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ORIGINAL ARTICLE

Volumetric magnetic resonance imaging analysis of multilevel upper airway surgery effects on pharyngeal structure

Kate Sutherland[1,2], Aimee B. Lowth[1,2], Nick Antic[3,4,†], A. Simon Carney[5,6], Peter G. Catcheside[3], Ching Li Chai-Coetzer[3,4], Michael Chia[7], John-Charles Hodge[8], Andrew Jones[9,10,11], Billingsley Kaambwa[12], Richard Lewis[13,14], Stuart MacKay[9,10,15], R. Doug McEvoy[3,4], Eng H. Ooi[6,16], Alison J. Pinczel[3], Nigel McArdle[17,18], Guy Rees[19], Bhajan Singh[17,18,20], Nicholas Stow[21], Edward M. Weaver[22,23], Richard J. Woodman[24], Charmaine M. Woods[6,16], Aeneas Yeo[7] and Peter A. Cistulli[1,2,*]

[1]Sleep Research Group, Charles Perkins Centre and Sydney Medical School, University of Sydney, Sydney, NSW, Australia, [2]Department of Respiratory and Sleep Medicine, Royal North Shore Hospital, Sydney, NSW, Australia, [3]Adelaide Institute for Sleep Health, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, [4]Respiratory and Sleep Service, Southern Adelaide Local Health Network, Adelaide, SA, Australia, [5]Southern ENT and Adelaide Sinus Centre, Flinders Private Hospital, Adelaide, SA, Australia, [6]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, [7]Department of Thoracic Medicine, Royal Adelaide Hospital, Adelaide, SA, Australia, [8]Ear Nose and Throat Department, Royal Adelaide Hospital, Adelaide, SA, Australia, [9]Illawarra Shoalhaven Local Health District, Wollongong, NSW, Australia, [10]Discipline of Medicine, University of Wollongong, Wollongong, NSW, Australia, [11]Illawarra Sleep Medicine Centre, Wollongong, NSW, Australia, [12]Health Economics, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, [13]Hollywood Medical Centre, Perth, WA, Australia, [14]Department of Otolaryngology, Head and Neck Surgery, Royal Perth Hospital, Perth, WA, Australia, [15]Illawarra ENT Head and Neck Clinic, Wollongong, NSW, Australia, [16]Department of Otolaryngology, Head and Neck Surgery, Flinders Medical Centre, Adelaide, SA, Australia, [17]West Australian Sleep Disorders Research Institute, Queen Elizabeth II Medical Centre, Perth, WA, Australia, [18]Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia, [19]Department ENT Surgery, The Memorial Hospital, Adelaide, SA, Australia, [20]Faculty of Human Sciences, University of Western Australia, Perth, WA, Australia, [21]The Woolcock Clinic, University of Sydney, Sydney, NSW, Australia, [22]Department of Otolaryngology/Head and Neck Surgery, University of Washington, Seattle, WA, Australia, [23]Seattle Veterans Affairs Medical Center, Seattle, WA, Australia and [24]Flinders Centre for Epidemiology and Biostatistics, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

[†]Deceased.

[*]Corresponding author. Peter A. Cistulli, Department of Respiratory and Sleep Medicine, 8A, Acute Services Building, Royal North Shore Hospital, Reserve Road, St Leonards, NSW 2065, Australia. Email: peter.cistulli@sydney.edu.au.

Abstract

Study Objectives: The Sleep Apnea Multilevel Surgery (SAMS) trial found that modified uvulopalatopharyngoplasty with tonsillectomy (if tonsils present) combined with radiofrequency tongue ablation reduced obstructive sleep apnea (OSA) severity and daytime sleepiness in moderate-severe OSA. This study aimed to investigate mechanisms of effect on apnea-hypopnea index (AHI) reduction by assessing changes in upper airway volumes (airway space, soft palate, tongue, and intra-tongue fat).

Methods: This is a case series analysis of 43 participants of 51 randomized to the surgical arm of the SAMS trial who underwent repeat magnetic resonance imaging (MRI). Upper airway volume, length, and cross-sectional area, soft palate and tongue volumes, and tongue fat were measured. Relationships between changes in anatomical structures and AHI were assessed.

Results: The participant sample was predominantly male (79%); mean ± SD age 42.7 ± 13.3 years, body mass index 30.8 ± 4.1 kg/m^2, and AHI 47.0 ± 22.3 events/hour. There were no, or minor, overall volumetric changes in the airway, soft palate, total tongue, or tongue fat volume. Post-surgery there was an increase in the minimum cross-sectional area by 0.1 cm^2 (95% confidence interval 0.04–0.2 cm^2) in the pharyngeal airway, but not statistically significant on corrected analysis. There was no association between anatomical changes and AHI improvement.

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Conclusions: This contemporary multilevel upper airway surgery has been shown to be an effective OSA treatment. The current anatomical investigation suggests there are not significant post-operative volumetric changes associated with OSA improvement 6-month post-surgery. This suggests that effect on OSA improvement is achieved without notable deformation of airway volume. Reduced need for neuromuscular compensation during wake following anatomical improvement via surgery could explain the lack of measurable volume change. Further research to understand the mechanisms of action of multilevel surgery is required.

Clinical Trial: This manuscript presents a planned image analysis of participants randomized to the surgical arm or the clinical trial multilevel airway surgery in patients with moderate-severe obstructive sleep apnea (OSA) who have failed medical management to assess change in OSA events and daytime sleepiness. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=266019&isReview=true Australian New Zealand Clinical Trials Registry ACTRN12514000338662, prospectively registered on March 31, 2014.

