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Upper Airway Anatomy: Factors to predict OSA severity and changes induced by Mandibular Repositioning Appliances

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Upper Airway Anatomy: Factors to predict OSA severity and changes induced by Mandibular Repositioning Appliances

A thesis submitted in partial satisfaction of the

Requirements for the degree Master of Science in Oral Biology

by

William Paul Boggess

2020

ABSTRACT OF THE DISSERTATION

Upper Airway Anatomy: Factors to predict OSA severity and changes induced by Mandibular Repositioning Appliances

by

William Paul Boggess

Master of Science in Oral Biology

University of California, Los Angeles, 2020

Professor Sanjay Mallya, Chair

Anatomic constriction and collapse of the upper airway are key to development of obstructive sleep apnea. The first aim of this study was to identify upper airway anatomic features that correlate with AHI severity. The second aim was to evaluate changes to the upper airway caused by mandibular repositioning appliances and to identify potential predictors of the therapeutic response. Our study did not identify any anatomic correlates of AHI severity, indicating the contribution of other factors to OSA development, in addition to anatomic constriction. Mandibular repositioning appliances induced a statistically significant increase in the velopharyngeal dimensions, suggesting that muscular repositioning of the tongue as well as the pharyngeal and palatal muscles may play a role in its therapeutic actions.

The thesis of William Paul Boggess is approved.

Sotirios Tetradis

Diana Messadi

Sherwin Arman

Sanjay Mallya, Committee Chair

University of California, Los Angeles

2020

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Introduction

Obstructive sleep apnea (OSA) is characterized by episodes of partial or complete obstruction of the upper airway during sleep, interrupting (apnea) or reducing (hypopnea) the flow of air, followed by transient awakening that leads to the resolution of the upper airway collapse [1]. The cause of the disease is multifactorial with the main causes being a reduction of the expansion forces of the pharyngeal dilator muscles and discoordination between the inspiratory activity of the muscle and respiratory effort[2]. There is growing evidence of OSA playing a role in the pathogenesis of cardiovascular and metabolic diseases and a strong association with increased mortality rates [3].

An overnight polysomnography study is the most reliable confirmation for an OSA diagnosis [4]. A common measurement for the severity of OSA is the Apnea-Hypopnea Index (AHI); which is an average that represents the combined number of apneas and hypopneas that occur per hour of sleep. OSA is divided into three types by the American Academy of Sleep Medicine (AASM).

- Mild OSA: AHI of 5-15 – involuntary sleepiness during activities that require little attention, such as watching tv or reading.
- Moderate OSA: AHI of 15-30 – involuntary sleepiness during activities that require some attention, such as meetings or presentations.

- Severe OSA: AHI of more than 30 – involuntary sleepiness during activities that require more active attention, such as talking or driving.

The prevalence of obstructive sleep apnea had a mean of 22% (range, 9-37%) in men and 17% (range, 4-50%) in women in eleven published epidemiological studies published between 1993 and 2013[5]. The gold standard for treatment of moderate to severe OSA is continuous positive airway pressure (CPAP) but treatment can be challenging because of low patient compliance and adherence to the treatment [6]. Mandibular repositioning appliances (MRAs) are an effective treatment for mild to moderate OSA. Short term (health outcomes at one month) show MRA therapy to be comparable to CPAP [7].

Upper Airway

The upper respiratory tract has a complex anatomical arrangement of skeletal muscles and soft tissues. The anatomy can be divided into 4 main segments. The nasopharynx that is superior to the hard palate, the velopharynx between the hard palate and the tip of the uvula, the oropharynx that is between the tip of the uvula and the tip of the epiglottis and the hypopharynx from the tip of the epiglottis to the vocal cords.

The musculature has an internal longitudinal layer and an external circular layer. The longitudinal layer consists of the salpingopharyngeus, palatopharyngeus and stylopharyngeus muscles and their function is to elevate

the pharynx and larynx during speech and swallowing. The circular layer consists of the superior, middle and inferior pharyngeal constrictor muscles which constrict the pharynx during swallowing.

The soft palate is a movable fold that extends the hard palate posteroinferiorly to the uvula and forms an incomplete septum between the mouth and the pharynx. The lower border is free and the most inferior portion is called the uvula. Its function is to close off the nasopharynx in swallowing, while suckling and during speech[8]. The relationship between uvula size and sleep-disordered breathing is lacking in data for objective interpretation. Uvular length > 15 mm is considered elongated [9]. OSA patients have significantly longer soft palate length and the percentage of the airway taken up by the soft palate is greater than non-OSA patients [10].

Minimum pharyngeal airway space in a patient with no apparent symptoms of OSA has a 7.6 mm mean and 6.5 mm median (range 5.4 mm, 25% to 9.3 mm, 75%)[11]. An area of constriction less than 37.4 mm^2 was found to predispose a subject to OSA [12].

Cone Beam Computed Tomography (CBCT)

Evaluation of OSA using polysomnography is time consuming and expensive[13]. Therefore, attempts have been made to search for imaging modalities that would directly reflect the status of the upper airway[14]. Dental radiography was revolutionized when cone beam computed tomography

(CBCT) became readily available in the late 1990's. Since then interest in it has rapidly increased in dental research and clinical practice among general dentists and specialists alike [15]. The ability to perform a three-dimensional evaluation of the upper airway coupled with the lower radiation dose compared to medical CT imaging makes CBCT a potentially attractive tool for the assessment of airway anatomy in OSA patients [16]. Despite low soft tissue resolution, CBCT shows high contrast between bone, empty spaces and soft tissues in general so the airway can be visualized ideally in relation to the hard tissue structures of the skull[17]. Reliability of the CBCT imaging has been evaluated in comparison to multidetector CT and the measurements of the upper airway space using CBCT were fairly accurate[18]. The reliability of upper airway analysis with CBCT has great variability between examiners but improves with examiner experience. Assessment of the oropharynx is the most reliable area of upper airway; however, the velopharynx and hypopharynx has generally low reliability between examiners [19]. Adequate training in CBCT analysis is needed to provide the highest level of measurement reliability [19]. In the supine position, the velopharynx is the most changeable site in the upper airway, when compared to the oropharynx and hypopharynx in the upright position[20].

Specific Aims

Specific Aim1: To examine whether anatomic features of the upper airway, as determined on CBCT scans correlate with OSA severity, as categorized by the AHI score.

Specific Aim1: To evaluate anatomic changes to the upper airway caused by an MRA and the impact of these changes on therapeutic success of the appliance.

Materials and Methods

Patients and recruitment:

The study population was recruited from OSA patients referred to the UCLA Orofacial Pain Clinic for MRA therapy.

The inclusion and exclusion criteria were as below:

Inclusion criteria

- Age: 25 years or older. This age group is selected to represent the broad age range of patients that are typically treated with MRA for OSA.
- Apnea-hypopnea index (AHI, as determined by polysomnography): 5-30, representing mild to moderate OSA.
- Adequate number of teeth in good health to support the dental appliance.

Exclusion criteria

- Inability to reliably keep appointments for the treatment and follow-up visits.
- Pregnant patients.

Severe dental disease.

This study was approved by the Institutional Review Board of UCLA.

Mandibular Repositioning Appliance

The mandibular repositioning appliance used in this study was the Adjustable Herbst Appliance. The appliance has customized maxillary and mandibular trays with telescopic arms. The trays do not come apart and allow 2-3 mm of lateral movement. The telescopic arms are adjustable at ¼ mm increments with a recommended maximum expansion of 5 mm. The pre-fabrication record of bite was recorded in the anterior end to end position.

Radiographic Imaging

CBCT scans were taken both before treatment and right after MRA delivery (n=43). An additional follow-up CBCT scan was taken on 12 subjects. All CBCT scans were taken by a NewTom 5G machine in an 18x16 field of view with a 14-bit gray scale. Scan times were 18 seconds (3.6 seconds emission time), 110 kV, and utilized an automatic exposure control that adjusted the milliampere based upon the patient's anatomic density. Data from the CBCT was reconstructed to produce 0.3mm slices.

CBCT volumes and Reference Planes

DICOM files from CBCT examinations were imported into Invivo6 (Anatomage, CA). To standardize anatomic positioning and measurements, the imaged volume was re-oriented in the three orthogonal planes as below (Figure 1):

Sagittal plane: Included anterior nasal spine (ANS), posterior nasal spine (PNS) and nasion (N)

Horizontal plane: Plane perpendicular to the midsagittal plane and including the ANS and PNS

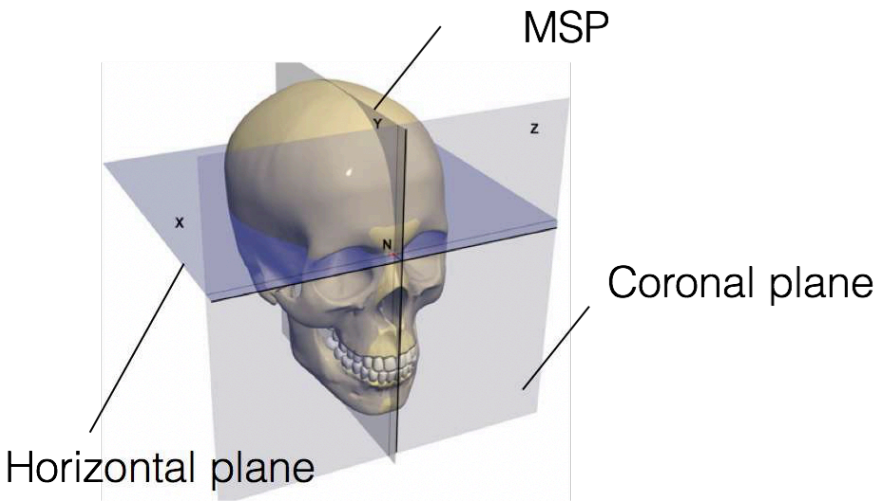


Figure 1: Orthogonal Planes

Upper Airway Assessment

The built-in airway module in InVivo was used to segment the upper airway from the palatal plane to the deepest point in the laryngeal vallecula (Figure 2). The software program automatically generates linear (antero-posterior) and area measurements at 0.5mm intervals along the airway length. Data was

exported in tabular format and imported into Graphpad Prism for further analyses. Summary statistic incudes the maximum, minimum and average Ap dimension and area measurement.

