the groups with movement.

Anatomical scans

To better understand the changes in upper airway size with mandible advancement on inspiratory dilatory pattern, anatomical scans were used to obtain volumetric measurements of the nasopharynx and oropharynx (Figure 1, B) and 2D nasopharyngeal and oropharyngeal cross-sectional area (CSA) measurements in both neutral and advanced mandible positions (Figure 1, C and D). The percentage of change between these two mandible positions was calculated (see Supplementary File for more details). Tongue and soft palate volumes were also measured on the images obtained with the mandible in neutral position because they can drastically impact upper airway size.

Statistical analysis

The primary outcome variable was inspiratory tongue movement, which was measured in both a neutral and advanced mandible position. Outcomes were defined before the study initiation along with the two hypotheses, based on previous studies [27, 28]. Statistical analysis was performed using SPSS (V24, IBM, Armonk, NY). Data are reported as mean ± standard deviation. For clarity, the specific statistical tests performed are listed with the results of the analysis. p values of less than 0.05 were considered significant.

Results

Inspiratory tongue movement was quantified for 87 (20 females) subjects out of 105 (82.9%). Dynamic scans were not completed for five participants due to claustrophobia or withdrawal partway through the scan, four participants did not have breathing information collected with the tagged images due to technical problems, and tongue movement could not be reliably quantified in nine participants due to poor image quality. Poor image quality was the consequence of large movement artifacts, such as those occurring during swallowing.

MAS treatment outcome was known for 72 (17 females) of these 87 participants (83.8%). Participants without a treatment outcome were either lost to follow-up (eight participants) or withdrew as they could not tolerate the MAS (six participants) or withdrew for personal reasons (one participant). Anatomical image quality was sufficient to quantify volumes in 60 of 72 participants (83.3%). Cross-sectional areas were quantified in all 72 participants.

Participant characteristics

Among these 72 participants, 16 participants had mild OSA, 27 had moderate OSA, and 29 had severe OSA before MAS treatment. They were largely middle aged (45 ± 11 years) male (17 females) and overweight (mean BMI 28.6 ± 4.8 kg/m^2). Age and BMI did not differ between OSA severity groups (one-way ANOVA, $p = 0.30$, and $p = 0.87$, respectively). The upper airway anatomical measurements with the mandible in neutral position were similar across OSA severity groups (one-way ANOVA, tongue

