2D and 3D Airway Analysis and Mandibular Advancement Treatment Outcome in Obstructive Sleep Apnea

BY

WHITNEY MOSTAFIZ
Sc.B., Brown University, 2008
D.M.D. Harvard School of Dental Medicine, 2012

THESIS

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Defense Committee:

Maria Therese S. Galang-Boquiren; Chair and Advisor
Budi Kusnoto
Grace Viana
David W. Carley, Biobehavioral Health Sciences, Medicine, Bioengineering

This thesis is dedicated to my family and friends who have helped support me during my orthodontics residency.

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LIST OF ABBREVIATIONS

2D	Two-Dimensional
3D	Three-Dimensional
AADSM	American Academy of Dental Sleep Medicine
AHI	Apnea-Hypopnea Index
ANS	Anterior Nasal Spine
A-P	Anteroposterior
BMI	Body Mass Index
BSSO	Bilateral Sagittal Split Osteotomy
C2	Second Cervical Vertebra
C3	Third Cervical Vertebra
C3ai	Anteroinferior Aspect of Third Cervical Vertebra
C4	Fourth Cervical Vertebra
C4ai	Anteroinferior Aspect of Fourth Cervical Vertebra
CBCT	Cone Beam Computed Tomography
CO_2	Carbon Dioxide
CPAP	Continuous Positive Airway Pressure
CR	Centric Relation
CSA	Cross-sectional Area
CT	Computed Tomography
DICOM	Digital Imaging and Communication in Medicine

LIST OF ABBREVIATIONS (continued)

EDS	Excessive Daytime Sleepiness
EMG	Electromyography
FH	Frankfurt Horizontal
Go	Point Gonion
H	Point Hyoid
ICC	Intraclass Correlation
IRB	Institutional Review Board
MAS	Mandibular Advancement Splint
mm	Millimeter
MMA	Maxillomandibular Advancement
MP-H	Mandibular Plane-Hyoid Bone
MRI	Magnetic Resonance Imaging
N	Point Nasion
NIH	National Institutes of Health
NREM	Non-Rapid Eye Movement
NS NREM	Non-supine Non-Rapid Eye Movement
NS REM	Non-supine Rapid Eye Movement
Or	Point Orbitale
OSA	Obstructive Sleep Apnea
OSAHS	Obstructive Sleep Apnea-Hypopnea Syndrome
PNS	Posterior Nasal Spine

LIST OF ABBREVIATIONS (continued)

PSG	Polysomnography
REM	Rapid Eye Movement
RDI	Respiratory Disturbance Index
RERA	Respiratory Effort-Related Arousals
RGn	Point Retrognathion
RME	Rapid Maxillary Expansion
S	Point Sella
SaO_2	Blood-Oxygen Saturation
SD	Standard Deviation
sdOSA	Supine-Dependent Obstructive Sleep Apnea
S NREM	Supine Non-Rapid Eye Movement
S REM	Supine Rapid Eye Movement
SVT	Supralaryngeal Vocal Chord Tract
TMJ	Temporomandibular Joint
TMD	Temporomandibular Disorders
TSD	Tongue Stabilizing Device
TT	Point Tongue Tip
UPPP	Uvulopalatopharyngoplasty

SUMMARY

Obstructive Sleep Apnea (OSA) is an extensive public health problem that imposes considerable morbidity. While nasally applied Continuous Positive Airway Pressure (CPAP) is highly effective, there are difficulties with treatment adherence. One well-tolerated alternative involves oral appliance therapy, such as a mandibular advancement splint (MAS), but success rates are difficult to predict. Our objective was to investigate oropharyngeal airway dimensions, dental protrusion with MAS, sleep characteristics, patient biometrics, and treatment response within an OSA patient sample.

Thirty-three adults were assessed retrospectively. Dolphin 3D was used to measure the airway on pre-treatment CBCTs. Patients used SomnoDent MAS appliances, which were titrated over a 6-8 weeks. Average dental protrusion and pre- and post-treatment polysomnograms (PSGs) were assessed. Initial OSA severity via Respiratory Disturbance Index (RDI), absolute and percent (%) changes in RDI, NREM and REM RDI, and supine and non-supine NREM and NREM RDI, and minimal blood-oxygen saturation (SaO_2) were analyzed.

Of the 33 patients assessed, 10 initially presented with mild OSA, while 15 and 8 had moderate and severe OSA, respectively. Pearson correlations were significant for change in RDI, change in NREM RDI, change in S REM RDI, NS NREM RDI, % change NS NREM RDI, change in S NREM RDI, and % change S

SUMMARY (continued)

NREM RDI. Pearson correlation also showed a high correlation between minimum CSA and airway volume.

Based on these significant linear associations, simple and simultaneous multiple regressions were conducted to investigate the best predictors of treatment response variables. A hierarchical method was used to create the multivariate models. Seven statistically significant models were found. Initial OSA severity was demonstrated as a primary predictor of treatment response in four models, as well as the combination of total airway volume and initial BMI in two models.

Patients with higher initial OSA severity and smaller total volume illustrated an increased treatment response to MAS therapy. In addition, decreases in airway volume due to skeletal rather than soft tissue obstruction may enable a better MAS treatment response. MAS therapy optimally targets the upper airway; patients with a more inferior minimum CSA showed greater MAS titration for a desirable outcome, but ultimately may illustrate a decreased treatment response. Future studies with a larger sample size, newer CBCT equipment, and standardized PSG analyses may be helpful to reassess MAS treatment response and these demonstrated relationships.

1. INTRODUCTION

1.1 Background

Obstructive Sleep Apnea (OSA) is an extensive public health problem that imposes considerable morbidity. While nasally applied Continuous Positive Airway Pressure (CPAP) is highly efficacious, its effectiveness in practice is limited by problems with treatment adherence. There is growing evidence that supports the importance of oral appliances, in particular using Mandibular Advancement Splints (MAS) as a treatment especially for mild to moderate OSA. Studies suggest that 60-70% of patients achieve a complete to partial clinical response to treatment (Mostafiz *et al.*, 2011). However, there are currently no reliable clinical methods for predicting MAS treatment response. Consequently, patients undergo inconvenient and expensive adjustments repeatedly only to find that the therapy may be ineffective. Thus, there is a need to develop clinically effective prediction models.

Although a number of studies have examined the potential influence of craniofacial factors on MAS treatment outcome using cephalometric x-rays, the results have been conflicting (Mostafiz *et al*., 2011). Because there is interplay between craniofacial soft tissue and skeletal structure in the pathophysiology of OSA, we hypothesize that these anatomical relationships likely influence the treatment response to MAS. Utilizing raw data from a published OSA study (Ma et *al.*, 2013), this study aims to help healthcare providers identify treatment response based on patients' baseline craniofacial dimensions.

1.2 Specific Aims

1. To identify the association between oropharyngeal airway dimensions derived from cone beam computed tomography (CBCT) and mandibular advancement splint (MAS) treatment response.

2. To identify the effect of mandibular protrusion on the association between oropharyngeal airway dimensions derived from CBCT and MAS treatment response.

3. To identify the effect of sleep state and position on the association between oropharyngeal airway dimensions derived from CBCT and MAS treatment response.

4. To identify the effect of initial OSA severity, body mass index (BMI), and neck circumference on the association between oropharyngeal airway dimensions derived from CBCT and MAS treatment response.

1.3. Research Hypotheses

1. Oropharyngeal 2D and 3D airway variables will be associated with MAS treatment response in terms of change in respiratory disturbance index (RDI) and change in minimum oxygen desaturation.

2. The association between oropharyngeal 2D and 3D airway variables with MAS treatment response will depend on sleep position, sleep state, mandibular protrusion, initial OSA severity, BMI, and neck circumference.

2. REVIEW OF THE LITERATURE

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder with significant co-morbidities and associated mortality (Malhotra & White, 2002). According to Flemons *et al.* (2004), OSA affects 24% of adult males and 9% of adult females and is the most common sleep-related breathing disorder. OSA manifests as recurrent episodes of upper airway obstruction during sleep, which leads to a decrease in blood-oxygen saturation (SaO_2), as initially defined by Guilleminault *et al.* (1976). Treatment remains challenging. Colin Sullivan introduced CPAP therapy to treat OSA as a splint to the airway (Sullivan *et al.*, 1981). While CPAP is the current gold standard of treatment, it often produces suboptimal results due to variable patient adherence (McArdle *et al.*, 1999). One well-tolerated alternative involves the use of oral appliance therapy, such as a mandibular advancement splint (MAS), but success rates are difficult to predict (Mostafiz *et al*., 2011). The understanding of the underlying mechanisms that offer treatment through oral appliances is poorly understood (Chan *et al*., 2010).

2.1 Sleep Apnea Definitions

An apnea is a cessation of airflow for at least ten seconds coupled with oxygen desaturation of at least 3% or an arousal. A hypopnea is defined by a reduction in the amplitude of airflow by >50% of the baseline measurement for at least 10 seconds, coupled with oxygen desaturation of at least 3% or an arousal

(Rechtschaffen & Kales, 1968). This reduction is measured using nasal pressure or thoracoabdominal wall movement. OSA is often characterized by intermittent apneic and hypopneic events. OSA is associated with oxyhemoglobin desaturation and arousals that lead to fragmented sleep and daytime sleepiness. OSA severity may be assessed clinically with the Apnea-Hypopnea Index (AHI), which accounts for the number of apneic and hypopneic events per hour via polysomnography (PSG). This is a useful diagnostic tool for sleep apnea (Shahar, 2014).

The term “apnea index” was first introduced in 1978 by Guilleminault and colleagues. In the 1980s, research groups began to endorse the AHI so that hypopneic events were included in analyses, as well. Since 1983, the respiratory disturbance index (RDI) evolved as another term for AHI (Shahar, 2014). The RDI includes apneas, hypopneas, as well as other airway disturbances.

According to Park *et al.* (2011), RDI is used in two different contexts. In the first definition of RDI, the chief difference between AHI and RDI is that RDI represents the frequency of apnea and hypopnea per hours of *recording time*. Meanwhile, AHI is based on these events per hours of *sleeping time*. In the clinical setting, many portable machines are not able to measure sleep status, which means that only RDI may be measured. In the second definition of RDI, RDI is a PSG measurement that averages the frequency of apnea, hypopnea, and respiratory effort-related arousals (RERA). AHI is the same measurement

but excludes RERA events. Shahar (2014) notes that the AHI measurement is dependent on physiological and technical variables that include sleep position (*i.e.* supine *versus* non-supine (NS)), sleep stage (*i.e.* rapid eye movement (REM) *versus* non-REM (NREM) sleep), device sensitivity and calibration. For the most part, scoring is done manually. Changes in AHI and RDI are useful in assessing success in OSA therapy. For the purposes of our study, we have employed the second definition of RDI because it embodies a more thorough PSG measurement.

Another distinction in apneas is that between central and mixed sleep apneas. Central apneas do not illustrate any change in respiratory effort, in contrast to obstructive sleep apnea. Therefore, there would be no nasal, chest, or abdominal activity during a central apneic event. According to Masood & Phillips (2000), idiopathic central sleep apnea-hypopnea syndrome occurs in the absence of upper airway obstruction. The authors note that it is theorized that individuals have an increased ventilatory response to CO_2, which causes them to hyperventilate and become hypocapnic. A central apnea-hypopnea event is characterized by reduced or absent breathing *and* respiratory efforts with a reduction of airflow that lasts 10 seconds or longer. Meanwhile mixed apneas initiate without respiratory effort initially, but then obstructive features persist once effort resumes (Gold *et al.*, 1985).

According to Flemons *et al.* (2004) and Bradley & Floras (2009), the OSA population in the US is most commonly Caucasian adults aged 30-60 years. Estimates of RDI scores of at least five occur in 24% males and 9% females; while 9% of males and 4% of females have RDI scores of at least 15. Prevalence is similar in the European population, as well. However, most individuals with OSA are asymptomatic and remain undiagnosed. This factor may have public health implications in relation to the morbidities that are a result of OSA. About 75-80% of those who may clinically benefit from OSA treatment remain undiagnosed (Bradley & Floras, 2009).

2.2 Evolution and Pathophysiology of OSA

From an evolutionary perspective, it has been proposed that anatomic shifts that enabled the progression of speech and language may have led to OSA as an indirect consequence. This pivotal point has been termed by Jared Diamond as “the great leap forward” (Davidson *et al.*, 2005). The evolution of spoken language appears to be linked with pharyngeal collapse during sleep, as only humans have both conditions (Davisdon *et al.*, 2005; Stupak, 2010). Aside from English bulldogs, humans are the only mammalian species that possess OSA (Davidson, 2003).

2.2.1 Pharyngeal Anatomic Shifts

The pharynx is a soft tissue surrounded by a bony scaffold. The pharynx’s size and shape are moldable in relationship to tension of the bony/soft tissues

and consequently, with growth (Abramson *et al.*, 2009). According to Schwab (2005), the lateral walls as well as the tongue, soft palate and soft tissues are larger in OSA patients. This leads to a decrease in functional airway size. Schwab (2005) additionally mentions that the retropalatal region of the oropharynx is the most common site of airway collapse in OSA patients.

Davidson (2003) and Davidson *et al.* (2005) propose that evolutionary anatomic shifts, unique to *Homo sapiens,* correlates with the development of speech. These changes comprise shortening of the mid-face which leads to a narrow and elongated supralaryngeal vocal chord tract (SVT). Meanwhile, the pharynx similarly becomes narrowed and elongated while the tongue shifts posteriorly. Finally, an acute bend in the SVT occurs to enhance speech, which angulates the cranial base. Assessing the horizontal (*i.e.* oral cavity) and vertical (*i.e.* pharynx) SVTs shows that forming an equal proportion of these linear measurements enables maximal vocal clarity (Davidson, 2003).

In particular relation to OSA, the sites between the nasopharynx and supraglottic larynx have been identified as primary sites of obstruction. Davidson *et al*. (2005) demonstrate that these anatomic changes in the upper respiratory tract contribute to OSA. Increases in RDI have been significantly associated with laryngeal descent, klinorynchy, and acute cranial base angulation, and such associations were independent of age and body mass index (BMI).

Laryngeal descent is measured linearly from the hyoid bone perpendicular distance to mandibular plane (MP-H). Laryngeal descent contributes to OSA by pulling the tongue into the oropharynx as well as creating a collapsible oropharyngeal segment of the vocal tract. Increased MP-H has been associated with OSA (Tsuiki *et al.,* 2008). Klinorynchy is a rotation exhibited by shortening of the mandible, measured as (1) linear point Gonion to point B or (2) angle Gonion-Nasion-Gnathion in lateral cephalograms. As mentioned previously, these two anatomic shifts affect the vocal cord anatomy as seen in the evolution of speech (Davidson *et al.*, 2005).

2.2.2 Skeletal and Dental Changes

In addition, acute cranial base angulation suggests an increase in the vertical dimension of the face and downward bend of the vocal chords. This leads to increased soft tissue in the posterior oral cavity, which has been correlated with OSA. During sleep, the tongue retro-positions into the oropharynx (Davidson *et al.*, 2005). Excessive soft tissue has been postulated as a contributing cause of OSA.

Davidson (2003) also cites changes in the dentition. *Homo sapiens* is the only primate species with impacted molars, and crowding is predominant. There is narrowing of the anteroposterior (A-P) dimension of the pharynx, as seen by decreased distance of posterior maxilla to anterior *foramen magnum*. The dental arches shorten and consequently expand laterally. Davidson (2003) believes

that dental lateral expansion may prevent the progression of OSA.

2.2.3 Nasal Anatomic Shifts

In addition, the prominence of the external nose may play a compensatory role in relation to OSA. Nasal obstruction has been shown as an independent risk factor for OSA (Stupak, 2010). A protrusive nose may compensate in supporting the upper airway, which has narrowed to enable speech in modern humans. A curvilinear intranasal airflow enhances nasopharynx opening. In contrast, earlier hominid species had a much more condensed nasal form.

During sleep, nasal airflow is greater than oral airflow. The angular force from the nasal to the pharyngeal airway elevates the soft palate and tongue towards the oral cavity, which opens the pharynx. This is seen as a compensatory mechanism to prevent pharyngeal collapse (Stupak, 2010). In earlier species, the pharynx was not constricted by speech requirements. Nostril openings, as a result, were more oriented with the plane of the face. Therefore, nasal airflow did not display the curvature as seen in modern human species and there is less lift of the palate and tongue.

Significant narrowing of the upper airway occurred during human evolutionary development to allow the tongue to modulate sound in the pharynx as well as de-nasalization of speech (Stupak, 2010). This shift, however, predisposes humans to the upper airway collapse during sleep, as noted.