Statement of Significance

Contemporary multilevel upper airway surgery has been demonstrated to be effective therapy for moderate-severe obstructive sleep apnea (OSA) in a randomized trial. However, anatomical effects of the surgery and relationship to efficacy in apnoea-hypopnea index reduction are unknown. Detailed 3D imaging found minimal anatomical changes following surgery, suggesting effective OSA treatment is achieved without significant tissue resection or major anatomical modification of the airway. This is the first longitudinal assessment of the macroscopic anatomy of the tongue plus intra-tongue fat, soft palate, and upper airway space following contemporary multilevel upper airway surgery.

Key words: obstructive sleep apnea; magnetic resonance imaging; multilevel upper airway surgery; tongue fat

Introduction

The Sleep Apnea Multilevel Surgery (SAMS) trial showed that combined modified uvulopalatopharygoplasty (UPPP_m) and radiofrequency-in-saline tongue ablation reduced obstructive sleep apnea (OSA) severity and improved daytime sleepiness compared to ongoing medical management in moderate or severe OSA patients unsuccessful with continuous positive airway pressure or mandibular advancement device therapy [1]. However, the mechanisms of apnea-hypopnea index (AHI) reduction following multilevel upper airway surgery for OSA are not fully understood.

Magnetic resonance imaging (MRI) allows for the assessment of upper airway soft volumes through segmentation as well as quantification of intra-tissue fat [2–4]. Volumetric analysis of the soft palate has shown a reduction following modified UPPP [5]. Effects of radiofrequency on tongue size have been assessed in small samples shortly post-surgery [6–8]. To our knowledge, there has been no assessment of combined upper airway effects following this multilevel surgical procedure after longer-term follow-up, and no assessment of the effect of radiofrequency ablation on tongue fat. Understanding the macroscopic effects on soft tissue structure following this intervention could help to elucidate mechanisms of action and aid in patient selection for surgical treatment of OSA.

The study aim was to quantify upper airway volume (airway space, soft palate, tongue, and intra-tongue fat) changes 6 months after surgery, and to assess whether these anatomical structures are associated with AHI improvement. We hypothesized that multilevel upper airway surgery results in macroscopic volume changes of increased upper airway space through volume reduction of surrounding soft tissues, and these volumetric changes are associated with AHI reduction.

Methods

Study subjects

Subjects were those in the surgical arm of the SAMS trial with baseline and follow-up (6 months) MRI scan and polysomnography. Inclusion/exclusion criteria, study protocol, and main results of the randomized controlled trial (RCT) have been previously published [1, 9]. In brief, the eligibility criteria were age 18–70 years, body mass index (BMI) <38 kg/m^2 and Epworth Sleepiness Scale >8, with moderate or severe OSA (AHI ≥15 events/hour) who had refused or been unsuccessful with device therapy [1, 9]. The study was performed at six Australian academic centers with human research ethics approval (Human Research Ethics Committee of Adelaide Institute for Sleep Health/Repatriation General Hospital/Flinders Medical Centre/Flinders Private Hospital, Adelaide, South Australia, protocol numbers EC00188, EC00271, EC00443, EC000266) and obtained written informed consent from all participants.

Study design

This study was a repeat case series study (before-after surgery) of upper airway anatomy to assess anatomical changes following surgery [1]. The sample size of those with MRI data in the surgical arm is sufficient to detect a change in upper airway anatomy of medium effect size (change/baseline standard deviation = 0.5) with significance level (α) = 0.05 and power ($1.0 - \beta$) = 90%.

Multilevel surgery intervention

The surgical intervention has previously been described [1, 9]. Briefly, the procedure consisted of UPPP_m with palatine tonsillectomy (if tonsils present) and submucosal insertions of a radiofrequency-in-saline wand into the tongue (7–9 points) [10]. The only tissues removed in this procedure were the palatine tonsils, submucosal lateral palatine fat pads and, in some cases, part of the uvula.

Magnetic resonance imaging

Upper airway imaging was performed at local diagnostic imaging practices according to a standardized imaging protocol. Spin-echo MRI was performed during wakefulness using 1.5T MRI scanners. Head position was standardized (Frankfort plane perpendicular to horizontal) and secured with foam pads. Participants were instructed to breathe normally through their nose, rest their tongue

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on the back of the front teeth with teeth lightly touching, and refrain from swallowing. Contiguous T1-weighted spin-echo axial images were obtained (50 slices, 3 mm thickness, 224 × 512 matrix). Additionally, mDixon sequences were acquired to allow quantification of intra-tongue fat [11, 12]. Of 51 participants randomized to surgery, 43 had available before-after scans of adequate quality for analysis (84.3%) and 31 with paired mDixon sequences (60%). There were no demographic differences between those with and without MRI data (see Online Supplement).

MRI analysis

Image analysis was performed using software 3D Slicer v4.10.1 (http://www.slicer.org) [13]. Volumetric analysis of upper airway structures (soft palate, tongue [genioglossus muscle and dorsum], airway space) was performed according to published manual segmentation protocols [2, 4, 14, 15], illustrated in Figure 1. Image analysis was performed by a single operator blinded to surgical status with measurement reproducibility confirmed (see Online Supplement). The upper airway was defined as the region between the hard palate and epiglottis base, and further subdivided into the velopharynx (hard palate to the tip of the uvula) and oropharynx (tip of the uvula to epiglottis base) (Figure 1, E). Airway cross-sectional area (CSA) and length (number of axial slices multiplied by slice thickness) were obtained. For the tongue, mDixon sequence images were used to quantify fat percentage (see Online Supplement for details). Soft palate length (posterior nasal spine ([P]NS) to uvula tip distance) and distance between the hyoid bone and the [P]NS ([P]NS-Hyoid) was measured on mid-sagittal images (Figure 1, F).

