UNIVERSITY OF CALIFORNIA

Los Angeles

Measuring Airway Changes After Treatment with the Maxillary Skeletal Expander Using Three Dimension Cone Beam Computed Tomography and Computational Fluid Dynamic Analysis

A thesis submitted in partial satisfaction

of the requirements for the degree

Master of Science in Oral Biology

by

Zachary Philip Hollander

2021

ABSTRACT OF THE THESIS

Measuring Airway Changes After Treatment with the Maxillary Skeletal
Expander Using Three Dimension Cone Beam Computed Tomography
and Computational Fluid Dynamic Analysis

by

Zachary Philip Hollander

Master of Science in Oral Biology

University of California, Los Angeles, 2021

Professor Benjamin M. Wu, Chair

Transverse maxillary deficiency is a common skeletal malocclusion that is diagnosed when the maxilla is narrow in relation to the mandible. The malocclusion develops during growth and usually does not correct without treatment. Some health problems thought to be associated with a narrow maxilla include narrowing of the pharyngeal airway and the nasal cavity and increased nasal resistance. In short, problems that make it more difficult to breath.

Adult patients seeking an alternative to surgical expansion can now turn to bone-borne expanders utilizing Temporary Anchorage Devices (TADs) such as the maxillary skeletal expander (MSE) which is able to orthopedically expand the maxilla transversely at any age. A preliminary study performed at UCLA suggested that patients treated with MSE had improvement in airway volume and airflow immediately following expansion.

This study investigated the effects of MSE on airway improvement using three-dimensional cone beamed computed tomography (CBCT) to measure volume changes in the upper airway and a computational fluid dynamic model (CFD) to evaluate the changes in airflow for sixteen patients at the UCLA Orthodontics Clinic at two timepoints: pre-expansion (T0) and post-expansion (T1).

Treatment with the MSE caused a statistically significant increase in the volume of the airway after expansion as compared with the control group. Furthermore, CFD analysis showed that treatment with the MSE caused a statistically significant reduction in the airway resistance. The airway resistance of the MSE group was no longer statistically different from the control group after expansion. There was no correlation between the volume increase and the decrease in airway resistance. Overall, there was a significant increase in total airway volume, oropharyngeal volume, nasopharyngeal volume, and nasal cavity volume with MSE treatment immediately after expansion, but there was no correlation between volume increase and the improvement in breathing metrics, namely airway resistance. These results suggest that treatment of maxillary constriction using the MSE appliance may show positive effects in improvement of the upper airway volumes and reduction of the upper airway resistance.

The thesis of Zachary Philip Hollander is approved.

Renate Lux

Min Lee

Benjamin M. Wu, Committee Chair

Table of Contents

List of Figures

Acknowledgements

I would like to acknowledge and thank Dr. Won Moon for serving as my PI and mentor at the outset of this investigation. He was instrumental in deciding to initiate this study as well as in treating the patients that participated in the study. I thank him for advising me throughout the course of the study and for providing unwavering support.

Introduction

Transverse maxillary arch deficiency is a common malocclusion with an incidence rate of 21% in children and 10% in adults[1–4]. It is often accompanied by unilateral or bilateral crossbite, dental crowding, high arch of palate and a narrow nasal cavity[2,5,6]. Etiology is multifactorial, but genetics as well as myofunctional disorders such as thumb sucking habit or low tongue posture are contributory factors[7,8]. Without treatment, arch deficiencies may necessitate either crowding that can lead to periodontal issues or functional shifting that can lead to joint pathology. Furthermore, if untreated we can see health problems brought on by narrowing of the pharyngeal airway and nasal cavity, increased nasal resistance, and airway stenosis due to posterior lingual displacement[9–11].

Maxillary expansion as an orthodontic treatment modality has been reported since the 1860s[12]. Rapid Maxillary Expansion (RME) aims to resolve maxillary transverse deficiencies, correct posterior dental crossbites, create arch space for relief of crowding, prevent maxillary canine impaction and reduce nocturnal enuresis[5,13,14]. Separation of the maxillary halves extends directly to the nasal cavity through lateral separation of the nasal walls and lowering of the palatal vault. There are reported benefits to the upper airway including improving allergic rhinitis, asthma, and recurrent ear or nasal infections[12,15]. Furthermore, many researchers have suggested that RME is a successful means of increasing the nasal permeability and reducing airway resistance, based on both objective and subjective evidence. Reduced airway resistance reduces negative pressure during ventilation, with promising results of RME shown in treatment of pediatric sleep disordered breathing, including obstructive sleep apnea[3,11,16,17]. Enlarged palatal space may also allow for improved tongue posture, which could facilitate increased airway space in the oropharynx.

The association between upper airway morphology, sleep-disordered breathing, and obstructive sleep apnea (OSA) has been studied and there is a general agreement that early management of these conditions may lead to better long-term medical and dental outcomes for patients[11,18]. Although the primary aim of RME is to exert force on the maxilla, studies have shown that the skeletal effects are much more extensive, occurring in all bones articulating with the maxilla as the airway[19]. Cistulli et al. investigated the effects of RME in a sample of ten patients with mild to moderate OSA; nine of them reported an improvement in snoring and daytime sleepiness and all patients demonstrated a reduction in the Respiratory Distress Index[20].

The interrelationship between respiratory obstruction, malocclusion, and facial growth continues to be debated after nearly a century of controversy. Interest in this subject has been rekindled, based on the possible role of craniofacial morphology, and especially the shape/dimension of the upper airways, on obstructive sleep apnea[9,21,22]. Upper airway obstructions that affect the breathing pattern can affect the width, length, and height of the maxillomandibular complex with a subsequent impact on the nasal cavity, retropalatal and retroglossal upper airway space[22].

OSA is reportedly diagnosed in 15-20% of middle-aged adults and up to 95% of the US population is underdiagnosed[16,18,20]. OSA is characterized by repeated occlusion of the upper airway and discontinuation of sleep. Airway restrictions affect both children and adults as they have serious long-lasting influence on dentition, speech, overall health, and craniofacial development[18,20]. Furthermore, poor quality of sleep seriously affects daily life with OSAS patients reporting daytime fatigue and headache, higher probability of accidents, and being more prone to serious health problems such as stroke, hypertension, and atherosclerosis. Numerous studies have reported an association between maxillary transverse deficiency and narrowing of the pharyngeal airway and nasal cavity[3,23–25]. In cases of considerable obstruction to the nasal airflow, the respiratory pattern can shift towards mouth breathing. Epidemiological studies have demonstrated a relationship between nasal airflow and snoring and correlations between nasal resistance measured by posterior rhinomanometry and severity of sleep apnea[12].

Several pathophysiological mechanisms have been suggested for the role of nasal pathology in OSA including the Starling resistor model, the instability of mouth breathing, and the nasal ventilatory reflex. In the Starling resistor model shown in Figure 1, the airway is related to a hollow tube in which increased nasal resistance will create a suction force that results in negative oropharyngeal pressure and pharyngeal collapse. In the instability of mouth breathing explanation, increased nasal resistance shifts nasal breathing to oral breathing leading to an unstable breathing pattern. There is a decrease in retroglossal dimension which leads to retraction of the tongue, narrowing of the pharyngeal lumen and increased vibration of the soft plate and pharynx[3].

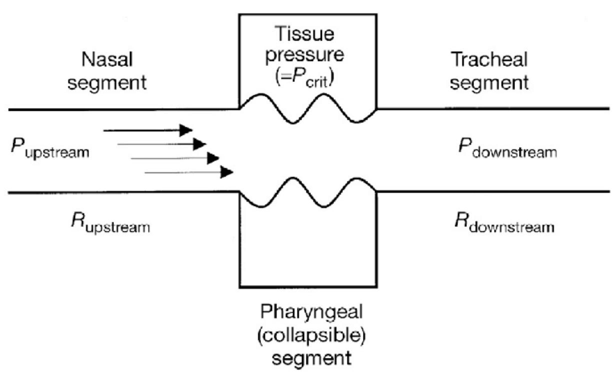


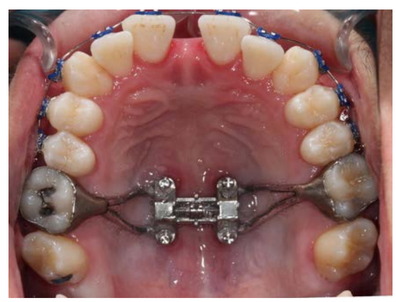
Figure 1: A diagram representation of the Starling resistor model illustrating the suction force that results in negative oropharyngeal pressure and pharyngeal collapse

There are a wide range of treatment options employed for OSA; however many remain unproven. Continuous positive airway pressure (CPAP) remains the gold standard, but this only treats the symptoms and not the underlying cause of the disease[20]. There are; however, several orthodontic treatment options that have shown promise in improving the airway and have been offered as treatment for OSA. Specifically, the use of RME has been suggested as a therapy for treatment of childhood OSA as it has been reported that RME separates the external walls of the nasal cavity laterally and causes lowering of the palatal vault along with straightening of the nasal septum[12]. This in turn increases the nasal volume, decreases nasal resistance, increases nasal airflow, and improves nasal breathing[26–29]. This is important because often, the orthodontist is the first clinician to evaluate and potentially detect an airway problem and it was already mentioned that early recognition and management of airway obstructions yield better health outcomes.