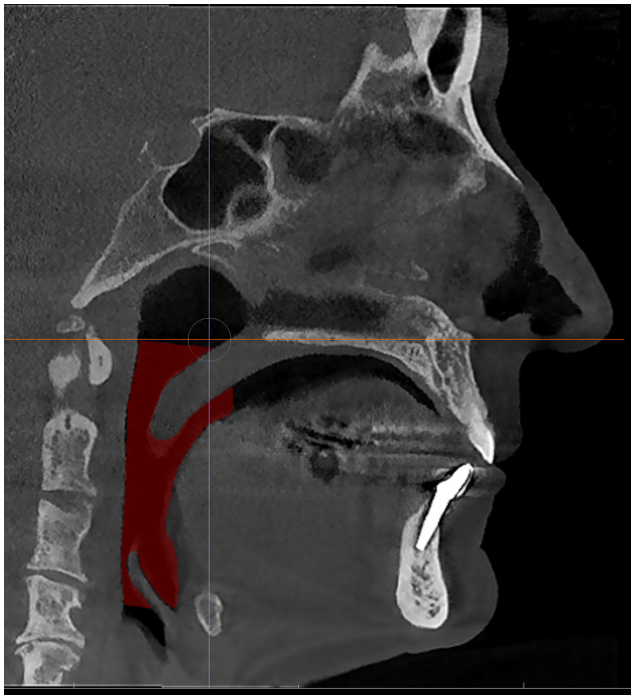


Figure 2: Airway Assessment

The area from the horizontal palatal plane to the tip of the uvula in the midsagittal plane was defined as the velopharynx. The deepest point of the laryngeal vallecula to the tip of the epiglottis was used as the hypopharynx. The tip of the epiglottis to the tip of the uvula was used as the oropharynx.

Each subject had their unique velopharynx, oropharynx and hypopharynx areas determined, the minimum cross-sectional area and minimum A-P length were obtained from the data chart for each level in the upper airway.

Data Analysis

Data sets obtained from the CBCT radiographs were transferred to Microsoft Excel. A single linear regression model for log-transformed AHI scores was utilized for the predictors at pre-treatment. For the posttreatment changes, pre and post comparisons in pharyngeal measurements were made. The lack of a model linking pharyngeal measurements to OSA severity limits the clinical relevance of any significant differences found. However, if a future model is found, these results could form the basis of a novel clinical intervention for OSA sufferers seeking treatment.

First, t-tests were conducted on the differences in measurement before and after the intervention with the mandibular repositioning device. For the three regions (velopharynx, oropharynx and hypopharynx), minimum cross-sectional area and minimum A-P length measurements were obtained. The null hypotheses were that the difference between pre and post measurements were zero while the alternative hypotheses were that there was a difference. Both absolute differences and percent differences were calculated and tested,

resulting in a total of 12 t-tests. Since there is presumably a degree of dependence between measurements of differences and percent differences, the Bonferroni correction applied was a reduction in alpha-level by a factor of six, not 12. If a p-value falls below 0.00833, it will be rejected. Criticism of the Bonferroni method commonly centers on its conservativeness with high numbers of tests[21]; however, for even any given test here, the rejection threshold is almost an order of magnitude stricter than the original threshold, so even with this modification, the standard is reasonably strict. For re-interpretation with a Bonferroni correction of 12, the rejected tests would be velopharynx area difference and length percent difference (alpha-level is 0.05/12, or 0.00416). Due to the dependent nature of the percent difference tests (for example, in these results, all significant differences also had significant percent differences and vice-versa), the Bonferroni correction of six is recommended at this time.

The single linear regression model for log-transformed AHI scores and the t-tests with the Bonferroni correction applied were completed by senior Master's students Zanyu Shi and Sean Campeau in the UCLA Department of Biostatistics. GraphPad Prism version 8.2.0 (435) was used for the anatomical analysis and graphing. Brown-Forsythe ANOVA tests were used for analysis between groups. Dunnett's T3 multiple comparisons tests were used for analysis of statistically significant results.

Predictive Factors

Prognostic factors analyzed in the pre-treatment upper airway were:

- Amount of A-P length constriction vs OSA severity
- Amount of cross-sectional area constriction vs OSA severity
- Level of A-P constriction vs OSA severity
- Level of cross-sectional area constriction vs OSA severity
- Validity of A-P Score
- Validity of Cross-sectional Area Score

Anatomical analysis in the pre-treatment airway:

- Differences between A-P constriction length in OSA severity groups
- Differences between cross-sectional constriction area in OSA severity groups
- Differences between level of constriction in OSA severity groups
- Differences between amount of constriction at each level in OSA severity groups

Prognostic factors analyzed in the post-delivery upper airway were:

- Does the MRA change the upper airway?
- What changes are observed? (positive, negative)
- Are significant changes correlated with specific upper airway levels?

Anatomical analysis of the post-delivery upper airway:

- Change in A-P constriction vs OSA severity (mm, %)
- Change in minimum cross-sectional area vs OSA severity (mm^2, %)
- Change in A-P constriction vs level (mm, %)

- Change in minimum cross-sectional area vs level (mm^2, %)

MRA analysis

- MRA advancement across all subjects (%)
- MRA advancement vs OSA severity (%)

Subjects recruited into the study received standard diagnostic and therapeutic clinical practices, non-standard or investigational practices were not used. The ages ranged from 29-88 years with a mean age of 69 years. The pre-treatment AHI numbers ranged from 1 to 47 with equal numbers of male and female subjects. Polysomnogram results for the subjects:

- AHI less than 5 or normal*: n= 5
- AHI between 5 but less than 15 or mild OSA: n=19
- AHI between 15 but less than 30 or moderate OSA: n=5
- AHI greater than 30 or severe OSA: n=3

  *Although these patients have an AHI score that is considered normal, each patient had OSA symptoms, and either a high Respiratory Distress Index (RDI) or high Respiratory Event index (REI).

The number of subjects recruited into the study and also received a pre-treatment CBCT radiograph was 62. The number of subjects with a pre-treatment AHI, pre-treatment CBCT radiograph and a CBCT radiograph at delivery of the MRA was 32. This group of 32 patients were the subjects evaluated in the study.

RESULTS

Summary of factors:

Variable	Coefficient	Number of cases	Estimate	Std. Error	t value	Pr(>|t|)
Velopharynx (Ref: >6mm n=6)	Intercept	-	1.7233	0.3338	5.1629	<0.0001
	Less than 6mm	26	0.5775	0.3703	1.5595	0.1294
Oropharynx (Ref: >6mm n=21)	Intercept	-	2.1494	0.1850	11.6171	<0.0001
	Less than 6mm	11	0.1254	0.3156	0.3975	0.6938
Hypopharynx (Ref: >6mm n=21)	intercept	-	2.1688	0.1854	11.7004	<0.0001
	Less than 6mm	11	0.0690	0.3162	0.2184	0.8286
AP Score (Ref: 0-3 n=16)	Intercept	-	2.0594	0.2097	9.8195	<0.0001
	6-9	16	0.2662	0.2966	0.8975	0.3766
Area Score (Ref: 0-3 n=17)	Intercept	-	2.1433	0.2058	10.4163	<0.0001
	5-15	15	0.1051	0.3005	0.3496	0.7291
Velopharynx (Ref: 50-90 mm^2 n=15)	Intercept	-	2.4740	0.2045	12.0989	<0.0001
	Greater than 90mm2	7	0.3025	0.3233	0.9355	0.3573
	Less than 50 mm2	10	-0.5521	0.3903	-1.4147	0.1678
Oropharynx (Ref: >90 mm^2 n=24)	Intercept	-	2.2096	0.1764	12.5283	<0.0001
	Between 50-90mm2	5	0.0340	0.6310	0.0539	0.9573
	Less than 50 mm2	3	0.0896	0.5291	0.1694	0.8667
Hypopharynx (Ref: >90 mm^2 n=22)	Intercept	-	2.1563	0.1795	12.0119	<0.0001
	Between 50-90mm2	3	-0.6998	0.5810	-1.2045	0.2381
	Less than 50 mm2	7	-0.3259	0.3654	-0.8920	0.3797
Level of Constriction A-P (ref: Hypo n=8)	Intercept	-	2.0181	0.2838	7.1109	<0.0001
	o	1	1.8321	0.8514	2.1518	0.0399
	v	23	0.1631	0.3295	0.4949	0.6244
Level of Constriction Area (ref: Hypo n=9)	Intercept	-	1.9712	0.2793	7.0568	<0.0001
	v	23	0.3080	0.3295	0.9347	0.3574

All factors to predict OSA severity that were analyzed in the pre-treatment airway showed no correlation to the AHI Score obtained after polysomnography ($p > 0.05$).