Statistical analysis

Statistical analysis was performed using SPSS (version 26.0, IBM Corporation). Continuous variables were assessed for normality of distribution (Shapiro-Wilk test). "Complete AHI response" was defined as post-surgery AHI <10 events/hour plus ≥50% AHI reduction, or "Incomplete" if both conditions were not met (alternative definitions presented in Online Supplement). Clinical characteristics of the complete and incomplete AHI response groups were compared using independent samples *t*-tests or Mann-Whitney tests as appropriate. As most MRI variables were not normally distributed (Shapiro-Wilk test, $p > 0.05$), comparison of pre- and post-surgery measures was by Wilcoxon Signed Rank tests. Differences in proportions were assessed via Fisher's exact tests. Linear regression was used to explore whether changes in each of the MRI measures related to AHI change (adjusting for age, sex, and any change in BMI between scans). Similarly, logistic regression was used to determine whether baseline anatomical characteristics or anatomical changes post-surgery were predictive of complete AHI response. The accepted level of statistical significance was adjusted using the Holm-Bonferroni method within each analysis to adjust for multiple comparisons. Values are reported as mean ± standard deviation or mean [95% confidence intervals] as indicated.

Results

Participant characteristics

Baseline clinical characteristics are shown in Table 1. The sample was predominantly male (79.1%) and on average mildly obese (BMI 30.8 ± 4.1 kg/m^2) with severe OSA (AHI 47.0 ± 22.3 events/hour). Forty participants (93%) had palatine tonsils removed as part of this surgical procedure, with prior palatine tonsillectomy in the remaining 3 participants. Ten (23.3%) of the 43 participants had a complete AHI response. These participants were younger than those with an incomplete AHI response (33.4 ± 13.8 vs. 45.6 ± 12.0 years, $p = 0.010$) and tended toward fewer males (40% vs. 15%, $p = 0.091$).

Changes in the upper airway structure following multilevel upper airway surgery

Pre- and post-surgery comparisons of upper airway structures are shown in Table 2. Overall, there were no changes in airway structures that reached the adjusted level of statistical significance. The exception was a reduction in uvula length ([P]NS-uvula distance, Figure 1), although there was no evidence of soft palate volume reduction. The uvula tip adopting a more superior location consequently moves the defined boundary between the velopharynx and the oropharynx (the uvula tip) resulting in a corresponding decrease in velopharyngeal volume as this region decreased in length, and an increase in oropharyngeal volume (Table 2). There was a tendency for overall airway length to reduce as indicated by a shortening of the [P]NS-Hyoid distance (−0.2 [95% CI −0.3, −0.03], $p = 0.032$), although not statistically significant. Within the velopharynx, there was a small increase in the minimum CSA (+0.1 [95% CI +0.04, +0.2] cm^2, $p = 0.004$), although this did not reach statistical significance. The other nonsignificant tendency was an increase in tongue volume on the post-surgical scan, corresponding to a mean percent change of 2.8 (95% CI +1.2, +4.5%, $p = 0.004$). There was no change in the intra-tongue fat tissue volume following surgery (Table 2). Mid-sagittal images of two participants (one complete AHI responder, one incomplete) before and after surgery are shown in Figure 2.

Relationship between changes in upper airway structure and OSA

The results of linear regression to examine the association between changes in upper airway structure and changes in AHI following surgery are shown in Table 3. None of the changes in airway dimensions (volume, cross-sectional area, or length) or soft tissue volumes related to change in AHI. The only MRI change measure with a tendency toward association with AHI change was the [P]NS-Hyoid distance, suggesting a decrease following surgery was associated with reduced AHI, although this did not reach statistical significance.

Predictors of complete AHI response to surgery from baseline anatomy and anatomical changes

Table 4 shows relationships between baseline clinical characteristics and MRI measurements and AHI-defined treatment complete AHI response to surgery. There were no statistically significant baseline predictors of complete AHI response to surgery. There was a trend for increasing age and soft palate volume to be negative predictors of AHI complete AHI response. Analysis to explore anatomical changes as predictors of complete AHI response are shown in Table 5. Changes in MRI measurements did not relate to the likelihood of being a complete AHI responder, although there was a trend for soft palate volume.