Traditionally, orthodontic treatment of a transverse deficiency is time sensitive because the circummaxillary sutures becomes more interdigitated with age, becoming fully fused during late adolescence – early adulthood, thereby increasing the resistance to expansion. Once the sutures are fused, RME appliances become less effective in achieving skeletal expansion, but rather the force applied leads to dentoalveolar tipping[30–33]. In more skeletally developed patients, dental tipping has potentially harmful implications such as dental dehiscence or fenestration as well as potential relapse of treatment as growth continues. Thus, in the adult patient, skeletal orthopedic expansion is necessary to prevent these issues while also correcting the maxillary deficiency. The conventional treatment of choice in adults is the surgically assisted rapid palatal expansion (SARPE). However, SARPE, is an invasive process that can result in lateral rotation of the 2 maxillary halves with minimal horizontal translation[3]. Furthermore, the procedure may be detrimental to the periodontium and has been shown to result in a large amount of relapse in the postretention period[30]. Nonetheless, like the RME improved breathing metrics such as airway volume and oxygen saturation in children, SARPE has been shown to increase upper airway volume in adults while also decreasing airflow resistance and improving nasal breathing[11].

Recently, a second alternative has been developed for adult patients, the mini-implant assisted rapid palatal expander (MARPE). Many designs of this device exist but the premise behind them is that temporary anchorage devices (TADs) are used in conjunction with a maxillary expander to transmit shear force to the maxilla, effectively forcing the mid palatal suture open as shown in Figure 2. Bone borne expanders have the ability to orthopedically correct transverse deficiency in skeletally developed adolescents and adults while decreasing the dental side effects compared with conventional RME[29,30]. The treatment with MARPE appliance has been shown to be helpful for relieving the symptoms of OSA in adult patients in several case studies[9,34,35]. Furthermore, in a randomized controlled trial in a population from age 8 to 13 years, it was shown that MARPE induced significantly higher nasal airway flow values and lower nasal resistance values than tooth-borne RME[35].

A



B

Figure 2: shows an occlusal view of a cemented MARPE appliance, this particular design is the Maxillary Skeletal Expander (MSE). Figure (A) shows the appliance before expansion, and (B) shows the expansion completed with an anterior visible diastema.

One MARPE design in particular used at UCLA Orthodontics Clinic has shown promising results in treating adults for maxillary transverse deficiency while also increasing nasal volume. A study utilized linear measurements on CBCT to measure various cross sections of both upper and lower nasal sections[19]. Furthermore, the study demonstrated that the skeletal changes associated with MSE treatment involve the maxilla with the fulcrum at the frontozygomatico suture in the coronal section and anterior skeletal segments at the lateral pterygomaxillary suture in the axial sections as shown in Figure 3. This study served as the jumping off point for quantifying the overall skeletal changes and increase in the bony housing

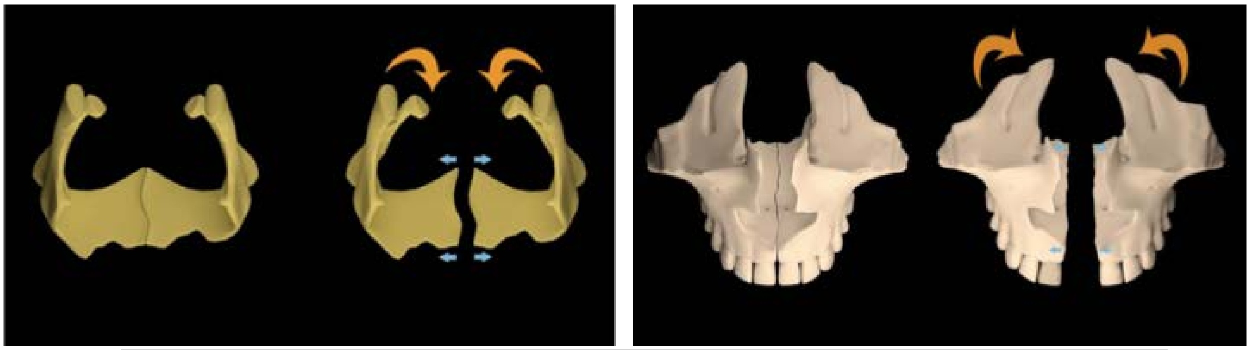


Figure 3: A representation of the orthopedic midface expansion produced by force applied by the MSE

of the nasal cavity stemming from MSE treatment. Nonetheless, linear measurements performed on individual CBCT cuts cannot accurately express the upper airways[11], which led to the initiation of several other studies to evaluate the effect of the MSE on the airway.

Measuring airway volume has advanced in the last ten years as commercial software has been developed that has the ability to reconstruct 3D models of airway from segmented CBCT data. It is now feasible to build an anatomically accurate model that includes the nasal cavity, nasopharynx, and oropharynx. With a more accurate 3D model of the airway, comparing the long verified pre and post airway volumes is not the only measurement that can be done. There have been several studies published that examined how flow rate of air changes after RPE treatment[17,36–38]. However, besides several case studies, there have been no studies published examining how flow rate of air changed after MARPE treatment. Furthermore, in these studies, airway changes with expansion appliances are not compared with controls. Therefore, this study will be the first to report on the effects of MARPE on airway change in a larger sample retrospective design with a matched control group.

Computational fluid dynamics (CFD) is a field of fluid mechanics that focuses on using the Reynolds Averaged Navier Stokes equation to calculate fluid flow and pressure through a defined volume. These calculations take into account nature of the fluid, initial flow rate, pressure, interaction with boundary conditions, and other variables to model how the fluid passes through the system, highlighting areas of increased fluid flow rate, pressure, and turbulence. CFD is noninvasive, convenient and reliable making it the most appropriate technique to simulate the internal flow dynamics of the upper airway. In addition, CFD provides an accurate simulation to the magnitudes of air pressure and airway resistance and thus a more precise evaluation of the airway function. Iwasaki et al., in a CFD study reported that in OSA children, the pharyngeal airway pressure during inspiration decreases with the reduction of nasal resistance by RME[24,39]. However, there is a lack of data on airway internal flow dynamics and patterns of airflow regarding MARPE treated adult patients. Therefore, the purpose of this study was to compare the effects of MSE treatment on airflow in the upper airway of adult patients using 3D modeling and CFD airflow simulation analyses with a matched control group. Specifically, we are attempting to understand if and how the MSE can serve as an alternative treatment for breathing problems in adult patients who also have narrow maxillary arch forms.

Preliminary Study

A retrospective case-control study had already been initiated at UCLA to compare the volume changes in the upper airway following treatment with MSE with a matched control. This case study strived to determine a reliable method of creating 3D models of the airway via segmentation of CBCT data. The method was based on validated publications describing strategies for segmenting the airway in cone-beam computed tomography[23]. CBCT scans of patients were exported in DICOM (Digital Imaging and Communications in Medicine) file format, and then read into AMIRA software. The CBCT files were reoriented in three planes, at which point the upper airway of interest was then segmented by setting the threshold between 1024 Hounsfield Units (HU) and -480 HU, and the anatomically accurate patient-specific models were reconstructed by removing soft tissue and bony structures, leaving only the airway area of interest as can be seen in Figure 4. A smoothing algorithm was then used to transform the 3D model into a smooth one and remove any “islands” without the loss of the patient-specific