Language development has a more powerful evolutionary force than the unwanted side effect of OSA. Therefore, one may conclude that OSA is an anatomic illness or side effect of natural selection for speech and language (Davidson, 2003).

2.2.4 Genetics and OSA Pathophysiology

Genetic factors involved with ventilatory and neurologic control have been noted in regards to the pathogenesis of OSA (Schwab, 2005). Several chromosomal defects are associated with sleep disordered breathing, including Treacher Collins Syndrome, Down Syndrome, Apert Syndrome, achondroplasia, and Pierre Robin Sequence. Shprintzen (2003) notes that these genetic disorders present with more acute cranial base angulations than average. A more acutely-angled skull base combined with a narrowing of the pharynx has been noted to increase the likelihood to develop OSA. In addition, Bayadi *et al.* (1990) demonstrate a familial line with an autosomal dominant transmission of OSA in three generations.

Finally, regional fat distribution has been shown to have a genetic component, which may have implications in the development of OSA (Schwab, 2005). Obesity is a strong risk factor for OSA. Schwab (2005) suggests that OSA patients have a genetic predisposition to regional fat distribution surrounding the upper airway, which presents as an upper body or abdominal obesity pattern.

It is unclear whether OSA was adversely selected. From an evolutionary stance, adverse health consequences that are resultant of OSA for the most part do not manifest until later adulthood (*i.e.* 40-60 years). This is after the majority of reproductive age and, at one point in time, *Homo sapiens* life expectancy (Davidson, 2003). Therefore, OSA could not have been a negative selection factor until about 10,000s of years after the above-mentioned anatomic shifts (Shprintzen, 2003). Furthermore, aging itself supports this theory; infants' and children's airways are more horizontally positioned than adults'. Humans experience two growth spurts: (1) when permanent dentition erupts, and (2) at puberty. During these times of growth, the face grows vertically and the pharyngeal airway becomes more vertical. This shift exacerbates the anatomic predisposition to OSA. Obstruction is a soft tissue phenomenon, since is it absent during the day and may occur at night or during sleep. However it is presumed that skeletal changes have repositioned the soft tissues, which lead to this obstruction. Other soft tissue changes that may contribute include floppy epiglottis or relaxed pharyngeal muscles (Davidson, 2003).

OSA pathophysiology is multifactorial in nature and highly variable in patients. Having a better understanding of the distinctive causes of OSA may aid in the selection of appropriate therapy and treatment modalities.

2.3 OSA Risk Factors

According to Flemons *et al.* (1999) the predominant risk factors for OSA are: (1) obesity, especially in upper body, (2) male gender in adults, (3) aging, (4) adenoid and tonsillar hypertrophy, particularly in children, (5) craniofacial abnormalities including mandibular and maxillary hypoplasia, (6) nasal obstruction, (7) endocrine abnormalities, such as hypothyroidism or acromegaly, and (8) family history.

Weight loss allows for improvement in OSA severity. Bradley & Floras (2009) indicate that a 10% weight gain increases the risk of developing OSA by six-times. According to Shelton *et al.* (1993), the presence of adipose tissue in the pharyngeal airway increases collapsibility. On a related note, men may have more fat in the pharyngeal airway than women (Young *et al.*, 2002). Similarly, Bixler *et al.* (1998) showed that older individuals (*i.e.* over 55 years) exhibited increased pharyngeal fat when compared to middle-aged individuals (*i.e.* 45-55 years). While the prevalence of OSA increases with age, clinical severity of OSA decreases with age when controlling for BMI.

2.3.1 Craniofacial Dimensions and OSA Risk

While the pathogenesis of OSA is complex, craniofacial structure is an important interacting factor. In addition to obesity, OSA patients may present with bony and soft-tissue craniofacial abnormalities as well as restricted oral

dimensions (Seto *et al.*, 2001; Battagel *et al.*, 2000). Both restricted hard-tissue dimensions and enlarged upper airway soft tissues compromise upper airway space, resulting in a smaller and more collapsible airway. Furthermore, habits such as smoking lead to nasal and pharyngeal narrowing due to soft tissue inflammation (Bradley & Floras, 2009). Ultimately, the size of the bony compartment relative to the amount of soft tissue contained within it will determine the degree of pressure exerted by surrounding tissues on the airway and influence its collapsibility, a concept that has been termed “anatomic balance” (Watanabe *et al.*, 2002). Although the mechanisms by which MAS decreases OSA events are still not well understood, increases in upper airway dimensions appear to be an important effect and craniofacial size is a likely mediator of this effect (Chan *et al.*, 2010).

According to Pirelli *et al.* (2004), many OSA patients present with craniofacial abnormalities that involve both jaws as well as skeletal structures within the respiratory dynamic space such as nasal septal deviation. Airflow is decreased and there is an increase in airway resistance. This condition early in life may cause a deformation in upper jaw development that leads to a reduced jaw size, which adversely affects anatomic balance.

Muscular activity in OSA patients has proven to be compensatory for a compromised upper airway that is present in these patients. Protective reflexes that increase upper-airway dilator activity maintain a patent airway. According to

Blumen *et al.* (2004), the *genioglossus* muscle exhibits increased activity to pull the tongue upward and forward. In addition, inspiratory resistance loading activates the *masseter* muscle and presents similar activity to pharyngeal airway muscles during apneic events while sleeping (Hollowell *et al.*, 1989). The anterior and posterior *temporalis* muscles also assist in maintaining a postural rest position in the mandible (Burdette & Gale, 1990). The activity in these muscles, in addition to the other jaw retracting muscles, may affect the amount of protrusion that is possible in oral appliances and may be directly related to treatment success (Tsuiki *et al*., 2004).

Compared with non-OSA subjects, OSA patients have a significantly larger tongue, indicating an anatomical imbalance of the upper airway (Mostafiz *et al.*, 2011). According to Tsuiki *et al.* (2008), a more caudal and larger tongue correlates with increased lower face cage and significantly longer MP-H distance. Tsuiki and colleagues (2008) hypothesize that the caudal displacement of the hyoid bone reflects this anatomical imbalance and excessive soft tissue, as it is a mobile bony structure.

2.4 **Clinical Consequences of OSA**

Untreated OSA exhibits significant morbidity and mortality costs. Floras (2014) propose several cardiovascular comorbidities, including hypertension, dysglycemia, atrial fibrillation, stroke, as well as heart failure in men. OSA episodes trigger activation of the sympathetic nervous system, which leads to a

rise, instead of fall, in nocturnal blood pressure. OSA interrupts the period of cardiac quiescence during acute pro-inflammatory events, which may contribute to exacerbating cardiovascular disease (Bradley & Floras, 2009). Cycles of hypoxia and CO_2 retention may adversely affect heart rate. According to the authors, hypoxia induces oxygen free radical production, which activates inflammatory pathways that impair vascular endothelial function. Furthermore, decreased cardiac output leads to a decrease in cerebral blood flow during OSA events.

There are adverse cognitive effects of OSA, as well. Increased daytime sleepiness and automobile accident rates occur in individuals with OSA. According to Jureyda & Shucard (2004), apneics possess a 2.3-7.3 times relative risk to have an automobile accident to non-apneics. Estimated costs for comorbodities have been calculated at $3.4 billion/year (Jureyda & Shucard, 2004).

In children, there are also concerns related to OSA or snoring. Gozal (1998) indicates a relationship between OSA and behavioral and learning deficits. Children also develop cardiac changes that comprise increased diastolic blood pressures and increased thickness of the left ventricle.

Snoring is the hallmark symptom of OSA in the pediatric population, which has been reported to range from 8-27% (Lipton & Gozal, 2003). Similar to the

adult population, pediatric patients experience considerable morbidities such as neurobehavioral, cardiovascular, as well as somatic growth deficits. The majority of children with OSA do not report excessive daytime sleepiness (EDS) as a major symptom, in contrast to adults. Alternatively, Ali *et al*. (1993) describe that up to 25% of parents of children with OSA notice hyperactivity and behavioral problems.

The chief source of obstruction in the pediatric population is a result of adenotonsillar hypertrophy (Nixon & Brouilette, 2005). In these patients, the most popular treatment is surgical removal of enlarged tonsils and/or adenoids. Lipton & Gozal (2003) note a reported success rate of 80% for this procedure. However, trends of increasing obesity in the pediatric population may lead to increasing OSA patients in the childhood and adolescent range.

The abundance of research investigates pediatric OSA patients in relationship to the transverse dimension of the oral cavity. In particular, orthodontic rapid maxillary expansion (RME) has been utilized to treat lateral crossbites ranging from six to 10 mm, wherein the maxillary dentition is narrower than the mandibular dentition in the transverse dimension. Ozbek *et al.* (2009) reported in a cephalometric study that tongue posture elevates about two mm after RME. They also demonstrated an association between nasal obstruction and low tongue posture regardless of RME treatment. Iwasaki *et al.* (2013) performed a CBCT study and also witnessed that tongue posture improved with

RME, although was still considered low. They noted that factors affecting tongue posture include mouth-breathing, nasal airway ventilation, arch width, and palatine tonsil hypertrophy. After RME, the intraoral airway volume decreased significantly. Additionally, total pharyngeal airway volume, retropalatal airway volume, and oropharyngeal airway volume all increased significantly in the RME group. The authors suggest that this enlargement of the pharyngeal airway may be a result of the improved tongue posture, which may or may not occur with improved nasal obstruction.

It has been hypothesized that improvement with RME treatment is linked to improved breathing and blood saturation in consequence (Kurol *et al.*, 1998). RME in children has been shown as an effective treatment for OSA, as well as nocturnal enuresis, indirectly. Computed tomography (CT) images confirm that expansion occurs in the maxillary dentition, maxilla, as well as in the nasal cavity. This anatomic shift allows for normal airflow and increased airway patency (Pirelli *et al.*, 2010). Although the studies are limited, it is reasonable to utilize RME as a preventative treatment in children with OSA.

2.5 **Diagnosis**

According to Flemons *et al.* (1999), to be diagnosed with obstructive sleep apnea-hypopnea syndrome (OSAHS), an individual must illustrate either EDS or two or more of the following: choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, and/or impaired

concentration. The other criterion needed for an OSAHS diagnosis is an RDI > 5, which is measured with an overnight sleep study by PSG. Meanwhile, a diagnosis of OSA only requires this final criterion. Flemons *et al.* (1999) also describes the severity of adult OSA based on the RDI: mild, RDI = 5-15; moderate, RDI = 15-30; and severe, RDI > 30. In children, any apneic or hypopneic event is indicative of OSA.

2.5.1 Diagnostic Imaging

The upper airway has been considered a significant contributing factor to OSA. Airway volume can be assessed two-dimensionally via lateral cephalometry or three-dimensionally via Magnetic Resonance Imaging (MRI) or CBCT. Traditionally, cephalometric radiographs have been obtained to assess the upper airway space. However, this modality is limiting in assessing the transverse or volumetric dimensions of the airway. Currently, 3D visualization of the airway with CBCT or MRI is the diagnostic gold standard. MRI offers superior soft tissue imaging; however, the cost may be unwarranted (Haskell *et al.* 2009). Meanwhile, fluoroscopy offers an alternative means to assess the airway through dynamic changes of the pharynx in different positions. This methodology successfully localizes the source of airway constriction, but cannot be related to specific anatomic structures such as with 3D imaging (Viviano, 2002).

2.5.1.1 Cone Beam Computed Tomography (CBCT)

3D imaging of the airway has helped in the understanding of these anatomic shifts. Furthermore, this technology has developed as an evaluative tool to assess OSA severity and treatment planning. Using boundaries of the hard palate, pharyngeal walls, epiglottis and tongue base, Abramson *et al.* (2009) assessed anatomic changes of the airway with age through CT. Adults had larger and more elliptical shaped airways compared to children. The steepest slope in regards to airway growth occurred during the transition of the primary to permanent dentitions (defined as ages 0-5 years, 12-16 years, respectively). In particular, growth occurred most in the transverse dimension and also increased in elliptical shape. There was no difference in morphology in males *vs.* females in all age groups.

CBCT has become well-accepted in orofacial diagnosis and treatment planning due to lower effective radiation dose, lower costs, easy access, and shorter acquisition times (Guijarro-Martínez & Swennen, 2011). Interest in upper airway 3D morphology in relation to OSA has increased. However, in a systematic review, Alsufyani *et al.* (2013) concluded that there is insufficient literature pertaining to the use of CBCT in order to assess treatment outcomes in regards to upper airway changes. Furthermore, most of these studies address the volumetric changes in the airway but do not have follow-up sleep studies to assess clinical OSA status. In 2011, Guijarro-Martínez & Swennen also

performed a systematic review. One study assessed upper airway and dentomaxillofacial morphology, and demonstrated that retrognathic patients had a decreased total airway volume. Children with class III malocclusion were shown to have a larger and flatter oropharyngeal airway in another study.

There have been several studies assessing the relationship between upper airway and OSA. In one study, only the ratio of airway cross-sectional area (CSA) showed significant differences between OSA and non-OSA patients (Shigeta *et al.*, 2008). When comparing the oropharynx in OSA and non-OSA patients, two studies showed a statistically significant smaller minimum CSA in OSA patients (Enciso *et al.*, 2010). Meanwhile another study (Ogawa *et al.*, 2005) showed significant differences in total airway volume and A-P diameter of the smallest CSA.

2.5.2 Three-Dimensional (3D) Imaging Software

Weissheimer *et al.* (2012) compared six different 3D airway analysis software programs: Dolphin3D®, InVivo Dental®, Ondemand3D®, Mimics®, OsiriX®, and ITK-Snap®. The authors noted that reliability was high in all programs. Mimics®, Dolphin3D®, OsiriX®, and ITK-Snap® showed less than 2% errors when compared to a known standard. Meanwhile, Ondemand3D® and InVivo Dental® had more than 5% errors. In addition, El and Palomo (2010) assessed Dolphin3D®, InVivoDental®, and OnDemand3D®, which were all shown to be reliable. However, these three programs were compatible only with

Windows operating systems. According to El and Palomo (2010), nasopharynx morphology is complex and its volume measurement is less reliable than oropharynx. Weissheimer *et al.* (2012) also mentioned that due to this complexity, they only evaluated oropharynx in their study.

To evaluate the size and shape of the airway, the volumetric information is processed via segmentation. Segmentation is defined as the construction of 3D virtual surface models (*i.e.* segmentations), which match volumetric data (Weissheimer *et al.*, 2012). Segmentation may be done manually or semiautomatically. When done manually, segmentation is completely slice-by-slice by the user. The software will stitch the segments to create a 3D volume. The manual approach is time-consuming and not practical in the clinical setting. Meanwhile, semiautomatic segmentation is often employed with these softwares and is significantly faster (El and Palomo, 2010). The semiautomatic segmentation process involves the software differentiating the air and surrounding soft tissues by using differences in density values (*i.e.* gray levels) of these structures. While each program is different in its method, many involve the placement of “seed points” in the cross-section of the airway, which identifies an initial threshold. Once the user determines this threshold, all voxels/gray levels within this interval will be selected to construct the volumetric representation of the airway. However, using a single threshold value for each CBCT scan is limiting and may lead to errors in volume analysis (Lenza *et al.*, 2010).

There are limited studies that assess threshold filtering with airway imaging. According to Alves *et al.* (2012), there is no standardization of an ideal threshold. Furthermore, the authors note that there is no established protocol amongst airway volume studies, wherein thresholds highly vary. Lenza *et al*. (2010) used one threshold value to assess the airway, which is more reproducible than using a dynamic threshold, but it may produce errors in making volumetric analyses. Furthermore, CBCT settings or different threshold values in 3D airway software analysis can lead to systematic differences in airway measurements (Guijarro-Martínez & Swennen, 2013). Weissheimer *et al.* (2012) noted that all programs that they evaluated underestimated the oropharynx segmentation when compared to a known gold standard. They specified that with OnDemand®, empty spaces were observed in axial, coronal, and sagittal slices, which represents the underestimation of airway volume. El and Palomo (2010) displayed similar results, noting that airway segmentation done using an interactive threshold technique showed high reliability but poor accuracy. Limitations were expressed in regards to InVivo® Dental software, wherein the user may only adjust thresholds in the 3D view. In contrast, all of the other softwares that Weissheimer and colleagues (2012) assessed allowed for viewing all of the 2D slices when segmenting the airway. These measurements are sensitive to the operator's visual discrimination of airway boundaries. Mah *et al.* (2010) explain that human vision is subject to lighting, fatigue, gray-scale discernment, and visual acuity.