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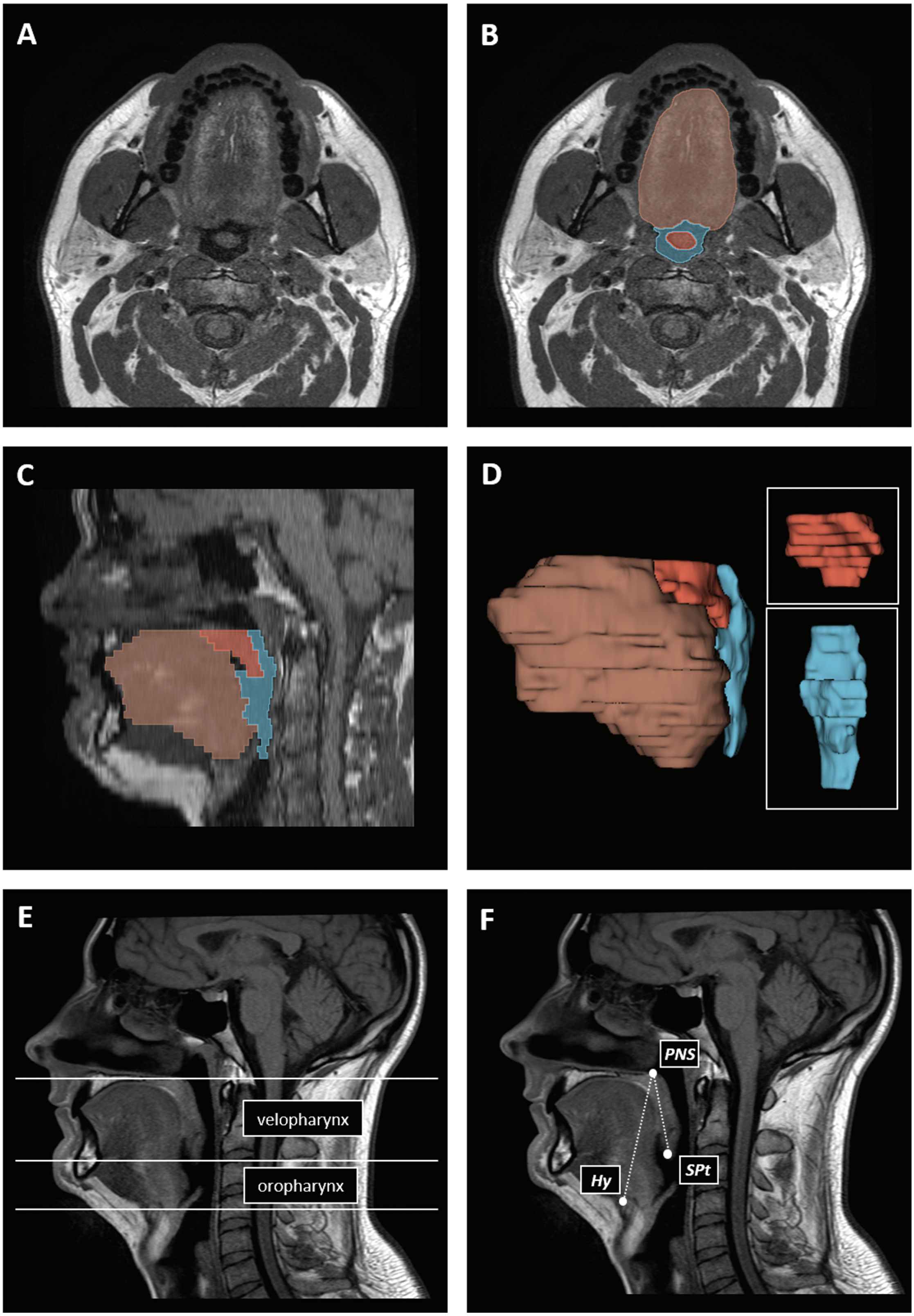

Figure 1. Magnetic resonance imaging analysis. (A) The axial image slice is used to segment the three structures of interest for volumetric analysis (upper airway space, soft palate, tongue). (B) Axial slice through the velopharynx with segmentation of the airway space (blue), soft palate (red), and tongue (pink). (C) Sagittal view of the segmentation on axial slices. (D) 3D reconstruction of the three segmentations. The Soft palate volume (red) and airway space (blue) are shown in full in the insets. (E) Boundaries of the airway regions. The velopharynx was defined as the region between the hard palate and the last slice of the soft palate (uvula tip). The oropharynx starts inferior to the uvula tip until the base of the epiglottis. (F) Landmarks used to calculate linear distances for tongue position ((P)NS-Hy), and soft palate length ([P] NS-SPt). The linear distance is indicated by the dotted line. Hy, hyoidal; [P]NS, posterior nasal spine; S, sella; and SPt, soft palate (uvula) tip.

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Table 1. Baseline characteristics of all and complete versus incomplete treatment response participants

	All	Complete response	Incomplete	*p*
N	43	10	33	
Demographics				
Age (years)	42.7 ± 13.3	33.4 ± 13.8	45.6 ± 12.0	0.010*
Gender (% male)	79.1	60.0	84.8	0.091
BMI (kg/m^2)	30.8 ± 4.1	31.1 ± 5.1	30.7 ± 3.9	0.795
AHI (events/hour)	47.0 ± 22.3	46.0 ± 28.4	47.1 ± 20.7	0.980

Complete response was defined as follow-up AHI <10 events/hour + 50% AHI reduction from baseline and compared to nonresponders using independent *t*-tests. Continuous measures are presented as mean ± standard deviation.
$^*p < 0.05$.

Discussion

This study provides a longitudinal assessment of the macroscopic anatomy of the tongue, soft palate, and upper airway following multilevel surgery (combined UPPP_m, radiofrequency tongue ablation ± tonsillectomy). The effectiveness of this surgical intervention compared to usual medical care in OSA patients for whom CPAP failed has been previously published [1]. There was a decrease in soft palate length (likely due to alterations of the uvula tip position) and a possible small increase in minimum CSA of the velopharynx; however, these changes were not associated with change in the apnea-hypopnea index. There were overall no volumetric changes in the airway, soft palate, tongue, or tongue fat. This suggests that the treatment effect of this surgery on OSA reduction occurs without major anatomical alteration of the tissues or upper airway space and suggests functional modulation of tissue properties or more

Table 2. Upper airway structural changes following multilevel upper airway surgery