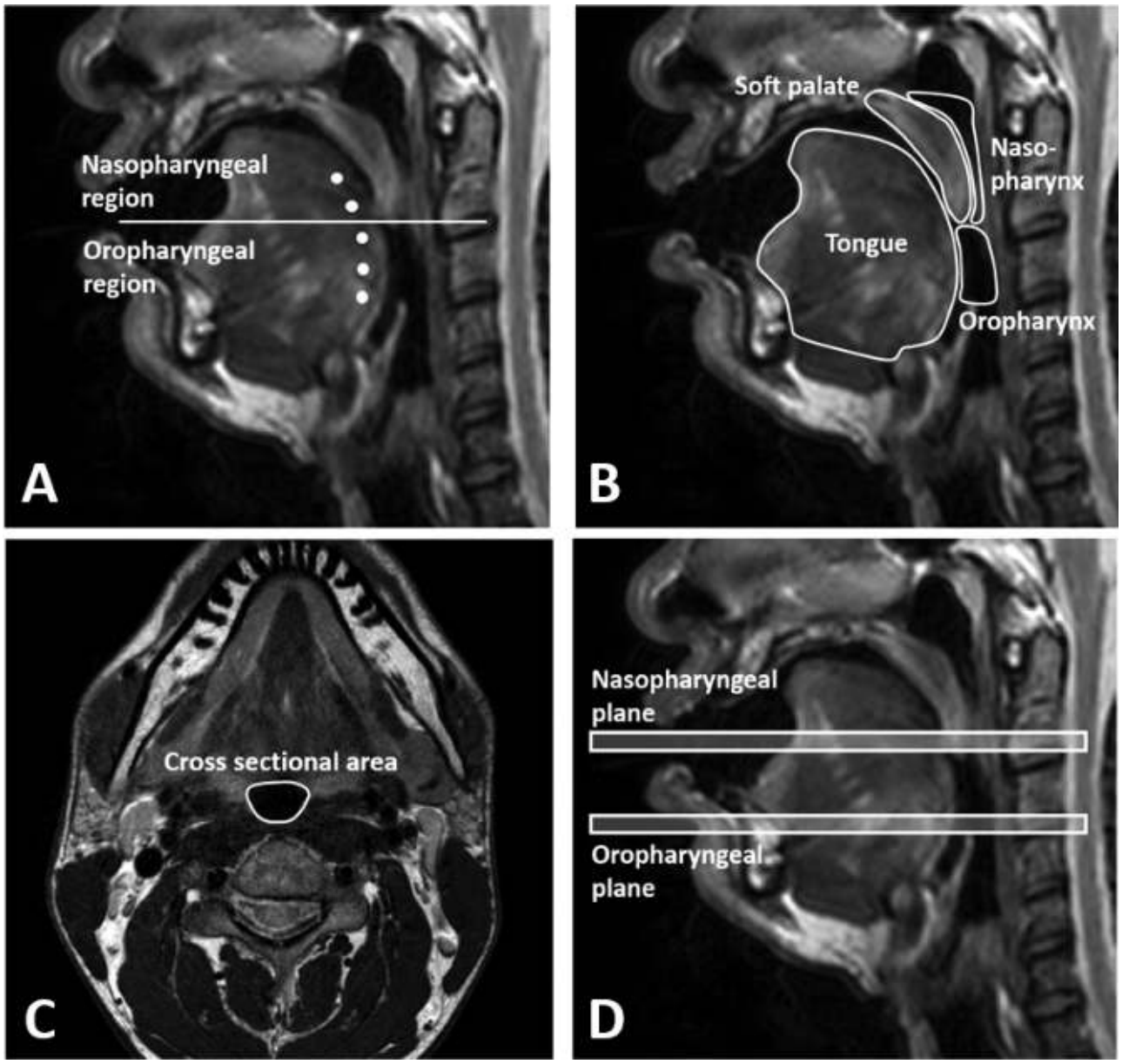

Figure 1. Imaging analysis. (A) Placement of tracking points at the posterior of the tongue, from the epiglottis to halfway up the soft palate, following the curvature of the tongue. Points are separated into nasopharyngeal points (above the base of the soft palate), and oropharyngeal points. (B) Outline of the tongue (excluding the geniohyoid), soft palate, nasopharynx, and oropharynx for volume measurements in the mid-sagittal slice. (C) Pharynx cross-sectional areas are measured by manually outlining the airway in two axial slices. (D) One slice is at the narrowest area of the nasopharynx, and the other slice is at the oropharynx, positioned above the epiglottis.

volume: $p = 0.81$, soft palate volume: $p = 0.29$, nasopharynx/oropharynx volumes: $p = 0.35/0.79$, nasopharyngeal/oropharyngeal CSAs: $p = 0.57/0.95$).

On therapy, 34 participants were responders, 9 were partial responders, and 29 nonresponders. Overall, mandibular advancement with MAS significantly decreased the AHI, increased the nasopharynx volume, and the narrowest cross-sectional area of the pharynx (see Table 1).

Inspiratory tongue movements

Table 2 reports tongue movement during inspiration by pattern and mandibular position. When the mandible was advanced, greater anterior nasopharyngeal movement of the tongue was associated with smaller nasopharyngeal volume (Spearman, $r = 0.28$, $p = 0.03$). There were no other significant associations between tongue movement and demographic variables or anatomical measurements.

