SLEEPJ, 2018, 1–12

doi: 10.1093/sleep/zsy021
Advance Access Publication Date: 26 March 2018
Original Article

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Anatomic predictors of response and mechanism of action of upper airway stimulation therapy in patients with obstructive sleep apnea

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Abstract

Study Objectives: Upper airway stimulation has been shown to be an effective treatment for some patients with obstructive sleep apnea. However, the mechanism by which hypoglossal nerve stimulation increases upper airway caliber is not clear. Therefore, the objective of this study was to identify the mechanism of action of upper airway stimulation. We hypothesized that, with upper airway stimulation, responders would show greater airway opening in the retroglossal (base of the tongue) region, greater hyoid movement toward the mandible, and greater anterior motion in the posterior, inferior region of the tongue compared with nonresponders.

Methods: Seven participants with obstructive sleep apnea who had been successfully treated with upper airway stimulation (responders) and six participants who were not successfully treated (nonresponders) underwent computed tomography imaging during wakefulness with and without hypoglossal nerve stimulation. Responders reduced their apnea–hypopnea index (AHI) by 22.63 ± 6.54 events per hour, whereas nonresponders had no change in their AHI (0.17 ± 14.04 events per hour). We examined differences in upper airway caliber, the volume of the upper airway soft tissue structures, craniofacial relationships, and centroid tongue and soft palate movement between responders and nonresponders with and without hypoglossal nerve stimulation.

Results: Our data indicate that compared with nonresponders, responders had a smaller baseline soft palate volume and, with stimulation, had (1) a greater increase in retroglossal airway size; (2) increased shortening of the mandible-hyoid distance; and (3) greater anterior displacement of the tongue.

Conclusions: These results suggest that smaller soft palate volumes at baseline and greater tongue movement anteriorly with stimulation improve the response to upper airway stimulation.

Statement of Significance

Upper airway stimulation is a new effective treatment for some continuous positive airway pressure-intolerant patients. This is the first study examining the mechanism of action of upper airway stimulation with computed tomography (CT) scanning. We used CT to examine differences in upper airway caliber, the volume of the upper airway soft tissue structures, craniofacial relationships, and centroid tongue and soft palate position in responders and nonresponders during upper airway stimulation in wakefulness. Our data indicate that compared with nonresponders, responders had a smaller baseline soft palate volume and, with stimulation, had (1) a greater increase in the retroglossal airway size; (2) increased shortening of the mandible-hyoid distance (hyoid movement towards the mandible); and (3) greater anterior displacement of the tongue (based on the tongue centroids).

Key words: obstructive sleep apnea; hypoglossal nerve stimulation; upper airway; tongue; CT scan

Submitted: 22 February, 2017; **Revised:** 13 October, 2017

Introduction

Upper airway stimulation (UAS) has emerged as an innovative and effective therapy for some patients with obstructive sleep apnea (OSA) who cannot tolerate continuous positive airway pressure (CPAP) [1]. After initial feasibility studies [2, 3], a recent large FDA pivotal study (the STAR [Stimulation Therapy for Apnea Reduction] trial) demonstrated that, on average, upper airway stimulation significantly reduced the apnea–hypopnea index (AHI) and improved self-reported quality of life measures in patients with OSA [1]. Long-term follow-up of the study participants in the STAR trial showed that upper airway stimulation remained effective over a 4 year period [4–6]. In a randomized controlled study, withdrawal of therapy for 1 week led to a return of OSA severity back to the baseline level, and reactivation of upper airway stimulation again resulted in reductions in the AHI [1, 7].

The mechanism of action by which upper airway stimulation improves upper airway caliber and reduces the AHI is currently unclear. It is thought that upper airway stimulation recruits the tongue protrusor muscles without activating the tongue retractor muscles [8–10]. Recruitment of the tongue protrusor muscles should result in anterior tongue-based displacement, reduced upper airway collapsibility [9], and increased inspiratory flow rate during sleep [11]. Visual assessment of upper airway changes during awake and propofol-induced sedation endoscopy has shown that upper airway stimulation increased both retroglossal (RG) area at the base of the tongue and retropalatal (RP) area posterior to the soft palate [12]. The same study also showed larger RP enlargement with upper airway stimulation among therapy responders compared with nonresponders. However, drug-induced sleep endoscopy only examines the lumen of the airway; it does not allow for examination of the changes in upper airway soft tissues or craniofacial structures with upper airway stimulation. Such data can be obtained with computed tomography (CT) scanning.

Therefore, the objectives of this investigation were to determine the mechanism of action of upper airway stimulation by examining quantitative measures of upper airway size and surrounding soft tissue and craniofacial relationships with CT scans in responders and nonresponders before and during upper airway stimulation. We hypothesized that, with upper airway stimulation, responders would show greater airway opening, movement of the hyoid towards the mandible and away from the spine, and larger soft tissue movement in the anterior and inferior directions compared with nonresponders. Portions of this investigation have been previously presented as an abstract [13].

Methods

Participants

Participants with moderate-to-severe OSA (AHI greater than 15 events per hour) were recruited from clinical trials of upper airway stimulation [1, 3]. All participants provided written informed consent at the implanting center. Participants were classified as either responders (defined as a reduction in AHI by at least 50% and residual AHI less than 20 events per hour) or nonresponders (showed an AHI improvement of less than 50% or residual AHI over 20 events per hour). Key exclusion criteria included body mass index (BMI) greater than 32 kg/m^2, neuromuscular diseases, and other significant medical conditions, such as severe restrictive or obstructive pulmonary disease, congestive heart failure, and recent myocardial infarction or severe cardiac arrhythmias. All participants received the upper airway stimulation system (Inspire Medical Systems, MN, USA), The Inspire device consists of three implanted components: an implanted pulse generator in the subclavicular area, a sensing lead in the intercostal muscles, and a stimulation lead on the right hypoglossal nerve. The pulse generator receives the ventilatory effort signal from the sensing lead and delivers electrical stimulation pulses to the right hypoglossal nerve (resulting in unilateral stimulation and movement of the tongue to the left) during the inspiratory phase through cuff electrodes on the stimulation lead. The upper airway stimulation system delivered unilateral stimulation during inspiration to the right hypoglossal nerve in all cases.

Data collection

All participants underwent an in-lab polysomnography (PSG) study before and after receiving the implant. The baseline PSG was conducted 1 to 2 months before the implant and the post-op PSG was performed after 12 months of using the implant. The primary outcome measure was AHI based on standard scoring criteria [14].

During a post-operative visit, CT scans of the upper airway were performed during a single slow, mouth-closed inhalation under two conditions: (1) without stimulation; and (2) during a 5 s period of stimulation during inspiration. The mouth stayed closed during the CT scanning among all participants in the study. Stimulation amplitude was delivered at the voltage level titrated during an in-lab sleep study and set for home use (in responders and nonresponders, the voltage chosen during CT scanning was the voltage that was most effective in reducing the AHI). The voltage level ranged from 1.4 to 2.6 V among participants. The participants were instructed to inhale slowly during the scans while supine in the CT scanner. The patient's head and neck posture was in a neutral position during the CT scanning. The total radiation dosage of the scan was approximately 0.2 millisievert (mSv), which was low but adequate for airway analysis [15].