	Baseline Median (IQR)	Post-surgery Median (IQR)	Change Mean (95% CI)	*p*
Airway volume (cm^3)				
Total	11.1 (4.4)	12.1 (5.0)	+0.4 (−1.0, +1.8)	0.538
Velopharynx	3.4 (1.8)	3.1 (1.8)	−0.5 (−0.9, −0.02)	0.039
Oropharynx	7.3 (4.0)	8.1 (4.2)	+0.9 (−0.4, +2.1)	0.151
Airway length (cm)				
Total	7.5 (1.5)	7.2 (1.5)	−0.1 (−0.3, −0.002)	0.058
Velopharynx	**3.3 (0.9)**	**3.0 (0.9)**	**−0.5 (−0.7, −0.3)**	**<0.001***
Oropharynx	**4.2 (0.9)**	**4.5 (0.9)**	**+0.4 (0.2, +0.6)**	**<0.001***
(P)NS-Hyoid	7.7 (1.2)	7.1 (1.3)	−0.2 (−0.3, −0.03)	0.032
Airway CSA (cm^2)				
Total				
Minimum	0.4 (0.2)	0.4 (0.2)	+0.1 (+0.01, +0.1)	0.016
Maximum	3.3 (1.2)	3.2 (1.3)	−0.1 (−0.5, +0.2)	0.534
Mean	1.4 (0.4)	1.6 (0.6)	+0.1 (−0.1, +0.2)	0.380
Velopharynx				
Minimum	0.4 (0.2)	0.4 (0.3)	+0.1 (+0.04, +0.2)	0.004
Maximum	2.4 (1.4)	2.5 (1.5)	−0.2 (−0.5, +0.1)	0.450
Mean	1.0 (0.5)	1.1 (0.4)	+0.03 (−0.1, +0.2)	0.429
Oropharynx				
Minimum	0.8 (0.6)	0.8 (0.6)	−0.02 (−0.2, +0.1)	0.308
Maximum	2.9 (1.1)	3.0 (1.3)	+0.1 (−0.3, +0.5)	0.617
Mean	1.7 (0.9)	1.8 (0.7)	+0.01 (−0.2, +0.2)	0.881
Soft palate				
Volume (cm^3)	6.5 (2.3)	6.6 (1.9)	+0.1 (−0.4, +0.6)	0.405
Length (cm)				
PNS-uvula tip	**3.6 (0.7)**	**3.2 (0.6)**	−0.4 (−0.6, −0.3)	**<0.001***
Tongue				
Volumes (cm^3)				
Total	96.5 (27.9)	97.7 (25.7)	+2.5 (0.9, +4.2)	0.004
Fat	27.3 (12.5)	26.8 (13.0)	+0.2 (−0.7, +1.1)	0.638
Fat proportion of tongue (%)	27.7 (11.7)	25.8 (9.8)	−0.3 (−1.3, 0.7)	0.494

Airway measurements (*N* = 43) are given for the total airway (hard palate to epiglottis base), as well as velopharynx (hard palate to soft palate tip), and oropharynx (soft palate tip to epiglottis base) regions. Airway length reflects the number of axial image slices between airway landmarks. Soft palate length was defined as the linear distance between the landmarks of the posterior nasal spine ((P)NS) and uvula tip ((P)NS-tip) on the mid-sagittal scan. Tongue tissue composition measures (tongue fat volume) were only available in a subset of participants (*N* = 31). Upper airway structures were compared between baseline and post-surgery scans using Wilcoxon Signed Rank Test, as the majority of variables were not normally distributed. * indicates statistical significance determined by the Holm-Bonferroni method ($p < 0.0028$). Significant differences also highlighted in bold text. (–) indicates that airway measurements reduce, (+) indicates that airway measurement increases. Baseline and Post-surgery data are presented as median (interquartile range).
CI, confidence interval; CSA, cross-sectional area.

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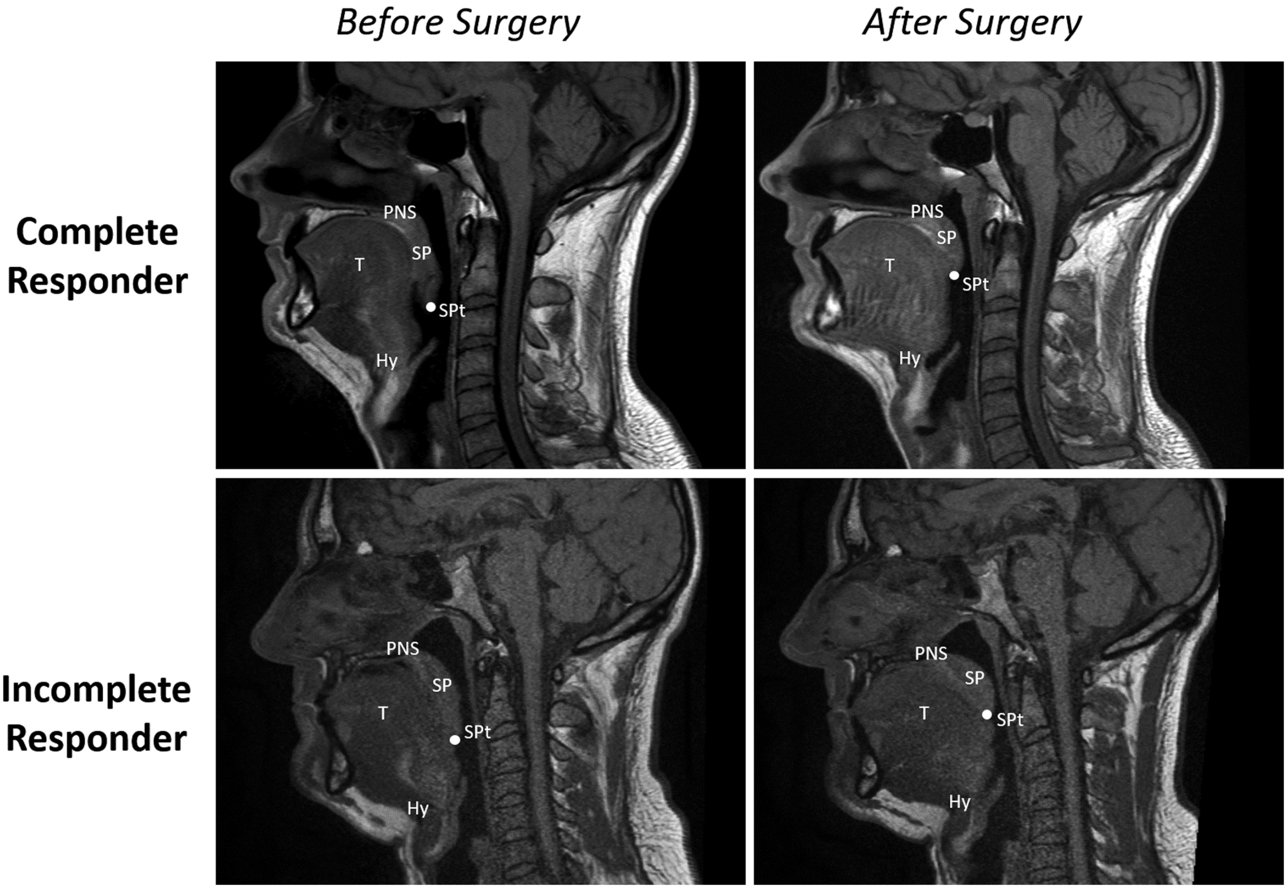