Summary of Changes:

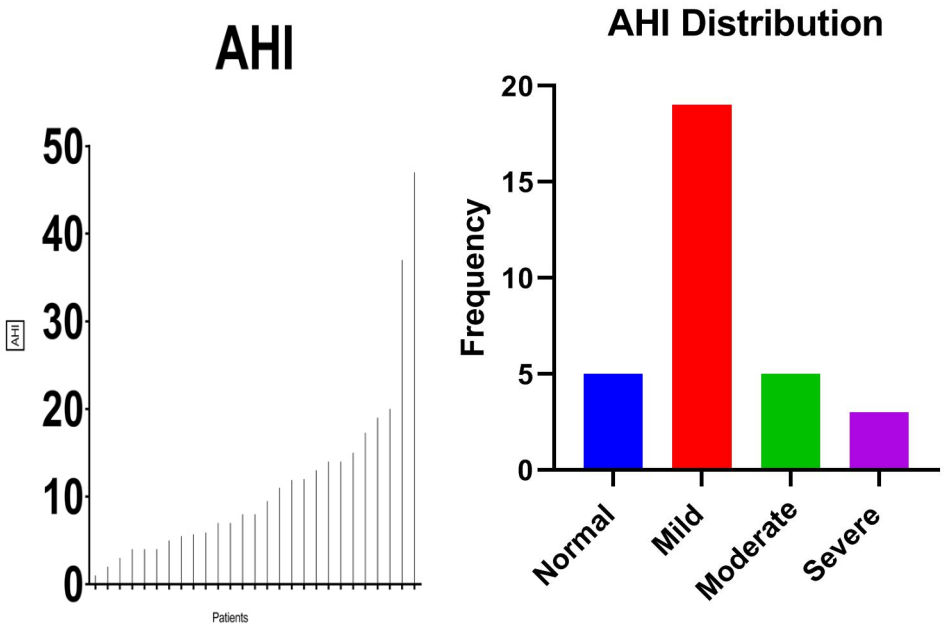
Velopharynx	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-2.7828	1.1090	1.0709	5.3842	0.00583	Yes
Change (%)	-50.19	21.93	39.60	189.34	0.00144	Yes
Change(mm^2)	-45.394	-2.507	26.593	176.948	0.00198	Yes
Change (%)	-31.99	37.17	56.43	553.23	0.00632	Yes

Oropharynx	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-5.3667	-0.2793	0.2028	6.3254	0.7260	No
Change (%)	-48.34	-3.75	13.30	128.44	0.1280	No
Change(mm^2)	-133.45	20.578	24.830	179.074	0.0718	No
Change (%)	-56.62	16.15	30.88	176.64	0.0052	Yes

Hypopharynx	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-7.7278	0.3527	0.2892	7.5667	0.6200	No
Change (%)	-62.78	9.41	16.23	188.25	0.0981	No
Change(mm^2)	-111.76	16.25	22.33	207.28	0.1200	No
Change (%)	-46.86	30.58	49.40	575.77	0.0201	No

All changes in area and A-P in the velopharynx and the percentage area change in the oropharynx were significantly positive ($p > 0.00833$).

Distribution of AHI score in the pretreatment airway.



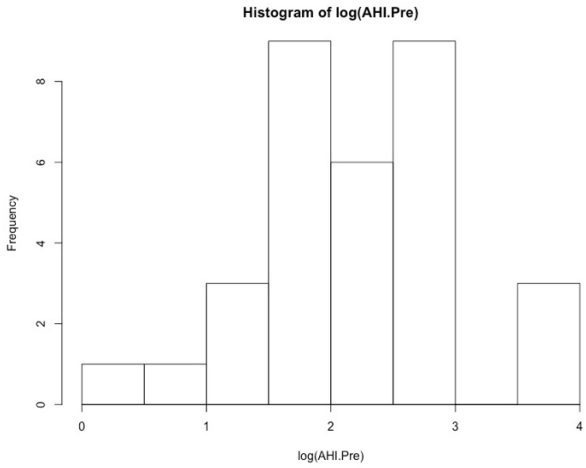
- **Normal** **n=5**
- **Mild** **n=19**
- **Moderate** **n=5**
- **Severe** **n=3**

The range of AHI Scores varied from the least severe at 1 to the most severe at 47.

All patients have OSA symptoms; yet, five patients had an AHI below 5 after the polysomnogram. Three of these patients were diagnosed with Upper Airway Resistance Syndrome while the remaining two patients had snoring, insomnia and daytime tiredness.

Due the distribution of AHI scores, a log-transformation was conducted on AHI scores to make its distribution more approximated to a normal distribution, which is a prerequisite for t-test and other parametric analysis.

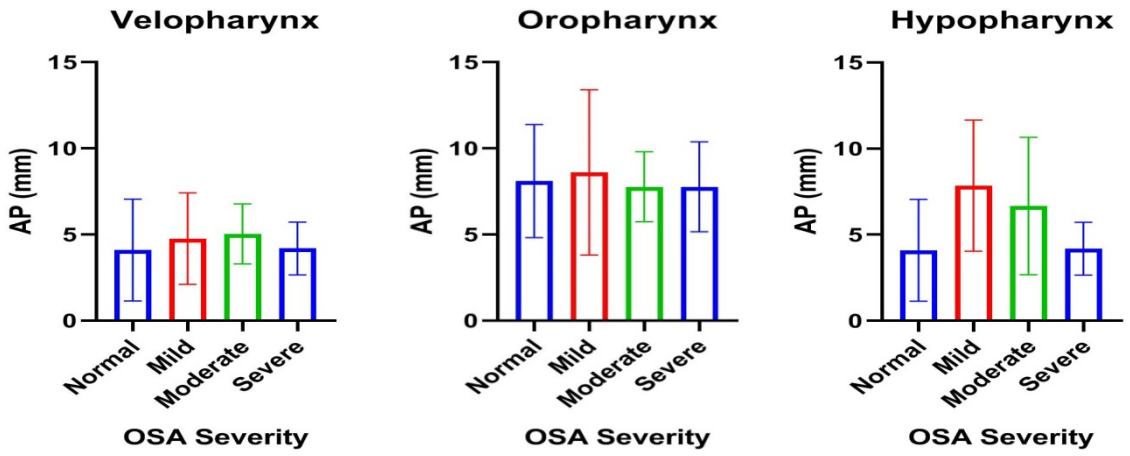
Log Transformation of AHI scores



Model for predictors

Single linear regression models for log-transformed AHI scores and the predictors on pre-treatment airways were utilized. The Single linear regression models test was used for correlation between single variables and the outcome AHI scores in the pre-treatment airway.

Is there a significant difference of the AP length among OSA severity groups at various segments of the upper airway?

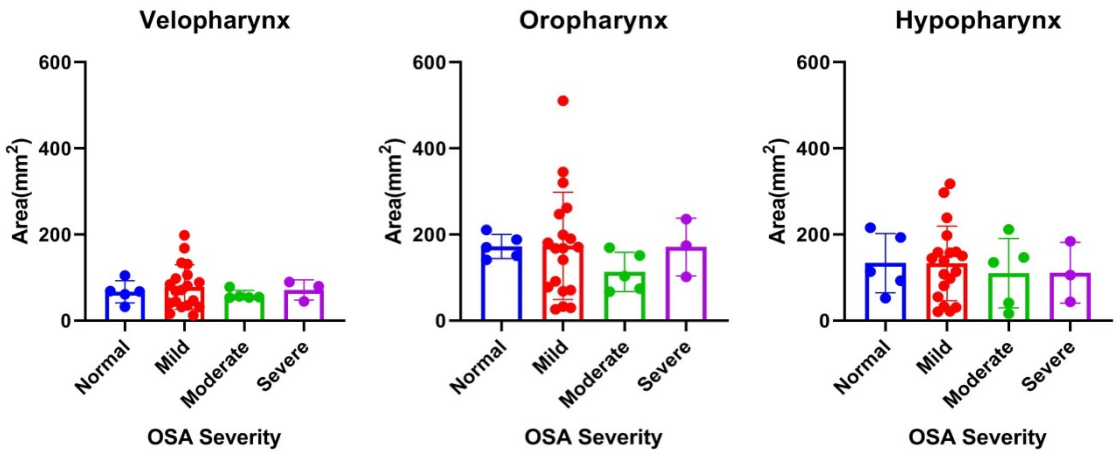


Brown-Forsythe ANOVA	F(DFn,DFD)	P value	Significant Difference
Velopharynx	0.2087(3,12.9)	0.8885	No
Oropharynx	0.1503 (3,16.6)	0.9280	No
Hypopharynx	2.700(3,13.2)	0.0881	No

The null hypothesis is that the average minimum A-P length at various levels of the upper airway is the same (Ho: L normal =L mild =L moderate =L severe).

The analysis of these data sets, failed to reject the null hypothesis.

