Evaluation of pharyngeal airway in response to Hypoglossal nerve stimulation and Continuous positive airway pressure.

by

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DEDICATION

This work is dedicated to my wonderful parents . You have encouraged and Supported me through this journey. You know how much I love and appreciate you.

To my wife, who listened to all of my heartaches and stresses throughout this time in my life.Thanks for always being there.

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ABSTRACT

Evaluation of pharyngeal airway in response to Hypoglossal nerve stimulation and Continuous positive airway pressure

The upper airway stimulation (UAS) using a unilateral implantable neurostimulator for the hypoglossal nerve is a relatively novel option for obstructive sleep apnea (OSA) patients. This may be specially useful to patients that cannot tolerate CPAP therapy. **Aim**: to introduce a new technology in treatment of OSA using a fully implanted system through stimulating the hypoglossal nerve, to evaluate pharyngeal changes in patients with an implanted UAS system. And to compare To compare the pharyngeal airway changes with implantable upper airway stimulation system and continuous positive airway pressure therapy. **Methods** seven patients with moderate or severe OSA who underwent surgical implantation for upper airway stimulation therapy were evaluated by cone-beam computed tomography scans in regular breathing, continuous positive airway pressure and upper airway stimulation. The upper airway was divided into Nasopharyngeal (NP), Oropharyngeal (OP) and Hypopharynx (HP). In addition, the most constrictive axial area (MinAx) was also recorded. Hyoid bone position and linear distance measurements were recorded **Results:** The results indicated that the increase of the NP,OP and HP volumes and dimensions in the upper airway stimulation was significantly greater than regular breathing. Similarly was greater than CPAP **Conclusion**: the upper airway stimulation enlarges the airway volume and dimensions. These results indicate that implanted UAS system appears to be a good option for treatment of OSA patients

LITERATURE REVIEW

Inadequate sleep contributes to heart disease, diabetes, depression, falls, accidents, impaired cognition, and a poor quality of life. In children and teens, sleep also supports growth and development. Sleep entails several functions, including recovery, biochemical refreshment, memory consolidation and emotional regulation [1]. There is some evidence to support the relationship between duration (too little or too much) and the risk of cardiovascular diseases, diabetes, obesity, depression and even cancer [2.]Modern sleep research became possible in 1924 when Hans Berger, a German psychiatrist, described the recording of human electroencephalography [3.] Loomis and colleagues in 1935 published a quantitative description of the four levels of sleep based on electroencephalogram (EEG) characteristics [4, 5.]

Upper airway Anatomy

The upper airway is an intricate structure composed of soft tissue and muscles that work in dynamic relationship to perform many different physiologic functions including respiration deglutition, and vocalization. According to Gray's Anatomy classification, the pharyngeal airway can be divided into three regions of interest, with one subdivision very relevant to orthodontics[6, 7.] Nasopharynx: between the nares and hard palate. Oropharynx: from the soft palate to the upper border of the epiglottis. The velopharynx or retro-palatal oropharynx is located between the soft palate and the posterior pharyngeal wall, is found within the Oropharynx.

Laryngopharynx or Hypopharynx: from the base of the tongue to the inferior border of the cricoid cartilage. The upper airway forms the passage for movement of air from the nose to the lungs and also participates in other physiological functions such as phonation and deglutition.[8] The properties of the upper airway are a compromise between these different functions, which variably require maintenance of patency of the airway .The muscles surrounding the airway that actively constrict and dilate the upper airway lumen [9] can be classified into four groups: Muscles regulating the position of the soft palate: ala nasi, tensor palatini, levator palatine Tongue: genioglossus, geniohyoid, hyoglossus styloglossus Hyoid apparatus: hyoglossus, genioglossus, digastric, geniohyoid, sternohyoid Posterolateral pharyngeal walls: palatoglossus, pharyngeal constrictors These groups of muscles interact in a complex fashion to determine the patency of the airway..[10] The main craniofacial bony structures that determine the airway size are the mandible and the hyoid bone these presumably act by providing the anchoring structures to which muscles and soft tissue attaches

The hyoid bone is strategic because, as a bone, it is more readily seen in radiographs as compared to muscles. The hyoid bone is the only bone in the head and neck region without a bony articulation. It lies freely suspended by the same muscles that are integrally related to pharyngeal region of the airway. The hyoid bone is a useful indicator of how the soft tissue is functioning. Its muscle attachments can be

described as belonging either to the suprahyoid or infrahyoid groups. Arising from the cartilages of the 2nd and 3rd branchial arches, the hyoid bone consists of a central body which projects posteriorly as a left and right greater horn. Attaching to the superior surface of the hyoid bone are the left and right lesser horns Moore 2007.[11] Papadopoulos et[12] al used the hyoid bones from 76 cadavers to demonstrate their lack of symmetry. Among their sample, almost 50% of hyoid bones were found to be asymmetric in the transverse dimension.

The hyoid bone position is determined by the combined activity of the suprahyoid and infrahyoid muscle groups, with the upper airway (UA) dilator muscles being of great importance.

Behlfelt et al in 1990[13] concluded that age was positively correlated with linear measurements of sagittal and vertical posture of the hyoid bone. They observed that children with enlarged tonsils had a more caudally positioned hyoid bone with respect to the mandibular plane (H-MP). Nelson et al[14] found that the Hyoid-Mandibular Plane (H-MP) distance increased over time, irrespective if the person was a snorer or not. Their study demonstrated that there was a trend for snorers to have a greater H-MP distance during the pre-pubertal and pubertal period ($P<0.10$). Likewise, adult snorers displayed a significantly larger H-MP distance ($P<0.05$) compared to non-snoring controls. Hyoid bone position can potentially be influenced by anatomic variables, neuromuscular control and even deposition of fat in the neck region.

Sforza et al[15] hypothesized that excessive submental fat deposition in obese patients could be responsible for moving the hyoid bone further inferiorly. Upon examining lateral cephalograms, Sforza et al[15] showed that differences in the position of the hyoid bone and measurements of the posterior airway space exist between control subjects and snorers. Verin et al[16] (2002) demonstrated that segmental upper airway resistance was correlated with the posterior airway space and the distance from the hyoid bone to the mandibular plane and the distance from the hyoid bone to the posterior pharyngeal wall (H-Ph) ($P < 0.05$). Patients with OSA displayed a greater upper airway resistance, which was linked to various anatomical variables, especially the position of the hyoid bone. A more downward and anterior position of the hyoid bone was demonstrated in OSA subjects compared to both snorers and normal subjects. The H-MP distances averaged 12±5mm in the control group, 18±3mm in the snorers' group, and 24±7mm in OSA patients, showing statistical significance at all levels. The anterior position of the Hyoid bone was not significantly different between control and snorers' group (35±5mm and 39±6mm respectively), but both were significantly smaller than in the OSA group (46±1mm).[16]

Normal sleep stages

Normal sleep architecture includes both quiet sleep (non-rapid eye movement [non-REM] sleep) and active sleep (rapid eye movement [REM] sleep). Non-REM sleep consists of four stages which are based largely on the original criteria of Loomis and colleagues [4, 5.] Stage I is a transitional period between wakefulness and sleep. Stage 2 predominates and comprises 45 to 50% of total sleep time. The four stages of non-REM sleep represent progressively deeper sleep marked by the increasing appearance of high-amplitude slow waves in stages 3 and 4, which are collectively known as delta sleep. Non-REM sleep is characterized by a general slowing of all levels of activity. Progression through all four stages of non-REM sleeps usually occurs rapidly after sleep onset. REM sleep occurs after non-REM sleep has been established, and the first REM period normally occurs after 70 to 90 minutes of non-REM sleep. The average duration of a period of REM sleep is about 20 minutes. The initial REM period of the night is usually very brief, but subsequent REM periods become longer. During an average night of REM/non-REM cycle progression, 4 to 6 REM periods normally occur at intervals of 60 to 90 minutes. REM sleep occupies about 20 to 25% of total sleep time in a healthy young adult.