Figure 2. Example of individual participants with achieving a complete and incomplete AHI response to the surgical intervention. Mid-sagittal images from two participants in different response categories are presented to visualize the appearance of the tongue, soft palate, and upper airway before and after surgery. The complete AHI responder is a 53-year-old male with baseline AHI 23.5 events/hour, which reduced to 2 events/hour (91.5% AHI reduction) following surgery. The incomplete AHI responder is a 42-year-old male with baseline AHI 42.1 and 39.7 events/hour following surgery (2.4% AHI decrease). These example images are to give a representative view of the airway, tongue, and soft palate before and six-months following surgery. A change in soft palate morphology can be observed in both, which would decrease the velopharyngeal volume as measured in this study. Apart from the obvious change in the uvula, the airway and tongue areas appear similar before and after the intervention in both cases. The pharyngeal airway appears black in the image. T, indicates the tongue tissue; Hy, indicates the position of the hyoid bone; PNS, posterior nasal spine on the maxilla; SP, indicates the soft palate tissue; and SPt, tip of the uvula on the soft palate.

microscopic anatomical changes beyond the sensitivity of the current methodology.

The surgical intervention included a modified UPPP which is a reconstructive procedure aiming to preserve mucosa whilst expanding the upper airway space [9]. Therefore, a lack of reduction in total soft palate volume is not surprising. The uvula is reconstructed in the process to create a neo-uvula (estimated reduction of ~50%–75%) [10]. This was demonstrated as a reduction of the soft palate length (measured as [P]NS-uvula tip distance). Similar studies of soft palate volume are limited, although a previous volumetric analysis of eighteen participants undergoing UPPP found an 18% reduction in soft palate volume using equivalent analysis methods [5]. This UPPP$_m$ procedure was based on the expansion sphincteroplasty technique and could explain differences in the volumetric changes.

Although not meeting the criteria for statical significance, there was a small increase in tongue volume following surgery of around 2 cm^3 (<3% of total volume). Radiofrequency procedures are proposed as a minimally invasive way to reduce tongue bulk [10, 16, 17]. However, imaging results on this have been somewhat contradictory to date. An MRI study of repeated scans on 18 participants with radiofrequency applied to the tongue base showed a 17% decrease in tongue volume after the final treatment, once volume initially increased in the days immediately following first treatment due to edema [7]. Although it is unclear whether the tongue volume measurement methods used in that study are directly comparable to this current study. In another study of 10 participants with repeat MRI 4–6 weeks after radiofrequency tongue procedure, no change in tongue volume, height, width, or length was observed [8]. The current study reflects the longest follow-up period (6 months) before repeat scanning and found a small increase in tongue volume. These latter two studies suggest that the mechanism of OSA reduction by radiofrequency applied to the tongue is not through reduction of tongue bulk, but rather through other means of tissue remodeling, such as stiffening, to reduce upper airway collapsibility. We can only speculate on why there was a tendency for tongue volume to increase. It is possible the volume increase observed represents tissue scarring, or with improved airway function there is a decrease in muscle activity to maintain patency and this is reflected in a small tongue volume increase. Alternatively, this finding may be a chance finding at random or spurious due to the limited sensitivity of the method to detect smaller tongue volume changes. Tongue volume

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Table 3. Relationship between upper airway structure and OSA changes following multilevel upper airway surgery

	Δ AHI		
Δ Airway measurements	R^2	*B* (95% CI)	*p*
Airway volume (cm^3)			
Total	0.2	1.2 (−0.4, 2.9)	0.145
Velopharynx	0.1	0.5 (−4.8, 5.7)	0.863
Oropharynx	0.2	1.5 (−0.4, 3.4)	0.113
Airway length (cm)			
Total	0.1	6.9 (−8.9, 22.8)	0.383
Velopharynx	0.1	−1.3 (−14.7, 12.1)	0.844
Oropharynx	0.1	4.1 (−8.9, 17.0)	0.531
(P)NS-Hyoid	0.2	19.6 (2.2, 37.0)	0.029
Minimum CSA (cm^2)			
Total	0.1	−12.2 (−58.4, 34.1)	0.597
Velopharynx	0.1	−12.2 (−47.5, 23.1)	0.489
Oropharynx	0.2	8.6 (−5.9, 23.1)	0.235
Soft palate			
Volume (cm^3)	0.1	1.7 (−2.9, 6.5)	0.460
Length (cm)	0.1	−0.7 (−2.4, 0.9)	0.370
Tongue			
Total volume (cm^3)	0.1	0.4 (−1.1, 1.9)	0.608
Tongue fat %	0.1	−1.5 (−5.5, 2.4)	0.431

Linear regression was used to assess whether changes in upper airway measurements related to changes in the apnea-hypopnea index (AHI). The models contain age, sex, and change in BMI as covariates. Tongue fat percent only available in $N = 31$. No upper airway structure changes significantly related to AHI change (Holm-Bonferroni adjusted level of significance, $p < 0.0036$).