2.5.2.1 Dolphin Imaging 3D®

Dolphin 3D® software is extremely popularized in the US, and enables accurate airway volume measurements with few (*i.e.* 1%) errors (Alves *et al.*, 2012). Weissheimer *et al.* (2012) emphasized its friendly interface, quick upper airway segmentation, good segmentation sensitivity, possibility of checking segmentation in 2D slices, and minimum CSA analysis. However, the disadvantages include its cost, lack of tools to correct or adjust airway segmentation in 2D slices, and incompatibility of its threshold interval units with other imaging softwares. The airway is selected through an automated program that differentiates between the airway and soft tissue densities. Alves and colleagues (2012) selected several thresholds in comparison to a known volume gold standard. According to their measurements, a threshold value of 73 was the most accurate.

Mattos *et al.* (2014) assessed linear, CSA, and volumetric measurements of the upper airway using CBCT and Dolphin 3D® software. The authors observed good intraexaminer and interexaminer reliability in the upper airway when measuring linearly in the A-P dimension as well as measuring sagittal area and volume. In regards to measurement errors, the greatest mean differences in linear measurements were in the transverse dimension at the level of the soft palate, tongue, and vallecula (interexaminer, 11.5%, 13.4%, and 16.1%, respectively). When measuring area, the greatest mean difference was at the

level of the vallecula (interexaminer, 13.3%). Meanwhile, volumetric data were below 10%.

Mattos *et al.* (2014) discuss important considerations when using the Dolphin airway/sinus tool. In particular, when performing the minimum CSA assessment, the operator must place the boundaries within the upper and lower limits that were previously chosen by the operator for volumetric measurements. If these boundaries are coincident with the upper or lower limits, the authors witnessed that in some cases the software will measure areas outside of the limits and underestimate the actual minimal CSA *vs.* obtaining the true minimal CSA.

2.5.3 CBCT Analysis Limitations

Guijarro-Martínez & Swennen (2013) highlight major obstacles with CBCT upper airway analysis. Particularly, the authors mention the impact of respiration phase, tongue position and mandibular morphology, longitudinal and cross-sectional 3D CBCT upper airway evaluation, and 3D anatomic definitions of the upper airway. For these reasons, it is difficult to compare data from different studies. Most studies do not control respiratory phase; the authors recommend that patients should avoid deglutition and movement during the scan. While increasing the time of the CBCT scan will lead to increased quality and accuracy, Weissheimer *et al.* (2012) note that this can lead to increased patient movement. These scans can last as long as 40 seconds; motion-related artifacts may

influence segmentation accuracy and negate the increased information obtained from a longer scan. In addition, Guijarro-Martínez & Swennen (2013) recommend positioning the mandible in a reproducible position such as maximum intercuspation or centric relation (CR).

Another concern is that head posture may affect the shape of the airway. Head posture may be assessed by evaluating craniocervical orientation (*i.e.* inclination of sella-nasion (SN) plane to a line through the cervical vertebrae). Using identifiable cephalometric landmarks from CBCT images allowed for consistent and reproducible analysis (Guijarro-Martínez & Swennen, 2013).

Patient positioning during data acquisition is an important factor. Upright position (*i.e.* natural head position) is recommended for baseline assessment of the upper airway morphology. Meanwhile the supine position is considered adequate for OSA research. According to Enciso *et al.* (2010), the NewTom device is ideal for OSA studies, as it is the only CBCT machine that images the patient in the supine position. Sutthiprapaporn *et al.* (2008) assessed these differences, particularly addressing the response of gravity on soft tissue structures. They found that the soft palate, epiglottis and entrance to the esophagus moved anteriorly and caudally when sitting upright. The hyoid bone only moved caudally. In addition, the CSA in the upright position was larger than in the supine position. In a cephalometric study of OSA subjects, it was evident that when head position changed from upright to supine, the velopharynx

significantly reduced in the A-P dimension and was the narrowest site in both body positions (Tsuiki *et al.*, 2003). This can be attributed to gravity and relaxation of the soft palate, tongue and change in hyoid bone position (Alsufyani *et al.*, 2013). In addition, another study showed that a change of 10 degrees in craniocervical angulation can produce a four mm change in posterior airway space (Muto *et al.*, 2002).

According to Mattos *et al.* (2014), the best approach in airway assessment is a thorough analysis, including linear measurements, area, and volume. The authors note that volumetric information alone might not necessarily represent or identify the locations of the relevant constrictions. In OSA studies, the most common measurements are to assess the minimum CSA of oropharynx and A-P and lateral dimension of this area (Enciso *et al.* 2010). The upper airway has been shown to be significantly smaller in OSA patients, as well as possessing a more spherical/elliptical shape when compared to non-OSA patients.

Scanning protocols such as modifications in milliamperes and kilovolts may influence the voxels' gray scale, which may affect volumetric measurements (Alves *et al.*, 2012). If the voxels' density is higher, higher software sensitivity may be required to be most similar to the true airway volume. However, the authors note that there is a lack of literature that assesses scanning protocol in relation to software threshold sensitivities, which needs further standardization.

2.5.4 Assessments of Sleep Position and Stage and OSA

A study by Camacho *et al.* (2014) was the first to perform CBCT assessments of the airway in both supine and upright positions in OSA patients. In the supine position, there were decreases in total airway volume as well as the CSA at the levels of the posterior nasal spine (PNS), uvula tip, retrolingual region, and tongue base. The total airway volume decreased by 32.6%, whereas the area at site of the minimum CSA decreased by 75.9%. Similarly, the authors suggest that the effect of gravity and tissue laxity produce these airway changes. Notably, one patient who had tonsillectomy and uvulopalatopharyngoplasty (UPPP) procedures did not exhibit these changes. This was most likely due to previous soft tissue removal.

In addition, there are differences between awake and asleep airway anatomy. Stationary position likely does not reflect the dynamic positions during sleep (Alsufyani *et al.*, 2013). During the transition from awake to NREM sleep there is a reduction in diaphragm and upper airway muscle activity. This leads to a two to five-fold increase in upper airway resistance. Furthermore, the prevalence of apneic events varies during NREM and REM sleep. OSA is more severe during REM sleep than during NREM sleep, wherein longer duration of apneas and a lower mean SaO_2 occurred in both sexes (Peregrim *et al.*, 2013). In regards to sleep states, on average REM sleep comprises about 25% of total sleep time (Carskadon and Dement, 2011). The authors note that while there is

a decrease in apneic events during NREM sleep, sleep efficiency is decreased in severe OSA patients, and in particular in the supine position.

Sleep position also affects apneic status as a result of changing soft tissue draping in the airway. Lee *et al.* (2014) were the first to assess upper airway changes when sleeping in supine *versus* lateral position in OSA patients. RDI has been shown to be two times greater in supine than non-supine in 50-70% OSA patients. Prevalence of obstruction at the soft palate, tongue base, and larynx decreased significantly after changing from a supine to lateral position. The authors concluded that obstruction in lateral position is mostly due to obstruction at the oropharyngeal lateral walls, which was not affected by sleep position. In the supine position, the most common structure contributing to obstruction was soft palate, occurring in 87.4% of patients, followed by the tongue base (76.5%), lateral wall (70.6%), and larynx (21.2%). In the lateral position, the lateral wall was the highest contributor to obstruction (60%), followed by soft palate (22.3%), tongue base (7.1%), and larynx (1.4%). Improvement in lateral wall was not significant, except when RDI severity was taken into consideration. In regards to soft tissue obstruction, patients with severe OSA showed significant improvement when changing to a lateral position, with exception of the lateral walls. Moderate OSA patients improved in all measured structures when changing to the lateral position. The most prominent changes were in the tongue base and larynx, regardless of OSA severity. Authors suggest that OSA patients without severe lateral wall collapse are likely

to be position-dependent apneics. UPPP can reduce lateral wall collapsibility, and consequently change patients from non-position-dependent to position-dependent apneics. In these patients, positional therapy is a useful treatment option. In women, RDI was higher in REM sleep than NREM sleep, in both supine and lateral sleep positions (Peregrim *et al.*, 2013). A similar tendency was observed in men, with only significance in the lateral body position.

Controlling for REM *vs.* NREM-related OSA events, Oksenberg *et al.* (2010) showed that REM-related OSA patients' disorders were significantly less severe than NREM-related OSA. REM-related OSA was more commonly found in mild-moderate OSA (93% patients), especially in women. NREM-related OSA patients had a higher RDI. This may be accounted for since the majority of total sleep time is spent in the NREM state. Sleep position during REM sleep in particular affected OSA events, in which supine posture was detrimental. Sleeping in the supine position increased frequency as well as severity of abnormal breathing events. In this study, when assessing for sleep stages and position, RDI REM supine > RDI NREM supine > RDI REM lateral > RDI NREM lateral. In addition, minimum SaO_2 levels were lower in the supine compared to the lateral sleep position in both REM-related and NREM-related OSA patients.

2.6 OSA Treatment

2.6.1 Continuous Positive Airway Pressure (CPAP)

Colin Sullivan introduced CPAP as a treatment for OSA in adults in 1981 (Sullivan *et al.*, 1981). The gold standard and first line in OSA therapy is CPAP. The mechanism involves air blown through the upper air passages, which comes from a mask worn over the mouth or nose. This air pressure keeps the throat open. CPAP therapy is highly effective, in which success rates are about 95% (Riley *et al*. 2000). While side effects are uncommon, according to Pépin *et al.* (1995), 25% may develop nasal congestion if used chronically.

Ultimately, the primary concern is poor patient tolerance, as patients tend to find CPAP uncomfortable. The mask limits mobility, and many patients complain about marks, noisiness, and a sense of claustrophobia. Patients often feel burdened cleaning the machine and find it bulky in regards to travel (Almeida *et al*., 2013). Compliance ranges from 65-80% (Pépin *et al.,* 1995) and CPAP usage is usually less than 50% of the night. Lowe (2012) compared CPAP wear is to oral appliance wear, and noted that patients tolerate oral appliances longer at night. Furthermore, most patients indicate a preference for oral appliance therapy. Imbedded compliance monitors suggest that oral appliances are worn between 6.6 and 6.8 hours per night compared with 4 hours per night for CPAP. Dentoskeletal movement has also been documented with CPAP wear, including anterior maxillary retrusion and incisor retroclination, chin setback, and a decrease in facial convexity (Lowe, 2012).

2.6.2 Behavior and Lifestyle Management

Several lifestyle modifications may decrease OSA symptoms. These include weight loss, changes in sleep position, and decreases in alcohol consumption (El *et al.,* 2011). Weight loss is extremely important in the management of OSA treatment (Davies *et al.,* 1992), especially as obesity is a risk factor. In addition, other factors include decreasing smoking and sleeping in a non-supine position.

2.6.3 Oral Appliances in the Management of OSA

In OSA patients, constriction has been seen more laterally than anteroposteriorly, with the narrowest part posterior to the soft palate. The amount of RDI reduction is significantly dependent on the amount of mandibular protrusion (Almeida *et al.*, 2002). Oral appliances keep the pharyngeal airway open wide enough to prevent snoring, apnea, and arousal (George, 2001). Protruding the mandible also advances the tongue anteriorly. Mandibular protrusion also moves the hyoid upward and backwards, reducing the MP-H cephalometric measurement (Battagel *et al.,* 1999). According to George (2001), therapeutic effects have been seen at 15 mm. However, a maximum forward mandibular position is not adequate since it may cause temporomandibular joint (TMJ) or muscle discomfort (Almeida *et al.,* 2002). Using an MAS stretches the elevator muscles and connective tissue, which are anchors against the force to return to CR (Almeida *et al.,* 2002). This force may change incisor angulation; however, using teeth in both arches as anchorage distributes the force and

minimizes dental movement. Therefore, similar to CPAP, where nasal pressure is titrated for each patient to reduce RDI, the concept of titration is important in relation to the amount of MAS protrusion in OSA treatment (Almeida *et al.*, 2002). With using MAS, Tsuiki *et al.* (2001) demonstrated that the A-P width of the velopharynx increases after two-thirds of maximum protrusion.

Many studies address A-P anatomical discrepancies in OSA patients, which are assisted with the use of lateral cephalometry. According to Tsuiki *et al*. (2001), a titratable oral appliance may enlarge the velopharynx and hypopharynx by increasing the A-P dimension, which was correlated with a reduced RDI. There was no change in CSA of the oropharynx. The retropalatal region was considered the most constricted and collapsible site (Tsuiki *et al.*, 2001).

Chan *et al.* (2010) performed a volumetric MRI evaluation of the upper airway with and without an MAS. Participants were assessed in the supine position, and it was shown that the MAS increased the upper airway volume particularly in the region of the velopharynx in the lateral dimension. This dimension has been seen as most constricted in OSA patients, in particular. Furthermore, the authors noted several bony and soft tissue dimensional changes that comprised raising the hyoid bone, lateral displacement of the parapharyngeal fat pads, and repositioning tongue muscles more anteriorly. It has been noted that CPAP mechanisms of action are similar by increasing airway volume and thinning out the lateral pharyngeal walls. Liu *et al.* (2000)

also hypothesize that this advancement may stretch the soft palate and stiffen the velopharynx through this mechanism which would diminish upper airway collapsibility.

While most appliances used to treat OSA are similar to the MAS design and mechanism, there are other appliances that have been used in a clinical setting. The tongue stabilizing device (TSD) is another oral appliance that is used, which protrudes and holds the tongue through suction.

Less is known about the TSD mechanism of action. According to Sutherland *et al.* (2011), TSDs may increase the velopharyngeal lateral as well as A-P diameter more than the MAS. However, the authors also indicate that compliance and comfort are decreased in comparison to the MAS. TSDs may be recommended for patients in which MAS therapy is contraindicated, such as reduced number for teeth, compromised dental health, periodontal disease, gag reflex, or unwanted dental side effects developing from using MAS.

The American Academy of Dental Sleep Medicine (AADSM) (1999) has recommended oral appliance therapy for mild-moderate OSA. CPAP remains the gold standard, and has been recommended as an initial therapeutic approach. MAS may be suitable for those who do not tolerate or respond to CPAP. In order to wear an oral appliance, patients need to maintain an adequate number of teeth that are well maintained. Ferguson *et al.* (2006)

recommend, at minimum, six teeth per arch as a means of retention and support for MAS.

There are myriad MAS designs that are marketed for treatment of OSA. The two broadest categories include either one-piece (Monobloc) or a two-piece design (Bibloc), which are either custom-made or pre-fabricated. Most appliances are constructed from a soft elastomeric material or hard acrylic (Yow, 2009). Custom appliances are more retentive, which better ensures fit and compliance during sleep. While one-piece appliances are rigid, two-piece designs offer limited mandibular movement in three dimensions. Henke *et al*. (2000) suggest that this movement may reduce the risk of TMJ pain and improve long-term compliance. Furthermore, many appliances are titratable in the sagittal dimension; this allows for individualized mandibular advancement.

Initially, an MAS is set between 50-75% of maximum mandibular protrusion (Ferguson *et al.*, 2006). Patients may titrate and continue advancement over a period of weeks to months. Titration is considered complete when associated symptoms are improved or maximal comfort has been reached. Ferguson *et al.* (2006) demonstrated that there was a relationship between the amount of MAS advancement and therapeutic effect. In addition, titration is important since patients may tolerate advancement over time (Walker-Engström *et al.*, 2002).

2.6.3.1 MAS Treatment Side Effects

Subjective side effects while using MAS are common, most frequently comprising TMJ pain, myofascial pain, tooth pain, TMJ sounds, dry mouth, gum irritation, and morning after occlusal changes (Martínez-Gomis *et al.*, 2010). TMJ problems from using MAS are myofascial, not intracapsular (George, 2001). Due to myostatic contraction, in which the muscle is held in a shortened position over the time, the muscle is shortened. However, most patients' bites will normalize after chewing or clenching after awakening. In a long-term study performed by Martínez-Gomis *et al.* (2010), occlusal changes involved a decreased number of posterior contacts; however, this tendency reversed during years 2-5 of treatment. In addition, Giannasi *et al.* (2009) confirmed that jaw noises and clicking sounds that were present at baseline disappeared or diminished over years of MAS usage.

Studies using cephalometric and MRI have shown no change in TMJ position or remodeling during the use of an MAS (Giannasi *et al.*, 2009; Almeida *et al.*, 2002). Almeida *et al.* (2002) demonstrate that patients preserved TMJ morphology before and after treatment and that they also maintained symmetrical masticatory musculature. The mandibular fossa and articular eminence outlines were preserved, and there were no changes in morphology and MRI signal intensity.