Participants with counterproductive inspiratory tongue movement patterns with the mandible in the neutral position had a larger nasopharyngeal cross-sectional area (83 ± 75mm^2, one-way ANOVA, $p = 0.002$) than those with minimal or beneficial movements (38 ± 26 mm^2 and 33 ± 18 mm^2, respectively, Sidak's multiple comparisons, $p < 0.003$). When the mandible was advanced, participants with counterproductive inspiratory tongue movement patterns had larger soft palate volume (9.4 ± 2.4 cm^3, one-way ANOVA, $p = 0.03$) than those with minimal movement (7.2 ± 1.8 cm^3, Sidak's comparison, $p = 0.03$), but

Table 1. Participant demographics, AHI and anatomical measurements are presented as mean ± standard deviation for each response category group with the mandible in neutral and advanced position

	Responders $n = 34$	Partial responders $n = 9$	Nonresponders $n = 29$	P values
Number (M:F)	23:11	7:2	25:4	$p = 0.25^{\$}$
AHI (events/h)	Baseline: 25.4 ± 14.0	Baseline: 47.1 ± 20.2	Baseline: 28.8 ± 18.0	$p_{interaction} < 0.001^{\&}$
	On therapy: 4.7 ± 2.9	On therapy: 16.4 ± 6.2	On therapy: 20.8 ± 11.2	$p_{mandible\ position} < 0.001$
				$p_{treatment\ response} < 0.001$
Age (years)	44 ± 13	49 ± 6	44 ± 11	$p = 0.44^{\wedge}$
BMI (kg/m^2)	28.1 ± 4.6	30.1 ± 5.6	28.8 ± 4.7	$p = 0.51^{\wedge}$
Maximal mandibular protrusion (mm)	6 ± 2	6 ± 1	6 ± 2	$p = 0.54^{\wedge}$
Genioglossus volume (cm^3)	87.5 ± 11.9	91.9 ± 12.5	96.5 ± 15.9	$p = 0.07^{\wedge}$
Soft palate volume (cm^3)	6.9 ± 1.6	7.5 ± 2.3	7.8 ± 2.0	$p = 0.23^{\wedge}$
Nasopharynx	Neutral: 5.0 ± 2.5	Neutral: 4.1 ± 1.5	Neutral: 4.7 ± 2.1	$p_{interaction} = 0.66^{\&}$
Volume (cm^3)	Advanced: 5.4 ± 2.2	Advanced: 4.6 ± 2.0	Advanced: 5.5 ± 2.7	$p_{mandible\ position} = 0.005$
				$p_{treatment\ response} = 0.70$
Narrowest CSA (mm^2)	Neutral: 39 ± 40	Neutral: 33 ± 20	Neutral: 47 ± 30	$p_{interaction} = 0.21^{\&}$
	Advanced: 46 ± 32	Advanced: 53 ± 40	Advanced: 63 ± 45	$p_{mandible\ position} < 0.001$
				$p_{treatment\ response} = 0.34$
Oropharynx	Neutral: 7.7 ± 3.4	Neutral: 5.4 ± 1.9	Neutral: 8.0 ± 5.1	$p_{interaction} = 0.86^{\&}$
Volume (cm^3)	Advanced: 7.9 ± 4.3	Advanced: 6.1 ± 1.9	Advanced: 8.4 ± 5.6	$p_{mandible\ position} = 0.17$
				$p_{treatment\ response} = 0.47$
CSA (mm^2)	Neutral: 200 ± 86	Neutral: 154 ± 63	Neutral: 200 ± 87	$p_{interaction} = 0.06^{\&}$
	Advanced: 211 ± 90	Advanced: 180 ± 79	Advanced: 216 ± 110	$p_{mandible\ position} = 0.83$
				$p_{treatment\ response} = 0.43$

Statistical differences between OSA response categories were assessed using one-way ANOVA (^) or repeated two-way ANOVA ($^{\&}$) to evaluate the effect of mandibular advancement on anatomical variables. The effect of gender on OSA response categories was assessed using a Fisher's exact test ($^{\$}$). All variables were assessed over all subjects ($n = 72$), except the volumes which were measured in 60 subjects (28 responders, 6 partial responders, and 26 nonresponders). One participant was underweight (BMI < 18.5 kg/m^2), 17 were normal range BMI (18.5 ≤ BMI < 25 kg/m^2), 28 were overweight (25≤ BMI <30 kg/m^2), and 26 were obese (BMI ≥ 30 kg/m^2). M, male; F, female; AHI, apnea–hypopnea index; CSA, cross-sectional area.