Table 4. Baseline predictors of complete response to multilevel upper airway surgery

	Predictive utility for complete response	
	Odds ratio (95% CI)	*p*
Baseline characteristics		
Age (years)	0.92 (0.85, 0.99)	0.019
Gender	0.27 (0.06, 1.30)	0.103
BMI (kg/m^2)	1.02 (0.86, 1.22)	0.490
AHI (events/hour)	1.0 (0.97, 1.03)	0.979
Airway measurements		
Airway volume (cm^3)		
Total	1.05 (0.88, 1.25)	0.116
Velopharynx	0.97 (0.64, 1.5)	0.879
Oropharynx	1.07 (0.89, 1.29)	0.487
Airway length (cm)		
Total	0.68 (0.31, 1.51)	0.348
Velopharynx	0.55 (0.15, 2.1)	0.383
Oropharynx	0.84 (0.34, 2.06)	0.697
(P)NS-Hyoid	0.87 (0.89, 1.06)	0.516
Minimum CSA (cm^2)		
Total	1.39 (0.01, 225.33)	0.900
Velopharynx	0.44 (0.01, 25.9)	0.690
Oropharynx	1.45 (0.29, 7.37)	0.652
Soft palate		
Volume (cm^3)	0.31 (0.13, 0.72)	0.007
Length (cm)	0.98 (0.86, 1.12)	0.779
Tongue		
Total volume (cm^3)	0.97 (0.92, 1.02)	0.967
Tongue fat %	1.01 (0.91, 1.12)	0.870

Univariate logistic regression was used to identify baseline predictors to identify responders to surgery. Complete response was defined on the basis of follow-up AHI < 10 events/hour + 50% AHI reduction from baseline ($N = 10$). No upper airway structure changes significantly related to AHI change (Holm-Bonferroni adjusted level of significance, $p < 0.0028$).

Table 5. Anatomical changes as predictors of complete response to multilevel upper airway surgery

	Predictive utility for complete response	
	Odds ratio (95% CI)	*p*
Δ Airway measurements		
Airway volume (cm^3)		
Total	0.9 (0.7, 1.2)	0.404
Velopharynx	1.0 (0.5, 2.1)	0.978
Oropharynx	0.9 (0.6, 1.2)	0.334
Airway length (cm)		
Total	1.1 (0.1, 8.0)	0.938
Velopharynx	4.2 (0.7, 25.2)	0.119
Oropharynx	0.16 (0.02, 1.86)	0.118
(P)NS-Hyoid	0.2 (0.02, 1.7)	0.127
Minimum CSA (cm^2)		
Total	6.2 (0.03, 1218.1)	0.500
Velopharynx	4.6 (0.6, 352.7)	0.490
Oropharynx	1.6 (0.3, 9.6)	0.631
Soft palate		
Volume (cm^3)	2.8 (1.2, 6.7)	0.022
Length (cm)	0.9 (0.7, 1.1)	0.350
Tongue		
Total volume (cm^3)	0.9 (0.7, 1.1)	0.160
Tongue fat %	0.7 (0.4, 1.2)	0.227

Logistic regression was used to identify any anatomical changes which could identify complete responders to surgery. The models for anatomical changes contain age, sex, and change in BMI as covariates. Complete response was defined on the basis of follow-up AHI < 10 events/hour + 50% AHI reduction from baseline ($N = 10$). No upper airway structure changes significantly related to AHI change (Holm-Bonferroni adjusted level of significance, $p < 0.0035$).

segmentation has excellent intra-rater reliability as performed by an experienced operator, however, the average percent difference in repeat measurement of tongue volume is around 2.5% for this dataset (data not shown). Therefore, the mean difference between the before and after surgical scans falls within this margin of error. A previous MRI analysis of tongue volume following transoral robotic glossectomy showed a 5.8% volume reduction following the procedure [5]. This would suggest that reduction through this minimally invasive radiofrequency procedure tongue volume reduction magnitude would be <5%, and hence potentially below the sensitivity of the MRI analysis method.

A novel aspect of this work is the assessment of tongue fat percentage following radiofrequency ablation. It is unknown if radiofrequency may have an effect on reducing tongue fat. Tongue fat deposition has been shown to be increased in OSA (33%) compared to BMI-matched non-apneics (28%) (AHI <10) using mDixon MRI techniques [3]. Decreased tongue fat volume mediates some of the effect of weight loss on OSA improvement [18]. Therefore, if tongue fat was reduced this could be a mechanism by which radiofrequency ablation reduces OSA. We found fat to comprise an average of 27% of total tongue tissue. This is slightly below the average observed in those without OSA (28%) in the study of Kim et al. [3], suggesting low tongue fat in our patient sample and possibly explaining why we found there was no difference in tongue fat percent following the intervention. Animal studies in porcine tongues have examined the lesion size resulting from radiofrequency coblation in the submucosa to be around 60 mm [3, 19, 20]. It is unclear how far the effect of coblation penetrates through the human tongue. The tongue "fatty streak" is likely inferior to the field and this may also explain the failure to identify an effect on tongue fat. Alternatively,

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it may be that the procedure does not specifically ablate fat tissue relative to nonfat tissue.