CT image analysis

The CT scans were reconstructed in the axial and sagittal orientations with a 3 mm slice thickness and manually examined using the Amira 4.1.2 image analysis software (Visage Imaging, San Diego, CA). There were four analysis domains: airway, soft tissue, craniofacial, and centroid movement of both the tongue and soft palate.

Airway measurements were obtained from the axial and sagittal images in the RP (plane of the hard palate to the caudal tip of the uvula) and RG regions (caudal tip of the uvula to the base of the epiglottis) (Figure 1A). Airway measurements included airway volume, airway length (distance from the hard palate to the base of the epiglottis), average cross-sectional area, and anterior–posterior and lateral dimensions at the middle slice in both RP and RG regions as well as at the levels of the minimum and maximum cross-sectional area in each region. As the UAS system causes protrusion of the tongue with movement of the tongue base, a

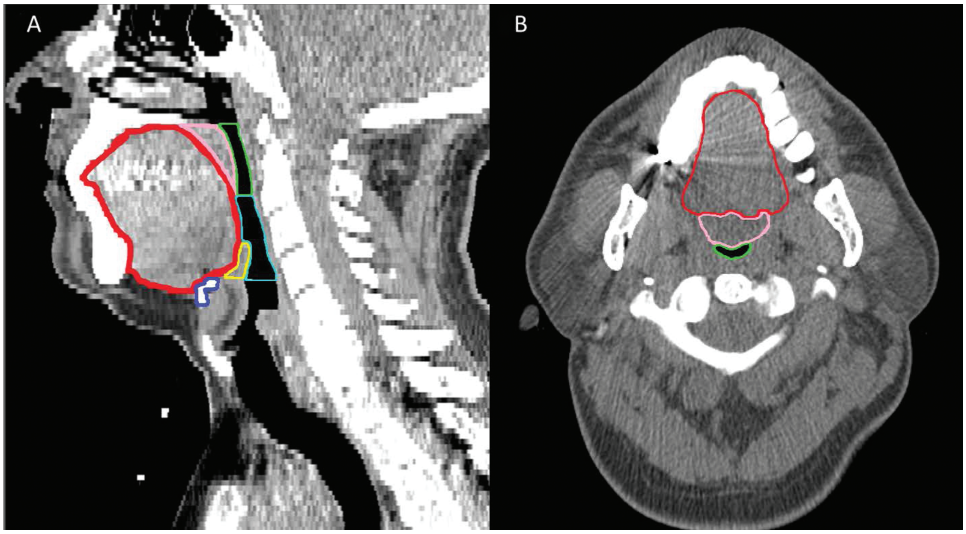

Figure 1. (A) Midsagittal view of the upper airway. The tongue is marked by a red border, soft palate by pink, RP airway by green, RG airway by cyan, epiglottis by yellow, and hyoid bone by blue. (B) Axial slice in the RP region showing the tongue outlined in red, soft palate in pink, and airway in green.

relatively larger RP than RG airway may hinder the effectiveness of UAS. Thus, the ratios of RP to RG airway volume and average cross-sectional area were also examined.

Soft tissue volumetric measurements were obtained from the axial images via manual segmentation of the soft palate, epiglottis, and tongue (digastric, genioglossus, geniohyoid, hyoglossus, mylohyoid, and styloglossus muscles) using techniques similar to our previous work [16–18] (Figure 1B). Due to the poorer soft tissue detail on CT imaging compared with MR imaging, our analysis method was adapted to utilize differences in voxel intensity [fat −130 to −70 Hounsfield Units (HU); bone 7000 to 3000 HU; soft tissues/muscle 40–60 HU] as a means of distinguishing between tissue types [19]. This use of variation in intensity, combined with simultaneous assessment of structures in the sagittal, coronal, and axial planes, allows visualization of the soft palate and tongue for volumetric reconstruction.

The craniofacial analysis focused on distances between the mandible, hyoid, and cervical vertebrae. Specific measures included the mandibular plane-to-hyoid (MPH) distance, distance between the posterior aspect of the body of the mandible to the anterior aspect of the hyoid bone, and distance from the posterior aspect of the hyoid to the anterior aspect of the C4 vertebra (Figure 2).

The three-dimensional centroids of the tongue and soft palate were used to compare the position of the centroid before and during upper airway stimulation, similar to a method described previously [20]. Centroid position was tracked along three axes, as the unilateral stimulation resulted in contralateral protrusion of the tongue. The mid-sagittal plane was used to separate the left and right regions of the tongue, the coronal plane at the junction of the soft and hard palate on the posterior nasal spine was used to differentiate the anterior and posterior regions of the tongue, and the axial plane at the superior aspect of the body of the mandible was used to separate the superior and inferior regions of the tongue (Figure 3). The centroid of each tongue region (eight regions in total), the total tongue, and the soft palate were measured, at baseline and during stimulation, as distances with respect to the plane of the hard palate (for movement in the inferior–superior axis), a coronal plane through the body of the mandible as visualized on the mid-sagittal line (for movement in the anterior–posterior axis), and distance from the mid-sagittal plane (for lateral movement). The difference in distances was determined in order to track centroid movement in each region as well as for the total tongue and soft palate. All image analysis was conducted by a single trained technologist at the Sleep Imaging Center at the University of Pennsylvania. The technologist was supervised by a physician (R.S.) and was blinded regarding participants' OSA severity and response to upper airway stimulation.

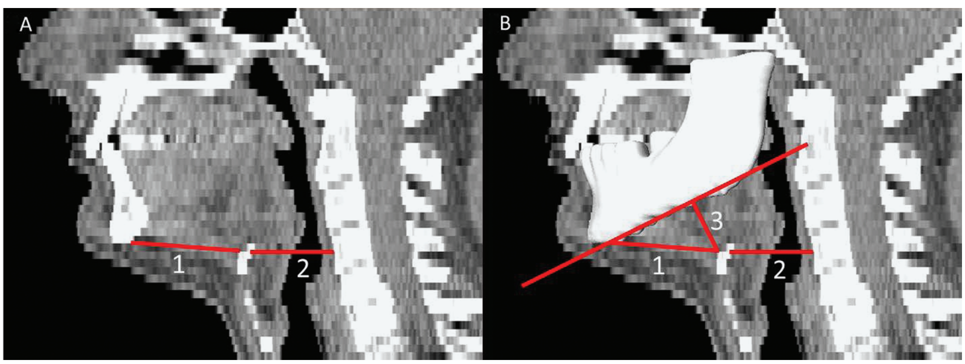

Figure 2. (A) Midsagittal image showing craniofacial measurements: 1—distance from mandible to hyoid; 2—distance from hyoid to C4 vertebra. (B) Measures 1 and 2 shown with mandibular reconstruction. 3—distance from MPH.