$^{*}p < 0.05$.

$^{**}p < 0.01$.

$^{***}p < 0.001$.

Table 2. Antero-posterior movement (mean ± standard deviation, mm) measured within the posterior tongue at the level of oropharynx and nasopharynx for the three dilation patterns observed during inspiration (anterior beneficial, minimal and posterior counterproductive) with the mandible in neutral and advanced positions

	Movement (mean ± standard deviation, mm)			
	Neutral		Advanced	
Airway dilation patterns	Nasopharynx	Oropharynx	Nasopharynx	Oropharynx
Beneficial	−0.41 ± 0.73	−1.26 ± 0.63	−0.29 ± 1.07	−1.65 ± 0.62
Minimal	0.02 ± 0.45	−0.01 ± 0.54	0.24 ± 0.45	−0.12 ± 0.47
Counterproductive	0.29 ± 1.05	1.60 ± 0.37	0.66 ± 1.41	1.55 ± 0.28

Movements of less than 1 mm were considered to be minimal. Negative displacements represent anterior movement.

not than those with beneficial movement (7.0 ± 1.5 cm^3, Sidak's comparison, $p = 0.05$).

Alterations in inspiratory tongue movement patterns with mandible position

A majority of the participants had minimal inspiratory tongue movement when the mandible was in both the neutral and advanced positions (Figure 2). There were no significant differences in proportions of pattern between mandible positions (Fisher's exact test, $p = 0.09$).

Mandibular advancement did not alter tongue movement patterns during inspiration for 60% (43/72) of the participants (Table 3). A large proportion of subjects with minimal movement in the neutral position did not change with advancement (78%, 35/45), while 75% (15/20) of the participants with beneficial and 57% (4/7) of the participants with counterproductive tongue movement in the neutral position had a different movement pattern with the mandible advanced. Among participants for whom advancement altered inspiratory tongue motion pattern, neutral inspiratory tongue movement patterns and the trajectories of change were not associated (McNemar's test, $p = 0.27$, Figure 3).

Compared with those for whom mandibular advancement did not alter inspiratory tongue movement, participants for whom advancement altered inspiratory tongue movement had a smaller increase in upper airway cross-sectional area with mandibular advancement (21 ± 53% vs 82 ± 160%, t-test

with unequal variances, $p = 0.02$), and larger soft palate volume (8.0 ± 1.9cm^3 vs. 6.9 ± 1.7cm^3, *t*-test with unequal variances, $p = 0.04$). Other demographic variables and anatomical measurements did not differ between these groups. There was no association between OSA severity or treatment response and whether inspiratory tongue movement pattern changed or not (Fisher's exact tests, $p = 0.86$, and $p = 0.08$, respectively).

Participants for whom advancement did not alter tongue movement pattern

Treatment outcome was not associated with inspiratory tongue movement patterns, but nonresponders had a larger cross-sectional upper airway with the mandible in neutral position (56 ± 35 mm^2, one-way ANOVA, $p = 0.04$) than responders (34 ± 19 mm^2, Sidak's comparison, $p = 0.049$), but not than partial responders (34 ± 21 mm^2, Sidak's comparison, $p = 0.15$). Partial responders had a higher AHI before MAS therapy (41.9 ± 13.5 events/h, one-way ANOVA, $p = 0.008$) than responders (22.9 ± 12.3 events/h Sidak's comparison, $p = 0.06$), but not than nonresponders (28.9 ± 15.9 events/h, Sidak's comparison, $p = 0.11$). Other demographic and anatomical measurements were not different between treatment response categories.