Temporomandibular Disorders (TMD) affect an estimated 12% of the population (Smith *et al.,* 2009), in which > 50% report poor sleep quality. Smith *et al.* (2009) reported that 28% of TMD subjects were diagnosed with OSA based on PSG. Of these, 73% were in the mild range (RDI = 5-14.9). They also presented with a trend towards hypoalgesia at the *masseter* site. However, long-term studies suggest that MAS treatment does not modify TMD prevalence in OSA patients (Martínez-Gomis, 2010). On the contrary, Giannasi *et al*. (2009) showed that TMD symptoms lessened with use of MAS.

The majority of long-term changes are dental. These changes primarily include reduction of overbite and overjet, which occurred after 12-30 months of treatment (Fritsch *et al.*, 2001). These reported changes were < one mm; however, Doff *et al.* (2010) observed greater changes of up to three mm. In addition, posterior open bites have been observed in 17.9% of patients (Perez *et al.*, 2013). While clinically, these changes may be small, patients must be informed of these potential long-term effects of MAS therapy.

2.6.3.2 Predictors of MAS Treatment Response

The literature indicates that not all patients who may receive MAS therapy achieve a clinically successful outcome (*i.e.* reduction in RDI). This contrasts with CPAP treatment, which is highly effective. Ascertaining diagnostic measurements that may predict treatment outcome would allow clinicians to be

more efficient. Patients would ultimately receive more effective care while minimizing time and resource costs as well as medical expenses.

Several studies assess MAS treatment outcome in relation to change in RDI. Largely, better success rates were seen in patients that originally had lower RDI values (Ferguson *et al.*, 2006). Consequently, the authors do not recommend MAS therapy as an initial line of therapy in patients who have been diagnosed with severe OSA. To predict a resultant RDI < 5 following MAS, Hoekema *et al.* (2007) noticed that smaller BMI, increased levels of maximum mandibular advancement, and a smaller initial RDI had fair predictive ability. Smaller neck circumference additionally suggests improved response (Mehta *et al.,* 2001).

The relationships between cephalometric variables and MAS treatment outcome has been assessed on a broad scale, but findings are inconsistent and investigation is warranted. Hoekema *et al.* (2007) reported that higher ANB angle, smaller SNB angle, and increases in overjet, overbite, and upper anterior face height were the best predictors for MAS treatment outcome. Based on lateral cephalometry, an increased ratio between tongue surface area and oral cavity enclosure CSA correlated with improved treatment response to MAS (Mostafiz *et al.*, 2011). Mayer and Meier-Ewert (1995) identified that shorter soft palate length and decreased MP-H distance enhance clinical outcome. It is noteworthy that cephalometric variables are typically obtained in an upright

position. Imaging and analysis of patients in the supine position, wherein OSA events occur, may offer more clinically pertinent information.

3D airway data have the potential to offer additional insight. Imaging done with awake nasopharyngoscopy has shown that MAS treatment modifies the lateral dimension of the velopharynx. Chan *et al.* (2010) suggest that an improvement in velopharyngeal caliber may be useful in predicting responsiveness to MAS therapy. Similarly, this may be attributed to an increase in volume of the velopharynx, which was assessed via MRI. According to Chan *et al.*, (2010) this effect does not occur in the non-responders in their sample. Abi-Ramia *et al.* (2010) demonstrated increases in total airway volume after seven months of appliance therapy by 1.1 ± 0.2 cm^3 ($15 \pm 6\%$). However, these measurements were not validated clinically since change in OSA status was not measured. Haskell *et al*. (2009) similarly saw increases in airway volume. The authors noted that the largest changes occurred more in the lateral dimension rather than anteroposteriorly, particularly at the level of the C2 vertebra. The minimal CSA changed by 0.4 ± 0.9 cm^2; the largest increase in A-P dimension was by 0.1 ± 0.2 cm and in the transverse dimension was by 0.4 ± 0.4 cm. As a result, the airway acquired a more elliptical cross-sectional shape (Haskell *et al.,* 2009).

The amount of protrusion achieved with the MAS is an elemental predictor of treatment outcome with this therapy. Mandibular protrusion diminishes

pharyngeal collapsibility and improves oxygenation, as previously noted. According to Kato *et al.* (2000), a two mm increase in mandibular advancement may improve RDI by 20%. In addition, patients who were able to protrude their mandible at least five mm exhibited higher success rates (Marklund *et al.*, 1998). The amount of vertical opening has not shown a significant effect on treatment outcome. Minimizing bite opening with appliance therapy is favored to better enable patient comfort as well as to reduce posterior rotation of the mandible (Pitsis *et al.*, 2002).

Studies assessing positional OSA and treatment response to MAS therapy are limited. According to Dieltjens *et al.* (2014), the prevalence and evolution of supine-dependent OSA (sdOSA) with use of MAS therapy is unknown. The authors assessed the prevalence of and conversion to sdOSA before and after MAS treatment in 237 patients. Initially, the prevalence of sdOSA ranged from 27- 67%, which decreased to 17.5-33.9% with MAS therapy. Additionally, the conversion from non-sdOSA to sdOSA patients increased from 23.0% initially to 37.5%. Investigating the physiological basis of this conversion is needed. Furthermore, the authors concluded that the presence of sdOSA at the baseline was not a significant factor in treatment success when using MAS therapy.

2.6.4 Surgical Treatment Options

Surgical options include soft tissue resections, such as UPPP, tonsillectomy, tongue resection or skeletal advancements such as Le Fort I and

Bilateral Sagittal Split Osteotomy (BSSO) advancement of the maxilla and mandible, respectively. In addition, other procedures include bariatric surgery and tracheostomy as OSA management options.

Tracheostomy has been performed since 1969, which circumvents the pharyngeal sites of obstruction (Hendler *et al*., 2001). There are many complications, however, such as infection, problems with speech, and esthetic concerns. In 1964, UPPP was introduced by Ikematsu as a treatment for habitual snoring. However, this procedure had a 50% failure rate and high morbidity. Wilhelmsson *et al.* (1999) evaluated 95 OSA patients in two treatment groups, comparing appliance and UPPP treatment options. Using a definition of success of an RDI < 10, the oral appliance group was 78% successful, and 51% of the patients in the UPPP group were successful after one year. Additionally, Walker-Engström et al. (2002) quantified an oral appliance success rate of 63% *vs.* 33% for UPPP after four years. Oral appliances had few adverse side effects, and repairs and adjustments were moderate. In comparison, 8% and 10% of the UPPP subjects complained of nasopharyngeal regurgitation and difficulty with swallowing.

Maxillomandibular advancement (MMA) was first suggested in 1979 as an alternative to tracheotomy procedures (El *et al.,* 2011). This procedure would advance the suprahyoid and velopharyngeal muscles and tendons. Studies show that these procedures lead to expansion in the retropalatal and retrolingual

airway (El *at al.,* 2011). Abramson *et* al. (2011) assessed airway changes following MMA via CBCT. The authors found that following surgery, the upper airway was larger in both sagittal and transverse planes in addition to decreasing in length. Consequently, airway resistance decreased. In 1983, Powell, Guilleminault, and Riley observed successful results from an intraoral horizontal sliding osteotomy of the anterior mandible, along with a BSSO. This procedure advances the genioglossus, mylohyoid, and anterior digastric muscles (Powell *et al*., 1983). Riley *et al.* (2000) suggest that 10 mm of mandibular advancement should be achieved at minimum. In addition, counterclockwise rotation of the occlusal plane may help increase posterior airway space. Furthermore, Brevi *et al.* (2011) reported that 93.3% patients' OSA conditions resolved with MMA.

Adenoidectomy and tonsillectomy have been popularized procedures in the pediatric population. One indication includes mouth-breathing. According to Caixeta *et al.* (2014), previous studies have demonstrated that mouth-breathing children commonly have smaller arch widths and lengths, a greater palatal depth, and a craniofacial growth disharmony. The authors' results demonstrate that the untreated mouth-breathers show increased palatal depth and decreased maxillary intercanine and intermolar molar width gains than those who were treated. Meanwhile, no association was found between adenotonsillectomy and mandibular changes. Caixeta *et al.* (2014) noted that the palatal depth increase might be attributed to a decreased growth rate of the transverse dimension of the maxillary arch as well as by the nasal cavity hypofunctionality seen in these

individuals. The tendency in mouth-breathers is to deepen the palatal roof, whereas a more normal growth pattern is established after tonsillectomy and adenoidectomy.

3. MATERIALS AND METHODS

A sample population from “Association between resting jaw muscle electromyographic activity and mandibular advancement splint outcome in patients with obstructive sleep apnea” (Ma *et al.*, 2013) with ethics approval was used retrospectively.

3.1 Retrospective De-identified Data

Data were obtained retrospectively from a prospective clinical study (Ma *et al.*, 2013). The data used in this current study were de-identified coded CBCT scans and pre- and post-MAS treatment PSG data. Information regarding patient demographics and MAS appliance titration was also obtained for the purposes of this study. The Office for the Protection of Research Subjects at the University concluded that our protocol (2013-0903) was IRB-exempt, since the research activity does not involve human subjects.

3.1.1 Subjects

Ma and colleagues (2013) recruited patients from the sleep clinics at Royal Prince Alfred, Royal North Shore, and the Woolcock Institute and from other sleep physicians (Sydney, Australia). Thirty-three patients completed the protocol. Inclusion criteria were at least two symptoms of OSA (snoring, witnessed apneas, fragmented sleep, daytime sleepiness), plus evidence of OSA on PSG (RDI ≥ 10), and age > 20 years. The presence of the C4 vertebra on

CBCT was also required. Exclusion factors included subjects that had periodontal disease, insufficient numbers of teeth (*i.e.* less than ten teeth in either dental arch), exaggerated gag reflex, evidence of TMD, or receiving treatment for OSA with a MAS within the last three months.

3.1.2 Clinical Records obtained

Impressions and bite registrations were taken to fabricate the MAS. CBCT scans were taken as a part of the pre-treatment records obtained. BMI and neck circumference measurements were recorded before and after MAS treatment. CBCTs were taken before treatment with the NewTom 3G (QR, Verona, Italy), utilizing a 12-inch field of view at 110 kV with an exposure time of 5.4 seconds in a standardized method. With the aid of a gantry beam, the patient's head was positioned with the Frankfort Horizontal (FH) plane perpendicular to the true horizontal. Foam pads were used to secure the head in this position. Throughout the scan, patients were asked to breathe normally through their nose and to refrain from swallowing. Patients were instructed to keep their mouths closed and to maintain a relaxed bite, with the tongue touching the front teeth. This author was able to obtain Digital Imaging and Communication in Medicine (DICOM) files and Dolphin Imaging 3D® software (version 11.7; Dolphin Imaging & Management Solutions, Chatsworth, California) was used for airway analysis.

All of Ma's subjects received a customized two-piece mandibular advancement splint (SomnoDent; SomnoMed, Crows Nest, New South Wales, Australia) for OSA treatment. Titration protocol was reported in their publication. Final mandibular protrusion, defined as the summation of the 75% maximal advancement measurement with average titration, was recorded for this study.

3.1.3 Polysomnography (PSG)

Deidentified initial and final PSGs were obtained. All PSGs were scored according to standard criteria (Rechtschaffen & Kales, 1968). Apneas were defined by a cession of airflow that lasted at least 10 seconds in association with oxygen desaturation of at least 3%, or an arousal (Mehta *et al.*, 2001). Hypopneas were defined by a reduction in the amplitude of airflow, as assessed with nasal pressure or thoracoabdominal wall movement by more than 50% of baseline for more than 10 seconds, in association with oxygen desaturation.

Since the literature is not consistent in defining response in terms of RDI, treatment response was assessed through several different measures. Patients were categorized by initial OSA severity as mild, moderate, or severe. Mild OSA had an RDI of 5-15/hour, moderate OSA had an RDI of 15-30/hour, and severe OSA was defined as having an RDI >30/hour (Flemons *et al*., 1999).

Treatment response was assessed by the absolute change in RDI and percentage (%) change in RDI. The absolute and % changes in RDI were further

categorized by sleep phase; *i.e.* absolute change and % change in NREM RDI and REM RDI. Absolute and % changes were then defined by sleep position and sleep phase; *i.e.* non-supine NREM (NS NREM) RDI, supine NREM (S NREM) RDI, non-supine REM (NS REM) RDI, and supine REM (S REM) RDI. Since some of the sleep centers did not describe RDI in terms of supine or non-supine without phasic data embedded in the PSG report, supine RDI and non-supine RDI could not be assessed in this study. Finally, treatment response was assessed by measuring the % change in minimum SaO_2. Figure 1 illustrates the stratification of the PSG variables.

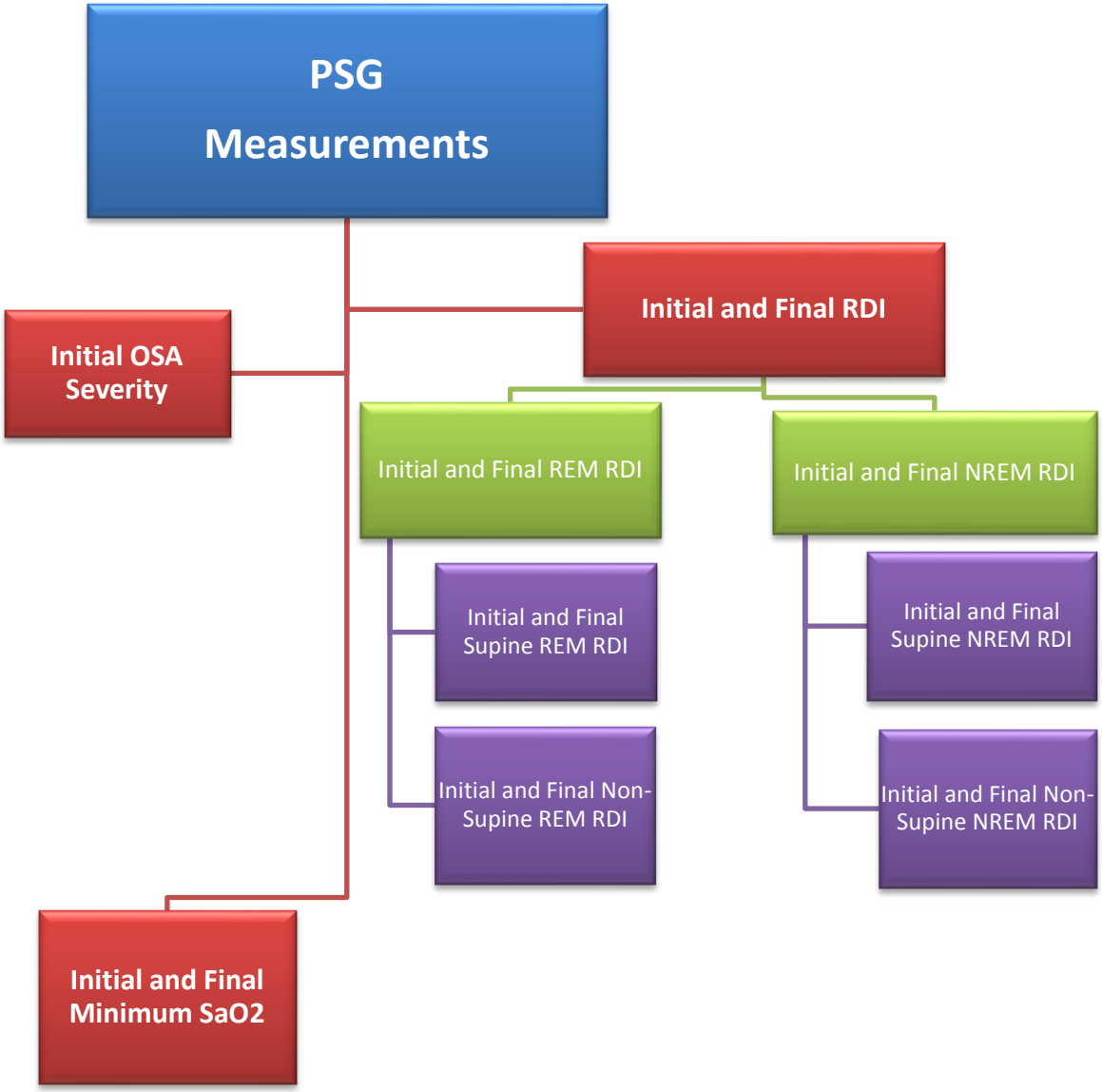


Figure 1. Stratification of PSG Variables.

3.2 Anatomical Definitions, Measurements, and Analyses

Volumetric upper airway measurements were performed with the use of Dolphin 3D® airway software utilizing previously described techniques (Mattos *et al.*, 2014; Guijarro-Martínez & Swennen, 2013; Chan *et al.*, 2010; Mehta *et al.*, 2008). All airway measurements were made by one assessor (WM), who was blinded to the subject's apneic status and was assessed for reliability by repeated measurements for n=10 after one week under the same conditions. Inter-reliability was also assessed for n=10 by a second assessor (AM).