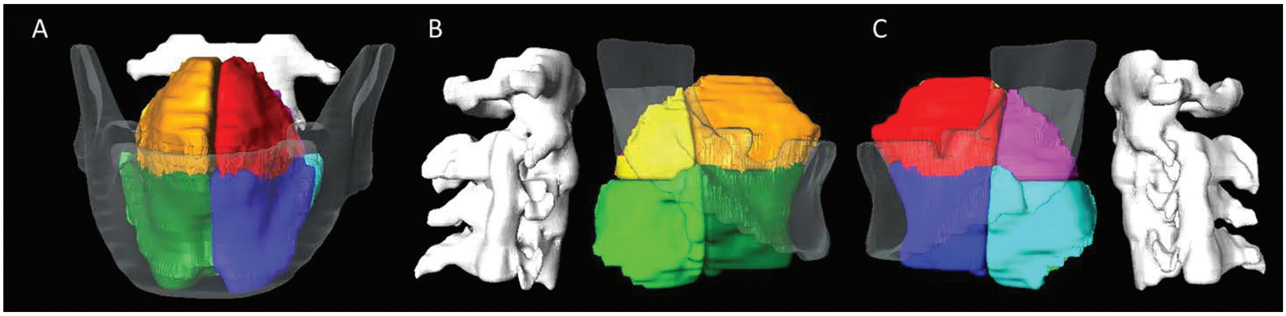

Figure 3. (A) Reconstruction of the tongue within the mandible from the front, showing the inferior/superior division at the level of the body of the mandible as well as the left/right division along the mid-sagittal plane. The tongue was divided into eight regions which enable greater resolution in tracking tongue motion with upper airway stimulation, as the stimulation results in contralateral protrusion of the tongue. (B) Sagittal view of the tongue from the right, showing the anterior and posterior division and the superior and inferior division. (C) Sagittal view of the tongue from the left, denoting the anterior and posterior division and the superior and inferior demarcation of the tongue. Mandible—translucent; spine–white. All the other colors reflect different tongue quadrants: orange—anterior superior right; red—anterior superior left; yellow—posterior superior right; pink—posterior superior left; dark green—anterior inferior right; dark blue—anterior inferior left; light green—posterior inferior right; light blue—posterior inferior left.

Statistical analysis

Continuous variables were summarized using means and standard deviations. Participant-specific change scores were calculated as values during stimulation minus baseline values. Assessments of whether there were significant changes from baseline within patient groups were performed using nonparametric signed-rank tests. To compare baseline or changes with stimulation between responders and nonresponders, we utilized nonparametric Wilcoxon rank-sum tests. Associations between baseline anatomy measures and centroid movement of the tongue and soft palate were assessed using nonparametric Spearman rank correlations. Given the exploratory nature of these analyses, statistical significance was based on a $p < 0.05$ for all analyses and a $p < 0.10$ was considered suggestive evidence for an association.

Results

Participant demographics and baseline anatomic measures

The stimulation amplitude was similar among responders and nonresponders (1.84 ± 0.26 vs. 1.62 ± 0.71 V, $p = 0.191$) and both groups had the same electrode configuration. Participant demographics are summarized in Table 1. All participants were male and Caucasian, reflecting the characteristics of the treated sample at the time, and all were diagnosed with moderate–severe OSA (AHI > 15 events per hour). Age and BMI were not significantly different between responder and nonresponder groups. In the responders, the mean ± SD AHI before treatment was 36.71 ± 9.71 events per hour and was reduced to 14.09 ± 4.86 events per hour with upper airway stimulation therapy. Nonresponders showed no improvement in AHI, from 29.68 ± 11.31 events per hour at baseline to 29.85 ± 23.31 events per hour with upper airway stimulation therapy. Differences in baseline anatomic measures between responders and nonresponders are shown in Table 2. Responders had significantly smaller baseline soft palate volumes than nonresponders (8789.33 vs. 11394.33 mm^3, $p = 0.032$) and suggestively smaller RP to RG airway volume ratio (0.58 vs. 0.95, $p = 0.086$); all other airway, soft tissue and craniofacial measures were similar between groups at baseline.

Differences in upper airway changes with upper airway stimulation

The changes in anterior–posterior and lateral airway dimensions and overall change in upper airway volume with upper airway stimulation are shown in representative participants in Figure 4, A and B. In the nonresponder (Figure 4A), there was an increase in RP airway volume with a decrease in RG airway volume. In the responder (Figure 4B), there was an increase in both the RP and RG airway volumes. In all the participants (Tables 3 and 4), there was no significant increase in RP airway volume with stimulation (712.57 ± 3403.86 mm^3, $p = 0.553$), but a suggestive increase in RG airway volume (1490.05 ± 4402.30 mm^3, $p = 0.087$) in our sample. Responders showed a nonsignificant trend towards greater mean increases in RP airway volume (1992.07 vs. −780.18 mm^3, $p = 0.116$) compared with nonresponders. In the RG region, responders showed a statistically greater increase in total RG airway volume (3481.20 vs. −832.95 mm^3, $p = 0.032$) and average

Table 1. Demographic information in responders and nonresponders

Characteristics	All participants (n = 13)	Responders (n = 7)	Nonresponder (n = 6)	P*
Age (years)	53.00 ± 9.15	50.32 ± 8.24	56.13 ± 9.89	0.252
BMI (kg/m²)	27.77 ± 1.57	27.74 ± 1.93	27.81 ± 1.20	0.775
Baseline AHI (events/hour)	33.47 ± 10.42	36.71 ± 9.17	29.68 ± 11.31	0.087
AHI with upper airway stimulation therapy (events/hour)	**21.36 ± 17.47**	**14.09 ± 4.86**	**29.85 ± 23.31**	**0.032**
AHI change (events/hour)	**−12.11 ± 15.60**	**−22.63 ± 6.54**	**0.17 ± 14.04**	**0.003**

*p-Value from nonparametric Wilcoxon rank-sum tests comparing values between responders and nonresponders. Values presented as Mean ± SD. Bold = statistically significant.

Table 2. Baseline anatomic data comparing responders and nonresponders

Upper airway measures	All participants (n = 13)	Responders (n = 7)	Nonresponders (n = 6)	P*
RP airway volume (mm³)	8642.98 ± 4986.41	6838.85 ± 3256.40	10747.79 ± 6089.03	0.199
Average RP airway area per slice (mm²)	214.95 ± 93.51	178.79 ± 54.04	257.13 ± 116.26	0.199
RG airway volume (mm³)	12429.94 ± 5760.36	12711.03 ± 5643.46	12102.00 ± 6417.00	0.668
Average RG airway area per slice (mm²)	309.34 ± 123.67	306.72 ± 122.33	312.4 ± 136.86	0.775
RP:RG airway volume ratio	0.75 ± 0.35	0.58 ± 0.19	0.95 ± 0.39	0.086
RP:RG average airway area per slice ratio	0.73 ± 0.26	0.63 ± 0.20	0.85 ± 0.29	0.153
Pharyngeal length (mm)	80.92 ± 7.63	80.35 ± 8.29	81.57 ± 7.50	0.568
Soft palate volume (mm³)	**9991.63 ± 2348.54**	**8789.33 ± 1811.37**	**11394.33 ± 2217.07**	**0.032**
Total tongue volume (mm³)	156558.7 ± 16222.3	157986.9 ± 11300.2	154892.5 ± 21729.5	0.568
Mandible–hyoid distance (mm)	41.00 ± 5.01	42.30 ± 5.55	39.49 ± 4.27	0.317
Mandibular plane–hyoid distance (mm)	27.24 ± 3.53	26.66 ± 4.00	27.92 ± 3.09	0.775
Hyoid–spine distance (mm)	40.17 ± 3.40	41.23 ± 4.11	38.93 ± 2.03	0.391

*p-Value from nonparametric Wilcoxon rank-sum tests comparing baseline values between responders and nonresponders. Values presented as Mean ± SD. Bold = statistically significant.