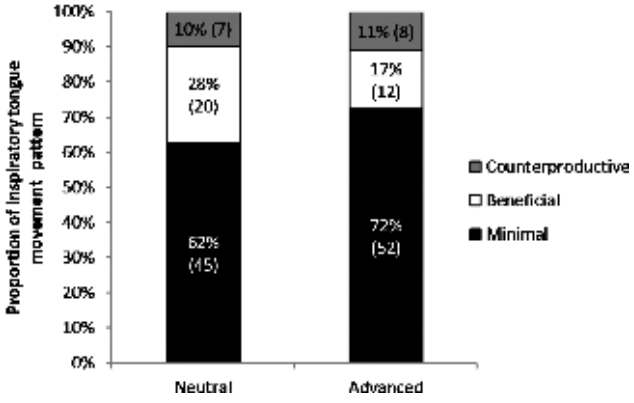

Figure 2. Distribution of inspiratory tongue movement patterns with the mandible in neutral and advanced positions. A majority of the participants had minimal inspiratory tongue movement in the neutral position. Individual changes in inspiratory dilatory patterns with mandibular advancement are reported in Table 3. Data labels: % (*n* participants).

Participants for whom advancement altered tongue movement patterns

When responders and the partial responder were taken together, therapeutic response to MAS were more commonly seen among those who convert to a beneficial pattern (ordinal regression, odds ratio = 4.0, $p = 0.09$; Figure 4), but this was not statistically significant. Participants who changed to a counterproductive tongue movement pattern had a larger percentage change in nasopharyngeal cross-sectional area (87 ± 67%, one-way ANOVA, $p = 0.005$) than those who changed to minimal (6 ± 40%, Sidak's comparison, $p = 0.005$) or beneficial (8 ± 38%, Sidak's comparison, $p = 0.02$). Other demographic and anatomical measurements were not different between trajectories of change.

Discussion

The main findings are: first, a majority of people with OSA maintained airway patency during inspiration without significant dilatory motion of the tongue (minimal inspiratory tongue movement). Second, MAS alters inspiratory tongue movement patterns in 40% of participants. These participants mostly had beneficial or counterproductive patterns during inspiration with the mandible in the neutral position and had only small increases in nasopharyngeal cross-sectional area with mandibular advancement. Third, while tongue inspiratory movement patterns were not directly associated with treatment outcome across the whole sample, in participants where MAS altered inspiratory tongue movement pattern, change to a beneficial inspiratory tongue movement pattern was more commonly seen in responders and the partial responders than in nonresponders.

Minimal inspiratory tongue movement

This study has reproduced the finding that airway patency can be maintained with minimal inspiratory tongue movement in subjects with large airways. This was demonstrated in a previous study where people without OSA with large airways had minimal movements in the tongue in inspiration [27], while those with narrower airways showed greater active dilation of the airway during inspiration. In overweight people with OSA during wakefulness [32], an upper airway cross-sectional area of 60–70 mm^2 is thought to be enough to maintain airway patency with minimal anterior tongue movement.

Table 3. Distribution of number of inspiratory tongue movement patterns observed in OSA subjects when the mandible was in neutral position and advanced with a MAS

	Neutral			
	Inspiratory tongue motion patterns	Minimal	Beneficial	Counterproductive	Total
Advanced	Minimal	35	13	4	52
	Beneficial	7	5	0	12
	Counterproductive	3	2	3	8
	Total	45	20	7	72

There were no subjects with counterproductive patterns which became beneficial when the mandible was advanced. Overall, there was no significant association between inspiratory tongue movement patterns in the two mandible positions (McNemar–Bowker test, $p = 0.27$).