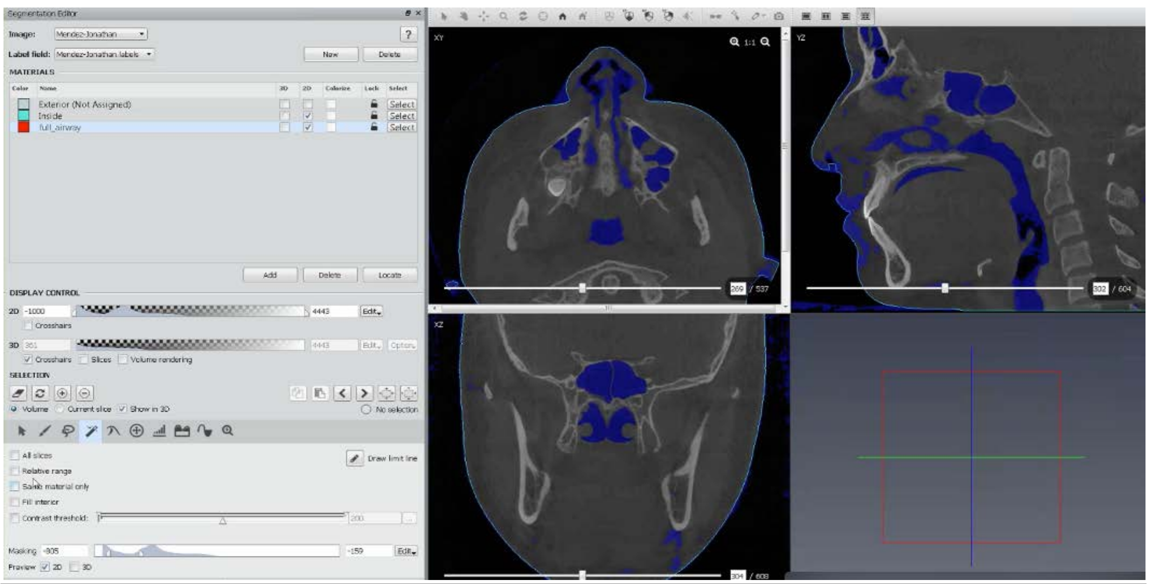


Figure 4: Amira automated segmentation selectively includes the airway as the area of interest

characters in the shape of the airway. The study utilized overall volume change and minimum cross sectional area to evaluate airway changes at two timepoints T0 (Pre-expansion) and T1 (Post-Expansion) for an experimental group of 2 orthodontic patients undergoing MSE expansion and a control group of 1 patient treated with conventional non expansion orthodontic treatment.

As shown in Figure 5, the results indicated that the MSE patient yielded close to 30% increase in minimum cross sectional area as well as volume. This was almost 2.5-3x what has been reported in the literature for other MARPE patients. Furthermore, the control patient minimum cross sectional area and volumes had increased between 5-10% as well, which was also not in line with the previously reported data. Therefore, the preliminary study provided the idea and groundwork for the present study, but required refinement to achieve more accurate 3D models before CFD analyses could be run.

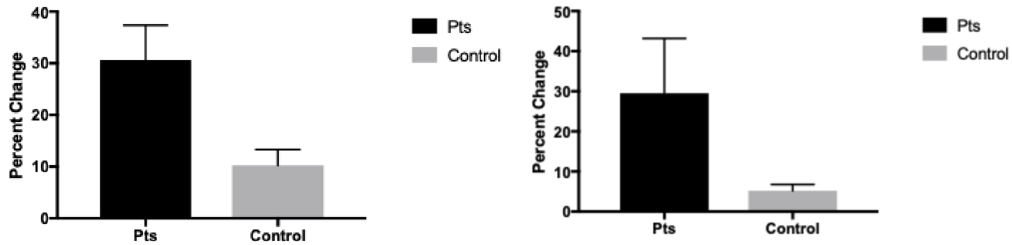


Figure 5: (a) Minimum cross sectional area increased in the MSE patients compared to the control. (b) Total Volume increased in the MSE patients compared to the control.

Objectives and Specific Aims

The goal of this study was to compare the effects of MSE treatment on airflow in the upper airway of adult patients using 3D modeling and CFD airflow simulation analyses with a matched control group. If we succeed in creating a physiologically accurate 3D model for CFD analyses, the future goal is to evaluate the long-term (post-orthodontic treatment) airway improvement following maxillary skeletal expansion. If treatment with MSE improved the airway volume and airflow measurements, then the MSE may serve as an alternative to surgical treatment for breathing problems in adult patients who also have narrow maxillary arch forms.

Aim 1: Review and refine the segmentation protocol to achieve more anatomically accurate 3D models to ensure there is no over / under selection of the airway

- Re-evaluate preliminary study method of segmentation and evaluate slice by slice where the inaccuracies in airway were introduced
- Refine segmentation protocol to eliminate inaccuracies in the 3D models

- Compare overall volume measurements as well as the separate volumes of the nasal cavity, nasopharynx and oropharynx at two timepoints: pre-expansion (T0) and post-expansion (T1)

Aim 2: Use the refined 3D models to run CFD analysis

- Compare airflow parameters such as pressure, wall strain, and airway resistance acquired from the CFD model at two timepoints pre-expansion (T0) and post-expansion (T1)

Materials and Methods

This research expanded on the preliminary study performed at the University of California, Los Angeles School of Dentistry in the Department of Orthodontics concerning the volumetric airway assessment following MSE treatment. The participants were selected for this study under IRB#17-000567 and patients participating in the study signed informed consent. The inclusion criteria for our sample required adult patients with a marked end to growth determined by CVMS staging with a diagnosis of maxillary transverse deficiency, successful opening of the midpalatal suture, non-extraction treatment, and availability of CBCT images obtained before expansion (T0) and immediately after expansion (T1). The exclusion criteria were: a history of orthodontic treatment and presence of craniofacial syndromes or systemic diseases. Data for 16 patients in the experimental group (12 women, 4 men) and 8 patients in the control group (5 women, 3 men) were collected retrospectively. The data at both timepoints was collected using the same protocol and outlined in the section below.

Aim 1

Patients in both the experimental and control groups received a full volume Cone Beam Computed Tomography scan of the head and neck using a NewTom 5G scanner. All scans included an 18x16 field of view with a 14-bit gray scale and voxel size of .3mm. Scan times were 18s (3.6s emission time) with 110 kV, and automatic exposure control. The initial NewTom provided baseline records of the patient before treatment and was diagnostic of the appropriate treatment for each patient. A new CBCT was taken in the experimental group immediately following the end of expansion to verify sutural opening, measure the magnitude of expansion, and rule out any abnormal skeletal changes or for the corresponding timepoint in the control group when progress records were needed. The data were sent directly to a personal computer and store in the DICOM (Digital Imagine and Communications in Medicine) format.

We used the same volume rendering software as the preliminary study, Amira, to construct the 3D surface models (STL file) of the pre and post treatment upper airway. We did not use the rendering software's automated threshold segmentation to remove the denser soft tissue and bony areas leaving the inverted air space, but rather hand traced the airway in every odd slice of the CBCT from the coronal view, then allowed the software to interpolate the airway to the even cuts. Although it has been validated that the airway is a void surrounded by hard and soft tissues, thereby making it possible to use the rendering software's threshold segmentation to

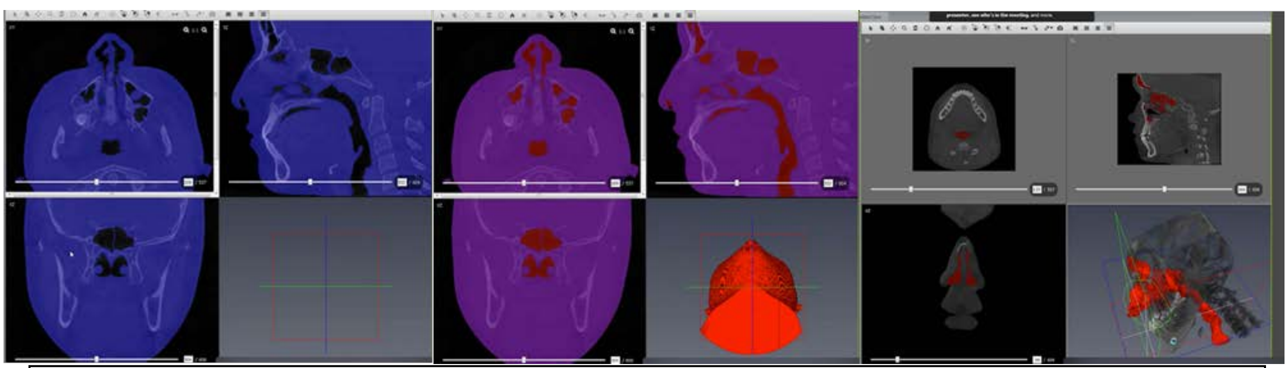


Figure 6: Automated threshold segmentation: selecting denser tissue to leave only the airway was an inaccurate technique leaving many slices with incomplete delineation of the airway and voids within the final segmented airway

select CT units within the airway, we did not find that the inverted airway exhibited significantly greater positive CT values than the denser surrounding soft tissue. To use the automated threshold segmentation smaller voxel size and a higher quality differentiation of gray values may be necessary. Figures 6 and 7 delineate the difference in project flow for the segmentation

Table 1: Definition of airway boundaries
ANS – anterior nasal spine, PNS – posterior nasal spine, S – Sella, N – nasion, CV – cervical vertebrae

	Anterior boundary	Posterior boundary	Superior boundary	Inferior boundary
Nasal cavity	Line connecting the ANS to the tip of the nasal bone	Line extending from S to the PNS	Line connecting N to S	Line extending from ANS to PNS
Nasopharynx	Line extending from S to the PNS	Line extending from S to the tip of the odontoid process	Line extending from S to the tip of the odontoid process	Line extending from PNS to the tip of the odontoid process
Oropharynx	Line extending from PNS to the tip of the epiglottis	Line extending from the tip of the odontoid process to the posterior superior border of CV4	Line extending from PNS to the tip of the odontoid process	Line extending from the base of the epiglottis to the posterior superior border of CV4

process between the preliminary study and this study. The overall airway volume was measured as well as separately at the nasal cavity, nasopharynx, and oropharynx. The anatomic boundaries and airway outlines used are in Table 1.