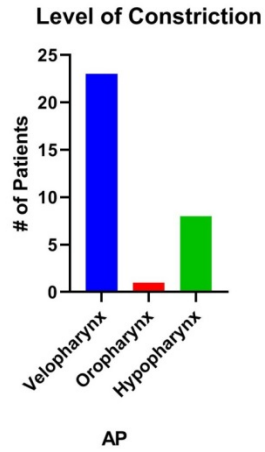
Is there a significant difference of the area of maximum constriction among OSA severity groups at various levels of the upper airway?



Brown-Forsythe ANOVA	F(DFn,DFD) (3, 28)	P value	Significant Difference
Velopharynx	0.3023 (3, 18.4)	0.5352	No
Oropharynx	0.4739 (3, 14.4)	0.3481	No
Hypopharynx	0.1466 (3, 13.1)	0.9110	No

The null hypothesis is that the average area of maximum constriction at various levels of the upper airway is the same (Ho: L normal =L mild =L moderate =L severe). The analysis of these data sets, failed to reject the null hypothesis.

At what level in the upper airway does the minimum A-P length occur?



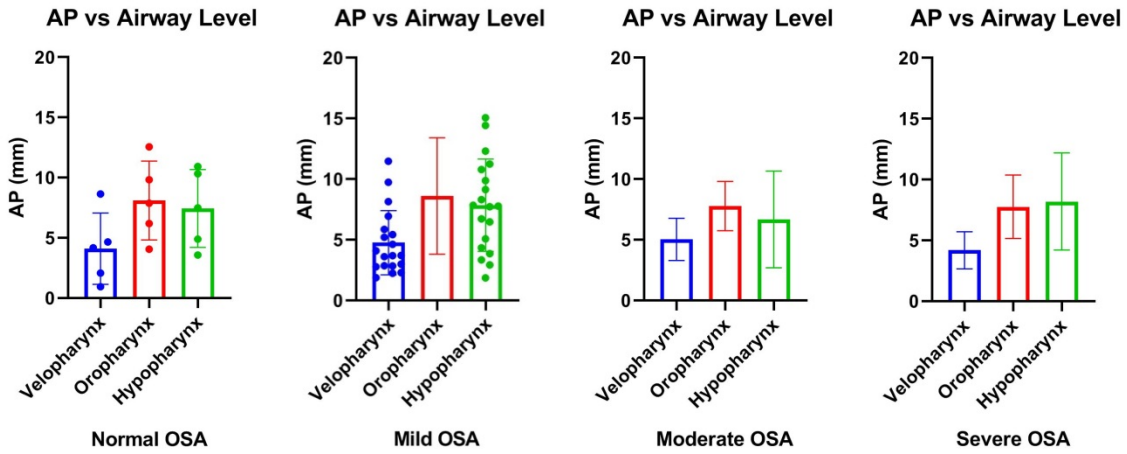
The minimum AP dimension occurred in the velopharynx 72% of the time. One patient has the minimum AP length in the oropharynx. In cases with the initial constriction in the velopharynx, this is the only constriction point below 6 mm in 57% if the patients.

Is there a significant difference of the AHI score among patients with initial A-P constriction at various levels of the upper airway?

Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
Level of Constriction (ref: Hypo n=8)	Intercept	-	<2.0181	0.2838	7.1109	<0.0001
	Oropharynx	1	<1.8321	0.8514	2.1518	0.0399
	Velopharynx	23	<0.1631	0.3295	0.4949	0.6244

The null hypothesis is that there is no difference in the effects of level of initial constriction to the AHI score (Ho: L velopharynx =L oropharynx =L hypopharynx). The analysis of these data sets, failed to reject the null hypothesis. The analysis of these data sets, failed to reject the null hypothesis in the velopharynx and hypopharynx. Even though the p-value in the oropharynx is less than 0.05; because only one patient is initially constricted at this level, evidence to reject the null hypothesis is weak.

Is there a significant difference of the AP length among various levels of the upper airway in different OSA severity groups?



Brown-Forsythe ANOVA	F(DFn,DFD)	P value	Significant Difference
Normal	2.302 (2, 12)	0.1428	No
Mild	5.318 (2, 45.3)	0.0084	Yes
Moderate	1.234 (2, 7.6)	0.3433	No
Severe	1.737 (2, 4.1)	0.2838	No

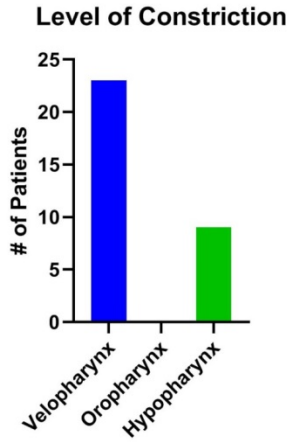
The null hypothesis is that the average minimum A-P length at various levels of the upper airway is the same (Ho: L velopharynx =L oropharynx =L hypopharynx). The analysis of these data sets, failed to reject the null hypothesis in the normal, moderate and severe OSA groups. There is a statistically significant difference in the constriction area for patients with mild OSA.

Among what levels in the upper airway is the difference noted for patients with mild OSA?

Dunnett's T3 multiple comparisons test (Mild)	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value	
Velopharynx vs. Oropharynx	-3.848	-7.407 to -0.2881	Yes	*	0.0143	A-B
Velopharynx vs. Hypopharynx	-3.090	-6.077 to -0.1039	Yes	*	0.0196	A-C
Oropharynx vs. Hypopharynx	0.7572	-3.167 to 4.682	No	ns	0.9303	B-C

A statistically significant difference is noted between the constriction area of the velopharynx vs the oropharynx and the velopharynx vs the hypopharynx in the mild OSA group.

At what level in the upper airway does the minimum cross-sectional area occur?



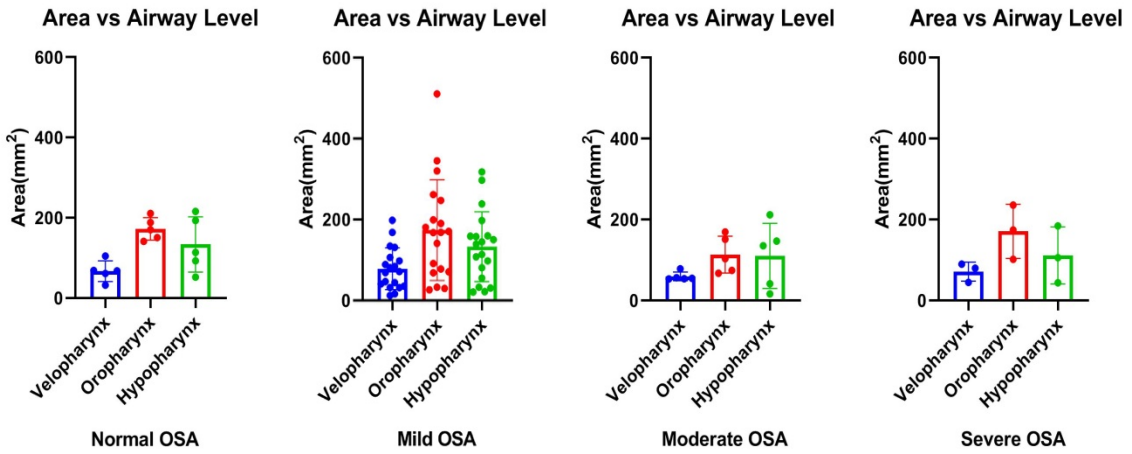
The minimum cross-sectional area occurred 72 % in the velopharynx. In cases with the initial constriction in the velopharynx, this is the only constriction point below 90 mm^2 in 74% if the patients. There were no patients that has the area of maximum constriction the oropharynx.

Is there a significant difference of the AHI score among patients with initial minimum cross-sectional area at various levels of the upper airway?

Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
Level of Constriction (ref: Hypo n=9)	Intercept	-	1.9712	0.2793	7.0568	<0.0001
	v	23	0.3080	0.3295	0.9347	0.3574

The null hypothesis is that there is no difference in the effects of level of initial constriction to the AHI score (Ho: L velopharynx =L oropharynx =L hypopharynx). The analysis of these data sets, failed to reject the null hypothesis.

Is there a significant difference of the cross-sectional area among various levels of the upper airway in different OSA severity groups?



Brown-Forsythe ANOVA	F(DFn,DFD)	P value	Significant Difference
Normal	6.854 (2,6.5)	0.0248	Yes
Mild	5.066 (2,39)	0.0111	Yes
Moderate	1.586 (2,6.5)	0.2748	No
Severe	2.245 (2, 4.4)	0.2120	No

The null hypothesis is that the average minimum cross-sectional area at various levels of the upper airway is the same (Ho: L velopharynx =L oropharynx =L hypopharynx). The analysis of these data sets, failed to reject the null hypothesis in the moderate and severe OSA groups. There is a statistically significant difference in the constriction area for patients with normal and mild OSA.

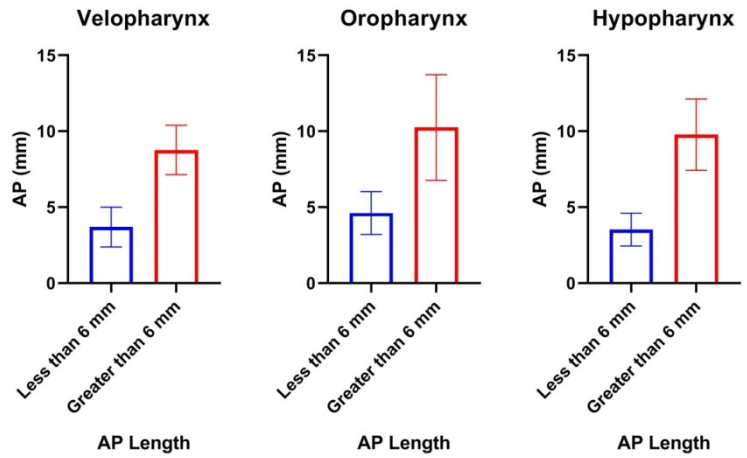
Between what levels in the upper airway is the difference noted?