Normal Sleep Influences on Respiration

In OSA, pharyngeal obstruction during sleep is central to the pathogenesis of the disorder. Therefore understanding how sleep influences breathing and patency of the

pharynx is important. marked changes in respiration occur during sleep [17.] With sleep onset, ventilation declines, and arterial carbon dioxide increases. Although ventilatory drive tends to decline during sleep, the fall in alveolar ventilation may be more importantly related to a sleep-associated change in respiratory mechanics. In young, healthy, non-obese men, inspiratory upper airway resistance is increased throughout normal non-REM and REM sleep relative to wakefulness and immediately returns to waking levels after arousal from sleep [18, 19.] Sleep thus renders the upper airway more collapsible than it is during wakefulness, Segmental pressure recordings across the upper airway during normal sleep in human beings have confirmed that the site of narrowing is in the pharynx behind the soft palate and tongue base [20.] Although many factors may contribute to partial pharyngeal collapse during normal sleep, sleep-related changes in upper airway muscle forces probably are most important [21.] Muscles that control the hyoid, tongue, and palatal structures that surround the pharynx include the geniohyoid, genioglossus, and tensor veli palatine muscles. During sleep several changes may occur in the balance between the forces of upper airway and diaphragm muscles that favor pharyngeal collapse. The activity of the upper airway dilator muscles decreases during sleep, [22] rendering the upper airway more collapsible.Because diaphragmatic activity is well maintained during sleep, [23] the balance of forces favors Collapse.

Classification of sleep disorders.

Recently, under the auspices of the American Academy of Sleep Medicine, a task force of experts was brought together to review the literature on sleep disorders. The results were published in 2005, in a revised edition of the international classification of sleep disorders .[24]The classification compromises eight sections.

I. Insomnia.

II. Sleep-related breathing disorders

III. Hypersomnia

IV. Circadian rhythm sleep disorders

V. Parasomnias

VI. Sleep-related movement disorders

VII. Isolated symptoms

VIII. Other sleep disorders and disorder associated with other conditions.

Breathing abnormalities detected during sleep are classified as apnea, hypopnea, respiratory effort related arousals, and hypoventilation. The apnea is the cessation, or near cessation, of airflow. It exists when airflow is less than 20 percent of baseline for at least ten seconds in adults.[25] Obstructive apnea occurs when airflow is absent or nearly absent, but ventilatory effort persists. Central apnea occurs when both airflow and ventilatory effort are absent. Mixed apnea, there is an interval during which there

is no respiratory effort and an interval during which there are obstructed respiratory efforts.

The Apnea–Hypopnea Index (AHI) is the total number of apneas and hypopneas per hour of sleep. The AHI is most commonly calculated per hour of total sleep, and it is the current defining measure of disease and disease risk.[26-28] However, an AHI is occasionally calculated per hour of non-REM sleep, per hour of REM sleep, or per hour of sleep in a certain position to provide insight into the sleep stage dependency or sleep position dependency. If AHI values are 4 or less, then the patient is within normal limits, after that the OSA is mild when 5<AHI<15, moderate when 15<AHI<29, and severe when AHI>30. [29]

Obstructive Sleep Apnea.

OSA is defined as [30] more than 15 apneas, hypopneas per hour of sleep (i.e., an AHI >15 events/hr) in an asymptomatic patient .Obstructive Sleep Apnea Syndrome (OSA) applies only to the latter definition. More than 75 percent of the apneas or hypopneas must have an obstructive pattern.

History of Obstructive Sleep Apnea.

Sleep Apnea Syndrome Obstructive sleep apnea has a remarkably short history considering the incidence and disabling symptoms of the syndrome. Burwell and colleagues published_the first description of the syndrome in 1956.[31] Their report

compared an obese, somnolent, polycythemia patient with the sleepy red-faced boy, Joe, in the Charles Dickens novel The Posthumous Papers of the Pickwick Club (1837). However, Burwell and colleagues did not link their patient's excessive daytime sleepiness to nocturnal sleep fragmentation. In 1966, Gastaut and colleagues were the first investigators to demonstrate repeated apneas in pickwickian patients during sleep.[32]

Epidemiology.

OSA is estimated to affect approximately 8% of men, and 2% of women, averaging 5% of the general population, with several of them going undiagnosed, thinking of themselves as healthy individuals.[33] In the US, there was a 12-fold increase in the annual number of patients diagnosed with sleep apnea between 1990 and 1998, from 108,000 to over 1.3 million.[34] Population- based studies suggest that 4 percent of and 2 percent of women aged more than 50 years suffer from OSA. However, OSA is often asymptomatic and the prevalence of patients with OSA, who do not present clinical syndrome, might be as high as 20-30% in middle aged population. Several studies have shown that OSA is a common disorder that represents a significant public health problem.[35] A large prevalence study found that undiagnosed sleep disordered breathing "is prevalent and has a wide range of severity in middle aged women and men".[36] Therefore, in the United States alone, more than 3 million men and 1.5 million women meet at least one definition of OSA. In the Wisconsin Sleep

Cohort Study, a random sample of 602 working men and women between 30 and 60 years of age underwent overnight polysomnography to determine the frequency of apneas and hypopneas during sleep. When the results were extrapolated to the general working population in this age range, the study group determined that 9% of men had 15 or more episodes of apnea and hypopnea per hour of sleep. [37]OSA affects men more often than women. Studies conducted with patients seen in sleep disorders clinics report that 8 to 10 times as many men as women have sleep apnea.[38,39] Postmenopausal women are at higher risk of developing OSA than are their premenopausal counterparts, [40] an effect that hormone replacement therapy could prevent or ameliorate.[41]OSA is also described in children with adenotonsillar hypertrophy.[42] OSA in children is a special case for several reasons. The presenting symptoms are more likely to be behavioral problems during the day and below expected performance in school.[43] in young women and before menopause, OSA presents with more complaints of fatigue and "depression" that snoring or sleepiness. There is more often a workup for hypothyroidism that is negative.[44] The special case of pregnancy is also a time when a women is more vulnerable to OSA because of edema and nasal congestion, progesterone and small lung volumes giving a higher loop gain.[45]