3.2.1 Oropharyngeal Dimensional Measurements

The upper airway was divided into three segments following the methods of Guijarro-Martínez & Swennen (2013): nasopharynx, oropharynx, and hypopharynx. Nasopharynx pertains to the nasal airway, soft palate and pharynx; the superior limit was defined with respect to the soft tissue contour of the pharyngeal wall. The inferior limit was defined as the plane parallel to FH, at the level of the posterior nasal spine (PNS), extended to the posterior wall limit of the pharynx. The anterior limit was the PNS, while the soft tissue contour of the pharynx confined the posterior limits. Next, the oropharynx superior limit was the inferior limit of the nasopharynx, while inferiorly, C3ai vertebra was defined as the limit. Similar anterior and posterior limits were used as with nasopharynx. The hypopharynx superior limit was the inferior limit of the oropharynx, extending inferiorly to the C4ai vertebra. Please refer to TABLE I and Figure 2.

TABLE I. AIRWAY MEASUREMENTS

Region	***Boundaries***	***Anatomic and Technical Definitions***
Nasopharynx	Anterior	Frontal plane, perpendicular to FH, passing through PNS
	Posterior	Pharyngeal wall soft tissue contour
	Upper	Pharyngeal wall soft tissue contour
	Lower	Plane, parallel to FH, passing through PNS
	Lateral	Pharyngeal wall soft tissue contour
Oropharynx	Anterior	Frontal plane, perpendicular to FH, passing through PNS
	Posterior	Pharyngeal wall soft tissue contour
	Upper	Lower boundary of Nasopharynx
	Lower	Plane, parallel to FH, passing through C3ai
	Lateral	Pharyngeal wall soft tissue contour
Hypopharynx	Anterior	Frontal plane, perpendicular to FH, passing through PNS
	Posterior	Pharyngeal wall soft tissue contour
	Upper	Lower boundary of Oropharynx
	Lower	Plane, parallel to FH, passing through C4ai
	Lateral	Pharyngeal wall soft tissue contour

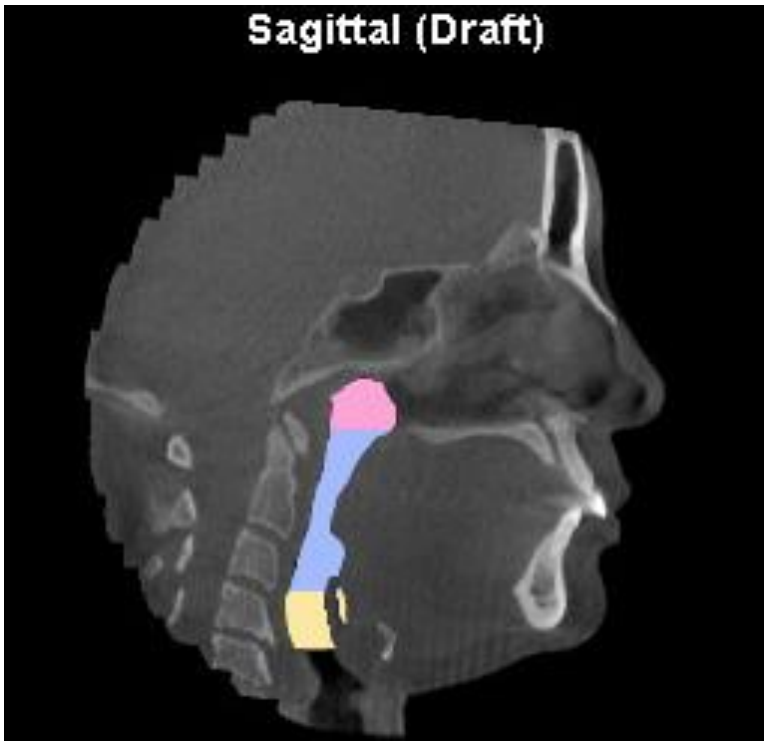


Figure 2. Airway Segments.
(Nasopharynx is pink, oropharynx is blue, hypopharynx is yellow)

Airway measurements were obtained from the CBCTs using the Dolphin 3D® software Sinus/Airway analysis. Specifically within the three segments, the segmental location and value of minimal axial CSA were recorded. At the level of each minimal axial CSA, the maximal transverse and A-P linear dimensions were recorded to assess the shape of the ellipse. In addition, a summation of the pharyngeal airway volume and vertical length segments was constructed. Airway

total volume and length were defined as the sums of these three airway segments. A diagram summarizing the progression of these measurements is illustrated in Figure 3.

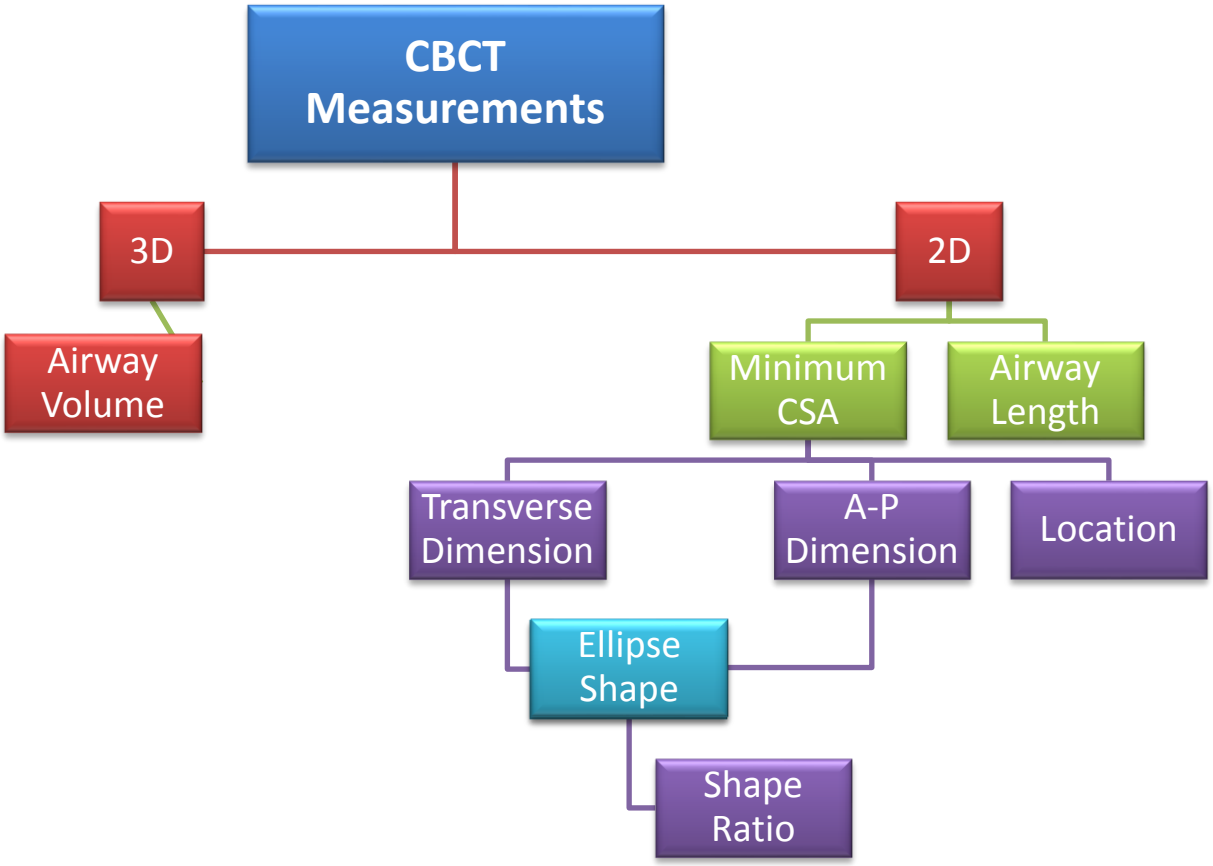
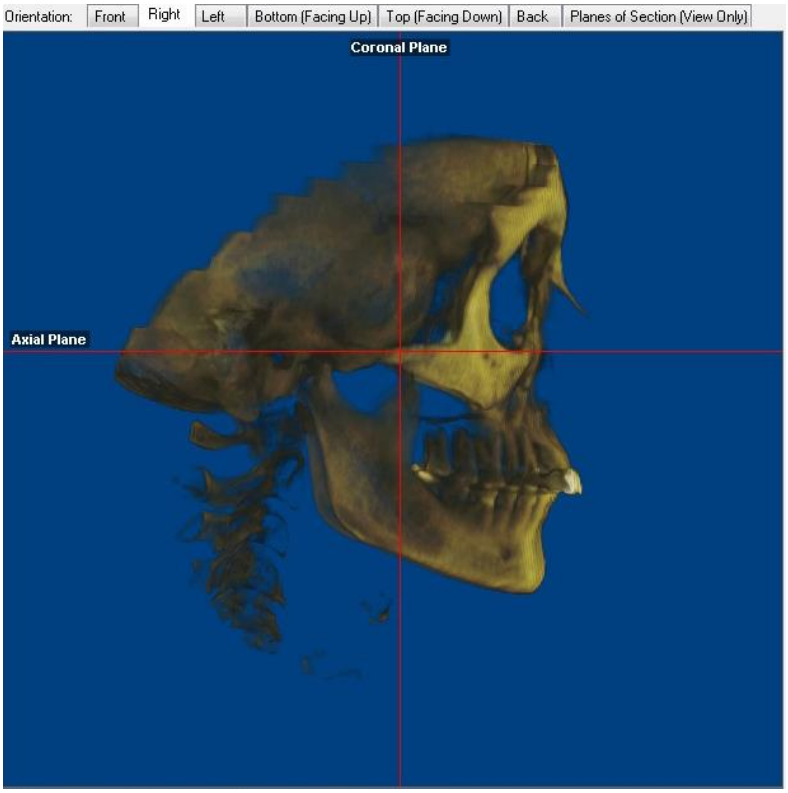
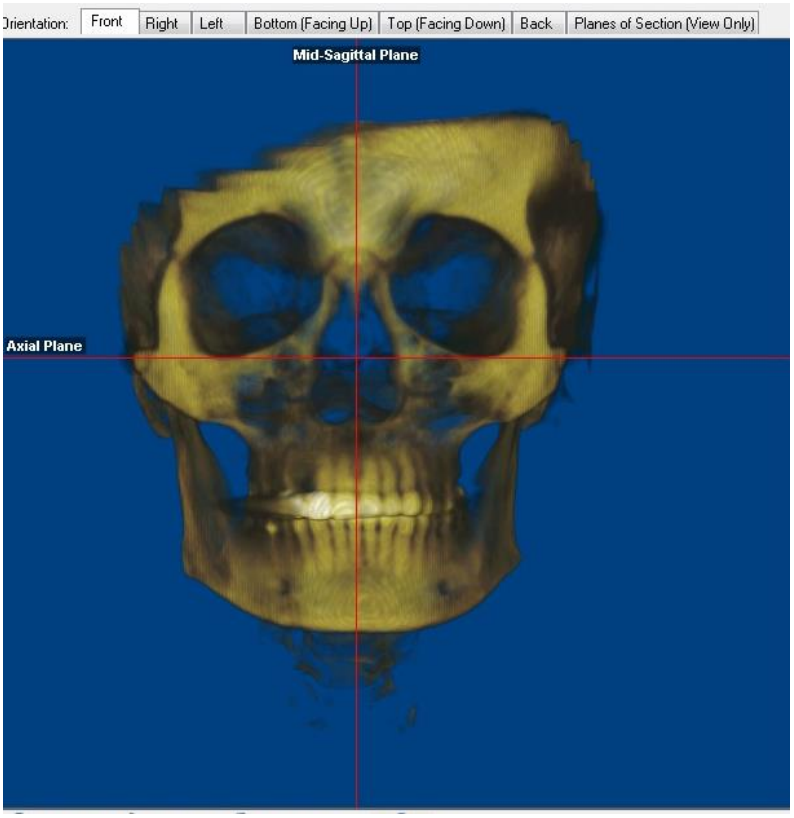


Figure 3. CBCT Measurement Model.

3.2.2 Airway Analysis Protocol

CBCT DICOM data were transferred into Dolphin3D® following these steps: Using the 3D module, click on “import new DICOM”. Next, use the “Orientation Calibration” button to adjust orientation so that the sagittal position is approximated to the perpendicular to FH plane, following the methods of Guijarro-Martínez & Swennen (2013). From the patient’s right side, the head was rotated either clockwise or counterclockwise until the FH plane was parallel to the horizontal reference plane (Figure 4). Next, the midsagittal plane slice was assessed from the coronal view. The vertical reference plane position was centered at point Nasion (N). The head again was rotated either clockwise or counterclockwise so that both orbital rims were coincident with the horizontal reference in this view, as well (Figure 5). Horizontal axial reference lines were made at the FH in the sagittal view and at the level of point Orbitale (Or) from the frontal view. N-vertical from the frontal view was used as a vertical reference. These three references were utilized in order to orient the skull in the 3D software.





Figures 4 and 5. CBCT Orientation Callibration.

Next, the sinus/airway analysis was used to perform airway volumetric, area, and linear measurements. Three volumetric and minimum CSA measurements and nine linear measurements were obtained. In the sinus/airway module, the skull was oriented as predefined. First, the axial slices were browsed manually until the airway was clearly identified and then a measurement area was defined (*i.e.* clipping boundary). These boundaries were defined manually by the operator. Measurements were performed in the nasopharynx, oropharynx, and hypopharynx segments individually.

Within each airway segment that was measured, yellow seed points were placed to identify the airway density to be assessed, which defined the region of interest (Figure 6). The airway sensitivity threshold was adjusted using a sliding scale function. This highlights the airway as a surface. The investigator manually chose the sensitivity based on percentage of airway selected. Noise was minimized while maximal airway volume was selected. This information was assessed by browsing through the airway slices in sagittal and axial views in order to confirm that the appropriate sensitivity was selected.

Figure 6. Clipping Boundary, Seed Point, and Sensitivity Adjustment.

Once complete, the “Update Volume” button was selected to find airway volume measurements, noted as the total airway volume (mm^3). In order to define the region wherein maximal airway restriction is located, the Enable ‘Minimal Axial Area’ button was checked, which highlights this individual slice (mm^2). Next the superior and posterior boundaries, which are identified by horizontal red dashed lines, were identified. The operator moved the red dashed

lines within the confines of the airway segment and clicked the “find” button to obtain the CSA value and location (Figure 7). It is important that these limits were confined to the airway segment outermost boundaries; an inaccurate read may result if positioned too far superior or posterior. Mattos *et al.* (2014) similarly discuss this critical detail in their study, as mentioned in the literature review.

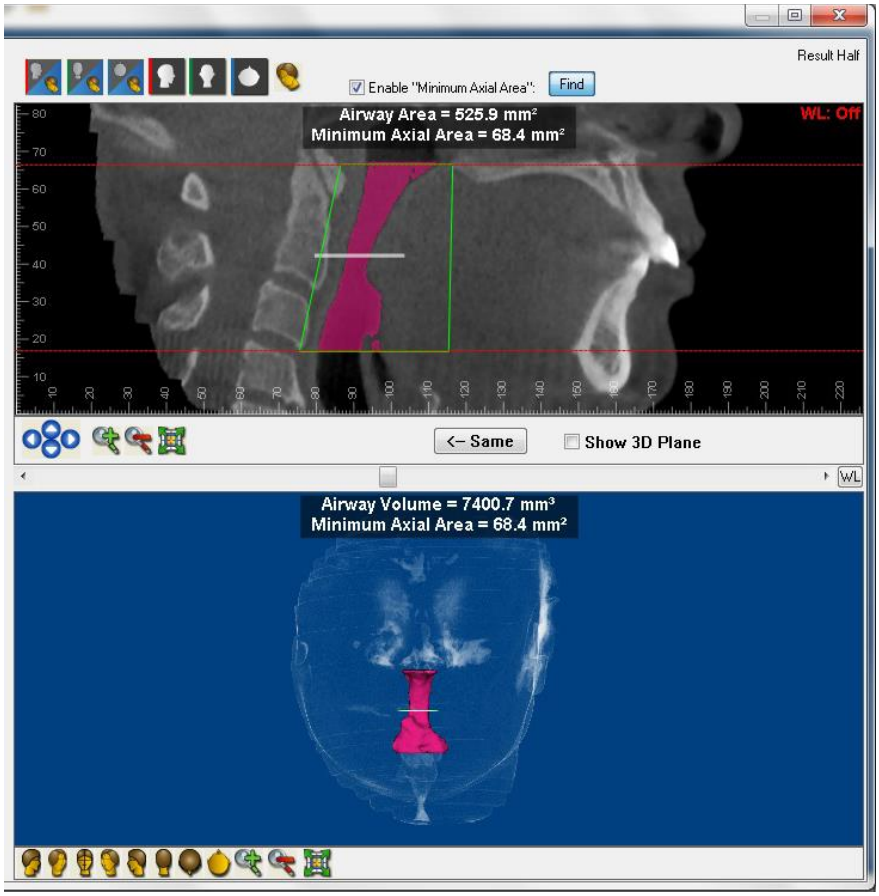


Figure 7. Airway Volume and Minimum CSA Calculation.