Dunnett's T3 multiple comparisons test (Normal)	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value	
Velopharynx vs. Oropharynx	-105.3	-164.0 to -46.52	Yes	***	0.0008	A-B
Velopharynx vs. Hypopharynx	-66.59	-200.9 to 67.73	No	ns	0.2373	A-C
Oropharynx vs. Hypopharynx	38.66	-97.23 to 174.6	No	ns	0.6070	B-C

Dunnett's T3 multiple comparisons test (Mild)	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value	
Velopharynx vs. Oropharynx	-95.30	-184.0 to -6.624	Yes	*	0.0151	A-B
Velopharynx vs. Hypopharynx	-54.33	-119.6 to 10.98	No	ns	0.0744	A-C
Oropharynx vs. Hypopharynx	40.96	-56.74 to 138.7	No	ns	0.5674	B-C

A statistically significant difference is noted between the constriction area of the velopharynx vs the oropharynx in both the normal and mild OSA groups.

Is there a significant difference between of A-P length between the airways with constriction less than 6 mm and greater than 6 mm?



There is a statistically significant difference between the mean lengths in airways that have a constriction less than 6 mm and those that have the minimum constriction greater than 6 mm (p=<0.0001).

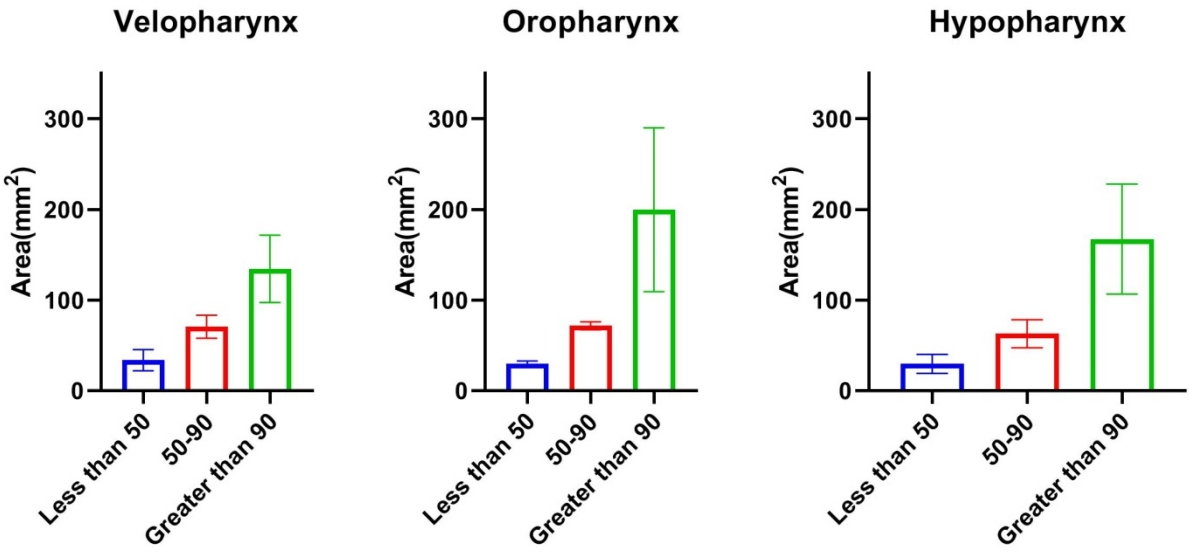
Does the amount of initial AP constriction correlate with OSA severity?

Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
Velopharynx	Intercept	-	1.7233	0.3338	5.1629	<0.0001
(Ref: >6mm n=6)	<6 mm	26	0.5775	0.3703	1.5595	0.1294
Oropharynx	Intercept	-	2.1494	0.1850	11.6171	<0.0001
(Ref: >6mm n=21)	<6 mm	11	0.1254	0.3156	0.3975	0.6938
Hypopharynx	Intercept	-	2.1688	0.1854	11.7004	<0.0001
(Ref: >6mm n=21)	<6 mm	11	0.069	0.3162	0.2184	0.8286

The null hypothesis is that there is no difference in the effects among the amount of initial constriction groups and the AHI score (Ho: L less than 6 mm =L greater than 6 mm). The analysis of these data sets, failed to reject the null hypothesis.

	AP(mm)	Normal	Mild	Moderate	Severe
Velopharynx	>6 n=6	1	4	1	0
	<6 n=26	4	15	4	3
Oropharynx	>6 n=21	4	12	3	2
	<6 n=11	1	7	2	1
Hypopharynx	>6 n=21	3	13	3	2
	<6 n=11	2	6	2	1

Is there a significant difference of the area of the airways among various airway parameters at various levels of the upper airway?



There is a statistically significant difference among the mean area in airways at various cutoff levels (p=<0.0001.

Does the amount of the initial area of constriction correlate with OSA severity?

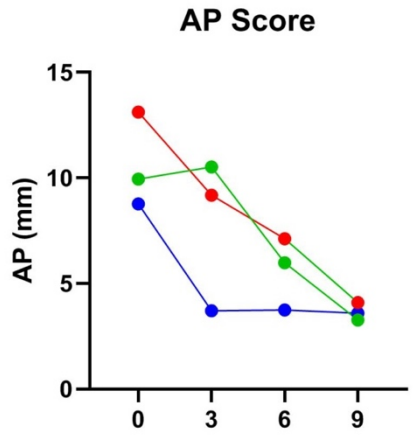
Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
Velopharynx (Ref: 50-90 mm^2 n=15)	Intercept	-	<2.4740	0.2045	12.0989	<0.0001
	>90 mm^2	7	0.3025	0.3233	0.9355	0.3573
	<50 mm^2	10	-0.5521	0.3903	-1.4147	0.1678
Oropharynx (Ref: >90 mm^2 n=24)	Intercept	-	<2.2096	0.1764	12.5283	<0.0001
	50-90 mm^2	5	0.0340	0.6310	0.0539	0.9573
	<50 mm^2	3	0.0896	0.5291	0.1694	0.8667
Hypopharynx (Ref: >90 mm^2 n=22)	Intercept	-	<2.1563	0.1795	12.0119	<0.0001
	50-90 mm^2	3	-0.6998	0.5810	-1.2045	0.2381
	<50 mm^2	7	-0.3259	0.3654	-0.8920	0.3797

The null hypothesis is that there is no difference in the effects among the amount of initial constriction groups and the AHI score (Ho: L less than 50 mm^2 =L 50 mm^2 to 90 mm^2 =L greater than 90 mm^2). The analysis of these data sets, failed to reject the null hypothesis.

	Area (mm^2)	Normal	Mild	Moderate	Severe
Velopharynx	<50 n=10	1	8	0	1
	50-90 n=15	3	5	5	2
	>90 n=7	1	6	0	0
Oropharynx	<50 n=3	0	3	0	0
	50-90 n=5	0	3	2	0
	>90 n=24	5	13	3	3
Hypopharynx	<50 n=7	0	4	2	1
	50-90 n=3	1	2	0	0
	>90 n=22	4	13	3	2

Is the AP Score a useful tool for upper airway analysis?

Velopharynx Oropharynx Hypopharynx



AP Score	0	3	6	9
Ave Airway (mm)	10.6	7.8	5.6	3.7

The AP Score is a value to indicate the severity of the AP constriction in the upper airway. Three points are given to each section of the upper airway (velopharynx, oropharynx and hypopharynx) that measures 6 mm or less. The higher the score, the greater the number of areas in the upper airway that have an AP constriction less than 6 mm and the average length of the airway is smaller; however, this index does not indicate at what level or levels the constriction occurs.

Is the AP Score a useful tool for predicting OSA severity?

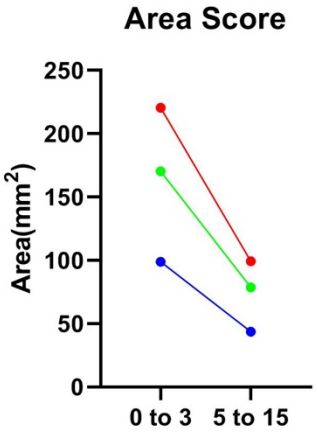
Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
AP Score (Ref: 0-3 n=16)	Intercept	-	<2.0594	0.2097	9.8195	<0.0001
	6-9	16	<0.2662	0.2966	0.8975	0.3766

The null hypothesis is that the A-P Score has no correlation with the AHI score (Ho: L 0-3 =L 6-9). The analysis of these data sets, failed to reject the null hypothesis.

AP Score	Normal	Mild	Moderate	Severe
9 n=6	0	5	1	0
6 n=10	3	3	2	2
3 n=10	1	7	1	1
0 n=6	1	4	1	0

Is the Area Score a useful tool for upper airway analysis?