Pathophysiology of Obstructive Sleep Apnea

The fundamental problem in OSA is collapse of the upper airway during sleep, a process that often requires arousal for termination. Obstructive apneas are associated with complete upper airway collapse, and hypopneas are associated with partial upper airway collapse. Both anatomic and neuromuscular factors are involved in the development of obstruction of the upper airway in OSA. The human pharynx can be considered as a collapsible tube that serves several purposes including speech, swallowing and respiration; it is not provided with a rigid skeletal support and, during normal inhalation, it undergoes numerous stresses promoting its collapse. Negative pressure within the airway and the presence of soft tissues and bony structures, which increase extra-luminal tissue pressures, can predispose the pharynx to collapse; on the other hand, the tonic and phasic contractile activity of the dilator muscles of the pharynx contribute to the maintenance of pharyngeal patency.[46] An imbalance between these opposite forces is responsible for the upper airway obstructions that recur in patients with sleep-disordered breathing. The disease has been associated with the presence of tonsillar and tongue hypertrophy, retrognathia and inferior displacement of hyoid bone. Obstructive apnea involves the sequence of cyclic events. With the initial onset of an obstructive sleep apnea, the upper airway collapses in the region of the pharynx, and airflow is impeded despite increasing ventilatoty effort Hypoventilation results in progressive asphyxia, which increasingly stimulates

breathing efforts against the occluded airway, typically until arousal occurs. With arousal, the upper airway opens, and airflow is restored. This series of events may be repeated hundreds of times each night, causing considerable exposure to hypoxia and hypercapnia and resulting in highly disrupted sleep. The anatomic location of upper airway obstruction may be anywhere from the nose to the glottis, with the most frequent site of primary obstruction being the velopharynx, at the level of the soft palate, and the oropharynx.[47] OSA in adults has been elucidated to result from increased upper airway resistance and airway closure due to anatomic factors (eg, nose,tongue, lateral pharyngeal walls, soft palate, tonsils and parapharyngeal fat pads) [48] and/or physiologic factors (eg, reduced reflex responses of tongue and soft palate muscles to negative airway pressure) that impair function of airway-dilating muscles and increase collapsibility.[49-51] Positional factors that may exacerbate upper airway resistance during sleep include mouth opening which increases collapsibility and/or decreases efficacy of dilator muscles[52] and a supine posture which facilitates the gravitational forces that displace the tongue and soft palate posteriorly.[53,54] While increased upper airway resistance occurs at multiple sites along the upper airway from the nasopharynx to the hypopharynx it is particularly prominent at the level of the oropharynx .[55] The immediate effects include hypoxia, arousal during sleep, and negative upper airway pressure. These may lead to potential long-term comorbidities such as hypertension,[56] cardiac-related sudden death while sleeping,[57] abnormalities

of glucose metabolism,[58] excessive daytime sleepiness leading to automobile accidents,[59]impaired quality of life[60] and cognitive dysfunction including daytime performance, memory, and learning.[61-64] OSA requires an understanding of what normally occurs in the upper airway with the onset of sleep, and what may cause these occurrences to result in compromised airway patency and/or sleep apnea. Three interacting factors play a critical role: the muscle activity of the dilators of the pharyngeal airway, the negative pressure generated during inspiration, which opposes the activity of the dilators, and the structural anatomy of the airway.[65]

Muscle Activity

Sauerland and Harper observed a progressive reduction in the activity of the genioglossus muscle during sleep in normal subjects.[66]As the tongue relaxes, it tends to fall backwards obstructing the upper airway. Other researchers have found a similar sleep-induced reduction in the activity of the medial pterygoid and tensor palatini muscles, meaning that the soft palate also tends to fall backwards. [67,68]As a result of these changes in muscle tone, the pharyngeal airway becomes narrower, contributing to the possibility of airway occlusion.[63] The oropharyngeal airway can be further compromised when sleeping supine, as gravitational forces tend to posteriorly displace the mandible and base of the tongue and narrowing the airway.[69]As the fast moving air moves through this narrow airway negative pressure is created thereby

sucking the tongue and soft palate downward. When this pressure is greater than them tension provided by the muscle dilators of the airway, the airway collapses.[63]

Structural Considerations

Anatomical narrowing of the airway can occur at any level in the pharynx. Abnormalities that lead to upper airway narrowing such as micrognathia, macroglossia, tonsillar or adenoidal hypertrophy, and bulky pharyngeal tissue typically associated with obesity are considered predictive factors of apnea. While these abnormalities are generally evident upon physical examination, other more subtle abnormalities can be seen only with specialized techniques. Using various imaging techniques, some investigators have demonstrated reduction in upper airway area during wakefulness or sleep in patients with OSA.[70,71] Through the use of acoustic reflections, others have demonstrated that total pharyngeal area is lower in patients with OSA than in controls.[72] In healthy subjects, the phasic activity of some dilator muscles has been found to decline during rapid eye movement sleep[73] and the pharyngeal cross-sectional area has been found to be smaller during sleep than during wakefulness.[74] Mechanisms from both chemoreceptors and mechanoreceptors which control the activity of pharyngeal dilator muscles are reduced during sleep.[75,76] it has been observed that during wakefulness the activity of pharyngeal dilator muscles in OSA patients is increased to overcome compromised pharyngeal anatomy.[77] This compensatory mechanism is lost during sleep leading to pharyngeal collapse.[78]From

an anatomic perspective, a narrow upper airway is generally more prone to collapse than a larger one. A number of imaging studies have demonstrated that during wakefulness the cross-sectional area of the upper airway in OSA patients is reduced compared with control subjects.[79]Accordingly, OSA is frequently associated with a number of alterations in upper airway anatomy that reduce the size of the pharynx. Excessive fat deposits, particularly enlarged parapharyngeal fat pads, have been described in patients with OSA. Thickness of the lateral parapharyngeal muscular walls also represents a relevant factor causing airway narrowing in apneic subjects.[79]Another anatomically based predisposing factor of pharyngeal collapse in OSA may be the length of the pharynx .[80] In fact, it has been observed that OSA patients have a greater length of the pharynx compared with those without OSA .[81]The disease has been associated with the presence of tonsillar and tongue hypertrophy, retrognathia and inferior displacement of the hyoid bone .[82]

Anatomic factors in OSA

In OSA patients, an excess of the soft tissue such as obesity, restriction in the size of bony compartment such as retrognathia or combination of these factors can cause an increase in extraluminal tissue pressure, thereby reducing the caliber of the upper airway.[83, 84] support of this anatomic model OSA, research studies have found differences in the bony and soft tissue structures in patients with OSA. There is high prevalence of OSA in patients with congenital craniofacial syndromes (such as

retrognathia and mandibular hypoplasia in patients with treacher Collins syndrome). However, cephalometric studies have identified more subtle skeletal abnormalities in OSA patients, including a reduction in length of the mandible and an inferiorly positioned hyoid bone. Hyoid position determines airway length, which can also influence airway collapsibility.[85]The genioglossus muscle, an extrinsic tongue muscle, is the largest upper airway dilating muscle. Its contraction leads to tongue protrusion and to widening of the orophar-yngeal airway in the anterior-posterior dimension. The genioglossus is innervated by the medial branch of Cranial Nerve 12 (hypoglossal nerve).This nerve receives input not only from the sleep-wake center of the brain but also from the respiratory pattern-generator neurons, chemoreceptors, and negative-pressure receptors of the airway. During inspiration, genioglossus activity increases to prevent collapse of the airway owing to negative airway pressure.[86]The soft palate comprises these 5muscles: the tensor veli palatini, the levator veli palatini,the musculus uvulae,the palatopharyngeus, and the palatoglossus. The tensor veli palatini controls palatal stiffness, the levator, palate elevation;and the musculus uvulae, uvular position and shape.The palatopharyngeus aids in palate position; the palatoglossus, tongue position. In patients with OSA, the velopharynx is a common site of obstruction. Therefore, these 5muscles are likely important for maintaining upper airway patency. The hyoid muscles act to pull the hyoid bone either anteriorly and upward (geniohyoid and mylohyoid) or caudally (sternohyoid and thyrohyoid).