Within the confines of the minimal CSA axial slice, two linear measurements were made by the operator. The largest A-P and transverse dimensions were measured (Figure 8). To perform these linear measurements, it was best to use the axial view. In addition, in the sagittal section, the vertical length of the airway segment was measured (Figure 9). Additional measurements included airway total height, which is a summation of the nasopharynx, oropharynx, and hypopharynx lengths, in the sagittal plane. Similarly, airway total volume was calculated as a sum of these three regions. The shape of the ellipse at the level of the minimal CSA was additionally assessed. A shape ratio was defined by dividing the A-P and transverse linear dimensions.

The 2D linear measurement tool was used to make these measurements manually. Zooming in the viewing window was a helpful action for accuracy in these measurements.

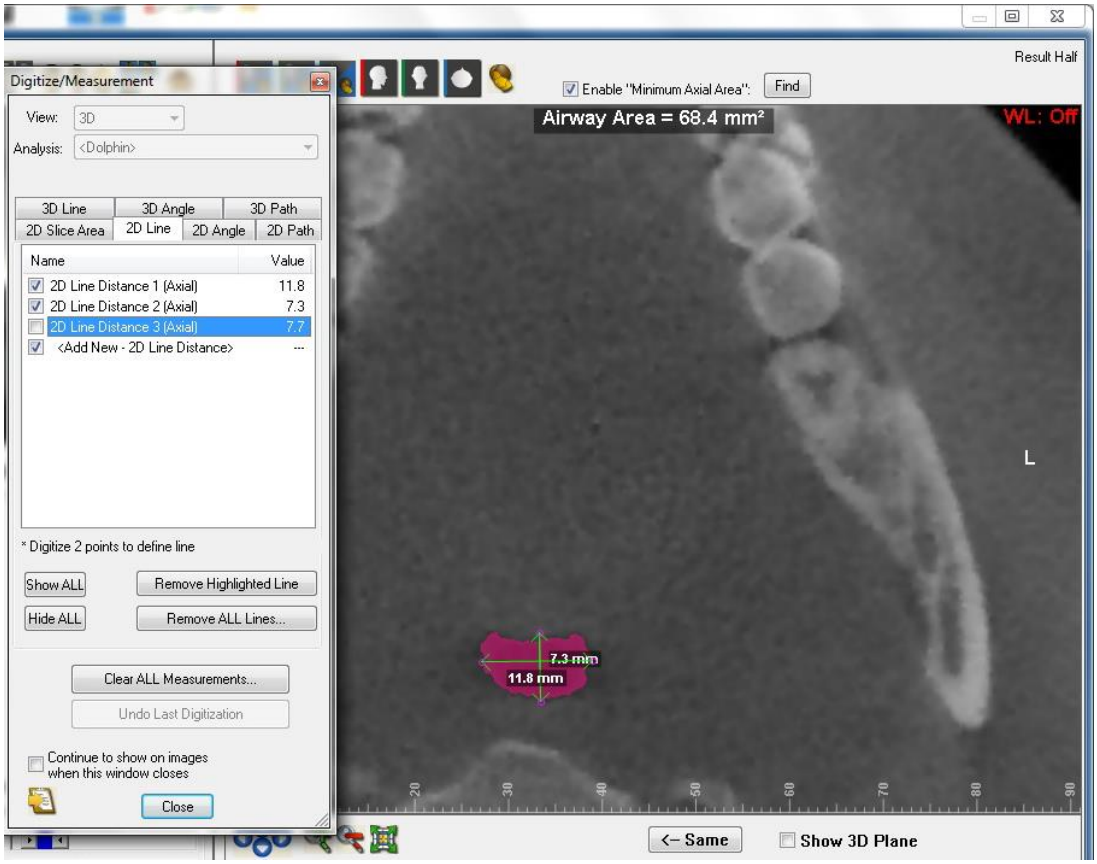


Figure 8. Minimum CSA and A-P and Transverse 2D measurements.

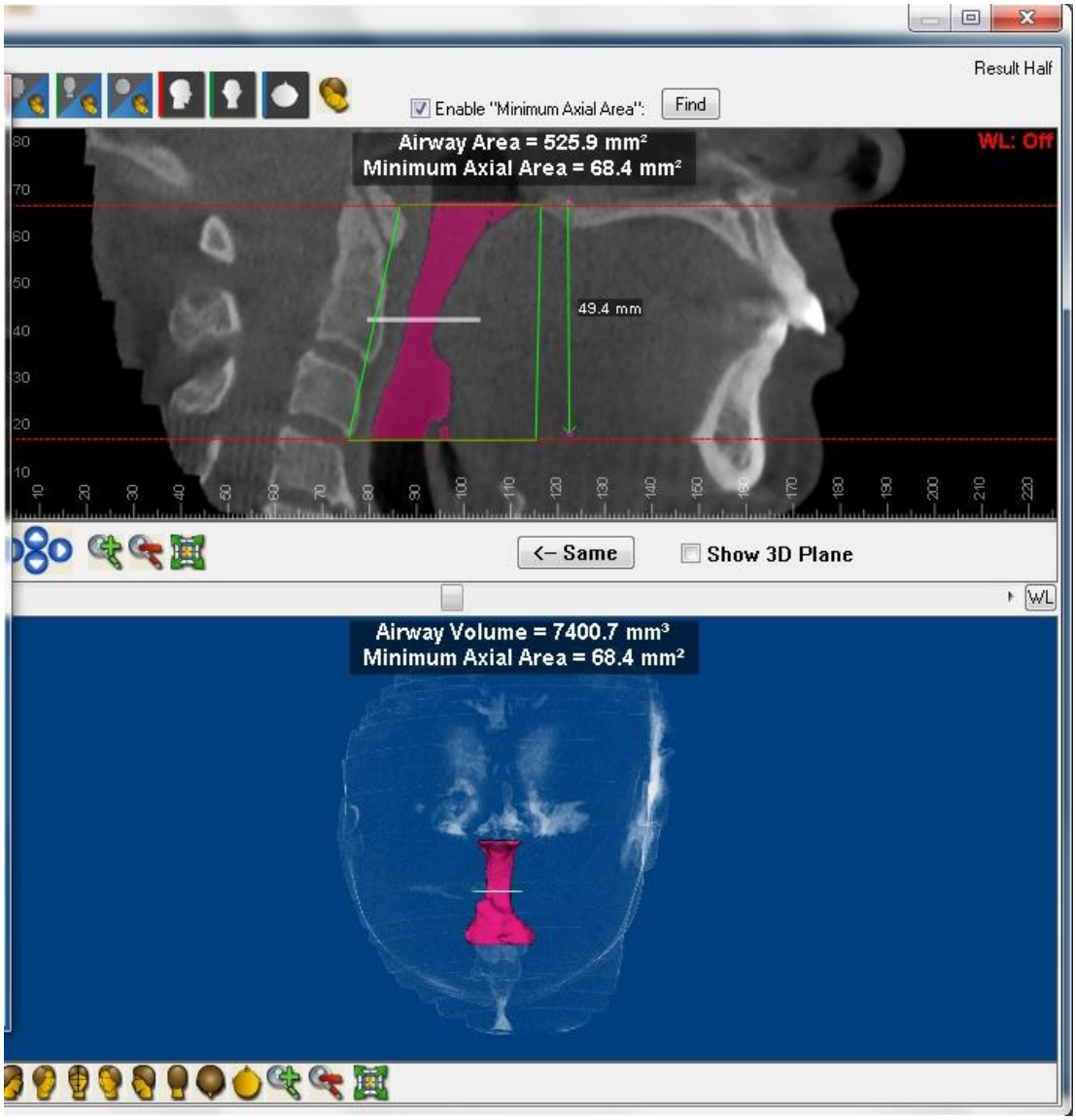


Figure 9. Vertical Measurement of Oropharynx.

3.3 Statistical Analysis

Student's paired t-test, descriptive statistics, Pearson correlation and regression analysis were conducted to investigate how well 2D and 3D airway variables, biometrics, mandibular protrusion and treatment response, individually and/ or in combination were related. Statistically significance was set at $p<0.05$. The paired t-tests based on results from coefficient of correlation were used to assess the test-retest reliability of the airway analysis method used in the study.

To assess whether the initial oropharyngeal 2D and/or 3D airway measurements, biometrics, OSA severity, and mandibular protrusion were associated with MAS treatment response (*i.e.* absolute and/or % change in RDI, NREM RDI, REM RDI, S NREM RDI, NS NREM RDI, S REM RDI, NS REM RDI, and minimum SaO_2), Pearson's correlations coefficients were estimated.

Based on significant coefficients of correlation, simple and multiple regressions were conducted to investigate the best predictors of PSG treatment response variables. A hierarchical method was used to assess how prediction by certain independent variables improved when adding additional variables. The R-squared values and tolerance indices of multicolinearity were inspected to investigate the usefulness of the selected set of PSG predictors. SPSS version 22.0 (IBM, Chicago, IL, USA) was used for the data analysis.

4. RESULTS

A sample of 33 subjects was analyzed for the study. From an original available sample of 40 subjects, five subjects were excluded because the C4ai vertebra were not captured in the diagnostic CBCTs, while two other patients were excluded for lack of follow-up PSGs and having rhinoplasty surgery during the MAS titration period. One detailed PSG report was not retrievable. In addition, because sleep position was not restricted, all sleep position and phase combinations were not observed in all of the PSG recordings. This consequently decreased the sample for these stratified measures. The intra- and inter-rater analyses showed highly significant correlations for all airway measures employed, ($r>0.80$; $p<0.001$).

4.1 Patient Demographics and Descriptive Statistics

Of the 33 participants in this study, 23 (69.7%) were male and 10 (30.3%) were female. There were 10 (30.3%), 15 (45.5%), and 8 (24.2%) patients initially diagnosed with mild, moderate, and severe OSA, respectively. When assessing the airway, in 22 patients (66.7%), the minimal CSA was located within the oropharynx. Five (15.2%) patients' minimal CSA were found in the nasopharynx, and six (18.2%) were found in the hypopharynx. Furthermore, the CSA ellipse shape illustrated a wider transverse dimension than A-P dimension. Descriptive statistics and frequencies are displayed in TABLE II and TABLE III.

TABLE II. DESCRIPTIVE STATISTICS

	N	Min.	Max.	Mean	Standard Deviation
Minimum CSA (mm^2)	33	14.40	112.00	63.18	24.10
Shape Ratio	33	0.15	2.93	0.61	0.46
Total Length (mm)	33	78.80	105.10	91.56	7.19
Total Volume (mm^3)	33	10507.70	32868.20	21660.65	6048.28
Total Protrusion (mm)	33	5.30	16.00	9.96	2.76
Age (years)	33	28.70	67.30	51.11	9.89
Neck Circumference (cm)	33	34.00	48.00	39.52	4.07
Initial BMI	33	20.82	38.42	27.98	4.54
Change in RDI	33	-62.60	4.80	-16.54	14.27
% Change RDI	33	-91.79	31.17	-58.06	29.79
Change NREM RDI	33	-69.00	6.10	-16.38	15.21
% Change NREM RDI	33	-95.27	84.72	-61.75	38.80
Change REM RDI	32	-54.50	20.00	-15.16	19.09
% Change REM RDI	31	-96.75	142.86	-31.02	53.90
Change S NREM RDI	28	-83.60	62.00	-20.59	27.57
% Change S NREM RDI	28	-100.00	413.33	-39.74	100.63
Change NS NREM RDI	31	-72.80	2.80	-12.03	17.31
% Change NS NREM RDI	26	-100.00	375.00	-56.91	93.45
Change S REM RDI	25	-104.60	37.50	-28.39	33.42
% Change S REM RDI	19	-97.70	74.29	-51.32	45.73
Change NS REM RDI	26	-45.90	33.20	-11.10	18.40
% Change NS REM RDI	21	-100.00	325.00	-23.18	104.32
Change Min SaO2 (%)	33	-8	37	4.33	8.48

TABLE III. FREQUENCIES

		Frequency	Percent	Valid Percent	Cumulative Percent
Location of Minimum CSA	Nasopharynx	5	15.2	15.2	15.2
	Oropharynx	22	66.7	66.7	81.8
	Hypopharynx	6	18.2	18.2	100.0
	Total	33	100.0	100.0	
Gender	Male	23	69.7	69.7	69.7
	Female	10	30.3	30.3	100.0
	Total	33	100.0	100.0	
Initial OSA Severity	Mild	10	30.3	30.3	30.3
	Moderate	15	45.5	45.5	75.8
	Severe	8	24.2	24.2	100.0
	Total	33	100.0	100.0	

4.2 **Initial Airway Measurements, Biometrics, OSA Severity, Total Protrusion, and MAS Treatment Response**

Statistically significant associations were found in MAS treatment response variables including: change in RDI, change in NREM RDI, change in

NS NREM RDI, % change in NS NREM RDI, change in S NREM RDI, % change in S NREM RDI, and change in S REM RDI. The bivariate associations were with minimum CSA, location of minimum CSA, total volume, initial neck circumference, initial BMI, initial OSA severity, and total protrusion. The range of the coefficient of correlations (r) and p-values ranging from: -0.74 to 0.47 and 0.046 to <0.001, respectively. No statistically significant associations with change in min SaO_2 were found (TABLE IV).

TABLE IV. SIGNIFICANT BIVARIATE TREATMENT RESPONSE ASSOCIATIONS

Bivariate correlations	Coefficient of Correlation (r)	P-value
Change NS NREM RDI and Minimum CSA	0.37	0.039
Change NS NREM RDI and Initial Neck Circumference	-0.50	0.004
Change NS NREM RDI and Initial BMI	-0.51	0.003
Change NS NREM RDI and Initial OSA Severity	-0.53	0.002
% Change NS NREM RDI and Location of Minimum CSA	0.44	0.026
% Change NS NREM RDI and Total Protrusion	0.45	0.023
Change S NREM RDI and Total Volume	0.42	0.028
Change S NREM RDI and Initial OSA Severity	-0.49	0.008
Change S REM RDI and Total Volume	0.40	0.046
Change in RDI and Initial OSA Severity	-0.74	<0.001
Change NREM RDI and Initial OSA Severity	-0.68	<0.001
% Change S NREM RDI and Initial BMI	0.47	0.011

Based on these significant coefficients of correlations, simple and multiple regressions were conducted to investigate the best predictors of PSG variables. A hierarchical method was used to assess how prediction by certain independent variables improves on the prediction by adding other variables.

A simple linear regression was conducted to investigate how well initial OSA severity predicts change in RDI. The result was statistically significant: F (1, 31) = 36.888, p-value<0.001. The identified equation to understand this relationship was change in RDI= 10.75-(14.07*initial OSA severity). The adjusted R^2 value was 0.53. This indicates that 53% of the variance in change in RDI was accounted for by the variance in initial OSA severity.

A multiple regression was conducted to investigate how a combination of initial OSA severity and total volume predicts change in RDI. The result F (2, 30) = 18.398, indicates that the combination of these variables significantly (p-value<0.001) predicts change in RDI. The adjusted R^2 value was 0.52. This indicates that 52% of the variance in change in RDI was accounted for by the variance in initial OSA and total volume. Only initial OSA severity significantly predicted change in RDI, p<0.001.

A simple regression was conducted to investigate how well initial OSA severity predicts change in NREM RDI. The results were statistically significant F (1, 31) = 26.334, p-value<0.001. The identified equation to understand this

relationship was change in NREM RDI= 10.35 - (13.79*initial OSA severity). The adjusted R^2 value was 0.44. This indicates that 44% of the variance in change in NREM RDI was accounted for by the variance in initial OSA severity.

A multiple regression was conducted to investigate how a combination of initial OSA severity, total protrusion, total volume, and location of minimum CSA predicts change in NREM RDI. The results, $F(4, 28) = 6.146$, indicates that the combination of these variables significantly predicts change in NREM RDI, (p-value=0.001). The adjusted R^2 value was lower at 0.39 and, only initial OSA severity significantly predicted change in NREM RDI, $p<0.001$.