Velopharynx Oropharynx Hypopharynx



Area Score	0 to 3	5 to 15
Average (mm^2)	163.3	73.9

The Area Score is a value to indicate the severity of the area constriction in the upper airway. Points are given to each section of the upper airway (velopharynx, oropharynx and hypopharynx). Zero points for the constriction area above 90 mm^2, three points for 50-90 mm^2 and five points for constriction areas below 50 mm^2. There is a large difference between the average area between Area Score groups.

Is the Area Score a useful tool for predicting OSA severity?

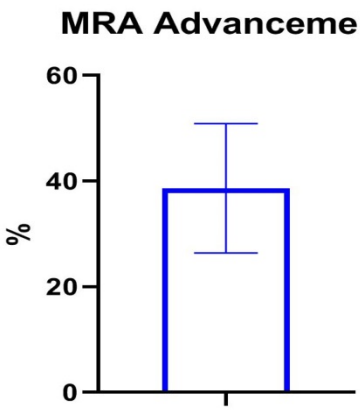
Variable	Coefficient	Number of cases	Estimate	Std.Error	t Value	Pr(>|t|)
Area Score (Ref: 0-3 n=17)	Intercept	-	<2.1433	0.2058	10.4163	<0.0001
	5-15	15	<0.1051	0.3005	0.3496	0.7291

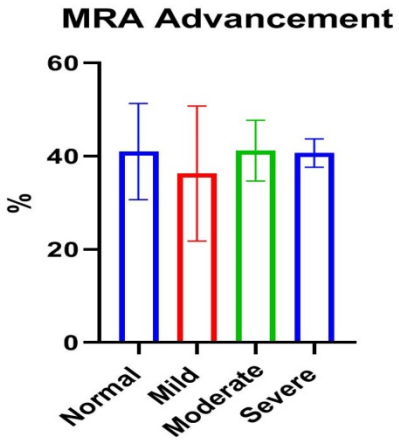
The null hypothesis is that the Area Score has no correlation with the AHI score (Ho: L 0-3 =L 5-15). The analysis of these data sets, failed to reject the null hypothesis.

Area Score	Normal	Mild	Moderate	Severe
0 to 3 n=17	4	9	2	2
5 to 15 n=15	1	10	3	1

MRA Post-Delivery Analysis

What was the percentage of mandibular advancement?





% Advancement	Total	Normal	Mild	Moderate	Severe
Number	32	5	19	5	3
Mean	38.65	41.00	36.28	41.20	40.67
Std. Dev	12.25	10.34	14.52	6.54	3.06
Std. Error	2.20	4.63	3.43	2.92	1.76

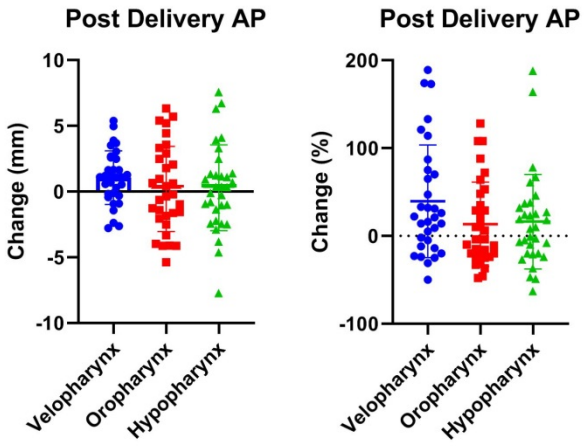
Advancement numbers were obtained clinically and the numbers used are 1) the amount in mm from maximum intercuspation to an anterior edge position and 2) the amount in mm from maximum intercuspation to maximum protrusion. The mean advance percentage was 38.65% across all the patients.

Is there a statistically significant difference between the amount of mandibular advancement between severities?

Dunnett's T3 multiple comparisons test	Mean Diff.	95.00% CI of diff.	Significant?	Summary	Adjusted P Value	
Normal vs. Mild	4.722	-16.73 to 26.18	No	ns	0.9476	A-B
Normal vs. Moderate	-0.2000	-22.30 to 21.90	No	ns	>0.9999	A-C
Normal vs. Severe	0.3333	-22.85 to 23.51	No	ns	>0.9999	A-D
Mild vs. Moderate	-4.922	-19.82 to 9.975	No	ns	0.8451	B-C
Mild vs. Severe	-4.389	-17.02 to 8.244	No	ns	0.8209	B-D
Moderate vs. Severe	0.5333	-14.12 to 15.18	No	ns	>0.9999	C-D

There was no statistically significant difference between the amount of advancement and severity of OSA.

What change is observed in the AP length at various levels of the upper airway after MRA delivery?

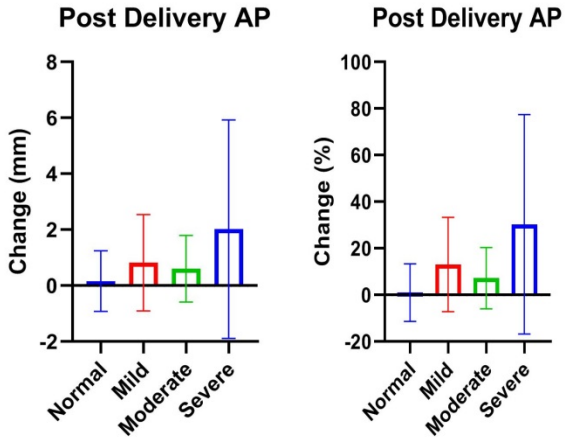


Change (mm)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Velopharynx	-2.783	5.384	8.167	1.071	2.046	0.3616
Oropharynx	-5.367	6.325	11.69	0.2028	3.242	0.5731
Hypopharynx	-7.728	7.567	15.29	0.2892	3.269	0.5779

Change (%)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Velopharynx	-50.00	189.0	239.0	39.53	64.05	11.32
Oropharynx	-48.00	128.0	176.0	13.28	48.02	8.488
Hypopharynx	-63.00	188.0	251.0	16.34	53.88	9.524

A large range of change is noted within each level of the upper airway even with mandibular advancement showing no statistical significance between patients.

What change is observed in the AP length among OSA severity groups after MRA delivery?

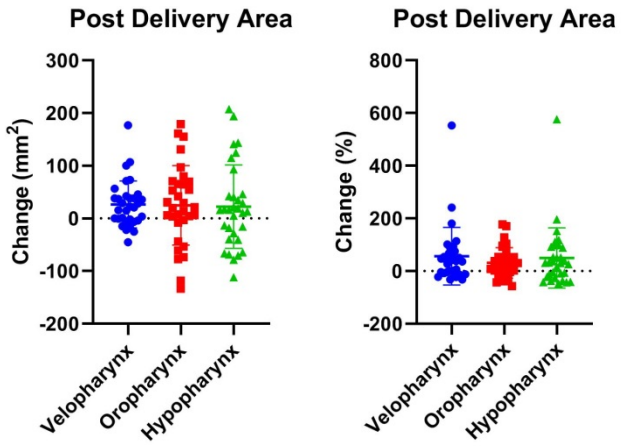


Change (mm)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Normal	-1.210	1.576	2.786	0.1594	1.084	0.4849
Mild	-3.046	5.089	8.135	0.8228	1.726	0.3959
Moderate	-0.7426	2.022	2.765	0.6036	1.195	0.5345
Severe	-2.481	4.520	7.001	2.020	3.906	2.255

Change (%)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Normal	-16.00	16.00	32.00	1.000	12.39	5.541
Mild	-24.00	71.00	95.00	13.11	20.27	4.650
Moderate	-7.000	24.00	31.00	7.200	13.18	5.894
Severe	-24.00	59.00	83.00	30.33	47.08	27.18

A large range of change is noted within each level of the upper airway even with mandibular advancement showing no statistical significance between patients.

What change is observed in the area at various levels of the upper airway after MRA delivery?

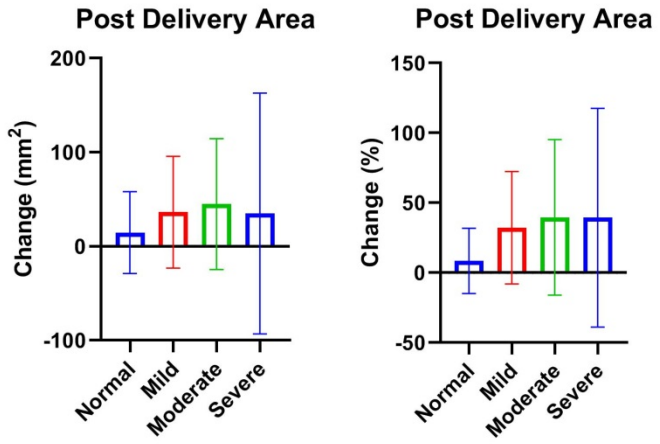


Change (mm²)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Velopharynx	-45.39	176.9	222.3	26.59	44.52	7.869
Oropharynx	-133.5	179.1	312.5	24.83	75.35	13.32
Hypopharynx	-111.8	207.3	319.0	22.33	79.07	13.98

Change (%)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Velopharynx	-32.00	553.0	585.0	56.44	109.0	19.26
Oropharynx	-57.00	177.0	234.0	30.94	58.18	10.28
Hypopharynx	-47.00	576.0	623.0	49.41	114.1	20.17

A large range of change is noted within each level of the upper airway even with mandibular advancement showing no statistical significance between patients.

What change is observed in the area among OSA severity groups after MRA delivery?