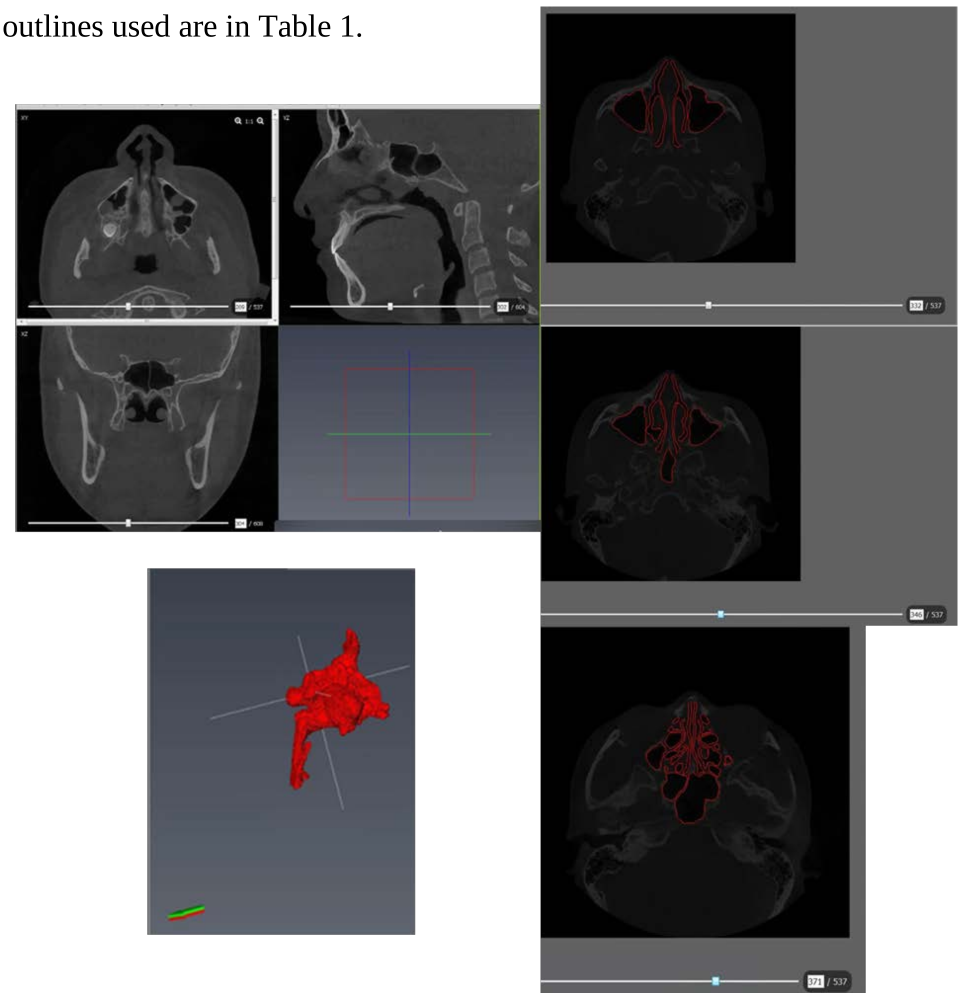


Figure 7: DICOM file uploaded in 3 planes followed by user delineation of the airway in sequential odd coronal slices and allowing the software to interpolate the even slices finally yielding the completed segmented airway.

Aim 2

After the segmentation of the CBCT data of the airway, the stereolithography (STL) files of the segments were imported into ANSYS 16.0 ICEM CFD for model repairing and mesh generating. As shown in Figure 8, unstructured tetrahedral volume mesh was then generated from the CBCT segmentation data in ANSYS ICEM CFD using the hybrid mesh scheme to spatially discretize fluid domain. A grid convergence analysis was performed by repeating the solution with five different element effect sizes meshes ranging from grid 1 to grid 5 to establish grid independence solutions. Grid 3, which kept effect size similar for pre and post expansion models at less than 1% was selected. Then the 3D models were imported into the Reynolds Average Navier Stokes CFD solver (ANSYS Fluent 16.0, Fluent Inc.).

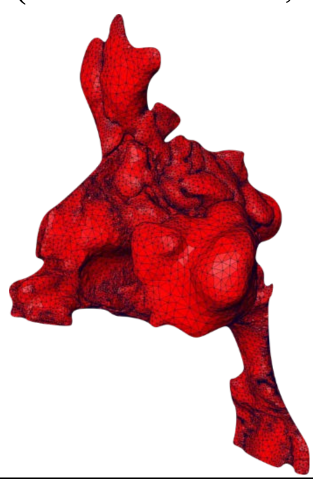


Figure 8: Tetrahedral mesh smoothing of the 3D segmented data

Flow simulations were performed with inspiratory upper airflow flow being modeled as inspiration is associated with negative pressures causing airway collapse, greater airflow pressure and velocity gradients. Steady laminar flow field was applied due to previous studies showing that fully developed turbulence would not be reached until a flow rate of 30L/min. The flow rate used for all subjects in this study was less than 20L/min – based on a flowrate of 300 mL/s, which represents an adult breathing at rest. Therefore, airflow was presumed as incompressible and laminar. Constant air density (1.1614 kg/m^3) and viscosity (1.846 x 10^{-5} kg/m-s) values were assumed. No-slip wall boundary conditions were imposed on the airway walls. The gravitational effect, heat source, heat transfer, phase change, and chemical reactions were all ignored. The pressure at the nostrils was set to be zero at inlet, and the velocity at outlet was adjusted to match with the constant volume flow rate of 300 mL/s. Pressure, wall strain, and resistance of airway were compared to assess the effect of MARPE expansion. The resistance of airway is defined as Resistance of airway = Pressure difference / Flow Rate. Finally, after analyzing the volume and CFD data independently, the volume data from AIM 1 was correlated with the CFD data to evaluate if volume change was related to airway change.

Results

Aim 1

The sample for the post expansion (T1) timepoint included sixteen patients in the treatment group with twelve females and four males. The mean age of the patients was 21.4 ± 3.7 years (range, 19.3 – 28.7 years). The average duration following the initiation of treatment (T0) was 61 days. Based on the preliminary study concerning expansion and volumetric airway analysis, significant differences were observed between pre- and post – operative measurements with an effect size of 1.6. Therefore, based on power analysis calculations with $\alpha=.05$ and power=.8, significance should be observed with N=8.

Testing of the study data using Shapiro-Wilk normality tests indicated that the data (T0 and T1) was normally distributed for pre- and post – expansion overall volume as well as at the nasal cavity, nasopharynx, and oropharynx. Therefore, the differences between the time points were tested using paired t-tests and Pearson correlation coefficients and between the groups using independent t-tests. A P-value <.05 was considered statistically significant. SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

In addition, testing was performed to standardize the experimental design and methods between segmentations. One examiner performed all measurements, to estimate intraexaminer reliability; three randomly selected data sets were re-evaluated after a week. The intraclass correlation coefficient (ICC) had high reliability (ICC >.90) showing there was no statistical significance between measurements.

Changes from Pretreatment (T0) to Postexpansion (T1) Within the Two Groups

In the expansion group, a significant increase ($P < .05$) was found in the nasal cavity volume, nasopharyngeal volume, oropharyngeal volume, and the total airway volume as can be seen in Table 2 and Figure 9. The average volume of the nasal cavity before treatment was 80448.9 mm^3, which increased by 9.21% immediately after expansion, the original average nasopharyngeal volume was 8572.6 mm^3, which increased 19.9% after expansion, the average oropharyngeal volume was 8624 mm^3, which increased 54% following expansion, and the original average total airway volume was 97645.6 mm^3 and experienced a 13.1% increase. The control group demonstrated no significant change in the parameters from T0 to T1 as shown in Table 3 and Figure 10.