The hyoid muscles are innervated by the hypoglossal (geniohyoid and thyrohoid), trigeminal (mylohyoid), facial (stylohyoid), and ansa cervicalis muscles (sternohyoid).[91]During wakefulness When individuals (with or without OSA) are awake, the upper airway dilator muscles, particularly the genioglossus muscle, have increased activity during inspiration. During expiration, they remain active, but at a decreased level. [87]During normal sleep with sleep initiation, the upper airway of healthy individuals (without OSA) decreases in diameter, resulting in an increase in airway resistance. However, shortly after the onset of sleep, genioglossus muscle activity begins to rise again, whereas the tensor veli palatine muscle continues to have very low activity which might explain why air way resistance generally remains elevated during sleep.[88]In patients with OSA during wakefulness, the upper airway dilator muscles (genioglossus, tensor veli palatini, and other palatal muscles) display a high activity level.[89] With the onset of sleep, upper airway dilator activity is reduced, both in patients with OSA and in healthy controls. However, in patients with OSA reduced upper airway dilator activity leads to airway collapse .Negative airway continue to build until arousal from sleep occurs and the airway reopens

Risk Factors for OSA

The prevalence of OSA increases with age[90] and reaches a plateau after the age of 60 years. Mechanisms proposed for the age-related increase in prevalence include increased deposition of fat in the para-pharyngeal area, lengthening of the soft palate

and changes in structures surrounding the pharynx.[91]The association between obesity and OSA has been noted in many studies.[92] Morbid obesity defined as a body mass index (BMI) of >30 kg/m2, is present in 60–90% of patients with OSA Central obesity characterized by a high waist: hip ratio or increased neck circumference is better correlated with OSA even in those with a normal BMI. Fat distribution around the neck results in increased extraluminal pressure and may affect the geometry of the airway making collapse more likely. Data suggest that weight gain has a greater effect on OSA than an equivalent weight loss.[93] OSA is more common in men.[104] The male predisposition for the disorder has been attributed to differences in anatomical and functional properties of the upper airway, differences in craniofacial morphology and fat deposition and different ventilatory responses to arousals from sleep.[94] Women with sleep apnea often do not report loud snoring, gasping and witnessed apneas, but may more frequently report symptoms of fatigue and lack of energy. Health care providers should have a lower index of suspicion for considering OSA in women[90] and there may be a non-response of the bed partner to the symptoms of obstructive breathing during sleep. Women tend to have a lower AHI in non-rapid eye movement (non- REM) sleep but have a similar AHI in REM sleep to men.[104] OSA prevalence is as high or higher in African-Americans and in Hispanics compared with Caucasians.[95] For a given age, sex, and BMI, Asians have greater disease severity than whites, despite their lesser degrees of obesity, probably due to differences in

craniofacial features, such as a more crowded UA, relative retrognathia and a shorter cranial base.[95] OSA is associated with craniofacial abnormalities such as retrognathia, tonsillar hypertrophy, enlarged tongue or soft palate, inferiorly positioned hyoid bone, maxillary and mandibular retropositions. Jaw abnormalities are important in thin OSA patients. [96] Smoking is associated with a higher prevalence of snoring and passive smoking has been linked with habitual snoring.[97] Alcohol can increase upper airway collapsibility by reducing the genioglossus muscle activity, prolonging apnea duration and exacerbating OSA. Acquired conditions such as acromegaly and hypothyroidism are also associated with OSA.[98]

Morbidity and mortality associated with OSA

OSA is a cause of systemic hypertension.[99] The mechanisms contributing to this include tonic elevation of sympathetic neural activity by the augmentation of peripheral chemoreflex sensitivity ,direct effects on sites of central sympathetic regulation and the disturbance of nocturnal renin and aldosterone levels due to severe sleep fragmentation.[100] OSA is associated with the development of ischemic heart disease.[101]Chronic intermittent hypoxia can induce oxidative stress and an inflammatory state and thus contribute to the development of atherosclerosis in OSA patients.[101] OSA also leads to abnormalities of coagulation (hypercoagulability) and excessive platelet activation.[101] Patients with OSA appear to be at increased risk of having a stroke.[102] The negative intra-thoracic pressure generated during an apnea

decreases cerebral blood flow predisposing to ischemic changes in some patients. Other risk factors for stroke, such as systemic hypertension, heart disease, impaired vascular endothelial function and pro inflammatory states may be exacerbated by OSA. There are insufficient data to support that treatment of OSA will reduce stroke risk or that treating OSA post-stroke leads to improvement in quality of life.[103] OSA may contribute to the development of pulmonary hypertension. The apnea- induced hypoxia appears to be the most important determinant of pulmonary hypertension .Development of right ventricular hypertrophy is related to the severity of OSA, but development of right heart failure requires additional alterations in daytime respiratory function and is associated with lung disease or morbid obesity.[104] OSA leads to neuropsychological impairment that includes deficits in attention, concentration, vigilance, manual dexterity, skills, memory, verbal fluency and executive function.[105] Sleepiness, depression, fatigue and obesity have an important impact on the person's quality of life. Patients report problems with relationships and sex, as well as concerns about poor memory and a fear of dying.[106] One of the most important complications and the one which has the greatest impact from the public health perspective is driving accidents.[107] Vigilance testing and driving simulators in studies assessing driving performance in OSA patients reveal that performance is markedly reduced and the impairment is not just limited to periods when patients actually fall asleep but also when they are awake due to reduced vigilance. Motor

vehicle crashes correlate with the degree of sleepiness and not the AHI. There is also evidence that OSA patients have an increased risk of work place accidents.[108]

Diagnosis of OSA

The presence or absence and predicting the severity of OSA must be determined before initiating any kind of treatment.[109] The gold standard of OSA diagnosis is clinical examination, daytime sleepiness and overnight polysomnography.[110] There are other tools that are more time efficient and clinically feasible. Screening questionnaires, indexes and cephalometric analyses are example of these clinical tools. Dentists must play a role in the diagnosis of obstructive sleep apnea hypopnea syndrome (OSA). The diagnosis of OSA begins with patient history, physical examination, and objective testing.[109]

Questionnaires and clinical prediction models

These questionnaires and models are usually developed with a large sample of subjects who have undergone formal diagnostic testing. Many such tools are available, but the most commonly used ones are the berlin questionnaire and the multivariable apnea prediction index (MAPI).[111, 112] such questionnaires incorporate clinical information such as gender, age, snoring, BMI, the occurrence of choking episodes, and the presence of hypertension.

Overall, prediction models tend to have high sensitivities but much lower specificities. Patients with OSA will ususally be identified correctly, but a significant

proportion of subjects without OSA may be identified incorrectly as having OSA. Therefore, these prediction models might have a role in disease exclusion, but their routine use in clinical practice remains limited. Incorporation of oral cavity measurements (palate height, overjet, and intermolar distances) in a prediction model maybe clinically useful screening tool for OSA.[113]

Polysomnography

Polysomnography performed in a sleep laboratory is the gold standard for the diagnosis of OSA. It involves continuous overnight recording of a minimum of 12 channels of sleep- and breathing-related measurements, such as electroencephalogram. Electro-oculogram, nasal airflow, oral airflow. Respiratory effort, oxygen saturation, body position and electrocardiogram.[114]

The severity of sleep apnea is assessed with the apnea-hypoapnea index, although other factors such as the degree of oxygen desaturation and the extent of sleep fragmentation are important for the clinical interpretation of OSA severity.

Generally, diagnosis of OSA can be based on a single night of testing, although night to night variability in results should be considered, especially if test results are negative for a patient with high clinical risk of OSA.