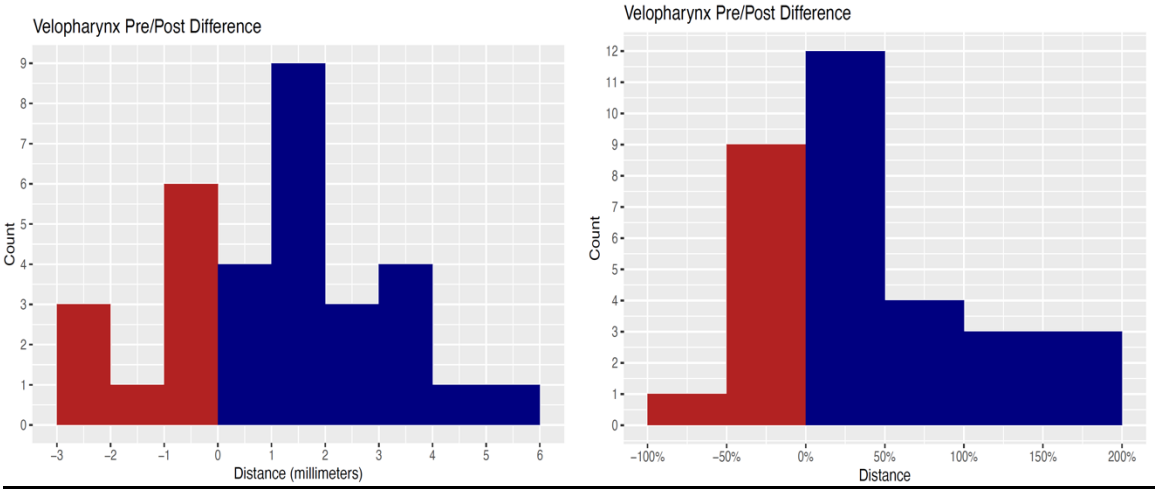


Change (mm^2)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Normal	-52.96	54.02	107.0	14.68	43.48	19.44
Mild	-96.48	158.1	254.6	36.26	59.37	13.62
Moderate	-41.21	136.1	177.3	44.87	69.61	31.13
Severe	-104.8	146.5	251.3	34.85	127.9	73.87

Change (%)	Minimum	Maximum	Range	Mean	Std. Dev	Std Error
Normal	-29.00	29.00	58.00	8.400	23.30	10.42
Mild	-33.00	146.0	179.0	32.16	40.23	9.229
Moderate	-15.00	128.0	143.0	39.60	55.70	24.91
Severe	-48.00	103.0	151.0	39.33	78.23	45.17

A large range of change is noted within each level of the upper airway even with mandibular advancement showing no statistical significance between patients.

Is the minimum A-P constriction change in the velopharynx statistically significant?



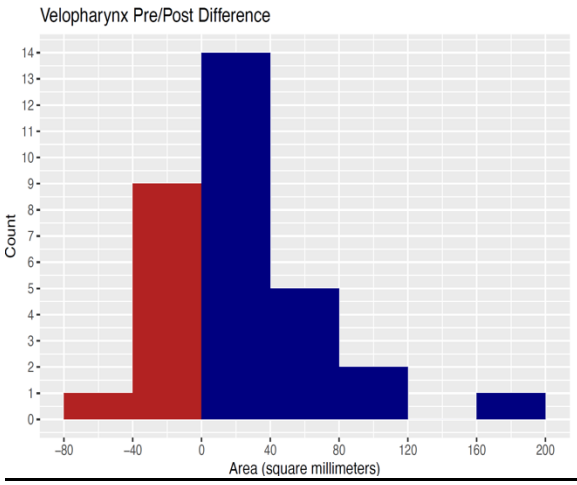
Velopharynx

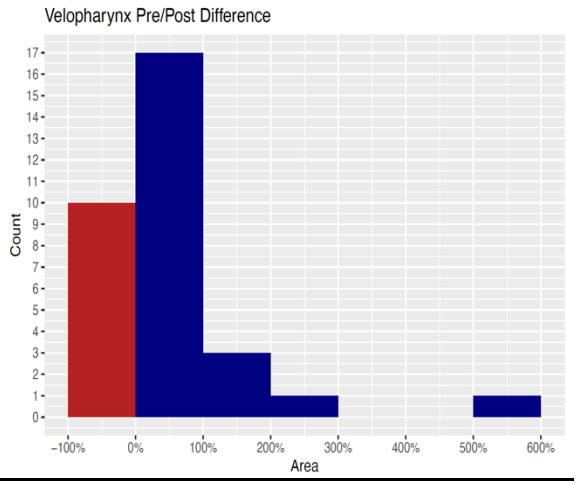
A-P length	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-2.7828	1.1090	1.0709	5.3842	0.00583	Yes
Change (%)	-50.19	21.93	39.60	189.34	0.00144	Yes

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of these data sets rejected the null hypothesis. The alternate hypothesis is that the MRA causes change in the airway after delivery. The analysis of these data sets with two-sided t-tests (p=0.05) and the Bonferroni correction applied (p=0.00833 significance value) supports the alternate hypothesis and the change was an increase.

The velopharynx had an overall mean positive change of 1.07 mm or 39.60%.

Is the minimum cross-sectional area change in the velopharynx statistically significant?





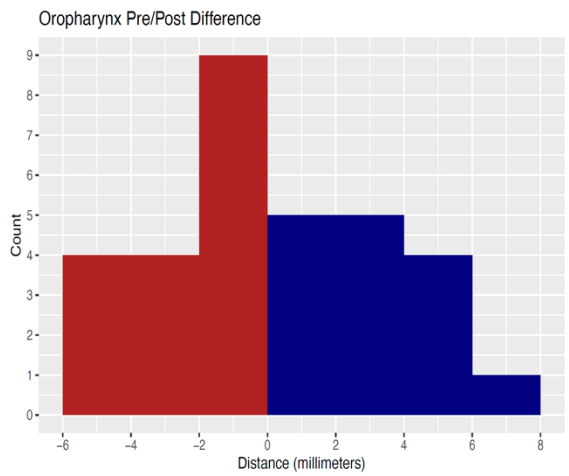
Velopharynx

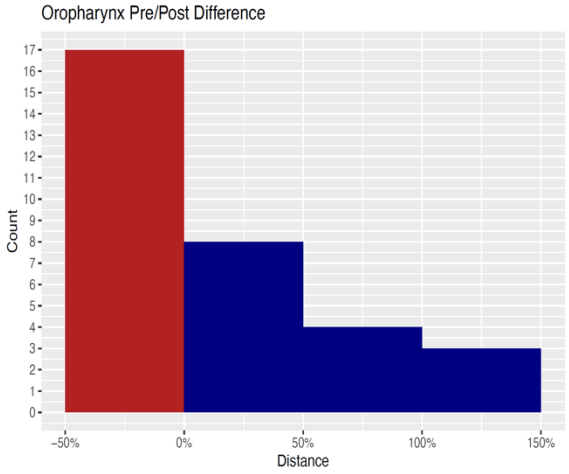
Area	Minimum	Median	Mean	Maximum	P Value	Significant
Change(mm^2)	-45.394	-2.507	26.593	176.948	0.00198	Yes
Change (%)	-31.99	37.17	56.43	553.23	0.00632	Yes

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of these data sets rejected the null hypothesis. The alternate hypothesis is that the MRA causes change in the airway after delivery. The analysis of these data sets with two-sided t-tests (p=0.05) and the Bonferroni correction applied (p=0.00833 significance value) supports the alternate hypothesis and the change was an increase.

The velopharynx had an overall mean positive change of 26.59 mm^2 or 56.43%.

Is the minimum A-P constriction change in the oropharynx statistically significant?





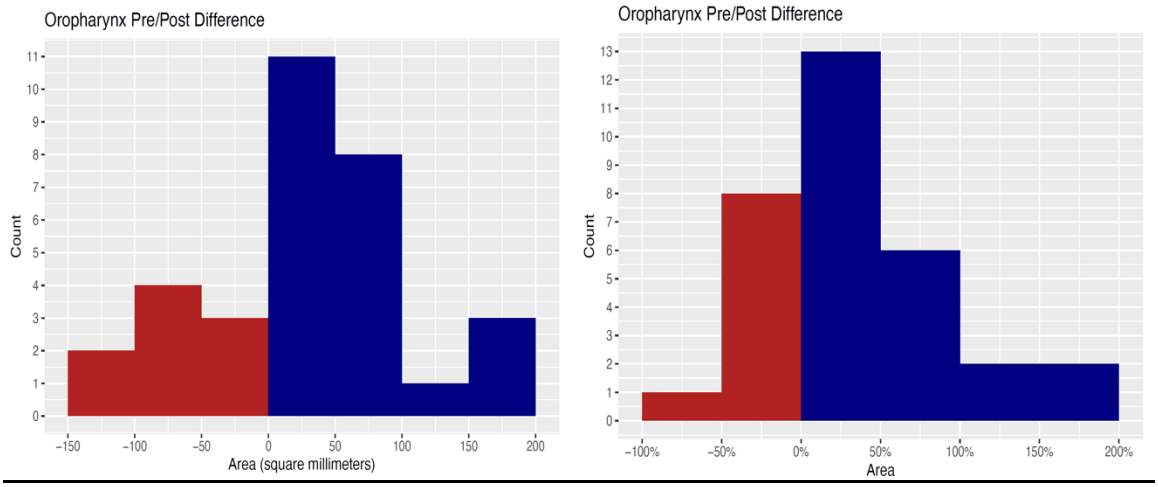
Oropharynx

A-P length	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-5.3667	-0.2793	0.2028	6.3254	0.7260	No
Change (%)	-48.34	-3.75	13.30	128.44	0.1280	No

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of these data sets failed to reject the null hypothesis.