Table 2: Parameters for the MSE Group, Pretreatment (T0), Postexpansion (T1)

	Mean (SD) T0	Mean (SD) T1	Mean (95% CI) T1-T0	% Change (T1-T0)	P Values (T1 vs T0)
Nasal Cavity volume, mm^3	80448.93 (15387.18)	87446.73 (15345.97)	6997.8 (4101.49, 9894.1)	9.21	<.001
Nasopharyngeal volume, mm^3	8572.62 (3354.84)	10191.66 (3808.14)	1619.04 (720.75, 2517.33)	19.99	0.002
Oropharyngeal volume, mm^3	8624.04 (4758.53)	12505.92 (6336.88)	3881.88 (1479.35, 6284.41)	54.88	0.004
Total airway volume, mm^3	97645.59 (19977.05)	110144.31 (21570.8)	12498.73 (10199.79, 14797.66)	13.07	<.001

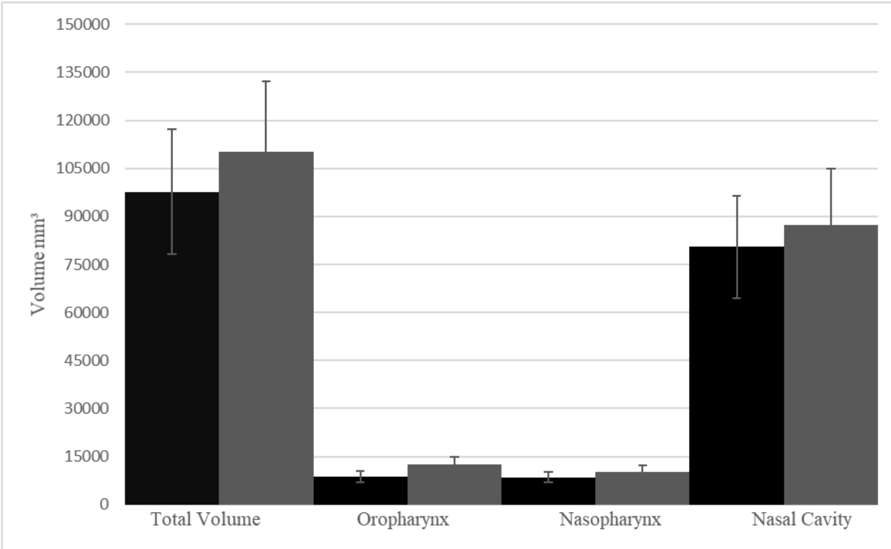


Figure 9: Changes in the Upper Airway after Maxillary Expansion, Pretreatment (T0) in Black Postexpansion (T1) in Grey

Table 3: Parameters for the Control Group, Pretreatment (T0), Postexpansion (T1)

	Mean (SD) T0	Mean (SD) T1	Mean (95% CI) T1-T0	% Change (T1-T0)	P Values (T1 vs T0)
Nasal Cavity volume, mm³	90067.34 (32198.19)	89148.31 (31436.1)	919.02 (-640.9, 2479.1)	-0.75	0.206
Nasopharyngeal volume, mm³	10359.22 (4551.1)	9204.27 (3548.4)	1154.96 (36.54, 2273.4)	-9.70%	0.125
Oropharyngeal volume, mm³	8392.13 (5759.1)	9092.9 (6203.6)	700.8 (-1651.7, 250.14)	10.10%	0.055
Total airway volume, mm³	108320.1 (37297.4)	107286.7 (37298)	1033.36 (-1197.7, 3264.4)	-0.87	0.31

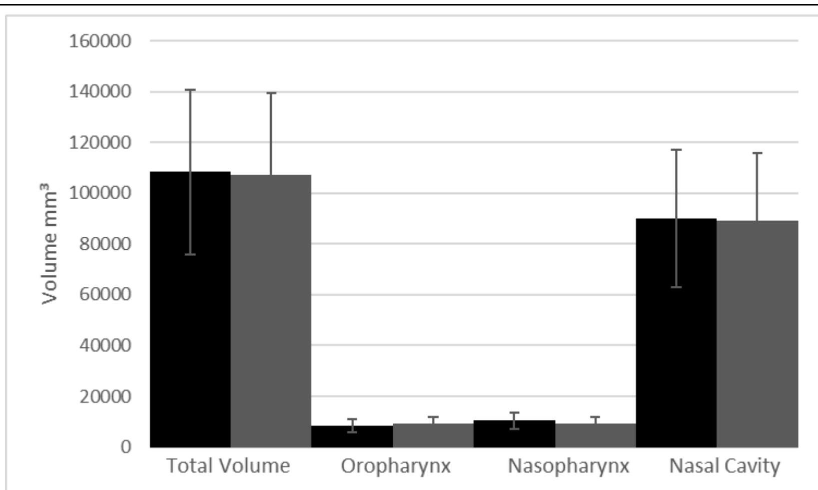


Figure 10 Changes in the Upper Airway in the Control Group, Pretreatment (T0) in Black & (T1) in Grey

Comparison of the Changes Between MSE and Control Groups

As shown in Table 4 and Figure 11, the results for the volumetric measurements between the groups showed significant increases in the change in total airway volume, nasopharyngeal volume, oropharyngeal volume, and the nasal cavity volume. Furthermore, we found there were no significant differences in the initial or second time point volumes of the total airway, nasopharynx, oropharynx, or nasal cavity between the MSE and control groups as shown in Table 5.

Table 4: Comparison of the Volumetric Changes Between MSE and Control Groups

	Mean Difference Between MSE and Control (95% CI)	P Value (MSE vs Control)
Change in Nasal Cavity volume, mm^3	7916.83 (4770.5, 11063.1)	<.001
Change in Nasopharyngeal volume, mm^3	2774 (1352.1, 4195.9)	0.001
Change in Oropharyngeal volume, mm^3	3181.1 (670.9, 5691.3)	0.016
Change in Total airway volume, mm^3	13532.09 (10549.6, 16514.6)	<.001

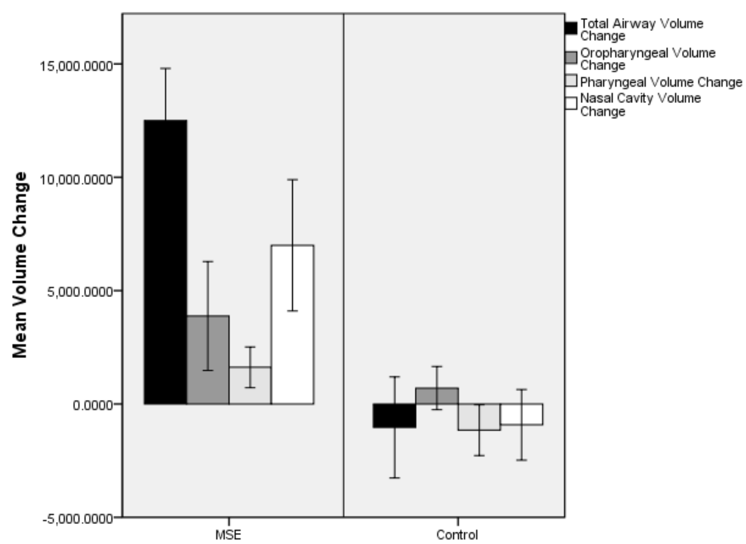


Figure 11: Comparison of the Volumetric Changes Between MSE and Control Groups

To determine any relationship between the changes in the airways within the groups, Pearson correlation coefficients and P values were calculated for changes from T0 to T1. In the

MSE group, Nasal Cavity volume change showed a moderately strong negative correlation with both Oropharyngeal volume change (r=-.53, P=.035) and Nasopharyngeal volume change (r=-.58, P=.019). In the control group, the Total Airway volume change showed a strong correlation with the Nasal Cavity volume change (r = .79, P =.021) and the Oropharyngeal volume change (r =.81, P=.017).

Table 5: Comparison of the Initial and Final Volumes of MSE and Control Groups

	Mean Difference Between MSE and Control (95% CI)	P Value (MSE vs Control)
Initial Total Airway Volume, mm^3	-10674.5 (-34682.2, 13333.3)	0.366
Final Total Airway Volume, mm^3	2857.61 (-21897, 27612.3)	0.813
Initial Nasopharyngeal volume, mm^3	-1786.6 (5178.2, 1605)	0.286
Final Nasopharyngeal volume, mm^3	987.4 (-2368.3, 4334.7)	0.547
Initial Oropharyngeal volume, mm^3	231.9 (-4346.37, 4810.2)	0.917
Final Orophayngeal volume, mm^3	3413.02 (-2239.8, 9065.8)	0.224
Initial Nasal Cavity volume, mm^3	-9618.4 (29523.1, 10286.3)	0.327
Final Nasal Cavity volume, mm^3	-1701.6 (-21273.4, 17870.2)	0.859

Aim 2

The sample for the CFD portion of the study included a subset of eight of the original volume patients and four of the original control patients. Testing of the study data using Shapiro-Wilk normality tests indicated that the data (T0 and T1) was normally distributed for initial and second time point pressure, wall strain, and airway resistance. Therefore, the differences between the time points were tested using paired t-tests and between the groups using independent t-tests.