RG cross-sectional area (96.65 vs. –29.12 mm², $p = 0.032$), as well as a suggestive difference in maximum RG cross-sectional area (155.96 vs. 0.65 mm², $p = 0.087$), compared with nonresponders. There was no significant or suggestive difference in pharyngeal length ($p = 0.391$) between responders and nonresponders.

Differences in upper airway soft tissue and craniofacial changes with upper airway stimulation

Soft palate and tongue volumes did not change significantly with stimulation. Mandible-to-hyoid distance decreased significantly overall (–6.93 ± 7.92 mm, $p = 0.009$) with stimulation (Table 5), with responders showing a significantly greater decrease than nonresponders (–11.41 vs. –1.71 mm, $p = 0.010$). MPH distance was significantly decreased with stimulation in all participants (–5.03 ± 5.36 mm, $p = 0.009$), but was not significantly different between responders and nonresponders ($p = 0.199$). Hyoid-to-spine distance significantly increased with stimulation in all participants (5.20 ± 5.87 mm, $p = 0.019$), with responders tending to show greater displacement than nonresponders (8.09 vs. 1.82 mm, $p = 0.063$).

Centroid tracking of soft tissue movement with upper airway stimulation

We also investigated the movement of the soft palate, the entire tongue (Figure 5), and with the tongue divided into eight regions along the three primary planes (axial, sagittal, and coronal; Figure 3). Soft palate movement did not differ between responders and nonresponders in anterior, inferior, or lateral displacement (Table 6). In all patients, stimulation resulted in tongue movement inferiorly (3.22 ± 2.80 mm, $p = 0.004$) and anteriorly (1.37 ± 2.56 mm, $p = 0.101$), with responders tending to show greater tongue motion in the anterior direction than nonresponders (2.54 vs. –0.01 mm, $p = 0.063$) (Table 6).

When the tongue was divided into eight regions, there were no significant differences in movement between responders and nonresponders; suggestive or trending differences were seen for a few regions. The greatest difference in movement was seen in the posterior inferior left and posterior inferior right regions of the tongue (Table 7). Responders tended to show greater motion in the posterior inferior left region anteriorly (2.33 vs. –0.18 mm, $p = 0.199$) and towards the left (1.98 vs. 0.77 mm, $p = 0.153$), and

Table 3. RP airway absolute changes with upper airway stimulation between responders and nonresponders

Measure	Baseline vs. stimulation difference: All participants (n = 13)	Responders (n = 7)	Nonresponders (n = 6)	P*
Pharyngeal length (mm)	0.71 ± 5.34	–0.89 ± 5.84	2.57 ± 4.44	0.391
RP airway volume (mm³)	712.57 ± 3403.86	1992.07 ± 3483.33	–780.18 ± 2877.64	0.116
Average RP area per slice (mm²)	36.31 ± 119.80	69.31 ± 129.27	–2.19 ± 105.30	0.317
Mid-RP AP distance (mm)	2.38 ± 6.10	2.64 ± 4.23	2.07 ± 8.23	0.391
Mid-RP lateral distance (mm)	–1.53 ± 3.66	–1.16 ± 2.74	–1.97 ± 4.77	0.617
Mid-RP cross-sectional area (mm²)	57.15 ± 184.83	101.47 ± 180.56†	5.44 ± 192.12	0.199
Min-RP AP distance (mm)	1.86 ± 4.05	2.99 ± 3.98	0.54 ± 4.05	0.317
Min-RP lateral distance (mm)	–2.12 ± 7.20	–0.01 ± 4.35	–4.59 ± 9.40	0.253
Min-RP cross-sectional area (mm²)	9.65 ± 75.92	38.60 ± 49.58†	–24.12 ± 91.33	0.199
Max-RP AP distance (mm)	1.19 ± 5.21	0.72 ± 2.07	1.75 ± 7.71	0.886
Max-RP lateral distance (mm)	0.40 ± 2.14	–0.30 ± 1.50	1.22 ± 2.61	0.153
Max-RP cross-sectional area (mm²)	17.37 ± 159.90	43.46 ± 209.25	–13.07 ± 82.18	0.775

*p-Value from nonparametric Wilcoxon rank-sum tests comparing change from baseline between responders and nonresponders.
†Within-group change significantly different from zero ($p < 0.05$ in signed rank-test); values presented as mean ± SD.