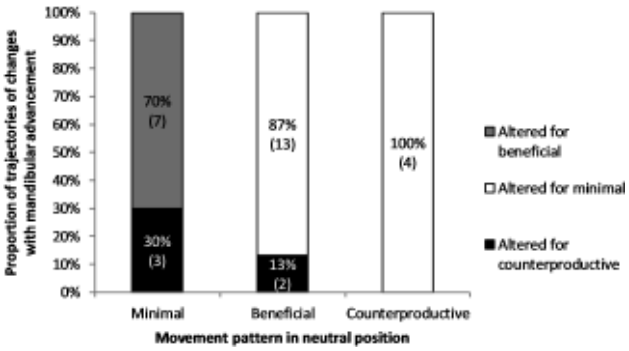

Figure 3. Proportion of trajectories of change in inspiratory tongue movement pattern with mandibular advancement for each movement patterns observed with no advancement. All subjects where MAS altered inspiratory patterns for beneficial patterns had minimal movement at neutral position. In a larger proportion, beneficial and counterproductive patterns with the mandible in neutral position became minimal patterns with the mandible advanced. Individual changes in inspiratory dilatory patterns with mandibular advancement are reported in Table 3. Data labels: % (*n* subjects).

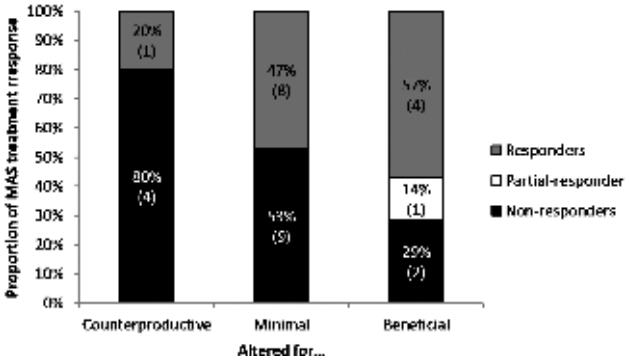

Figure 4. Proportion of MAS treatment response categories for each trajectory of inspiratory tongue movement change with mandibular advancement. Individual changes in inspiratory dilatory patterns with mandibular advancement are reported in Table 3. Data labels: % (number of participants).

However, results of inspiratory dilatory movement with the mandible in the neutral position from this study and the previous ones mentioned above cannot be directly compared because participants in this study wore a MAS device during the MRI scan, and not in the other studies. It is possible that the presence of the device altered the upper airway geometry and so the inspiratory dilatory movement. Specifically, the device may anatomically confine the tongue in the oral cavity and reduce its movement. With the device in the mouth when the mandible is in neutral position, the tongue may be less able to move forward during inspiration. This could explain the difference in results between studies, and explain why a higher proportion of minimal motion pattern was observed for people with severe OSA in this study compared to another study [33]. However, this needs to be confirmed in further studies.

The observed lack of movement could also indicate an inadequate neuromechanical response to increased load, potentially caused, at least in part, by neuropathy in the tongue [34–36]. Neuropathy was also suggested as a possible explanation for the minimal inspiratory patterns previously reported in people with severe OSA with the mandible in a neutral position, in comparison to controls and people with mild OSA who displayed beneficial movement patterns [28]. In contrast, healthy obese individuals without OSA but with narrow airways have been reported to show beneficial movement patterns during inspiration [28]. Severe motor unit neuropathy could potentially reduce anterior movement, although there is no evidence that the genioglossus is weakened to such a great extent [37]. The motor neuropathy, associated with enlarged motor units that has been observed in people with OSA [35, 36, 38], theoretically may result in more force for the same drive rather than reduce movement, although this has not been formally assessed to date. On the other hand, sensory neuropathy, which could reduce reflex drive through the lack of sensory input related to changes in negative pressure, could be a potential cause of the reduced tongue movement observed in the current study. However, the link between motor unit size and/or activity and tongue movement needs to be verified with measures of these factors in the same participants.