The oropharynx had an overall mean positive change of 0.2028 mm or 13.3%.

Is the minimum cross-sectional area change in the oropharynx statistically significant?



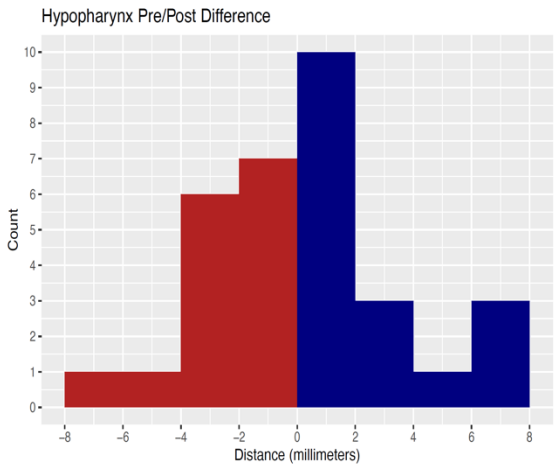
Oropharynx

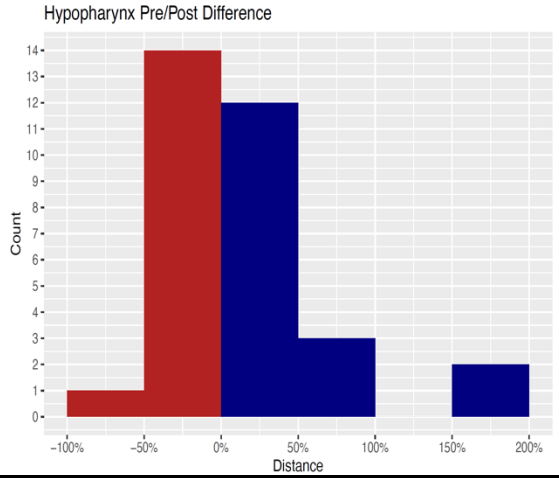
Area	Minimum	Median	Mean	Maximum	P Value	Significant
Change(mm^2)	-133.45	20.578	24.830	179.074	0.0718	No
Change (%)	-56.62	16.15	30.88	176.64	0.0052	Yes

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of the area data sets failed to reject the null hypothesis. The analysis of the percentage change data sets rejected the null hypothesis. The alternate hypothesis is that the MRA causes change in the airway after delivery. The analysis of the percentage change data sets with two-sided t-tests (p=0.05) and the Bonferroni correction applied (p=0.00833 significance value) supports the alternate hypothesis and the change was an increase.

The oropharynx had an overall mean positive change of 24.83 mm^2 or 30.88%.

Is the minimum A-P constriction change in the oropharynx statistically significant?





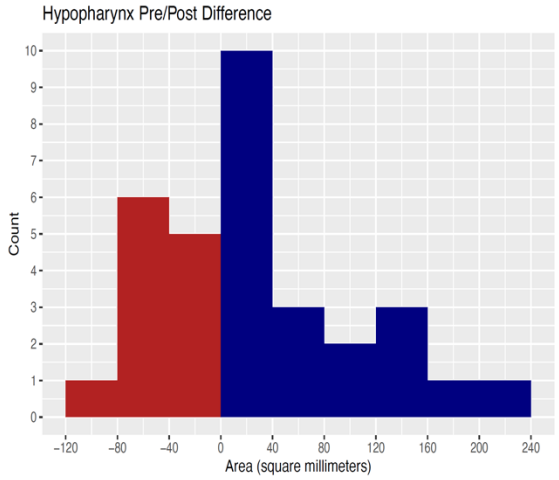
Hypopharynx

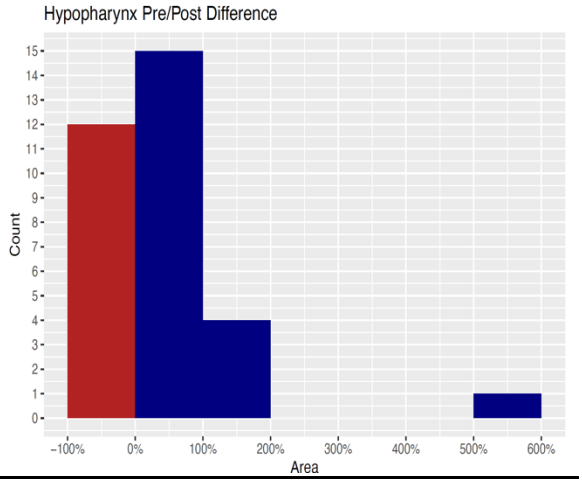
A-P length	Minimum	Median	Mean	Maximum	P Value	Significant
Change (mm)	-7.7278	0.3527	0.2892	7.5667	0.6200	No
Change (%)	-62.78	9.41	16.23	188.25	0.0981	No

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of these data sets failed to reject the null hypothesis.

The hypopharynx had an overall mean positive change of 0.2892 mm or 16.23%.

Is the minimum cross-sectional area change in the hypopharynx statistically significant?





Hypopharynx

Area	Minimum	Median	Mean	Maximum	P Value	Significant
Change(mm^2)	-111.76	16.25	22.33	207.28	0.1200	No
Change (%)	-46.86	30.58	49.40	575.77	0.0201	No

The null hypothesis is that the difference between the pretreatment and post-delivery airway is zero. The analysis of these data sets failed to reject the null hypothesis.

The Hypopharynx had an overall mean positive change of 22.33 mm^2 or 49.4%.

Discussion

Several upper airway and anatomical variables surrounding the upper airway have been used as possible predictors for OSA severity or variables for treatment success. The most common variables are related to the constricted site, including the AP dimension and minimum cross-sectional area, and in additional attributes of the entire oropharyngeal airway including average area, total volume and total length were noted among others[22]. In addition to the airway anatomy *per se*, craniofacial anatomic characteristics have been correlated with risk of OSA occurrence. In a 2016 meta-analysis of 25 studies, Neelapu found a strong correlation between total anterior facial height and reduced pharyngeal airway area and inferior position of the hyoid in OSA patients [4]. This meta-analysis focused on lateral cephalometric radiographs but suggested well-controlled clinical trials using 3-dimentional imaging are required to elucidate the precise relationship between craniofacial disharmony and OSA[4]. In this study, analysis of the average area showed no strong evidence to prove effects or correlation with the AHI score or OSA severity, suggesting that such summary statistics are not of practical value to recognizing OSA risk or severity.

Momany found that the narrowest cross-sectional area had a significant negative correlation with AHI. In this study, patients with AHI scores greater than 5 were compared to patients with Berlin questionnaire scores showing low or no risk of OSA [12]. In our study, the narrowest cross-sectional area showed no significant correlation with the AHI score; however, all of the subjects included in

our study had OSA symptoms and/or AHI scores greater than 5. In future studies, the addition of a control group with low or no risk of OSA would be beneficial to recognize the specificity of airway anatomic features for OSA recognition and management.

Nevertheless, the presence of a narrow airway is a known risk factor for OSA. A previous study correlated the narrowest cross-sectional area with likelihood of OSA and found that the risk was highest when the upper airway area was less than 52 mm^2, intermediate with an upper airway area between 52 mm^2 and 110 mm^2, and unlikely with an upper airway area larger than 110 mm^2 [23]. The mean AHI score was 41.8 with a SD of 17.7. Although this study was done on a group of patients with significantly higher AHI scores, the approximate probability limits were used in our study. Since our study only had 3 subjects with severe AHI, strong evidence supporting Lowe's probability numbers were weak and we found no correlation with AHI scores in our current study.

The currently used primary parameter to indicate success with MRA therapy is a reduction in the initial AHI score by 50%. Due to limitation in the number of patients with post-delivery AHI scores, the indicator for success was changed to a significant probability to observe an increase in the area of constriction after MRA delivery. The first question that needs to be answered is whether mandibular advancement with and MRA changes the upper airway. There were observed changes at all levels of the upper airway after MRA delivery. The AP and cross-sectional area constrictions were assessed in the velopharynx,

oropharynx and hypopharynx. Both positive and negative changes were detected at each level of constriction but the only section of the upper airway that showed a statistically significant change in the AP and cross-sectional area constrictions was the velopharynx and the change was positive. The oropharynx had a statistically significant change in the percentage change of the minimum cross-sectional area which was also positive. No parameter assessed in the upper airway showed a significant negative change.

In the pre-treatment airway, a majority of the patients (72%) had their most constricted AP and area in the velopharynx. This percentage correlates closely with studies showing successful treatment for OSA with an MRA at 76.2% [24]. In over half of these patients, the velopharynx is the only level of the upper airway that has a significant constriction (A-P length less than 6 mm and/or minimum cross-sectional area less than 90 mm^2).

Conclusion

1. MRA therapy typically increases the AP dimension and cross-sectional area of the velopharynx. In contrast, MRA therapy did not reliably increase oropharynx and hypopharynx dimensions.
2. AP length and minimum cross-sectional area of constriction did not correlate with OSA category, suggesting that factors other than the anatomic constriction play a role in OSA development.

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