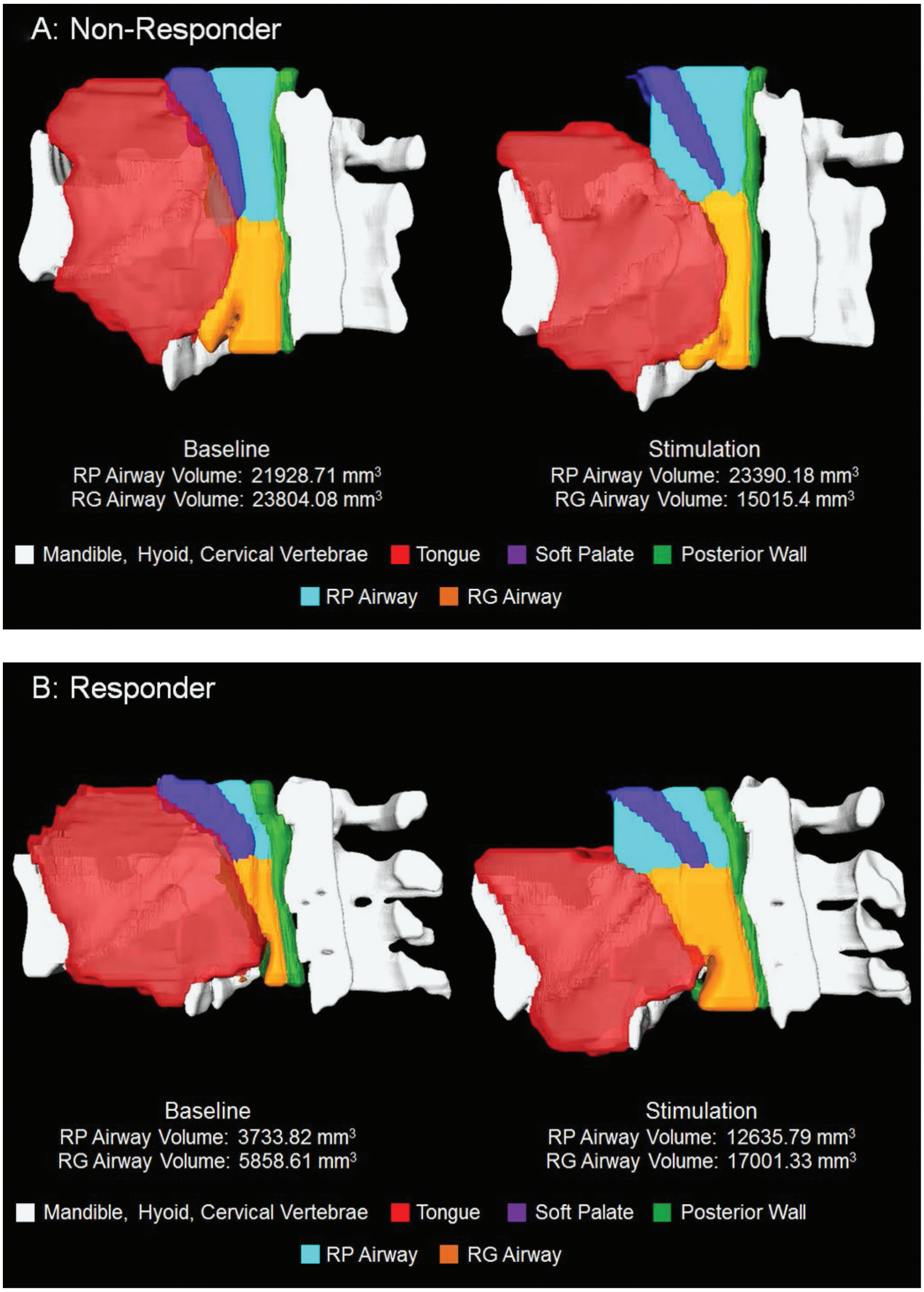

Figure 4. (A) Midsagittal reconstruction of a representative nonresponder before and during stimulation. The stimulation caused tongue tip protrusion and inferior displacement but also resulted in tongue base retrusion causing narrowing of the RG airway. The mandible is visible behind the tongue (translucent red). (B) Midsagittal reconstruction of a representative responder before and during stimulation. The stimulation caused anterior and inferior displacement of the tongue and hyoid bone with a resultant increase in the RP and RG airway. The mandible is visible behind the tongue (translucent red).

in the posterior inferior right region, responders showed greater motion anteriorly (3.46 vs. 0.60 mm, p = 0.116) and towards the right (1.40 mm right vs. 0.10 mm left, p = 0.116). Nonresponders tended to show greater inferior motion in the posterior inferior right region (2.01 vs. –0.90 mm, p = 0.116).

Anterior displacement was more pronounced in responders in the anterior inferior right (0.59 vs. –0.79 mm, p = 0.199), posterior superior left (0.71 vs. –1.16 mm, p = 0.116) and posterior superior right (1.65 vs. 0.27 mm, p = 0.153) regions. Nonresponders tended to show greater inferior displacement in the anterior superior left (3.59 vs. 0.95 mm, p = 0.199), anterior superior right (3.97 vs. 1.99 mm, p = 0.153), and posterior superior left (2.79 vs. 0.54 mm, p = 0.199) regions.

Lateral displacement was similar between responders and nonresponders in the anterior superior left, anterior superior right, anterior inferior left, and anterior inferior right regions. In the posterior inferior left region, responders tended to show greater displacement towards the left than nonresponders (1.98 vs. 0.77 mm, p = 0.153). On average, responders showed opposite movement than nonresponders in the posterior superior right (1.29 mm right vs. 0.46 mm left, p = 0.087) and posterior inferior right (1.40 mm right vs. 0.10 mm left, p = 0.116) regions.

Table 4. RG airway absolute changes with upper airway stimulation between responders and nonresponders

	Baseline vs. stimulation difference			
	All participants	Responders	Nonresponders	
Measure	(*n* = 13)	(*n* = 7)	(*n* = 6)	*P**
RG airway volume (mm³)	**1490.05 ± 4402.30**	**3481.20 ± 3450.68**†	**−832.95 ± 4494.20**	**0.032**
Average RG area per slice (mm²)	**38.60 ± 127.49**	**96.65 ± 78.02**†	**−29.12 ± 146.57**	**0.032**
Mid-RG AP distance (mm)	2.10 ± 5.39	2.66 ± 5.03	1.44 ± 6.20	0.668
Mid-RG lateral distance (mm)	2.67 ± 4.41†	2.84 ± 5.00	2.47 ± 4.07	0.886
Mid-RG cross-sectional area (mm²)	11.16 ± 146.24	46.67 ± 89.65	−30.26 ± 194.57	0.568
Min-RG AP distance (mm)	1.47 ± 5.70	1.47 ± 6.01	1.48 ± 5.90	>0.999
Min-RG lateral distance (mm)	4.15 ± 4.50†	3.26 ± 4.93	5.18 ± 4.13†	0.568
Min-RG cross-sectional area (mm²)	−4.65 ± 145.74	12.27 ± 130.40	−24.38 ± 172.34	0.391
Max-RG AP distance (mm)	3.85 ± 5.14†	5.54 ± 4.01†	1.89 ± 5.96	0.199
Max-RG lateral distance (mm)	4.04 ± 5.45†	3.63 ± 5.20	4.52 ± 6.19	>0.999
Max-RG cross-sectional area (mm²)	84.28 ± 160.90	155.96 ± 106.33†	0.65 ± 181.59	0.087

**p*-Value from nonparametric Wilcoxon rank-sum tests comparing change from baseline between responders and nonresponders.
†Within-group change significantly different from zero ($p < 0.05$ in signed-rank test); values presented as mean ± SD. Bold = statistically significant.

Correlation of baseline anatomic measures with tongue movement

To explore whether baseline anatomic variables could predict the magnitude of tongue movement, correlations between anatomic measures and total tongue and soft palate centroid movement were examined (Tables 8 and 9). No significant correlations were found for any anatomic measures at baseline and tongue or soft palate displacement. RP airway volume had