A multiple regression was conducted to investigate how a combination of initial OSA severity and total volume, predicts change in S NREM RDI. The results, $F(2, 25) = 6.403$, indicates that the combination of these variables significantly predicts change in S NREM RDI, (p-value=0.006). The adjusted R^2 value was 0.29. Only initial OSA severity significantly predicted change in S NREM RDI, (p-value=0.019) when both variables are included in the regression. Change in S NREM RDI was also predicted from a combination of initial OSA severity, initial BMI, initial neck circumference and total volume, $F(4, 23) = 4.961$, p-value= 0.005. The adjusted R^2 value was 0.37. In this model, only total volume and initial BMI significantly predicted the change in S NREM RDI when all four variables were included, p-value=0.010 and 0.039, respectively. Adding the variable combination showed higher R^2 change.

A simple regression was conducted to investigate how well initial BMI predicts % change in S NREM RDI. The results were statistically significant *F* (1, 26) = 7.409, p-value=0.011. The identified equation to understand this relationship was % change in S NREM RDI= -327.79+(-10.252*initial BMI). The adjusted R^2 value was 0.22. This indicates that 22% of the variance in % change in S NREM RDI was accounted for by the variance in initial BMI.

A multiple regression was conducted to investigate how a combination model predicted the % change in S NREM RDI from a combination of initial BMI, initial OSA severity, location of minimum CSA, and total volume; F (4, 23) = 5.294, p-value=0.004. The adjusted R^2 value was 0.39, and initial BMI and total volume significantly predicted % change in S NREM RDI, ($p<0.001$ and 0.017), respectively. Adding the combination of these variables showed higher R^2 change.

A simple regression was conducted to investigate how initial OSA severity predicts change in NS NREM RDI. The results were statistically significant F (1, 29) = 11.027, p-value= 0.002. The adjusted R^2 value was 0.25. This indicates that 25% of the variance in change NS NREM RDI was accounted for by the variance in initial OSA severity.

Multivariate regression was performed, assessing the change in NS NREM RDI in combination with minimum CSA, neck circumference, initial BMI, and initial OSA severity; $F(4, 26) = 6.457$, p-value= 0.001. The adjusted R^2 value was 0.42 and higher than the previous adjusted R^2 in the regression with only initial OSA severity variable. This indicates that 42% of the variance in change NS NREM RDI was explained by the combination from these four variables: minimum CSA, neck circumference, initial BMI, and initial OSA severity model. But, only initial OSA severity significantly predicted change in NS NREM RDI when all four variables were included ($p=0.007$).

A model that explained % change in NS NREM RDI from a combination of location of minimum CSA and total protrusion was significant; $F(2, 23) = 4.871$, p-value= 0.017. The adjusted R^2 value was 0.24. However, both variables did not significantly predict % change in NS NREM RDI, ($p>0.05$). Adding different combinations from the independent variables showed similar results.

A model to predict change in S REM RDI from total volume did not show significance, $p>0.05$. Adding different combinations from the independent variables did not indicate any improvement on the results of the regression. Initial OSA severity was identified to be a predictor for the majority of the PSG variables. The multivariate regression results indicated that only change in S NREM RDI and % change in S NREM RDI may significantly be explained by the combination of two variables: total volume and initial BMI (TABLES V AND VI).

TABLE V. MULTIVARIATE REGRESSION RESULTS

Dependent Variable	Independent Variables	Correlation Model Summary			ANOVA			Coefficients
		R	R Square	Adjusted R Square	df	F	Sig.	Sig.
Change in RDI	Total Volume	0.74	0.55	0.52	2, 30	18.398	<0.001	0.484
	Initial OSA Severity							<0.001
Change in NREM RDI	Total Protrusion	0.68	0.47	0.39	4, 28	6.146	0.001	0.545
	Total Volume							0.758
	Location of Min. CSA							0.702
	Initial OSA Severity							<0.001
Change S NREM RDI	Total Volume	0.58	0.34	0.29	2, 25	6.403	0.006	0.064
	Initial OSA Severity							0.019
Change S NREM RDI	Neck Circumference	0.68	0.46	0.37	4, 23	4.961	0.005	0.201
	Initial BMI							0.039
	Total Volume							0.010
	Initial OSA Severity							0.080
% Change S NREM RDI	Initial BMI	0.69	0.48	0.39	4, 23	5.294	0.004	<0.001
	Total Volume							0.017
	Location of Min. CSA							0.147
	Initial OSA Severity							0.143
Change NS NREM RDI	Min. CSA	0.71	0.50	0.42	4, 26	6.46	0.001	0.144
	Neck Circumference							0.866
	Initial BMI							0.171
	Initial OSA Severity							0.007
% Change NS NREM RDI	Total Protrusion	0.55	0.30	0.24	2, 23	4.87	0.017	0.085
	Location of Min. CSA							0.074

TABLE VI. SELECTED MODELS

	Dependent Variable	Model Equation
Multivariate Models	% Change in S NREM RDI	–724.672 + (0.008 * Total Volume) – (32.831 * Initial OSA Severity) + (17.337 * Initial BMI) + (39.995 * Location of Min. CSA)
	Change in S NREM RDI	-51.635 + (0.002 * Total Volume) + (12.349 * Initial OSA Severity) + (3.772 * Initial BMI) – (2.561 * Neck Circumference)

4.3 Additional Findings

There were two airway relationships that were associated. A statistically significant high correlation found was between total volume (mm^3) and minimum CSA (mm^2), $r = 0.733$, $p<0.001$ (TABLE VII, Figure 10). Additionally, a statistically moderate significant correlation found was between total protrusion and location of minimum CSA, $r = 0.457$, $p=0.008$ (TABLE VIII, Figure 11).

TABLE VII. CORRELATIONS

		Total Volume (mm^3)
Minimum CSA	Pearson Correlation	.733
	Sig. (2-tailed)	.000
	N	33

TABLE VIII. CORRELATIONS

		Protrusion (mm)
Location of Minimum CSA	Pearson Correlation	.457
	Sig. (2-tailed)	.008
	N	33

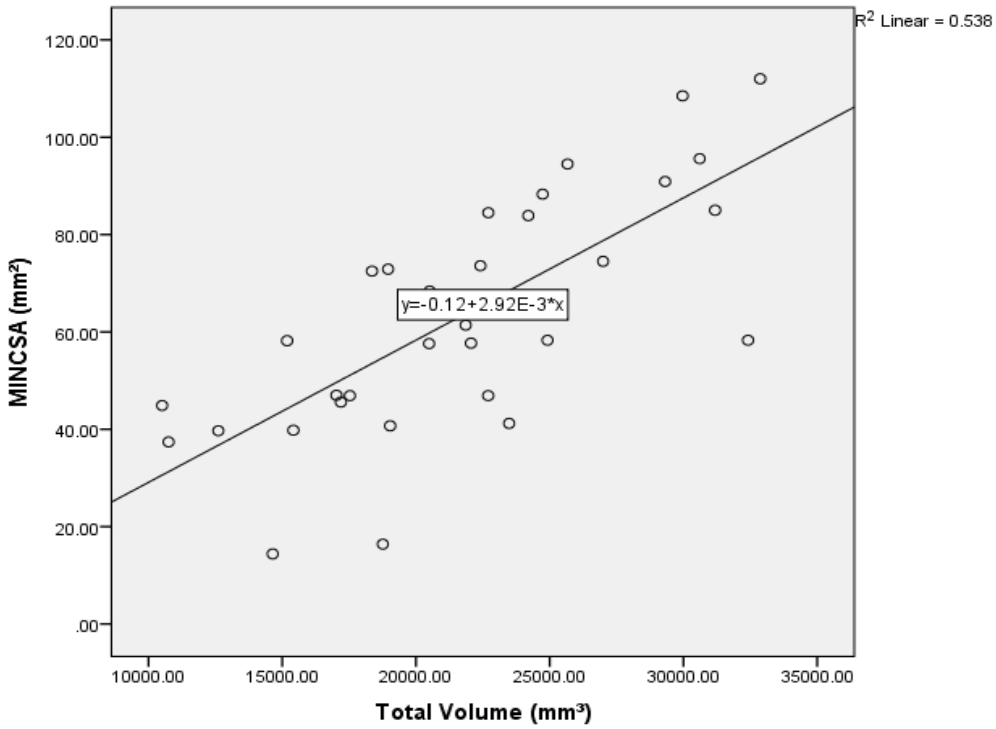


Figure 10. Linear Regression Model Predicting Minimal CSA and Total Volume

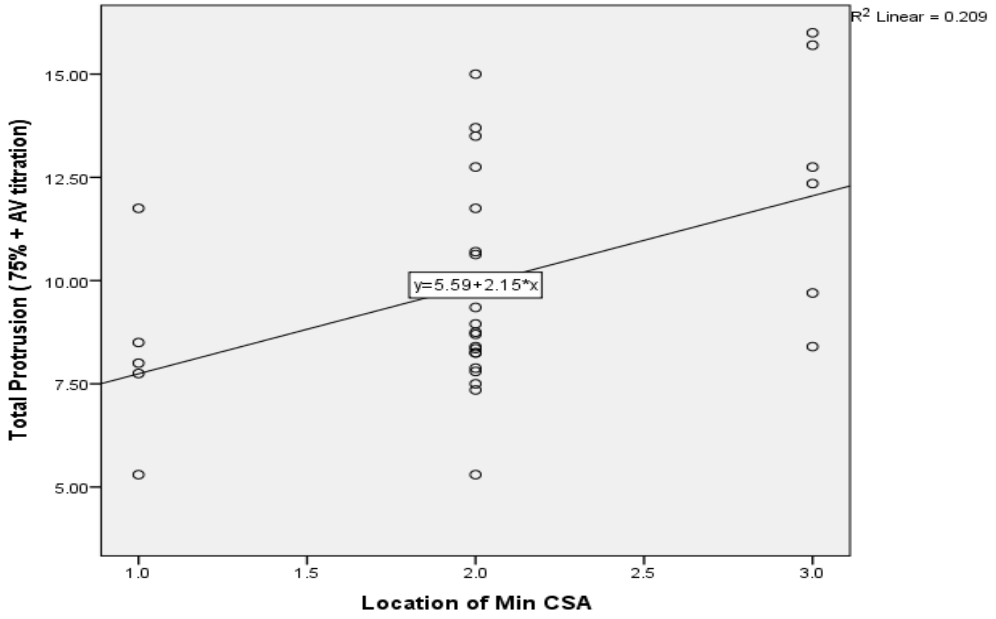


Figure 11. Linear Regression Model Predicting Total Protrusion and Location of Minimum CSA

5. DISCUSSION

The aim of this study was to identify 2D and 3D features of the airway, along with the amount of mandibular protrusion, initial OSA severity, BMI, neck circumference, and sleep characteristics that may explain MAS treatment response. There is limited and conflicting information in the literature in regards to predictors of MAS therapeutic response. Most studies comprise 2D assessments of the airway based on lateral cephalometry. Furthermore, many 3D studies evaluate airway changes with treatment but lack follow-up PSG studies, which directly measure the clinical outcome of MAS treatment. This study includes the combination past customary measures as well as contemporary 3D measurements in the determination of treatment response. A follow-up CBCT to assess changes in the airway with the MAS appliance was not performed, but this sort of evaluation has been documented in the literature.

The majority of participants (75.8%) in the study were initially diagnosed as mild to moderate apneics, which is a representative sample of the recommended treatment population of OSA with MAS therapy according to the AADSM (1999). Although taken in the awake state, the CBCTs were taken in the supine position, which is important to consider in terms of simulating airway anatomic features. The NewTom CBCT is ideal for OSA studies, since it is the only machine that assesses patients in the supine position (Enciso *et al.*, 2010). As mentioned by Camacho *et al.* (2014), there are decreases in overall airway

volume and minimal CSA in the supine position at the levels of the PNS, uvula tip, retrolingual region, and tongue base. Sutthiprapaporn *et al*. (2008) also saw a decrease in minimum CSA in the supine position, when compared to upright. When assessing the airway based on lateral cephalometry, a comparison of upright to supine positioning illustrated A-P reductions in the velopharynx region (Tsuiki *et al.*, 2013).

The value of the minimum CSA was strongly correlated with total airway volume. This suggests that overall airway form is proportionally distributed. In addition, the location of the minimum CSA within the pharyngeal airway was statistically significant, most commonly located in the oropharynx. This is consistent with the literature (Enciso *et al.*, 2010). Based on these associations, measuring total airway volume may aid in assessing airway anatomy in terms of the site of airway constriction as well as the relative amount of constriction. OSA patients exhibit an overall decrease in airway volume, as well as a decreased A-P dimension at the location of the minimum CSA (Ogawa *et al.*, 2005). Similarly, the upper airway in OSA patients has been shown to be more elliptical when compared to non-OSA patients (Enciso *et al.*, 2010), which was a consistent feature with our study sample. 32 of the 33 patients exhibited a wider ellipse in the transverse dimension. Nevertheless, airway shape did not illustrate any predictive relationships with MAS treatment response.

5.1 **Airway Variables and MAS Treatment Response**

There were 12 statistically significant correlations with treatment response. There were no associations with change in minimum SaO_2 as a treatment response measure. Of these correlations, one was in terms of change in RDI, one was in terms of change in NREM RDI, six were change or % change in NS NREM RDI, three were change or % change in S NREM RDI, and one was in terms of change in S REM RDI.

It is important to consider that there were more data and evidence during NREM apneic events. More time is spent in NREM sleep; therefore less data were collected in REM sleep phase when calculating RDI. This makes REM data less accurate and more variable. NREM information is a more accurate estimate of RDI in a limited sample size with two PSG reports, there are less missing data in NREM, as well. This may explain why there was only one significant correlation in REM sleep, when stratifying by sleep phases. Additionally, the analyses were also limited by the PSG report stratification based on sleep center variability; many reports did not illustrate RDI in terms of sleep position alone, but stratified by sleep phase, then position.

Initial OSA severity was negatively correlated with RDI changes in four measures: change in NS NREM RDI, change in S NREM RDI, change in NREM RDI, and change in RDI. As mentioned, REM data are limited, and may explain why there was not a significant relationship extracted when controlling for REM

sleep phase only. Based on these negative correlations, RDI measures decrease as OSA severity increases, suggesting that an absolute treatment response is greater in more severe apneics. However, it is also important to assess % change, especially since data is limited in sample size. This removes the linear effect that is illustrated when explaining a relationship based on initial OSA severity. Consequently, a relative proportional response potential is measured when assessing % change, which controls for initial OSA severity (*i.e.* changes in relation to baseline RDI).

When assessing % changes, there were three significant bivariate correlations. In regards to % change in NS NREM RDI, there was a positive correlation with the location of minimum CSA and with total protrusion. Meanwhile, % change in S NREM RDI was positively associated with initial BMI. These three relationships indicate that there may be greater treatment capacity for patients with a lower initial BMI, more superiorly located minimum CSA, and decreased amount of mandibular protrusion. On a related note, Hoekema *et al.* (2007) also saw that smaller BMI values were predictive of RDI < 5 with MAS treatment.

Positive correlations suggest a decreased treatment response when measured in terms of absolute change and % change in RDI. Interestingly, there was a positive correlation between change in NS NREM RDI and the value of the minimum CSA. While this was the weakest correlation in the results (r=0.37),

this suggests that those who are more constricted initially may have a better absolute treatment response in terms of apneic events during NS NREM sleep.

Another surprising finding was that the amount of protrusion was positively correlated with % change in NS NREM RDI. As this does not correspond with a positive treatment response, as in overall reduction in RDI, one may infer that patients who tolerated higher amounts of titration may have a decreased treatment response capacity.

Change in S NREM RDI and S REM RDI were both positively correlated with initial total airway volume. Although change in S RDI was not directly documented in the PSG reports, we can infer from the above correlations that S RDI change was correlated with total airway volume. While correlations with total airway volume were significant in the supine position in both NREM and REM sleep phases, this relationship was not present in non-supine sleep. The positive correlation suggests that, while in the supine sleep position, larger initial airway volume measures, which were also measured in the supine posture may reflect decreased therapeutic potential for mandibular advancement therapy. This interpretation is plausible, as individuals with relatively normal airway volume at baseline would not be expected to benefit as much from mandibular repositioning.