Upper airway imaging in OSA

Airway imaging techniques used in the diagnosis of OSA have greatly improved with the further understanding of OSA pathophysiology.[115] Treatment planning and evaluation of surgical and non- surgical therapies which target specific areas of obstruction are now possible with newer imaging modalities. Airway imaging can be done using numerous techniques such as acoustic reflection, fluoroscopy, and nasopharyngoscopy.[116] However, the most common airway imaging modalities are lateral cephalometric radiography, magnetic resonance imaging (MRI), and computed tomography (CT).

Lateral Cephalometric Radiography

Cephalometry involves the use of standardized lateral radiograph of the head and neck to assess craniofacial and soft tissue structures of the upper airway. This technique must be performed in a standardized fashion as the patient's head is stabilized by a cephalostat. This method is widely available, esily performed, inexpensive, and can be useful in the evaluation of oral appliances or orthognathic surgery. However, cephalometrics has several disadvantages that it is a static, two dimensional representation of a three dimensional object.Studies using cephalometrics have demonstrated craniofacial differences between patients with sleep apnea and normal control subjects.[117] The most commonly reported craniofacial characteristics of non-obese patients with sleep disorder breathing include a small

corpus length retrognathic mandible, a narrower posterior airway space, enlargement of the tongue and soft palate, inferiorly position of hyoid bone and a retrognathic maxilla.[118, 119] Mandibular or maxillary position can be evaluated by a number of methods including the SNA and SNB angles. Patients with skeletal deficiencies are more likely to have obstruction at the base of the tongue or at the level of the soft palate. Riley and colleagues determined that obstructive sleep apnea patients had an inferiorly positioned hyoid bone, a longer-than-normal soft palate, and a narrowing at the base of the tongue.[120] In 1984, McNamara described his cephalometric technique[121] which included assessment of the upper airway. He suggested the taking of two measurements, one for the upper pharynx, and the other for the lower pharynx dimension. The upper pharynx dimension was described as the minimum distance between the upper soft palate, and the nearest point of the posterior pharynx wall. It was determined that this distance increases with age, with its norm established at 17.4±3.4mm. The lower pharynx dimension is the minimum distance between the posterior wall of the pharynx and a point seen in the cephalograms as the intersection between the posterior contours of the tongue with the lower border of the mandible. The lower pharynx dimension was not seen to change with age, and its norm was determined to be 11.3±3.3mm for females, and 13.5±4.3mm for males.

Acoustic Reflection

Acoustic reflection is a noninvasive imaging technique based on the analysis of sound

waves reflected from upper airway structures. The phase and amplitude of the reflected sound waves can be used to determine the cross-sectional area of the airway. The technique is generally performed through the mouth, is free of radiation and because it is both fast and reproducible, permits dynamic imaging of the upper airway. However, acoustic reflection does not provide direct information on airway structure or anatomy or show the soft tissue structures, it only indicates the size of the airway lumen. Studies using acoustic reflection have demonstrated that the upper airway of apneic controls.[122]

Fluoroscopy

Fluroscopy has been used to assess dynamic closure and sites of obstruction in the upper airway.patients with OSA Somnofluoroscopy has demonstrated that upper airway closure occurs in the retropalatal region for most patients. Although fluoroscopy provides a dynamic evaluation of the upper airway during wakefulness and sleep, high radiation exposure, superimposition of the upper airway soft tissue structures and the possible need for sedation to attain sleep make this technique impractical for routine use.[123]

Nasopharyngoscopy

Nasopharyngoscopy is an accessible and in expensive method used to evaluate nasal passages oropharynx, and vocal cords of patients in multiple positions and in awake and asleep states. Although it is invasive and requires nasal anesthesia, it does not

involve radiation exposure. The combination of nasopharyngoscopy with the muller maneuver has been shown to add important information on possible sites of airway obstruction.[124]

Cone Beam Computed Tomography

Cone Beam Computed tomography (CBCT) is a medical imaging modality, which has been applied in different fields of medicine (e.g. cardiac imaging, radiotherapy). CBCT is very popular in orthodontics, and brought 3D radiography to clinical orthodontics. The principle behind this technique is a cone-shaped x-ray bundle, with the x-ray source and detector (Image Intensifier or Flat Panel Detector) rotating around a point (or field) of interest of the patient.

Osorio et al[125] suggested that CBCT has the potential to eventually emerge as a comprehensive and practical system to evaluate the airway, and could become an excellent research and teaching tool for understanding the normal and abnormal airway. The axial plane, which is not visualized on a lateral cephalogram, is the most physiologically relevant plane because it is perpendicular to the airflow. The airway can be accurately assessed through segmentation. In medical imaging, segmentation is defined as the construction of 3D virtual surface models to match the volumetric data.[126] Upper airway segmentation can be performed either manually or semi automatically. Proper analysis of the airway starts with orientation of the 3D image,

adjusting all three planes of space. CBCT has been used to evaluate the common sites of obstruction in 3 dimensions with OSA Patients.[127]Many studies have shown that OSA patients have smaller airway cross-sectional areas and volumes than do normal subjects. However, CBCT is static, not dynamic, imaging, and static imaging correlates poorly with OSA.[128] few studies have shown significant dynamic airway changes in OSA patients with dynamic3-dimensional computed tomography imaging.[127]

Dynamic Computed Tomography

CT scanning is widely available and is performed while the patient is in the supine position. It is ideal for imaging craniofacial structures and the lumen of the upper airway. Three-dimensional volumetric reconstructions can be obtained by reconstruction of axial CT images. Ultrafast or dynamic CT can be performed with electron beam CT, which provides excellent temporal (50- millisecond) and spatial resolution to assess dynamic changes of the upper airway dimensions during a respiratory cycle.[129]Most studies using CT to assess airway caliber during wakefulness and sleep have demonstrated narrowing in the retroplalatal region of patients with OSA.[130] Dynamic CT provides a more physiologically significant assessment of the upper airway compared with standard CT imaging due to its ability to capture the dynamic component of sleep apnea, while carrying the same drawbacks as standard CT.[115]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses electromagnetic energy and radio waves to assess various types of soft tissue without exposing the patient to ionizing radiation.[131] MRI has equal resolution, but much greater contrast than CT scanning this is especially useful in studying OSA as it allows more detailed visualization of soft tissues of the pharyngeal airway. The limitations of using MRI include: the large size of the MRI machine, noisy scans, taking several minutes for a scan, claustrophobic effects of being inside the machine, and its relative expense. These limitations negate its use as a routine imaging assessment for patients with OSA.[115]

Treatment for Obstructive Sleep Apnea

Non-surgical and surgical therapies can be used in the treatment of OSA. Non-surgical therapies include diet and lifestyle modification,[132] pharmacologic agents,[133] nasal positive airway devices,[134] and oral appliances.[135] Surgical options for the treatment of OSA include nasal reconstruction, uvulopalatopharyngoplasty (UPPP),[136] uvulopalatopharyngo-glossoplasty, uvulopalatal flap,[136] radiofrequency ablation to the base of the tongue,[136] mandibular osteotomy with genioglossus advancement,[136] hyoid suspension,[136]tracheotomy, tonsillectomy and adenoidectomy,[131] distraction osteogenesis, and maxillomandibular advancement osteotomy.[135]