In the expansion group, Table 6 shows that significant differences were found from initial to post expansion in the average pressure drop from inlet to outlet as well as in average wall strain and in the airway resistance. Airway resistance after expansion in the MSE group significantly reduced on average 47.8%. Furthermore, as shown in Table 7, the control group did not exhibit any significant differences from initial to the second time point with regards to pressure drop, average wall strain or airway resistance. Airway resistance in the control group increased on average 1.4%.

Table 6: CFD Results of the MSE Group for Initial and Post-Expansion

	Mean T0 (SD)	Mean T1 (SD)	Mean (95% CI) T0-T1	P Value
Average Pressure Drop (Pa)	24.37 (6.2)	12.9 (4.8)	11.47 (9.03, 13.89)	<.001
Average Wall Strain (1/s)	2808.9 (443.3)	1911.5 (345.5)	897.5 (392.9, 1402.2)	0.004
Airway Resistance (1/ms)	63662.5 (16580.6)	37062.5 (13702.1)	26600 (9912.2, 43287.8)	0.007

Table 7: CFD Results of the Control Group for Initial and Post-Expansion

	Mean T0 (SD)	Mean T1 (SD)	Mean (95% CI) T0-T1	P Value
Average Pressure Drop (Pa)	8.92 (2.31)	8.99 (2.04)	-.065 (-.84, .71)	0.807
Average Wall Strain (1/s)	1797.5 (585.1)	1797.9 (583.2)	-.37 (-23.7,22.9)	0.963
Airway Resistance (1/ms)	25625 (6637.9)	25825 (5848.9)	-200 (-2420.1, 2020.1)	0.793

Between the expansion and control groups there were significant differences in each of the CFD measurements at the initial time point; however, as shown in Table 8 after expansion in the MSE group, there were no significant differences noted between the groups for average pressure drop, average wall strain, or airway resistance.

Figures 12 shows the pressure and velocity distribution in the upper airway for a representative experimental patient. In the pre-treatment image, the pressure falls slowly as flow passes around the turbinates in the nasal cavity, however, distal to the nasal cavity at the entrance to the nasopharynx, we can see abrubt pressure drop and flow acceleration as the airway narrows. After expansion, the magnitude of the pressure drop decreased and the acceleration in the pharynx is less apparent.

Table 8: Comparison of the MSE and Control CFD Results at T0 and T1

	Mean Difference Between MSE and Control (95% CI)	P Value (MSE vs. Control)
Initial Average Pressure Drop	15.44 (8.15, 22.74)	0.001
Initial Average Wall Strain	1011.45 (342.6, 1680.3)	0.007
Initial Airway Resistance	38037.5 (18470, 57604.9)	0.001
T1 Average Pressure Drop	3.91 (-1.77, 9.59)	0.156
T1 Average Wall Strain	113.53 (-474.3, 701.3)	0.676
T1 Airway Resistance	11237.5 (-5003.9, 27478.9)	0.154

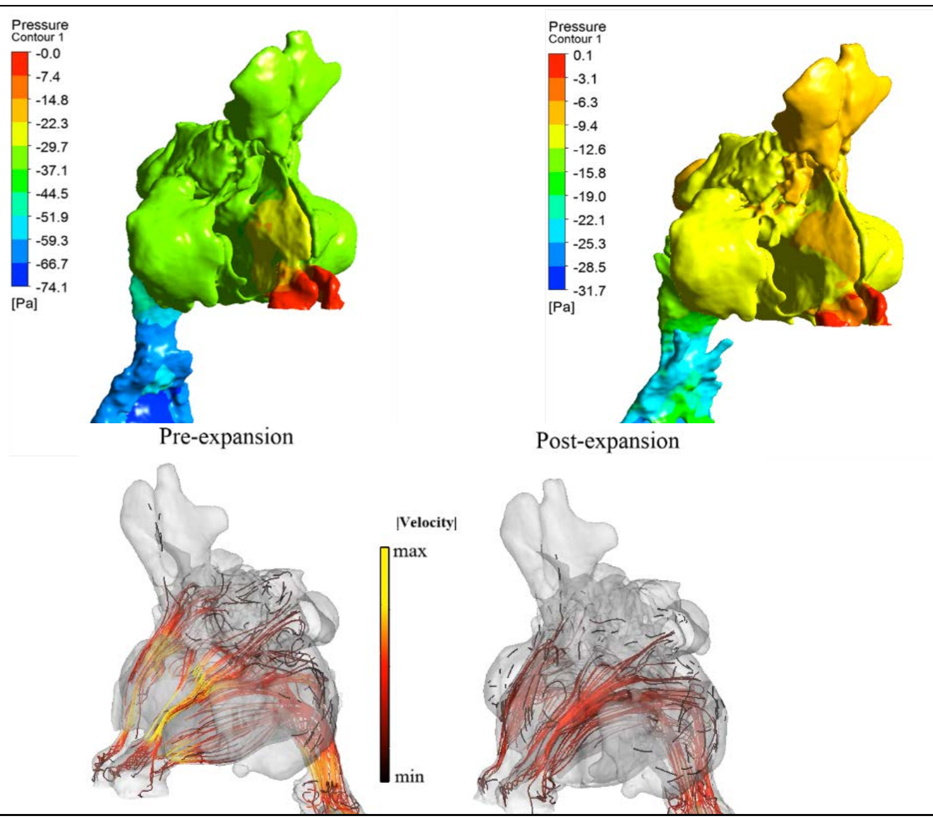


Figure 12 Pressure and Velocity profile from CFD simulation of an MSE patient at T0 and T1

Next, the volume measurements for total volume, oropharynx, nasopharynx, and nasal cavity were correlated with the CFD airway measurements. Pearson correlations were calculated; however, no significant relationships were determined between changes in the volume of the airway and the CFD metrics of airflow.

Discussion

Maxillary transverse deficiency is a common skeletal discrepancy that has been associated with various physiologic airway problems and linked with airway diseases such as OSA. Previous studies have reported that maxillary expansion with both traditional RME and MARPE results in increased nasal and oral cavity. Nonetheless, there is limited research examining the airway changes after treatment with MSE in non-growing patients. A preliminary study at UCLA demonstrated that patients who received MSE treatment showed improvement in airway volume measurements immediately following expansion.

In this present retrospective study, we assessed the effects of MSE expansion on the airway by evaluating the changes and comparing them with a control group. The findings of this study are significant, because it is the first to directly address the effects of MSE on the airway in comparison with controls. We demonstrated that nonsurgical maxillary expansion contributed to an increase in the volume of the upper airway in non-growing adult patients.

We carried out a more accurate and reliable segmentation method in this study as opposed to using the automated segmentation. While it has been validated that the airway is a void surrounded by hard and soft tissues, thereby making it possible to use the rendering software's threshold segmentation to select CT units within the airway, we did not find that the inverted airway exhibited significantly greater positive CT values than the denser surrounding soft tissue. To use the automated threshold segmentation smaller voxel size and a higher quality differentiation of gray values may be necessary from the DICOM files. We contend that that non-significant changes in the airway present in the control samples is an indication of our accuracy in segmentation for multiple patients over two time points. The literature points to the idea that there should be minimal change to the airway in control patients treated with non-expansion, non-extraction, non-surgical treatment plans[40–42]. Furthermore, the significant volume increases we noted for the MSE patients after expansion are in line with previously reported studies on MARPE patients[1,9,11]. In fact, Mehta et al. reported in 2020 to have found a 14.4% increase in nasal cavity volume, 21.8% change in nasopharyngeal volume, 19.2% increase in oropharyngeal volume, and a 20.5% increase in total airway volume. This study was performed on patients aged 11 – 15, therefore still growing, so we expect the airway changes to be greater than our reported 9% increase in nasal cavity volume, 19.9% increase in nasopharyngeal, 54% change in oropharyngeal volume, and 13% increase in total airway volume.

The oropharyngeal increase in the MSE and control patients were both unexpectedly larger, though the oropharynx is often the site of the most constricted portion of the airway, which if increased could signify the greatest improvement in breathing. Still, the nasal cavity exhibited the largest amount of increase, which is in line with previous research and logic as the expansion appliance is positioned directly below the nasal cavity and would directly influence changes on the nasal cavity[34,43]. In fact, the maxillary bones form approximately 50% of the nasal cavities anatomic structure; therefore, treatment that alters the morphology of the maxillary dental arch, would affect the geometry and function of the nasal cavity. Conversely, the nasopharynx and oropharynx would not be directly affected by the appliance due to the resistance from the zygomatic buttress and pterygomaxillary junction[19]. However, tongue positioning and an adaptive physiologic response may explain the improvement by the pharyngeal soft tissues. Studies have shown that patients with maxillary transverse deficiency often have low tongue posture, which may cause narrowing of the pharynx[44]; however, maxillary expansion allows for improved tongue posture and an enlargement of the pharyngeal space.