There is also a positive correlation for initial BMI and the % change in S NREM RDI. Therefore, when controlling for initial OSA severity, in the supine position, patients with higher BMIs had decreased improvement in treatment response, as well. These results suggest that, for any given initial OSA severity, individuals with a higher BMI are likely to show less improvement with MAS. This is reasonable because BMI correlates with parapharyngeal fat depositions, which may impair the improvement that is expected from MAS therapy. According to Lee *et al.* (2014), supine RDI is twice as severe compared to lateral sleep RDI, wherein obstruction was primarily found at the soft palate, followed by tongue base, lateral wall, and larynx. This is further supported by Oksenberg *et al.* (2010) who demonstrated that S REM RDI > S NREM RDI > NS REM RDI > NS NREM RDI, in which supine sleep has increased frequency and severity of abnormal breathing events. MAS therapy, by design, advances the tongue, and alleviates this site of obstruction. When controlling for initial OSA severity, patients with increased BMI while sleeping in the supine position may not be able to overcome the anatomical burden as effectively as individuals with lower BMI. As a result, MAS therapy may not reach its potential effectiveness.

Initial BMI had a positive correlation with % change in S NREM RDI and a negative correlation with change in NS NREM RDI. Initial neck circumference also had a negative correlation with change in NS NREM RDI. This suggests the possibility that increased BMI, which is an indirect measure of increased presence of soft tissue volume, has a detrimental effect on treatment response

especially in the supine position. Several soft tissue structures have been shown to be affected by gravity on soft tissue structures, including the soft palate, epiglottis and entrance to the esophagus moved posteriorly and rostrally when supine (Sutthiprapaporn *et al.,* 2008). In the non-supine position, primary sites of obstruction occur at the oropharyngeal lateral walls (Lee *et al.*, 2014). In regards to increased soft tissue in terms of BMI or neck circumference, MAS treatment may enhance treatment response in the non-supine position by relieving obstruction of the oropharyngeal walls.

5.2 **Multivariate Regression Models of MAS Treatment Response**

There were seven significant explanatory models that enhanced the understanding of MAS treatment response. None of the multivariate models significantly explained REM RDI treatment response. As previously mentioned, this is likely due to the decreased data and information assessed during REM sleep in the PSG, which limits accuracy and statistical power. Since more sleep time occurs in the NREM phase, there is less missing data. As a result, NREM treatment responses may be more accurately estimated in the present study. One model significantly describes treatment-related change in RDI, another describes change in NREM RDI, respectively; while two models account for changes in S NREM RDI, one model accounts for % change in S NREM RDI, one model explains for change in NS NREM RDI and finally one model expresses % change in NS NREM RDI. As supine apneic events are more severe and frequent (Lee *et al.*, 2014), it is noteworthy that many of these models

predict S NREM RDI. Four of the models include initial OSA severity as the only significant independent variable in the model. Initial OSA severity is used as a widespread clinical indicator and predictor of treatment response (Ferguson *et al.* 2006), which is reinforced in many of the regression models as it was a significant contributor. In the models explaining change in S NREM RDI as well as % change in S NREM RDI, both initial BMI and total airway volume were the two significant predictors. Meanwhile, the model explaining % change in NS NREM RDI was significant, but the independent variables as predictors were not significant.

The bivariate correlations explain about 10-25% of the variance in relationship to MAS treatment response. When adding variables in the multivariate models, there is an improvement in explaining about 23-52% of the treatment response variance. In the strongest model, initial OSA severity and total volume explained 52% of the variance in change in RDI (r^2=0.52), which was most strongly predicted by initial OSA severity. Change in RDI was negatively associated with initial OSA severity, while total volume exhibited positive correlations with changes in supine RDI; this suggests that patients with smaller airway volumes and increased OSA severity at baseline may exhibit a greater amount of treatment response potential with MAS treatment.

In regards to change in NREM RDI, initial OSA severity, total protrusion, total volume, and the location of the minimum CSA contributed to this model.

Again, initial OSA severity was the significant predictor. Similar to overall RDI, this suggests that initial OSA severity corresponds to increased improvements in NREM RDI with MAS treatment. When stratified into change in NS and S NREM RDI, two models also include initial OSA severity as a significant explanatory variable.

In the multivariate models, total volume significantly contributed to regressions in change and % change S NREM RDI as well as total RDI. Both the total volume in combination with initial BMI significantly contributed to the two regressions involving change in S NREM RDI and % change in S NREM RDI. Initial BMI positively correlated with % change in S NREM RDI, and volume also positively correlated with change in S NREM RDI. This suggests that there are decreases in absolute and relative treatment response potential in terms of S NREM RDI based on these two features. In addition, Dieltjens *et al.* (2014) demonstrated that MAS therapy affects supine-dependent OSA, in particular. Prevalence of sdOSA initially ranged from 27-67%, which decreased to 17.5-33.9% after MAS treatment. As previously mentioned, Hoekema *et al.* (2007) saw that smaller BMI values were predictive of RDI < 5 with MAS treatment. Therefore, patients with an initially smaller BMI and airway volume may have enhanced treatment outcome potential with MAS treatment, particularly in the supine position. This combination of features may help explain MAS therapeutic mechanisms. We propose that mandibular advancement therapy will have a proportionately diminishing response based on initial airway volume and BMI.

This may due to a higher absolute potential to increase the airway dimension through MAS therapy with an initially smaller airway volume, especially if coupled with a lower BMI and consequently decreased soft tissue obstructors. This suggests a poorly positioned (*i.e.* retrognathic) mandible. A well-positioned jaw is more likely associated with a more optimized airway volume and minimal CSA. Through the mechanism of MAS, a well-positioned jaw may have lesser therapeutic potential. Having a follow-up CBCT comparative assessment of the airway with MAS appliance in place would help validate this conjecture.

In the supine position, OSA patients have been shown to have decreases in total airway volume and CSA at the uvula tip, retrolingual region, and tongue base (Camacho *et al.*, 2014). This was attributed to the effect of gravity and tissue laxity. Lee *et al.* (2014) also saw that when comparing supine to lateral positions, the most significant changes in obstruction sites were in the tongue base and larynx regions, regardless of OSA severity. Soft tissue measures are related to BMI assessments, indirectly speaking. OSA patients have a genetic predisposition to regional fat distribution surrounding the upper airway (Schwab, 2005). The presence of adipose tissue in the pharyngeal airway increases collapsibility (Shelton *et al.*, 1993). It has been shown that pharyngeal fat increases with age, as well (Bixler *et al.*, 1998). Decreased amounts of soft tissue will also enhance therapeutic effect, as the presence and effect of these soft tissue obstructers will be diminished. Therefore, patients who may have decreased airway volumetric dimensions due to retrognathia (*i.e.* skeletal

causes) rather than obesity (*i.e.* soft tissue causes) may have a better treatment response to MAS treatment, especially when in the supine position.

The location of the minimum CSA was positively correlated with the amount of total protrusion. Ferguson *et al.* (2006) show that the amount of MAS advancement is associated with treatment response. This additionally implies that the mechanism of MAS and orofacial anatomy are intertwined, as tongue muscles are repositioned more anteriorly (Chan *et al.*, 2010). Based on MAS appliance mechanism, our results reinforce that MAS treatment is most optimal for treating airway constriction that is located in the less inferior regions of the airway.

In addition, both the location of the minimum CSA as well as amount of total protrusion were individually significant in correlating to % change in NS NREM RDI, as well as correlating in a multivariate explanatory model. Consequently, based on MAS mechanics and these findings, it is possible that more inferiorly located regions of airway constrictions may require increased anterior repositioning of the tongue base to achieve a desirable clinical outcome. However, both the location of the minimal CSA and amount of total protrusion were positively correlated to % change in NS NREM RDI. Since the % change removes initial OSA severity as a factor, this suggests it may be more difficult to achieve a desirable clinical outcome when the location of airway constriction is in

lower aspects of the airway or when an increased amount of protrusion is required.

It has been documented that increases in mandibular advancement are associated with enhanced treatment outcome (Almeida *et al.*, 2002; Kato *et al*., 2000; Marklund *et al*., 1998). Several studies show that MAS treatment increases upper airway volume, especially in the velopharynx region (Liu *et al.*, 2000; Tsuiki *et al.*, 2001; Chan *et al.*, 2010). Velopharynx pertains to the airway region in vicinity of the velum/soft palate, a soft-tissue landmark; the velopharynx is inclusive of the oropharynx, which we based on bony landmarks. Haskell *et al*. (2009) witnessed the largest changes in the airway with MAS advancement at the level of the C2 vertebra, which corresponds with our definition of the oropharynx. Since the MAS treatment targets the airway posterior to the soft palate, further protrusion in a patient with constricted hypopharynx may lead to less optimum results.

5.3 **Limitations and Future Research Considerations**

Participants elected MAS treatment over CPAP, allowing for potential of sample bias. More than one sleep center was used for initial and follow-up MAS PSGs, which may lead to decreased standardization in technique and PSG recording. Initial and follow-up sites for an individual patient varied in some instances. This may lead to errors that are resultant of different PSG sensitivities or differences in manual scoring the studies. Furthermore, the time lapse

between baseline and follow-up recordings was not standardized, which ranged from 28-263 days. A more immediate follow-up after titration would have been preferable. A post-titration CBCT would also provide information to better understand MAS treatment mechanics and restrictions.

There were limitations with both the software and DICOM image quality of the CBCTs. The NewTom 3G is an older machine, possibly accounting for the grainy quality and lack in sharp soft tissue detail in the CBCTs. Consequently, defining the airway density in Dolphin3D ® was challenging, particularly in the nasopharynx. This seems to be a common challenge in other studies, as well. Obtaining a most complete airway density without voids led to the selection of noise that was outside the confines of the pharyngeal airway. While the user may visibly discern the airway boundaries, since the software is semi-automated it was not possible to manually select and adjust the density threshold to the desired precision. This limitation leads to a source of error in volumetric measurements of the airway. In particular, the nasopharynx region illustrated the largest discrepancy due to the complex nature of the airway anatomy, which has been observed in past literature, as well (El and Palomo, 2010). The authors note that segmentation technique is highly reliable, but has poor accuracy. Weissheimer *et al.* (2012) additionally witnessed that all segmentation softwares that they assessed underestimated the oropharynx when compared to a known standard. Additionally, based on possible differences in CBCT settings or techniques, sensitivity thresholds were not consistent. Lack of calibration of

scanning protocol in conjunction with establishing software threshold sensitivities has been identified in the literature, as well (Alves *et al.*, 2012). In future studies, it would be useful to develop a standardized protocol with better quality CBCTs. Additionally, developments in the airway software wherein the operator can manually eliminate noise or select unidentified airway segments would be helpful.

Future studies with a larger sample size would be helpful to reinforce the validity of this study's findings. In addition, a non-OSA group as a control could be useful in understanding these connections. However, it may be difficult to justify obtaining CBCT studies on this patient population.

5.4 **Conclusions**

Oropharyngeal 2D and 3D airway variables including total volume, location, and value of the minimum CSA were associated with treatment response in terms of change and % change in RDI. Significant relationships were also found when RDI was stratified based on sleep phase, sleep position, and initial OSA severity. Changes in minimum SaO_2 were not related to any airway features or changes in treatment response. There also were correlations between dental protrusion and initial biometrics with treatment response variables. Multivariate models explained treatment response, wherein initial OSA severity was demonstrated as a primary predictor in four models, and the combination of total airway volume and initial BMI were additional predictors in two models.

Patients with higher initial OSA severity may have increased treatment response to MAS therapy. Patients with decreases in total airway volume due to a skeletal rather than a soft tissue obstruction may also be better MAS treatment responders. Since MAS targets upper airway, more inferiorly located airway constriction requires increases in MAS titration to achieve a desirable clinical outcome, but ultimately decreased treatment response potential. Future studies are indicated to further explore these associations.

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APPENDIX A

1. Ethics Approval from University of Sydney

Professor M Ali Darendeliler BDS PhD DipOrth CertifOrth PrivDoc MRACDS (Orth)
Professor and Chair ASO-NSW, Discipline of Orthodontics
Head, Department of Orthodontics, Sydney Dental Hospital, SSWAHS

26th November 2012

Department of Orthodontics
M/C 841
College of Dentistry
University of Illinois at Chicago
801 South Paulina Street
Chicago, IL 60612-7211

Re: Ethics Approval for Research

Dear Sir/Madam

I confirm that Dr. Whitney Mostafiz visited the Discipline of Orthodontics, University of Sydney in March-May 2012 to be involved with a research protocol. Dr. Mostafiz's research topic is: **Influence of oral cavity volume on oral appliance treatment outcome in obstructive sleep apnea**, which was conducted under my supervision. Dr. Mostafiz performed lateral cephalometric analyses from converted CBCT images on obstructive sleep apnea patients. We obtained ethics approval to include Dr. Mostafiz in the research protocol. Data were deidentified and a department statistician performed intra-rater reliability.

I give full permission for Dr. Mostafiz to use the deidentified data she collected at University of Sydney while at the University of Illinois at Chicago College of Dentistry.

Please contact me if you need further information.

Yours sincerely

M Ali Darendeliler

Faculty of Dentistry
Discipline of Orthodontics
Sydney Dental Hospital C12
Rm 2.21, Lvl 2, 2 Chalmers Street
Surry Hills NSW 2010 Australia

T +61 2 9351 8329
F +61 2 9351 8336
E ali.darendeliler@sydney.edu.au
sydney.edu.au

ABN 15 211 513 464
CRICOS 00026A

APPENDIX A CONTINUED

2. University of Illinois at Chicago Exemption

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Determination Notice
Research Activity Does Not Involve "Human Subjects"

September 15, 2013

Whitney Mostafiz, Sc.B, DMD
Orthodontics
801 S. Paulina St., Room 131
M/C 841
Chicago, IL 60612
Phone: (516) 765-6488 / Fax: (312) 996-0873

RE: Research Protocol # 2013-0903
"2D and 3D Orofacial Dimensions & Mandibular Advancement Splint Treatment Outcome in Obstructive Sleep Apnea Patients"

Sponsor: None

Dear Dr. Mostafiz:

The above proposal was reviewed on September 15, 2013 by OPRS staff/members of IRB #2. From the information you have provided, the proposal does not appear to involve "human subjects" as defined in 45 CFR 46. 102(f).

The specific definition of human subject under 45 CFR 46.102(f) is:

> *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) data through intervention or interaction with the individual, or
> (2) identifiable private information.

APPENDIX A CONTINUED

> *Intervention* includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

All the documents associated with this proposal will be kept on file in the OPRS and a copy of this letter is being provided to your Department Head for the department's research files.

If you have any questions or need further help, please contact the OPRS office at (312) 996-1711 or me at (312) 355-2908. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Charles W. Hoehne
Assistant Director
Office for the Protection of Research Subjects

cc: Carlotta A. Evans, Orthodontics, M/C 841
Maria Therese S. Galang, Orthodontics, M/C 841

VITA

NAME:	Whitney Robyn Mostafiz
EDUCATION:	Sc.B., Human Biology, Brown University, Providence, Rhode Island, 2008
	D.M.D., Doctor of Dental Medicine, Harvard School of Dental Medicine, Boston, Massachussets, 2012
HONORS:	The Harvard Odontological Society Award, Harvard Scholol of Dental Medicine, Boston, Massachussets, 2012
	Emma Gildersleeve Lane Fund Recipient, Harvard Medical School, Boston, Massachussets, 2012
	International Student Representative Outstanding Service Award, Alpha Omega International Dental Fraternity, 2011
	Graduate Student Research Award, American Academy of Dental Sleep Medicine, San Antonio, Texas, 2010
	Student Research Fellowship Recipient, American Association of Dental Research, 2010
	George W. Hage Prize in Human Biology Recipient, Brown University, Providence, Rhode Island, 2008
	Anne Crosby Emery Fellowship Recipient, Brown University, Providence, Rhode Island, 2008
PROFESSIONAL MEMBERSHIP:	American Association of Orthodontists American Dental Assocation Alpha Omega International Dental Fraternity Chicago Dental Society American Association of Dental Research American Academy of Dental Sleep Medicine
ABSTRACTS:	Sutherland K, Mostafiz W, Dalci O, Malhotra A, Srinivasan V, Darendeliler MA, Cistulli PA. Influence of oral dimensions on mandibular advancement splint treatment outcome in obstructive sleep apnoea. *Sleep Biol. Rhythms*, 8(Suppl 1): A2, 2010.
	Mostafiz W, Gidmark N, Swartz S. Histology and morphology of Cyprinid pharyngeal dentition in relation to diet; *Integr.*

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Mostafiz WR, Grine FE, Thompson VP, Bromage TG. A new method for the quantification of enamel prism imaging; *J. Dent. Res*, 86 Special Issue A, 2007.

PUBLICATIONS: Mostafiz W, Dalci O, Sutherland K, Malhotra A, Srinivasan V, Darendeliler MA, Cistulli P. Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. *Chest*, 139:1331-9, 2011