Diet and life style modification

Weight loss should be recommended for all overweight patients with sleep-disordered breathing as it results in improvement of OSA[137] presumably by reducing pharyngeal collapsibility[138] and/or ventilator instability.[139] Kajaste et al[137] reported the most improvement in OSA is following 6 months of a weight reduction program, at which point patients started to regain their weight. Peppard et al[140] reported that a 10% weight loss predicted a 26% decrease in the AHI. However, because weight loss results in variable changes in the upper airway, it is not known what degree of weight reduction is necessary to adequately treat OSA.[138] Furthermore, it is important to realize that diets, behavior modification, exercise, and medications may produce either a short term weight loss with most patients regaining the lost weight.[141] Anderson et al[142] conducted a meta-analysis of patients who participated in structured diets and exercise weight loss programs and concluded that there was only a 3.2% loss of body weight after 5 years. In fact OSA may predispose patients to weight gain due to decreased activity levels that result from sleep deprivation.[143] Smoking and alcohol consumption, have been shown to increase airway resistance. Smoking has been shown to produce upper airway edema that results in upper airway resistance. Thus, OSA patients are advised to avoid smoking tobacco.[144] Alcohol is a respiratory depressant that may exacerbate pre-existing OSA, and thus should be avoided at least four hours prior to sleep.[144]

Pharmacologic Agents

Several drugs have been used in the treatment of obstructive sleep apnea syndrome with variable results. The carbonic anhydrase inhibitor acetazolamide stimulates respiration by producing a metabolic acidosis. This drug reduced the number of apneas and decreased the severity of oxygen desaturations in a group of patients with central sleep apnea.[145] However, in several cases, acetazolamide given to patients with mild obstructive sleep apnea produced more frequent obstructive apneas of longer duration.[146] Therefore acetazolamide is probably not indicated in the management of obstructive sleep apnea syndrome. Some patients with obstructive sleep apnea benefit from the respiratory stimulant effect of progesterone, especially those with the obesity-hypoventilation syndrome.[147-150] Progesterone increases alveolar ventilation and improves oxygenation, but its effect on frequency of apnea is limited. Major side effects that limit its long-term use include decreased libido, alopecia, and impotence. The tricyclic antidepressant protriptyline is the most effective and best studied drug for the treatment of obstructive sleep apnea.[151]In a study of 12 patients, Smith and colleagues showed a reduction in apnea frequency and oxygen desaturation during non-REM sleep, in addition to a decrease in REM sleep.[152]

Positive Airway Pressure (PAP)

The positive airway pressure (PAP) is the treatment of choice for all levels of OSA, showing positive outcomes in reducing the AHI.[153] PAP may be delivered as continuous (CPAP), bilevel (BPAP), or automatic (APAP) modes, can be all be used in the treatment of OSA. CPAP is the most commonly used non-surgical therapy and was first introduced in 1981 as a treatment modality for OSA.[154] CPAP is the most effective method to manage OSA. It improves subjective and objective measures of sleepiness[155] by acting as a pneumatic splint to elevate and maintain a constant pressure along the upper airway during inspiration and expiration.[156] The most significant effect is enlargement of the airway by dimensional changes of the lateral pharyngeal walls.[157] In addition to structural changes, CPAP augments the tone of the upper airway dilator muscles thereby reducing susceptibility to collapse.[158] McArdle et al[159] reported that patients improve sleep quality and daytime sleepiness following month of using CPAP. Ballester et al[160] compared treating moderate and severe OSA patients for 3 months with conservative modalities (eg, avoiding sedatives and alcohol, weight loss, sleeping on their side) to CPAP plus conservative modalities and measuring success by improved symptoms (eg, snoring,nocturia, dry mouth, morning headaches), day time function, perceived health status, and quality of life. A meta-analysis conducted by Patel et al[155] found that patients with severe OSA benefit the most from CPAP. Despite the uniform success of this therapy, patient compliance

remains a problem. Compliance rates at 12 months have been reported as low as 54%.[161] the average nightly use of CPAP is 4.8 hours and the rate of use is usually determined in the first week of use. Overall approximately one-third of patients love CPAP, one-third struggle with CPAP but eventually tolerate it, and one-third hate CPAP and never use it. Patient dissatisfaction results from nasal dryness and congestion, sore throat, dryness of the skin and eyes, claustrophobia, and the inability to tolerate the noise, discomfort or mask. Careful patient selection and follow-up are essential if nasal CPAP is selected as a treatment modality

Oral appliances

Patients who are intolerant of CPAP therapy or those who refuse surgery are candidates for oral appliances, and are most commonly used for patients with mild to moderate OSA.[162] Increase in the posterior oropharyngeal airway space and reduction in the collapsibility of the upper airway during sleep is the goal of oral appliance therapy.[162] Tongue-retaining or mandibular-repositioning are the two categories for oral appliances. Tongue-retaining oral appliances position the tongue in an anterior direction through negative pressure, and are indicated for patients for those who have few or no teeth, macroglossia, or cannot adequately posture their mandible forward.[162, 163]Mandibular-repositioning devices help to posture the mandible and associated structures, such as the tongue and hyoid bone, in an anterior direction, thus increasing both the anterior-posterior and lateral dimensions of the upper airway. [162,

[164] While these devices are effective with success rates at 54% defined as reducing AHI to less than 10 and a resolution of symptoms, they are not without negative side-effects.[165] he most common dental side effects from oral devices includes proclination of the mandibular incisors, retroclination of the maxillary incisors, mesial movement of the mandibular molars, and a decrease in the SNB angle after long term usage.[166]

Surgical Treatment

Surgery is most indicated when conservative therapeutic approaches are unsuccessful or not tolerated well. The goal of surgical treatment for OSA is to target site specific areas that are causes for upper airway obstruction. Typically surgery should increase the upper airway size resulting in a decrease in airway resistance, thereby reducing the pressure effort to breath.[162] Patients that have well-identified underlying skeletal abnormalities in cases of moderate to severe OSA are also indicated for surgery.[167] Surgical prerequisites include an apnea-hypopnea index greater than 15 (AHI), or apnea index greater than 5 (AI),[167] a respiratory disturbance index (RDI) greater than 15-20,[168] lowest oxyhemoglobin desaturation less than 90%, and excessive daytime sleepiness. Patients must be psychologically and medically stable and willing to accept surgery.[169] Three categories typically govern upper airway surgical procedures for the treatment of OSA: (1) procedures that directly enlarge the upper airway; (2) changing the soft tissue elements and or skeletal anatomy by specialized procedures that increase the upper airway and as a last resort option, (3) a tracheotomy that

bypasses that pharyngeal portion of the upper airway.[170] Surgical treatment is typically staged into 2 phases. Stage I surgery is considered to be more conservative and site-specific and addresses obstructions in the palatal and tongue base area without movement of the jaw(s) or teeth. A multi-level approach may target areas such as:the nose, the oropharynx (the retropalatal and retroglossal airway) and the hypopharynx. This stage also includes nasal surgery, uvulopalatopharyngoplasty (UPPP), and base of tongue surgery (which includes genioglossal advancement, modified genioplasty, radiofrequency ablation, and hyoid myotomy).[162] Stage I therapy is usually conducted in a stepwise manner according to a methodical protocol where less invasive surgical procedures are first attempted and progressively treated with more surgery based on clinical symptoms. This may result in unnecessary additional surgery, which may be painful and expensive, and behave as a deterrent for patients to look for definitive surgical treatment. [169]Stage II surgery includes maxillomandibular advancement (MMA). MMA is an invasive procedure that surgically moves the maxilla and mandible anteriorly, along with their muscular attachments, to increase the airway space of the nasopharynx, oropharynx, and hypopharynx[162] to enhance the neuromuscular tone of the dilator muscles.[169]