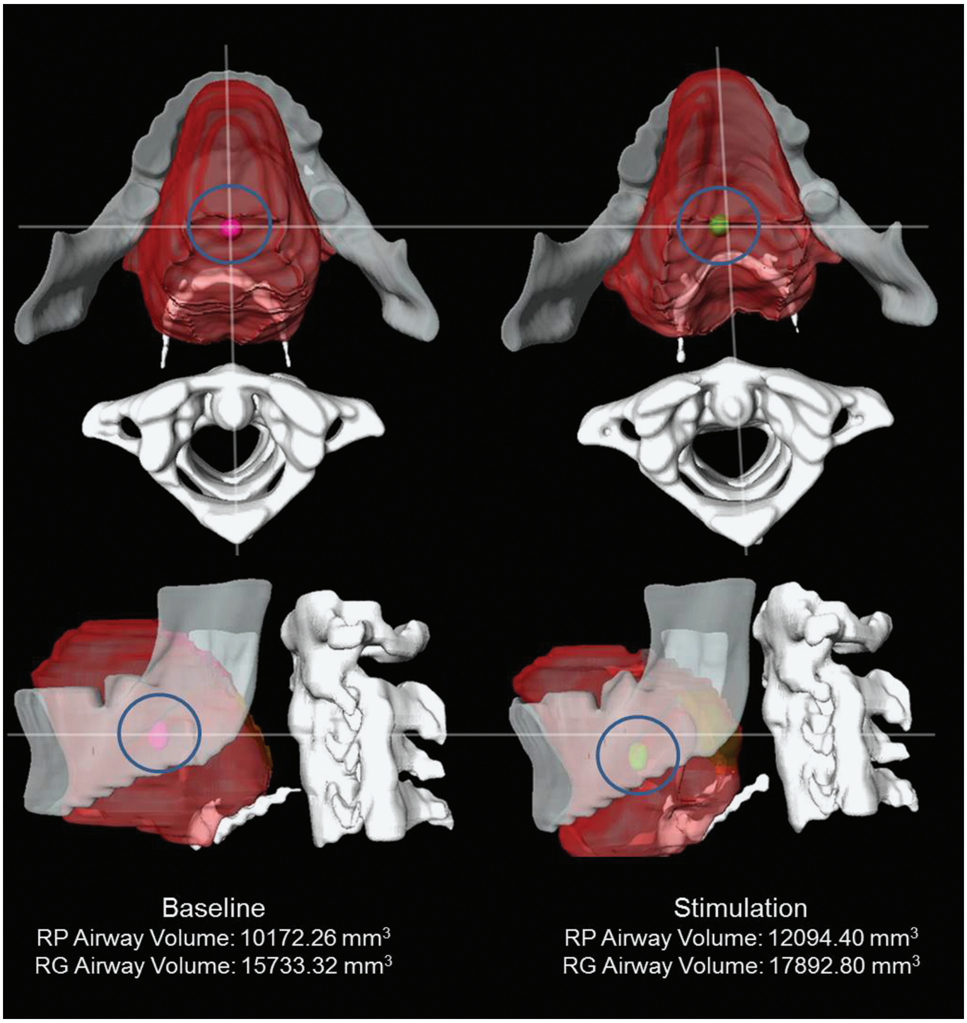

Figure 5. 3D reconstruction of a responder showing the location of the total tongue centroid (circled) of the tongue at baseline and with stimulation. The centroid tended to shift anteriorly and inferiorly with stimulation, with responders showing greater anterior deviation towards the left.

Table 5. Absolute craniofacial measure changes with upper airway stimulation between responders and nonresponders

	Baseline vs. stimulation difference			
	All participants	Responders	Nonresponders	
Measure	(n = 13)	(n = 7)	(n = 6)	P*
Mandible-hyoid distance (mm)	**−6.93 ± 7.92**†	**−11.41 ± 7.44**†	**−1.71 ± 4.82**	**0.010**
Mandibular plane–hyoid distance (mm)	−5.03 ± 5.36†	−6.86 ± 5.69†	−2.91 ± 4.48	0.199
Hyoid–spine distance (mm)	5.20 ± 5.87†	8.09 ± 5.40†	1.82 ± 4.72	0.063

*p-Value from nonparametric Wilcoxon rank-sum tests comparing change from baseline between responders and nonresponders.
†Within-group change significantly different from zero ($p < 0.05$ in signed-rank test); values presented as mean ± SD. Bold = statistically significant.

Table 6. Absolute soft palate and total tongue centroid changes with upper airway stimulation between responders and nonresponders

	Baseline vs. stimulation difference			
	All participants	Responders	Nonresponders	
Measure	(n = 13)	(n = 7)	(n = 6)	P*
Soft palate anterior displacement (mm)	0.72 ± 2.99	2.04 ± 3.41	−0.82 ± 1.52	0.116
Soft palate inferior displacement (mm)	0.46 ± 2.03	1.16 ± 1.45	−0.36 ± 2.43	0.252
Soft palate lateral displacement (mm)	0.22 ± 1.05 to the right	0.25 ± 1.24 to the right	0.17 ± 0.90 to the right	0.519
Total tongue anterior displacement (mm)	1.37 ± 2.56	2.54 ± 2.01†	−0.01 ± 2.59	0.063
Total tongue inferior displacement (mm)	3.22 ± 2.80†	2.78 ± 2.39†	3.73 ± 3.36†	0.668
Total tongue lateral displacement (mm)	0.40 ± 1.53 to the left	0.52 ± 1.53 to the left	0.26 ± 1.68 to the left	0.568

*p-Value from nonparametric Wilcoxon rank-sum tests comparing change from baseline between responders and nonresponders; values presented as mean ± SD.

a suggestive positive correlation with anterior tongue displacement ($\rho = 0.52$, $p = 0.067$). Total tongue volume showed nonsignificant negative correlations with anterior displacement ($\rho = -0.43$, $p = 0.138$) and lateral displacement ($\rho = -0.46$, $p = 0.117$), whereas soft palate volume did not correlate with soft palate movement.

Discussion

Upper airway stimulation is a new, effective treatment for some CPAP-intolerant patients. This is the first study examining the mechanism of action of upper airway stimulation with CT scanning. We used CT scans to examine differences in upper airway caliber, the volume of the upper airway soft tissue structures, craniofacial relationships, and centroid tongue movement in responders and nonresponders during upper airway stimulation in wakefulness. Our data indicate that when compared with nonresponders, responders had a smaller baseline soft palate volume and, with stimulation, tended to have (1) a greater increase in RG airway size, (2) increased shortening of the mandible–hyoid distance (hyoid movement towards the mandible, away from the spine), and (3) greater total anterior displacement of the tongue (based on the tongue centroids).

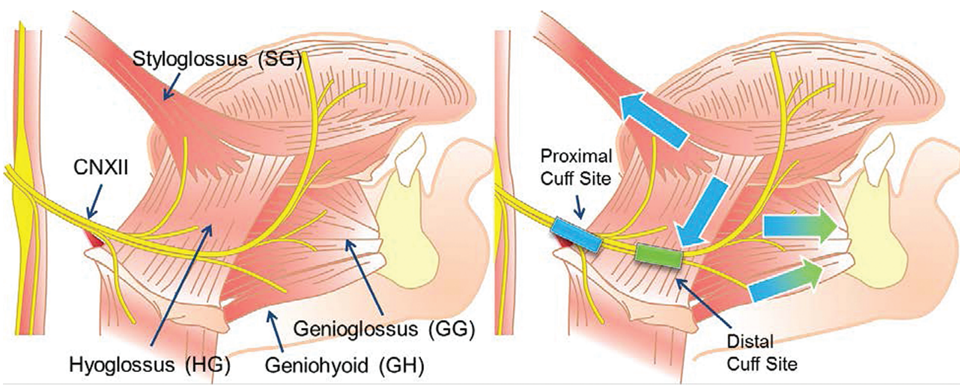

Figure 6. Left image shows the hypoglossal nerve and its branches in to the styloglossus, hyoglossus, genioglossus, and geniohyoid muscles. Note insertion of the SG near the tip of the tongue as well as on the hyoglossus. Right image shows the two cuff placement sites, where the proximal site results in all four muscle activations while the distal site only activates two muscles. Colors denote this difference (proximal results in all four arrows, distal only the green arrows).