Effects of mandibular advancement on inspiratory tongue movements

Heterogeneity in inspiratory tongue movement is thought to reflect different physiological responses to a compromised airway anatomy when the mandible is in a neutral position [28]. However, it could also inform our understanding of the mechanisms of action of MAS depending on how dilatory movements change with mandibular advancement, as this reflects the physiological response to changes in airway anatomy as a result of mandibular advancement. In our study, inspiratory tongue movement was altered by mandibular advancement in 40% of participants. This is similar to a previous study which found no systematic differences in inspiratory tongue movement between neutral and advanced mandibles in healthy normal range BMI participants without OSA [39].

Among those for whom inspiratory tongue movement pattern was not altered, a large proportion (35/43, 81%) had minimal dilatory movement. Two factors might contribute to this finding—OSA-induced neuropathy and anatomical confinement of the tongue in the oral cavity with the temporary MAS in situ. OSA-induced neuropathy in the tongue would be expected to reduce dilatory movement irrespective of mandibular advancement, consistent with there being minimal movement in both mandible positions, and why improving the anatomy may not be sufficient to initiate anterior movement of the tongue. The bulk of the MAS device may also be exacerbating anatomical confinement of the tongue in the oral cavity and reducing its freedom of movement, thereby reducing dilatory movement in response to the neural drive that is present. These potential explanations are supported by the observation that most of these individuals had a nasopharyngeal cross-sectional area well below the previously suggested threshold to maintain airflow without active dilatory movement of the tongue (mean 40 ± 27 mm^2 compared with 60–70 mm^2) [27], which could be a result of both narrowing of the airway lumen due to the MAS, and an inadequate response to this narrowed airway via the pharyngeal negative pressure reflex.

In contrast, people with beneficial or counterproductive inspiratory tongue movement patterns with the mandible in neutral position were more likely to display a different pattern with mandibular advancement. Inspiratory movement

larger than 1 mm in the neutral position has also been reported in people with OSA and is likely reflective of effective neural drive in the genioglossus [32]. The genioglossus is innervated by separate sub-branches of the medial branches of the hypoglossal nerve [40] that may contribute to these changes in inspiratory movement patterns with mandibular advancement, potentially by varying the neural drive to the horizontal and oblique compartments of the genioglossus (i.e. nasopharyngeal and oropharyngeal posterior of the tongue) to adapt inspiratory tongue movement to the upper airway geometry [32], altered tongue position and muscle fiber directions. Among those who changed their inspiratory movement to a beneficial pattern, a large majority were complete or partial responders, suggesting that the genioglossus was more effective at dilating the airway with MAS. Greater anterior movement of the tongue with the mandible advanced could indicate these individuals have increased genioglossus EMG activity with mandibular advancement which has been reported in OSA patients awake seated [41] and supine [20]. It could also reflect an effective response to the airway negative pressure excitatory reflex associated with a narrow upper airway, as those with a beneficial pattern had a smaller relative change in nasopharyngeal cross-sectional area with mandibular advancement.

For those individuals for whom mandibular advancement altered inspiratory tongue movement patterns to minimal or counterproductive patterns, one possible explanation could be that the soft tissue rearrangements from mandibular advancement exacerbated the anatomical confinement of the tongue. Anterior inspiratory tongue movement may not be possible due to a lack of space in the oral cavity [42], as the tongue is a muscular hydrostat [43]. Another possible explanation could be that regional neural drive became ineffective with mandibular advancement at opening a local portion of the airway due to the new tongue position and muscle fiber orientation. Both explanation could in turn lead to minimal or counterproductive movement patterns where part of the tongue moves posteriorly to compensate for anterior movement elsewhere. Patients who changed to counterproductive patterns had the largest increase in nasopharyngeal cross-sectional area with mandibular advancement and were more likely to be nonresponders. Nonresponders also had a larger nasopharyngeal cross-sectional area with the mandible advanced (48 ± 38 mm^2) than responders and the partial responder (39 ± 13 and 31 mm^2, respectively). This provides further evidence that anatomical enlargement of the upper airway may not be the only mechanism underlying MAS efficacy, and may shed light on why it is so difficult to predict MAS treatment outcome from static upper airway anatomy alone. Positive treatment outcome has rarely been associated with a larger upper airway with MAS [44, 45], although it is thought that mandibular advancement reduces upper airway collapsibility primarily by passively increasing the lateral dimensions of the airway [46–50]. These patients and particularly those who changed to a counterproductive pattern, may benefit from a smaller degree of mandibular advancement, consistent with previous findings that upper airway collapsibility tends to improve in the first half of mandibular advancement for nonresponders in contrast to responders for whom it occurs toward maximal advancement [18]. A smaller upper airway may initiate beneficial inspiratory tongue motion by increasing the pressure swings, provided there is not too much anatomical confinement, thereby increasing neural drive to the genioglossus via the negative pharyngeal pressure reflex to potentially enhance MAS efficacy, but this needs to be confirmed.