The initial and final volumes of neither the total volume nor any of the smaller segments were found to be significantly different between the MSE and control groups. This may be an indication that the volume of the airway may not be the best determinant of airway improvement. However, we must be careful making that assessment, because the patients in this study were selected based on presence of maxillary transverse discrepancy for orthodontic treatment rather than the presence of breathing impairment. Still, it was an unexpected result as we expected that there may have been significant differences between the initial volumes of the MSE and control groups that became not significant after expansion. Nonetheless, we did see that between the MSE and control group, there were significant differences between the changes in the volume from T0 to T1. Therefore, this confirms that expansion significantly changed the airway volume of the experimental group patients relative to the control group patients; however, not to the degree that there was any difference in the overall volumes between the groups. We can still see that the mean initial total airway volume and mean initial nasopharyngeal volume of the MSE group was less than the control group, however, after expansion, the mean total airway volume and mean nasopharyngeal volume were greater than in the control group.

In light of these findings regarding the volume of the airway, it would be worthwhile to look into the initial and final as well as change in cross sectional areas of the airway models going forward. Previous studies have shown that minimum cross sectional area of the upper airway increases with expansion and may be a critical factor in breathing improvement[1,9,45], however, it has not been compared to control patients. Furthermore, in adolescent patients, MARPE was found to significantly increase the nasophayngeal cross-sectional area only, but this is often the site of the lowest cross-sectional area of the area[1]. In the future, we plan to find an accurate way to determine minimum cross sectional area of the airway segments. Previous studies have used Dolphin to determine the minimum cross sectional airways, but we have already moved away from that technique as it is less accurate than evaluating a three-dimensional model.

In previous studies on children and several case studies on adults, the apnea-hypopnea index values decreases after expansion[12]. These studies showed that even minor changes in the anterior nasal volume can contribute to a decrease in the respiratory airway resistance. They also reported positive effects in terms of reduction in pressure, velocity, and resistance of airway to help us understand the key mechanisms behind relieving the symptoms of breathing disorders as a result of expansion. The CFD analysis is considered the most appropriate technique to simulate the internal flow dynamics of the upper airway. It provides accurate simulation of the magnitudes of air pressure, velocity, and airway resistance. Prior studies have reported that pharyngeal airway pressure during inspiration decreases with the reduction of nasal resistance by conventional RME in children[16,25,38,46–48]. Furthermore, case studies of adult patients with OSAS treated with MARPE using CFD analysis also found that MARPE improves airflow and decreases resistance[9,34]. This is important because the investigation of diseases involving the upper respiratory tract requires a good understanding of the complex interaction between the air flowing through the system and the tissues of the upper airway.

This study differs from previous studies by assessing the effect of MSE on adult non-growing patients who were diagnosed with maxillary constriction and comparing them with a group of control patients using CFD analysis. The MSE patients in this study showed a reduction in airway pressure, wall strain, and in upper airway resistance. These findings are in accordance with previous literature that suggests that expansion of the nasal cavity floor can benefit patients with a constricted maxillary arch and nasal airflow problem[9,44]. These results suggest that the cross-sectional area of the narrowest part of the upper airway increased, indicating a decreased collapsibility of the airway, which will consequently improve the breathing function as well as the sleep quality. Future studies are planned to compare the CFD breathing results with the clinical objective / subjective metrics of breathing.

The control patients did not show significant differences in the CFD metrics from T0 to T1, which is what we expected as they only underwent dental changes. The comparison of the CFD results between the MSE and control patient groups showed significant differences at the initial timepoint, but no differences at the second time point. Therefore, we can conclude that the expansion in the MSE patient group yielded airflow similar to that in the control patients, while previously it had been deficient. This suggests that the MSE may improve the breathing function in patients with maxillary transverse deficiency. Furthermore, since it has been demonstrated that the fast changing period of the upper airway is below 19 years old[36] and all of the patients in this study were older than 19, the growth potential impact can be ignored.

There was no indication that volume changes would be indicative of improvement in breathing function as there were no significant relationships determined by the Pearson correlation analysis. In the future we would be interested in re-evaluating a relationship between CFD metrics and cross sectional airway area relationships.

The present study has several limitations. First, the patients were awake during the CBCT scans and standing in an upright posture. Second, the patients did not complete a sleep study or a sleepiness questionnaire and we're assumed to all have the same flow rate. In addition, the airway is not a rigid structure, and the fluid-structure interaction resulting from the airway's soft tissue was not taken into consideration in this study. Future studies planned would be to increase the sample size of the patients run in the CFD analysis while also adding velocity determination to the output data. We would also attempt to validate the CFD analysis by 3D printing a model of the airway and running an in vitro study to determine the accuracy of our computer model. Furthermore, as discussed above we plan on evaluating the change in cross sectional area and correlating the minimum cross sectional area of the airway with the CFD data. We would also plan to evaluate the long term effects of the MSE with the addition of a third timepoint that evaluates our patients after the completion of fixed appliance orthodontic treatment. Our preliminary results from three patients that have completed treatment indicates that the total airway volume reduces 5% from the T1 timepoint and that airway resistance increases 11% from the T1 timepoint. Still, this would correspond to a 36% reduction in airway resistance from the start of treatment. We look forward to continuing to increase the sample size and evaluating the data.

Conclusion

Following MSE expansion, increases in the total volume of the airway as well as at the nasal cavity, nasopharynx, and oropharynx were found to be statistically significant when compared to T0 pre-expansion. Furthermore, when compared to the control group, the change in volume was found to be significantly different; indicating that the volume of the airway was increased following MSE treatment. We also found that MSE treatment led to significant improvement in breathing quality as measured by airway resistance when compared to the control group. However, there was no correlation between the changes in volume and airway resistance. Therefore, the use of MSE appliance in correction of maxillary deficiency showed positive effects in improvement of the airway resistance in the upper airway.

References

1. Mehta S, Wang D, Kuo C-L, et al. Long-term effects of mini-screw–assisted rapid palatal expansion on airway: *The Angle Orthodontist* 2020;00(00).

2. McNamara JA. Maxillary transverse deficiency. *American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics* 2000;117(5):567–70.

3. Brunetto DP, Sant'Anna EF, Machado AW, Moon W. Non-surgical treatment of transverse deficiency in adults using microimplant-assisted rapid palatal expansion (MARPE). *Dental Press Journal of Orthodontics* 2017;22(1):110–25.

4. Basciftci FA, Karaman AI. Effects of a Modified Acrylic Bonded Rapid Maxillary Expansion Appliance and Vertical Chin Cap on Dentofacial Structures. *Angle Orthodontist* 2002;72(1):61–71.

5. AJ Haas. Rapid expansion of the maxillary dental arch and nasal cavity by opening the midpalatal suture. *The Angle Orthodontist* 1961;31(2):73–90.

6. Moon W. Class III treatment by combining facemask (FM) and maxillary skeletal expander (MSE). *Seminars in Orthodontics* 2018;24(1):95–107. Available at: http://dx.doi.org/10.1053/j.sodo.2018.01.009.

7. Melsen B. Palatal growth studied on human autopsy material. A histologic microradiographic study. *American Journal of Orthodontics* 1975;68(1):42–54.

8. Takeuchi M, Tanaka E, Nonoyama D, Aoyama J, Tanne K. An adult case of skeletal open bite with a severely narrowed maxillary dental arch. *The Angle orthodontist* 2002;72(4):362–70.

9. Zhao T, Zhang X, Ngan P, et al. Effects of Maxillary Skeletal Expansion on Upper Airway Airflow: A Computational Fluid Dynamics Analysis. *Journal of Craniofacial Surgery* 2020;31(1):e6–10.

10. Storto CJ, Garcez AS, Suzuki H, et al. Assessment of respiratory muscle strength and airflow before and after microimplant-assisted rapid palatal expansion. *Angle Orthodontist* 2019;89(5):713–20.

11. Smith T, Ghoneima A, Stewart K, et al. Three-dimensional computed tomography analysis of airway volume changes after rapid maxillary expansion. *American Journal of Orthodontics and*

Dentofacial Orthopedics 2012;141(5):618–26.

12. Buck LM, Dalci O, Ali Darendeliler M, Papageorgiou SN, Papadopoulou AK. Volumetric upper airway changes after rapid maxillary expansion: A systematic review and meta-analysis. *European Journal of Orthodontics* 2017;39(5):463–73.

13. Bishara SE, Staley RN. Maxillary expansion: Clinical implications. *American Journal of Orthodontics and Dentofacial Orthopedics* 1987;91(1):3–14.