Tracheostomy

Tracheostomy was the first efficacious surgical procedure for treating obstructive sleep apnea, performed by Kuhlo and colleagues in 1969.[171] It is almost 100% curative in relieving the signs and symptoms of obstructive sleep apnea because it bypasses all the potential obstructive sites in the upper airway. After tracheostomy there is a rapid and striking reduction in daytime somnolence and a marked improvement in sleep architecture due to a major reduction in the frequency of arousals. Sinus dysrhythmias, bradycardia, pulmonary hypertension, hypoxemia, and apnea all improve dramatically with the procedure. Tracheostomy clearly is an effective surgical treatment for patients with obstructive apnea. The disadvantages of a permanent tracheostomy can have a devastating effect on sleep apnea patients. Almost all patients experience psychological depression from the social and medical problems associated with a lifelong tracheostomy. Because of these disadvantages and complications, a permanent tracheostomy should be reserved for severe cases of obstructive sleep apnea with significant cardiovascular symptoms. Simmons and colleagues have suggested that tracheostomy should be the primary therapy for all patients who spend substantial time in severe oxygen desaturations below 50% and for those who have life-threatening cardiac dysrhythmias during sleep apnea.[172]

Nasal Surgery

Significant obstruction in the nasal cavity has been shown to cause excessive daytime sleepiness, sleep fragmentation, hypopneas, and periodic breathing during sleep.[173] In most patients with moderate to severe obstructive sleep apnea, nasal obstruction is not the major contributing factor. The obstruction may be due to a deviated nasal septum, nasal polyps, or enlargement of the turbinates. In these patients septoplasty, nasal polypectomy, or turbinectomies are usually helpful only as adjunctive surgical procedures in the treatment of obstructive sleep apnea

Uvulopalatopharyngoplasty

The oropharynx and soft palate can cause significant airway obstruction during sleep. At least 10% of persons over the age of 40 years snore regularly and significantly. Loud and intermittent snoring is found in almost all patients with obstructive sleep apnea. In many cases habitual snoring is present for many years before sleep apnea is diagnosed. Ikematsu followed a large number of habitual snorers over several years and found that 91% of these patients had decreased oropharyngeal dimensions and longer soft palates and uvulas than normal subjects.[174] He was able to eliminate their snoring by surgically excising the excessive soft tissue in the palatal folds and partially excising the uvula. With minor modifications, Simmons and colleagues and Fujita and colleagues popularized the uvulopalatopharyngoplasty (UPPP) for the treatment of obstructive sleep apnea.[172] UPPP results in symptomatic improvement in the patient and eliminates habitual snoring in almost all cases. However, reports show

that significant objective improvement on the postoperative polysomnogram ranges only from 41 to 66%.[172] this procedure only eliminates the obstruction at the level of the soft palate and does not address obstructions occurring in the hypopharyngeal and base of tongue areas. Many patients have more than one site of obstruction. If UPPP is performed when the presurgical evaluation demonstrates obstruction localized to the soft palate–tonsil area, then the success rate of the surgical procedure approaches 90% treating obstructive sleep apnea.[175]

Laser-Assisted Uvulopalatoplasty

In the late 1980s Dr. Yves-Victor Kamami (Paris, France) designed a procedure to reshape and recontour the soft palate under local anesthesia with a CO2 laser to treat snoring and selected patients with obstructive sleep apnea syndrome.[176] He originally named the procedure "laser resection of the palatopharynx" or LRPP In the early 1990s in the United States, Dr. Yosef Krespi modified the procedure and renamed it "laser-assisted uvulopalatoplasty"or LAUP. He initially used the procedure to treat loud habitual snoring. In a study of 280 patients treated in the office under local anesthesia, 84% were cured with an average of 2.7 sessions.[177] Overall results for obstructive sleep apnea patients treated with LAUP are far less encouraging, with an average successful surgical response of 52.2%.[178] Based on these findings the current main indications for LAUP include loud habitual snoring, upper airway resistance syndrome, and mild obstructive sleep apnea (apnea index < 20). The most common

complication following LAUP is a moderate to severe sore throat. Patients experience pain 8 to 10 days after surgery and reach their peak pain intensity on the fourth or fifth postoperative day.

Orthognathic Surgery Procedures

Various orthognathic surgical procedures have been described for the treatment of obstructive sleep apnea. The majority of patients have airway obstruction at the level of the soft palate and at the base of the tongue. Orthognathic surgical procedures can change the size of the airway in several regions. Mandibular advancement and genial advancement work by changing the position of the mandible and hyoid bone with subsequent effects on the genioglossus and hyoglossus muscles. Obstructive sleep apnea patients with identifiable craniofacial anomalies can clearly benefit from a variety of these procedures.

Mandibular Advancement

Total mandibular advancement was the first orthognathic surgical procedure used in the treatment of obstructive sleep apnea. Kuo and colleagues in 1979 and Bear and Priest in 1980 reported complete reversal of sleep apnea symptoms in patients with horizontal mandibular deficiency treated by mandibular advancement.[179] More recently Alvarez and colleagues reported the successful treatment of an edentulous patient with sleep apnea by mandibular and genial advancement.[180]The exact reason for how mandibular advancement improves obstructive sleep apnea is not clearly

known, but the suspected effect is the pulling of the tongue forward off the pharyngeal wall. This effect is created by anteriorly moving the insertion of the genioglossus and geniohyoid muscles. If this were the only factor, then anterior chin procedures would be equally effective as total mandibular procedures. Variations of geniotomies have been designed to maximally pull the tongue muscles forward.

Genioglossal Advancement and Genioplasty

Anterior reposition of the genial tubercle and genioglossus muscle is the goal of a genioglossal advancement. The procedure places tension on the base of tongue, and thus tends to reduce prolapse into the posterior airway during sleep.[162] The patient cure rates from a genioglossal advancement varies from 35-60% depending upon OSA severity.[181] Potential complication from genioglossal advancement surgery include mandibular fracture, lower incisor root lesions infection, permanent anesthesia, and seromas.[181] A modified genioplasty is a technique that advances the genioglossus muscle and chin used for patients with microgenia. The primary goal of a genioplasty is improvement in facial esthetics, a secondary benefit of surgery is an increase in airway volume, thus decreasing the likelihood of hypopharyngeal airway collapse.[162]

Genial Advancement with Hyoid Suspension

In 1984 Riley and colleagues described an alternative technique in which an inferior mandibular osteotomy and an associated hyoid suspension were used in the treatment

of obstructive sleep apnea .[182] this technique is similar to a horizontal mandibular osteotomy, which is commonly used for advancement genioplasty. The osteotomy is designed to include the genial tubercle on the inner cortex of the anterior mandible where the genioglossus muscle attaches. Repositioning the anteroinferior segment of the mandible forward with the attached genioglossus muscle theoretically pulls the tongue forward and improves the hypopharyngeal airway. Sleep apnea who were treated with inferior mandibular osteotomy and hyoid suspension.[183] all responders to surgery showed significant improvement in their RDI and oxygen desaturation events. In 1994 Riley and colleagues reported on a new modified technique for hyoid suspension that fixed the hyoid to the thyroid cartilage instead of the anterior margin of the mandible.[184] the most serious reported complication from a hyoid suspension has been severe aspiration in one patient, in which the thyrohyoid membrane was totally sectioned. Other complications have included wound infections, transient sensory disturbances of the mental nerve, and mandibular fracture. An advantage to hyoid suspension is that it circumvents the need for maxillomandibular fixation and does not affect the occlusion. Maxillomandibular Advancement Combined advancement of the maxilla and mandible with or without hyoid suspension is the most recent and efficacious surgical procedure for the treatment of obstructive sleep apnea. The surgical technique includes a standard Le Fort I osteotomy in combination with a mandibular sagittal split osteotomy for advancement of the maxilla and