Limitations

This study has several limitations. First, participants were imaged awake so we cannot confirm that the same dilatory motion changes occur during sleep. This was done because there are good reasons to think that these wakefulness measures might be related to dilator muscle function during sleep. It has been shown that much of the phasic inspiratory component of genioglossus activity is driven by the negative pharyngeal pressure reflex, which is present during both wakefulness and sleep, although it is diminished in magnitude during REM sleep [51, 52]. Conceptually, if MAS alters the nadir pharyngeal pressure during sleep (as it does during wakefulness), then it could similarly alter the dilatory function of the genioglossus during sleep via this reflex mechanism, despite the drop in tonic neural drive during sleep. Indeed, there is some data to suggest that MAS is less efficacious for patients with REM-predominant OSA [53], which would be consistent with the attenuation of the reflex in REM sleep limiting the improvement of dilatory muscle function. Bamagoos et al. [18], albeit in a small sample, recently showed that muscle responsiveness to pharyngeal pressure drops was variable between OSA patients, with some appearing to have substantially improved muscle responsiveness to negative pharyngeal pressure with mandibular advancement. Other possible mechanisms include that the MAS may improve dilatory muscle geometry, making them more efficient at opening the airway (e.g. by orienting the muscles more perpendicular to the airway), which in turn may improve their recruitment, via the "neuromechanical matching" principle [42, 54]. Second, we were likely underpowered to detect a statistically significant association with alteration in movement patterns and treatment outcome. Our hypothesis was that mandibular advancement would alter inspiratory tongue movement patterns in all participants, and not just in 40%. Thus, the study was not designed for this subgroup analysis. Third, different oral appliances were used for the imaging and clinical treatment, because the SomnoDent Flex device was not MRI compatible. We do not expect that the effect on the upper airway enlargement differs much between devices, since 70% of the maximal advancement was used for both devices and the efficacy of the Apneaguard and custom acrylic splints is similar [55, 56]. Fourth, there are probably fewer morbidly obese patients in this study than in the general OSA population. Possible reasons include increased risk of discomfort and weight limits of the MRI scanner, or decreased likelihood to be referred for a trial of MAS therapy by their sleep physician. Similarly, there may be fewer older patients who met the dental criteria for MAS treatment. Therefore, we cannot be certain that our findings would generalize to older OSA patients and those with higher BMI.

Conclusion

Advancement of the mandible changed the inspiratory tongue movement in approximately 40% of people with OSA undergoing a trial of MAS therapy. In particular, the subgroup

of patients in whom there was an improvement in dilator muscle function with the mandible advanced were more likely to benefit from MAS therapy. In contrast, those whose inspiratory movement pattern with MAS became counterproductive with advancement were less likely to benefit from MAS therapy. This indicates that a complex interaction between anatomical and inspiratory dilatory function influences an individual's response to MAS therapy, rather than anatomical changes alone.

Supplementary material

Supplementary material is available at *SLEEP* online.

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