Table 7. Regional tongue centroid changes with upper airway stimulation between responders and nonresponders

Measure	Baseline vs. stimulation difference: All participants (n = 13)	Responders (n = 7)	Nonresponders (n = 6)	P*
Anterior, superior, left				
Anterior displacement (mm)	0.53 ± 2.61	0.39 ± 2.05	0.69 ± 3.36	0.475
Inferior displacement (mm)	2.17 ± 3.03†	0.95 ± 2.19	3.59 ± 3.43	0.199
Lateral displacement (mm)	0.21 ± 2.04 right	0.35 ± 2.51 right	0.06 ± 1.56 right	0.886
Anterior, superior, right				
Anterior displacement (mm)	0.72 ± 2.07	0.85 ± 1.77	0.56 ± 2.54	0.475
Inferior displacement (mm)	2.90 ± 2.65†	1.99 ± 2.24	3.97 ± 2.89†	0.153
Lateral displacement (mm)	0.30 ± 1.52 right	0.14 ± 1.60 right	0.49 ± 1.54 right	0.475
Anterior, inferior, left				
Anterior displacement (mm)	0.34 ± 2.79	0.55 ± 3.11	0.10 ± 2.63	0.431
Inferior displacement (mm)	3.99 ± 2.38†	4.13 ± 2.18†	3.83 ± 2.79†	>0.999
Lateral displacement (mm)	0.38 ± 2.23 left	0.44 ± 2.78 left	0.30 ± 1.63 left	0.775
Anterior, inferior, right				
Anterior displacement (mm)	−0.05 ± 2.25	0.59 ± 2.60	−0.79 ± 1.69	0.199
Inferior displacement (mm)	3.67 ± 2.67†	3.71 ± 1.92†	3.62 ± 3.56	0.886
Lateral displacement (mm)	0.98 ± 2.33 right	1.58 ± 2.79 right	0.28 ± 1.62 right	0.391
Posterior, superior, left				
Anterior displacement (mm)	−0.15 ± 2.38	0.71 ± 1.87	−1.16 ± 2.68	0.116
Inferior displacement (mm)	1.58 ± 3.36	0.54 ± 1.26	2.79 ± 4.69	0.199
Lateral displacement (mm)	0.47 ± 2.58 left	1.14 ± 3.01 left	0.31 ± 1.94 right	0.391
Posterior, superior, right				
Anterior displacement (mm)	1.02 ± 3.45	1.65 ± 2.59	0.27 ± 4.39	0.153
Inferior displacement (mm)	2.38 ± 3.61†	1.69 ± 2.43	3.19 ± 4.77	0.391
Lateral displacement (mm)	0.48 ± 1.97 right	1.29 ± 1.71 right	0.46 ± 1.97 left	0.087
Posterior, inferior, left				
Anterior displacement (mm)	1.17 ± 2.92	2.33 ± 2.65	−0.18 ± 2.84	0.199
Inferior displacement (mm)	1.13 ± 3.25	0.24 ± 2.21	2.17 ± 4.13	0.253
Lateral displacement (mm)	1.42 ± 2.27 left	1.98 ± 2.64 left	0.77 ± 1.75 left	0.153
Posterior, inferior, right				
Anterior displacement (mm)	2.14 ± 2.89†	3.46 ± 2.71†	0.60 ± 2.44	0.116
Inferior displacement (mm)	0.44 ± 4.29	−0.90 ± 3.75	2.01 ± 4.67	0.116
Lateral displacement (mm)	0.71 ± 1.47 right	1.40 ± 1.41 right†	0.10 ± 1.16 left	0.116

*p-Value from nonparametric Wilcoxon rank-sum tests comparing change from baseline between responders and nonresponders.
†Within-group change significantly different from zero ($p < 0.05$ in signed-rank test); values presented as mean ± SD.

Our data indicate that baseline CT upper airway measurements have limited predictive value for determining who will be a responder to upper airway stimulation, albeit in this small sample. Baseline airway measurements (volume or average cross-sectional area in the RP or RG regions), pharyngeal length, tongue size, and craniofacial measurements (MPH distance, hyoid–spine distance, MPH) were not different between responders and nonresponders in this study of response to upper airway stimulation. However, a small soft palate was associated with responding to upper airway stimulation using unilateral electrical stimulation of the hypoglossal nerve synchronized with ventilatory effort during sleep. These data suggest that the size

Table 8. Correlations† between baseline anatomic measures and total tongue movement

Upper airway measure	Anterior displacement ρ	Anterior displacement P	Inferior displacement ρ	Inferior displacement P	Lateral displacement ρ	Lateral displacement P
RP airway volume (mm³)	0.52	0.067	0.30	0.315	0.09	0.761
Average RP airway area per slice (mm²)	0.46	0.112	0.23	0.448	0.13	0.667
RG airway volume (mm³)	0.18	0.565	−0.08	0.789	0.41	0.168
Average RG airway area per slice (mm²)	0.20	0.517	0.06	0.844	0.27	0.373
Pharyngeal length (mm)	0.10	0.734	−0.20	0.517	0.15	0.628
Soft palate volume (mm³)	0.06	0.844	0.30	0.324	0.14	0.641
Total tongue volume (mm³)	−0.43	0.138	−0.35	0.238	−0.46	0.117
Mandible–hyoid distance (mm)	−0.03	0.915	0.27	0.364	0.06	0.845
Mandibular plane-hyoid distance (mm)	0.31	0.297	0.09	0.762	0.25	0.415
Hyoid-spine distance (mm)	−0.30	0.325	0.30	0.325	0.06	0.845

†Spearman rank correlation between total tongue displacement and baseline anatomy measure.

Table 9. Correlations† between baseline anatomic measures and soft palate movement

	Anterior displacement		Inferior displacement		Lateral displacement	
Upper airway measure	ρ	P	ρ	P	ρ	P
RP airway volume (mm³)	0.32	0.288	0.12	0.693	0.02	0.936
Average RP airway area per slice (mm²)	0.40	0.174	0.06	0.858	0.03	0.921
RG airway volume (mm³)	0.45	0.127	−0.18	0.565	−0.12	0.687
Average RG airway area per slice (mm²)	0.20	0.517	0.08	0.795	−0.34	0.250
Pharyngeal length (mm)	0.50	0.081	−0.43	0.146	−0.10	0.740
Soft palate volume (mm³)	0.32	0.279	0.08	0.802	−0.02	0.936
Total tongue volume (mm³)	−0.13	0.680	0.19	0.534	−0.45	0.121
Mandible–hyoid distance (mm)	−0.49	0.089	0.39	0.186	−0.11	0.727
Mandibular plane-hyoid distance (mm)	0.36	0.223	−0.13	0.673	−0.01	0.985
Hyoid-spine distance (mm)	−0.23	0.459	0.44	0.135	−0.48	0.093

†Spearman rank correlation between soft palate displacement and baseline anatomy measure.

of the soft palate could be used to determine good candidates for upper airway stimulation.