Our MRI analysis used a definition of the velopharyngeal airway common in MRI analysis studies [2, 4]. However, in studies such as this where the intervention is likely to change this landmark, the uvula tip may not be an appropriate choice because of the resulting decrease in retropalatal airway volume [5], which is difficult to interpret and may confound these results. A definition of regional airway boundaries based on bony landmarks may be more appropriate for future studies where there is a soft palate intervention. Although all participants with identifiable palatine tonsils had them removed (*N* = 40) there was no significant overall volume increase of the upper airway. This is a counterintuitive finding as soft tissue was removed and it would be expected to translate into an increase in airway space. In people with compromised airways, such as in OSA, pharyngeal dilator muscle activity is increased during wakefulness, most likely to compensate for anatomical compromise to maintain airway patency [21]. Surgical intervention to address anatomical compromise is likely to reduce neuromuscular compensation during wake and potentially mask a volumetric improvement by MRI methods. Unfortunately, we do not have corresponding data on muscle activity during wake, or volumetric analysis during sleep to confirm this. However, reduced AHI during sleep is consistent with these concepts. Given the extended 6-month period before the follow-up scan it is also possible that remodeling of the airway space in terms of soft palate position, connective tissue, or scarring helps to explain the lack of observable volume change. Although not statistically significant when adjusted for multiple comparisons, we did find some evidence for an increase in the minimum CSA of the velopharynx regardless of the lack of volume change. Poiseuille's Law predicts that airflow through the upper airway (first-pass approximation of a cylindrical tube) is proportional to the fourth power of airway radius and inversely proportional to airway length. Thus, although AHI changes and minimal CSA were not correlated, the small possible increase in minimum CSA of the airway, in the order of 6 mm^2 (+28%), could have importantly contributed to improved airflow and AHI, despite no overall velopharyngeal volume change detected by this methodology.

Overall, this anatomical investigation of the soft palate, tongue tissue, and airway space, combined with the SAMS trial result showing an approximate 60% reduction in AHI post-surgery, suggest that a significant OSA treatment effect is achieved with very little alteration of the macroscopic airway anatomy as measured by awake MRI. Hence, the effect of this surgical intervention on reducing upper airway collapsibility may largely be through changes in tissue properties to make the airway stiffer and less collapsible. Although we are not able to assess tissue properties in the current study, future studies using imaging methods such as elastography to measure changes in tongue stiffness and dynamic imaging of respiratory movements could provide important insights [22–24]. Additionally, sleep MRI or sleep endoscopy methods, although technically challenging, may be needed to help understand the anatomical changes related to OSA improvement. Ultimately the lack of association found between the anatomical measurements in this analysis and AHI changes means it remains unclear which aspects of the multilevel surgery are driving its effect. Future studies of additional anatomical factors and functional effects of this intervention are needed to further refine the surgical intervention and best select responders to surgery to further improve patient outcomes.

Despite the use of comprehensive MRI measures of the anatomical effects of multilevel upper airway surgery, this study has limitations. We did not have a control group for this study as the costs versus the limited benefit of MRI scans in SAMS trial control participants were not considered to be sufficiently justified. A control group would enable measures from two-time points to be compared in those without the intervention to assess any measurement differences between scans. A control group would have been preferable to test for potential systematic changes over time without surgical intervention. However, imaging was performed under a standardized protocol and analysis with careful instructions for subject positioning. Systematic time-dependent changes in a control group would likely be smaller than anatomical changes in the surgical intervention group which were minimal. A previous publication of this method of soft tissue volumetric analysis collected scans at two time points in nine participants and showed excellent reproducibility of the tongue and soft palate volume measurements between scans (intra-class correlation coefficient >0.9) [25]. Thus, MRI scanning was considered likely to be sufficiently sensitive and reproducible to detect within-subject changes with surgery. Although the lack of control group is a limitation of the study, given the predominantly negative findings in terms of anatomical changes in the intervention group, control group data are unlikely to alter the interpretation of the main findings of this study. With 43 participants of whom 10 were complete AHI responders we were underpowered to detect any smaller anatomical changes, although it is not clear that smaller changes would be clinically meaningful. There could be sources of variation related to the multicenter nature of the study in that different scanners were used, although a standardized image acquisition protocol was developed and our results are predominantly assessing within-subject changes. Comparing images from two different time points may also create subtle differences in head, jaw, or tongue posture which may additionally confound, despite standardizing the head position. Our assessment of airway CSA was in the plane of the scan (axial) and this does not necessarily reflect the most important boundaries influencing airflow; however overall anatomical changes should be detected by this method. The imaging protocol was also performed during stable breathing in wakefulness and over a number of respiratory cycles. This means the airway space boundaries analysed are an average of their appearance across inspiration and expiration. Although we would expect an overall change in airway configuration following the intervention could be detected [2, 5], it is possible that more subtle airway changes that are more evident on inspiration or expiration could be masked. Respiratory-gated or dynamic images would be needed in future studies to investigate this possibility. Additionally, imaging is performed in the supine body position only and airway changes may be different in the lateral position. Therefore, the analyzed airway space was assessed when wake neuromuscular influences favor airway patency and where averaging between inspiration and expiration may also mask potentially important sleep and respiratory cycle-dependent changes. The lack of any association between airway space and OSA improvement could therefore be lost due to imaging in wakefulness and structures which change with the onset of sleep and the associated withdrawal of muscle tone.

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Conclusions

This contemporary multilevel upper airway surgery has been shown to be an effective OSA treatment. The current anatomical investigation suggests that there were not significant post-operative volumetric changes associated with that improvement 6-month post-surgery. This suggests that effect on OSA improvement is achieved without notable changes to airway and soft tissue volumes. Reduced need for neuromuscular compensation during wake following anatomical improvement via surgery could explain the lack of measurable volume change. Further research to understand the mechanisms of action of multilevel surgery is required.

Supplementary material

Supplementary material is available at *SLEEP* online.

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