14. De Toffol L, Pavoni C, Baccetti T, Franchi L, Cozza P. Orthopedic treatment outcomes in Class III malocclusion. *Angle Orthodontist* 2008;78(3):561–73.

15. Juliana C, Silva A, Suzuki H, Garcez K. Assessment of respiratory muscle strength and airflow before and after microimplant-assisted rapid palatal expansion. 2019;89(5):713–20.

16. Shah DH, Kim KB, McQuilling MW, Movahed R, Shah AH, Kim YI. Computational fluid dynamics for the assessment of upper airway changes in skeletal Class III patients treated with mandibular setback surgery. *Angle Orthodontist* 2016;86(6):976–82.

17. Wootton DM, Sin S, Luo H, et al. Computational fluid dynamics upper airway effective compliance, critical closing pressure, and obstructive sleep apnea severity in obese adolescent girls. *Journal of Applied Physiology* 2016;121(4):925–31.

18. Iwasaki T, Takemoto Y, Inada E, et al. The effect of rapid maxillary expansion on pharyngeal airway pressure during inspiration evaluated using computational fluid dynamics. *International Journal of Pediatric Otorhinolaryngology* 2014;78(8):1258–64.

19. Cantarella D, Dominguez-Mompell R, Moschik C, et al. Midfacial changes in the coronal plane induced by microimplant-supported skeletal expander, studied with cone-beam computed tomography images. *American Journal of Orthodontics and Dentofacial Orthopedics* 2018;154(3):337–45.

20. Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. *Sleep* 1998;21(8):831–5.

21. Melsen B, Melsen F. The postnatal development of the palatomaxillary region studied on human autopsy material. *American Journal of Orthodontics* 1982;82(4):329–42.

22. Bakor SF, Enlow DH, Pontes P, De Biase NG. Craniofacial growth variations in nasal-breathing, oral-breathing, and tracheotomized children. *American Journal of Orthodontics and Dentofacial Orthopedics* 2011;140(4):486–92.

23. Mylavarapu G, Murugappan S, Mihaescu M, Kalra M, Khosla S, Gutmark E. Validation of computational fluid dynamics methodology used for human upper airway flow simulations. *Journal of Biomechanics* 2009;42(10):1553–9.

24. Iwasaki T, Takemoto Y, Inada E, et al. The effect of rapid maxillary expansion on pharyngeal airway pressure during inspiration evaluated using computational fluid dynamics. *International Journal of Pediatric Otorhinolaryngology* 2014;78(8):1258–64. Available at: http://dx.doi.org/10.1016/j.ijporl.2014.05.004.

25. Persak SC, Sin S, McDonough JM, Arens R, Wootton DM. Noninvasive estimation of pharyngeal airway resistance and compliance in children based on volume-gated dynamic MRI and computational fluid dynamics. *Journal of Applied Physiology* 2011;111(6):1819–27.

26. Liou EJW, Chen PKT. New orthodontic and orthopaedic managements on the premaxillary deformities in patients with bilateral cleft before alveolar bone grafting. *Annals of the College of Surgeons of Hong Kong* 2003;7(3):73–82.

27. Chung JC. Redirecting the growth pattern with rapid maxillary expander and chin cup treatment: changing breathing pattern from oral to nasal. *World journal of orthodontics* 2006;7(3):236–53.

28. Proffit WR, Fields HW, Moray LJ. Prevalence of malocclusion and orthodontic treatment need in the United States: estimates from the NHANES III survey. *The International journal of adult orthodontics and orthognathic surgery* 1998.

29. Suzuki H, Moon W, Previdente LH, Suzuki SS, Garcez AS, Consolaro A. Miniscrew-assisted rapid palatal expander (MARPE): The quest for pure orthopedic movement. *Dental Press Journal of Orthodontics* 2016;21(4):17–23.

30. Ngan P, Moon W. Evolution of Class III treatment in orthodontics. *American Journal of Orthodontics and Dentofacial Orthopedics* 2015;148(1):22–36.

31. Moon W, Wu KW, MacGinnis M, et al. The efficacy of maxillary protraction protocols with the micro-implant-assisted rapid palatal expander (MARPE) and the novel N2 mini-implant—a finite element study. *Progress in Orthodontics* 2015;16(16):1–14.

32. MacGinnis M, Chu H, Youssef G, Wu KW, Machado AW, Moon W. The effects of micro-implant assisted rapid palatal expansion (MARPE) on the nasomaxillary complex--a finite element method (FEM) analysis. *Progress in orthodontics* 2014;15(52):1–15.

33. Carlson C, Sung J, McComb RW, MacHado AW, Moon W. Microimplant-assisted rapid palatal expansion appliance to orthopedically correct transverse maxillary deficiency in an adult. *American Journal of Orthodontics and Dentofacial Orthopedics* 2016;149(5):716–28.

34. Hur JS, Kim HH, Choi JY, Suh SH, Baek SH. Investigation of the effects of miniscrew-assisted rapid palatal expansion on airflow in the upper airway of an adult patient with obstructive sleep apnea syndrome using computational fluidstructure interaction analysis. *Korean Journal of Orthodontics* 2017;47(6):353–64.

35. Kim SY, Park YC, Lee KJ, et al. Assessment of changes in the nasal airway after nonsurgical miniscrew-assisted rapid maxillary expansion in young adults. *Angle Orthodontist* 2018;88(4):435–41.

36. Kim DW, Chung SK, Na Y. Numerical study on the air conditioning characteristics of the human nasal cavity. *Computers in Biology and Medicine* 2017;86(December 2016):18–30. Available at: http://dx.doi.org/10.1016/j.compbiomed.2017.04.018.

37. Yu CC, Hsiao H Da, Lee LC, et al. Computational fluid dynamic study on obstructive sleep apnea syndrome treated with maxillomandibular advancement. *Journal of Craniofacial Surgery*

2009;20(2):426–30.

38. De Backer JW, Vanderveken OM, Vos WG, et al. Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. *Journal of Biomechanics* 2007;40(16):3708–14.

39. Iwasaki T, Saitoh I, Takemoto Y, et al. Improvement of nasal airway ventilation after rapid maxillary expansion evaluated with computational fluid dynamics. *American Journal of Orthodontics and Dentofacial Orthopedics* 2012;141(3):269–78. Available at: http://dx.doi.org/10.1016/j.ajodo.2011.08.025.

40. Alsufyani NA, Hess A, Noga M, et al. New algorithm for semiautomatic segmentation of nasal cavity and pharyngeal airway in comparison with manual segmentation using cone-beam computed tomography. *American Journal of Orthodontics and Dentofacial Orthopedics* 2016;150(4):703–12.

41. De Water VR, Saridin JK, Bouw F, Murawska MM, Koudstaal MJ. Measuring upper airway volume: Accuracy and reliability of dolphin 3d software compared to manual segmentation in craniosynostosis patients. *Journal of Oral and Maxillofacial Surgery* 2014;72(1):139–44. Available at: http://dx.doi.org/10.1016/j.joms.2013.07.034.

42. Alves M, Baratieri C, Mattos CT, et al. Is the airway volume being correctly analyzed? *American Journal of Orthodontics and Dentofacial Orthopedics* 2012;141(5):657–61.

43. Yi F, Liu S, Lei L, et al. Changes of the upper airway and bone in microimplant-assisted rapid palatal expansion: A cone-beam computed tomography (CBCT) study. *Journal of X-Ray Science and Technology* 2020;28(2):271–83.

44. Ghoneima A, AlBarakati S, Jiang F, Kula K, Wasfy T. Computational fluid dynamics analysis of the upper airway after rapid maxillary expansion: a case report. *Progress in Orthodontics* 2015;16(1). Available at: ???

45. Oliveira De Felippe NL, Da Silveira AC, Viana G, Kusnoto B, Smith B, Evans CA. Relationship between rapid maxillary expansion and nasal cavity size and airway resistance: Short- and long-term effects. *American Journal of Orthodontics and Dentofacial Orthopedics* 2008;134(3):370–82.

46. Inthavong K, Ma J, Shang Y, et al. Geometry and airflow dynamics analysis in the nasal cavity during inhalation. *Clinical Biomechanics* 2019;66(October):97–106. Available at: https://doi.org/10.1016/j.clinbiomech.2017.10.006.

47. Zheng Z, Liu H, Xu Q, et al. Computational fluid dynamics simulation of the upper airway response to large incisor retraction in adult class i bimaxillary protrusion patients. *Scientific Reports* 2017;7(April):1–8.

48. Xu C, Sin SH, McDonough JM, et al. Computational fluid dynamics modeling of the upper airway of children with obstructive sleep apnea syndrome in steady flow. *Journal of Biomechanics* 2006;39(11):2043–54.