The movement of the hyoid towards the mandible may be an important biomechanical change explaining why upper airway stimulation is successful. Studies utilizing surgical movement of the hyoid bone (anteriorly or inferiorly) or hyoid suspension in patients with sleep apnea have shown improvement in the AHI, although this surgery is often performed in conjunction with other ablative upper airway surgeries [21, 22]. The muscles that form the lateral walls of the upper airway originate on the styloid process and terminate on the hyoid. Moving the hyoid bone inferiorly or anteriorly would stiffen the lateral walls potentially reducing apnea. Upper airway stimulation may have a similar mechanism of action by moving the hyoid bone anteriorly towards the mandible.

The centroid analysis revealed that differences in tongue motion may also relate to patient response to upper airway stimulation. Since the implant stimulates the right hypoglossal nerve (CN-XII), the expected tongue motion is leftward protrusion towards the lips. In responders, anterior tongue motion was observed, whereas there was a trend for nonresponders to have neutral anterior–posterior movement. Using the regional centroid tracking, although no statistically significant differences were found, we observed anterior motion in all regions of the tongue in responders, whereas nonresponders tended to show anterior motion in the anterior regions, but neutral or posterior displacement in the posterior regions of the tongue. This bidirectional movement could explain the reduced response to upper airway stimulation.

Given this potential importance of tongue displacement in response to upper airway stimulation, we explored whether any baseline measures were correlated with tongue and soft palate movement. Within our small sample, the correlations observed between larger RP airway volume and more anterior tongue displacement and between larger total tongue volume and less tongue displacement in both the anterior and lateral directions were suggestive but not statistically significant. Future studies in larger samples should examine possible baseline anatomic predictors of tongue movement with upper airway stimulation.

Another reason that upper airway stimulation may not be effective could relate to cuff placement around the hypoglossal nerve. Distal placement recruits protrusor muscles (genioglossus and geniohyoid; Figure 6). The genioglossus muscle pulls the tongue base forward and the geniohyoid muscle pulls the hyoid anteriorly towards the mandible. Both the genioglossus and geniohyoid attach to the anterior body of the hyoid and anterior displacement of the hyoid would increase airway volume in the RG region. Proximal cuff placement recruits tongue protrusor and retractor muscles (styloglossus and hyoglossus) together (Figure 6). The styloglossus muscle retracts and elevates the tongue and the hyoglossus muscle retracts and depresses the tongue [23–25]. Proximal cuff placement, therefore, will result in the tongue being partially retracted, reducing airway volume in the RP and RG regions. However, distal placement will cause tongue tip protrusion along with tongue base movement anteriorly increasing airway volume in both RP and RG regions. Thus, patients with distal cuff placement should show greater improvement in AHI with upper airway stimulation than patients with a proximal cuff placement. When we reexamined our 13 participants, we found that those with a distal cuff placement showed greater average improvement in AHI [26]. Proximal cuff placement also reduced anterior and inferior motion of the tongue tip [26].

Moreover, there may be other upper airway anatomic and physiologic factors that influence the effectiveness of upper airway stimulation. For instance, the amount of fat in the tongue and different tongue fiber orientations may be important in determining whether upper airway stimulation is effective. Tongue fat has been shown to be increased in obese patients with sleep apnea [27, 28]. The amount of fat in the tongue in patients with sleep apnea is variable and the distribution is heterogeneous, with more fat at the base of the tongue [27, 28]. It is difficult to measure tongue fat with CT scans. However, once hypoglossal nerve stimulation is compatible with magnetic resonance imaging, it will be important to measure tongue fat to see if it predicts treatment response. Furthermore, chronic upper airway stimulation may, in turn, decrease tongue fat. The tongue is made up of intrinsic (superior and inferior longitudinal, transverse, vertical) and extrinsic (genioglossus, styloglossus, hyoglossus, palatoglossus) muscles [23–25]. Different fiber orientations of both the intrinsic and extrinsic tongue muscles may affect tongue protrusion and the effectiveness of upper airway stimulation. Finally, there are a number of important physiological factors [airway collapsibility (P_{crit}), loop gain, pharyngeal muscle responsiveness, and arousal threshold] that are thought to be important in the pathogenesis of sleep apnea [29, 30]. Each of these factors may be important predictors for determining the effectiveness of upper airway stimulation.

There are important strengths and limitations to our investigation. Because our sample size was small, we were unable to detect statistically significant differences between responders and nonresponders for a number of the measurements, although trends in the dataset were evident. Moreover, the study was performed under awake conditions and the observed effect and mechanism of upper airway stimulation may be different during sleep. However, performing CT scanning awake and asleep would increase the radiation dosage, increasing the risk of such a study. The CT scans were performed during slow inhalation. Lung volumes, which can affect upper airway behavior, were not controlled during the CT imaging. However, both responders and nonresponders underwent identical imaging protocols, and since the BMI was not different between the responders and nonresponders, lung volume changes should have been similar between these two groups. Another limitation is that we included only male and Caucasian participants in the study sample; although reflecting patients treated at that time, this, nonetheless, limits the generalizability of results to females or other ethnicities. Importantly, this sample was similar to the pivotal STAR trial (1) in terms of primary demographics, including age ($p = 0.612$), BMI ($p = 0.417$), gender ($p = 0.217$), race ($p > 0.999$), and AHI ($p = 0.660$). Although the sample size was small and the study was performed during wakefulness, this is the first study that utilized CT scanning to examine the mechanism of action related to upper airway stimulation. Furthermore, we utilized sophisticated upper airway imaging analysis techniques, including examining the centroid of the soft palate and tongue in multiple quadrants to understand how the tongue or soft palate moves with upper airway stimulation.

In conclusion, baseline soft palate volumes were greater in nonresponders compared with responders undergoing hypoglossal nerve stimulation. Hyoid movement was greater with stimulation in responders than nonresponders, due to increased tongue base recruitment. These differences were reflected as greater increases in RG airway volume and average cross-sectional area with upper airway stimulation in responders compared with nonresponders. These results suggest that larger soft palate volumes at baseline and impaired tongue movement anteriorly with stimulation may hinder response to upper airway stimulation.

Funding

J.V., O.M.V., P.V.H., and W.D. received research grant from Inspire Medical Systems for the clinical investigation.

Author Contributions

Conception and design: R.J.S., J.V., O.M.V., P.V.H., W.G.V., J.W.D., Q.N., and W.D. Data acquisition: O.M.V., P.V.H., W.G.V., J.W.D., and W.D. Analysis and interpretation: S.H.W., B.T.K., and R.J.S. Drafting of the manuscript: R.J.S., S.H.W., and B.T.K. Critical revision: R.J.S., S.H.W., B.T.K., J.V., O.M.V., P.V.H., W.G.V., J.W.D., Q.N., and W.D. Final approval of the version to be published: J.V., O.M.V., P.V.H., W.G.V., J.W.D., W.D., B.T.K., and R.J.S.

Notes

Conflicts of interest statement. Q.N. works for Inspire Medical Systems. O.M.V. received research support from SomnoMed Ltd., Inspire Medical Systems Inc., Nyxoah, and ReVent. O.M.V. is a consultant for Nyxoah and Philips Electronics B.V. The other authors of this paper have nothing to disclose and there are no conflicts of interest related to the investigation. There is no off-label use.

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