mandible. This surgery may result in a significant facial change, which is most often favorable. Several authors have described the use of maxillomandibular advancement (MMA) in treating large series of obstructive sleep apnea patients.[196-201] In a series of 23 patients, Waite and colleagues performed a high sliding horizontal geniotomy without the hyoid myotomy and Suspension.[185] All patients were reevaluated by polysomnography at 6 weeks postoperatively. The surgical success with MMA was 65% based on a postsurgical RDI of less than 10. Riley and colleagues reported the largest series of obstructive sleep apnea patients treated with MMA in which 98% (89 of 91) were successfully treated based on a postoperative RDI of less than 20 with at least a 50% reduction in the RDI compared to the preoperative study.[186] It should be noted that 67 of the 91 patients (74%) did not receive phase 1 therapy based on their two-phase protocol for reconstruction of the upper airway. In 1997,Hochban and colleagues reported a 98% success rate on 38 obstructive sleep apnea patients consecutively treated with a 10 mm MMA as the primary surgery, without any adjunctive procedures.[187] Their criteria for success were based on the more rigid postoperative RDI of less than 10. Patient selection for MMA was based on subjective symptoms of excessive daytime sleepiness, an RDI of greater than 20, and specific craniofacial characteristics determined cephalometrically. Only 2 patients who were morbidly obese were treated surgically. Based on their excellent results the authors concluded that a stepwise algorithm of staged surgical procedures was not

justified. In a series of 50 obstructive sleep apnea patients consecutively treated with MMA, Prinsell reported a 100% success rate based on a postoperative RDI of less than 15, an apnea index (AI) of less than 5, or a reduction in the RDI and AI of greater than 60%.[189] In 1999 Lee and colleagues proposed a three-stage protocol for the surgical treatment of obstructive sleep apnea patients.[190] Bettega and colleagues treated 51 consecutive obstructive sleep apnea patients according to the Stanford two-step surgical procedure.[191] Forty- four patients had phase 1 surgery with a success rate of 22.7% (10 of 44). Twenty patients underwent MMA as part of phase 2 in the protocol. Of these, 75% (15 of 20) were considered to be surgical responders based on a postoperative RDI of less than 15 and at least a 50% reduction in the RDI. Of the 5 failures, 3 had postoperative RDIs of less than 20. The PAS consistently increases with maxillomandibular advancement. However, there is no direct relationship between the gain in PAS and the remission of sleep apnea. MMA is effective for patients who have obstruction at the base of the tongue. This surgical treatment is the most efficacious procedure for expanding the pharyngeal airway and improving or eliminating obstructive sleep apnea. It remains the best current alternative to tracheostomy.[192] the long-term skeletal stability of MMA has been shown to be quite good. Louis and colleagues showed a mean relapse of 0.9 ± 1.8 mm among 20 maxillary advancement patients who underwent MMA for obstructive sleep apnea.[193]

Upper airway stimulation

Upper airway stimulation (UAS) using a unilateral implantable neurostimulator for the hypoglossal nerve is a relatively novel therapy for the treatment of moderate to severe OSA patients that are intolerant to CPAP therapy. The potential of the hypoglossal nerve stimulation as a therapeutic approach for the treatment of OSA was initially described by Eisele et al.[194] and Schwartz et al.[195] The branches of the hypoglossal nerve that innervate the genioglossus predominantly contain efferent (motor) fibers, such stimulation of those branches activate the genioglossus muscle with minimal afferent (sensory) feedback. Patients with AHI>65 and/or BMI>32, are not good candidates for this therapy, due to decreased likelihood of response to treatment. This therapy is also contraindicated when central and mixed apneas represent 25% or more of the AHI, and neurological problems in the upper airway due to a condition or previous procedures. The device is implanted in the chest, and has a small generator, a breathing sensor lead, and a stimulation lead. The patient can turn the therapy on before bedtime and off in the morning through a remote control. When the device is activated it senses the person's breathing patterns, delivering mild stimulation in order to keep the airway open, acting in a similar way than a pacemaker. The hypoglossal nerve is accessed through a horizontal incision in the upper neck at the inferior border of the submandibular gland. The median time for

surgical implantation has been reported as 140 minutes (65-360min), with most patients spending the night at the hospital.[196]

In 1989, Miki et al.[197] isolated the upper airway from the lower airway by performing tracheotomy in six dogs and examined the relationship between the frequency of stimulation of the genioglossus and upper airway resistance. They demonstrated stability in upper airway patency with graded increases in stimulation frequencies of the genioglossus muscle in awake, spontaneously breathing canines. In 1992, Schwartz et al.[198] implanted bilateral hypoglossal nerve stimulators in 18 decerebrate felines and illustrated that increases in stimulation frequencies bear a direct relationship with VI max via decreases in critical closing pressure. Animal studies have confirmed that the genioglossus muscle is the primary upper airway dilator and tongue protrusor, whereas the hyoglossus and styloglossus are tongue retrusor muscles that contribute to airway collapse.[199-202]

Initial human studies examining the tolerability of transcutaneous upper airway stimulation in the asleep, supine state bore mixed results.[203-207] Schwartz et al.[208] reported in 1996 the feasibility and efficacy of lingual musculature stimulation without causing arousals. Fine-wire Teflon-coated electrodes were used for intramuscular stimulation of the lingual muscle in nine participants with OSA.

Tongue muscle stimulation in consecutive breaths decreased the frequency of obstructive episodes in a subset of participants without causing arousal.

Oliven et al.[209] demonstrated the airway effects of selective stimulation of protrusor and retrusor muscles. Selective intramuscular stimulation of the genioglossus significantly increased stability of airway, whereas selective stimulation of the styloglossus and hyoglossus increased collapsibility of airway). Co-activation of both protrusor and retrusor muscles resulted in a net improvement in airflow.[210] Nasopharyngoscopy was used to demonstrate that genioglossus stimulation can result in enlargement and stabilization of not only the retrolingual portion of the airway but also the retropalatal space. Because OSA frequently involves multilevel collapsibility, this was a key observation suggesting that hypoglossal nerve stimulation has the potential to affect multiple levels of the pharyngeal airway rather than the tongue base alone.

Implantable nerve stimulation technology has been available and applied successfully in other medical conditions: sacral nerve stimulation for incontinence, vagal nerve stimulation for seizures, spinal cord stimulation for pain, and deep brain stimulation for tremors.[211-213] In 2001, a pilot study reported the results of eight participants receiving an implantable hypoglossal nerve stimulator (Inspire I, Inspire Medical Systems, Maple Grove, MN) for OSA.[214] Sleep studies were performed at 1, 3, and 6

mo postoperatively and apnea hypopnea index (AHI) results were reported individually for non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. Seven of the eight participants had significant reductions in their AHI. Despite the encouraging results, electrode breakage and sensor malfunction occurred in five of eight participants, precluding use beyond the 6-month study period. Following the published technical limitations of the human pilot study, multiple investigators and medical device companies spent a decade improving the product prior to the launch of two larger trials with results available as of 2011.[215,216] Eastwood et al.[215] reported on the safety and effectiveness in a Phase II trial of a new generation implantable hypoglossal nerve stimulator (HGNS) therapy system (HGNS, Apnex MedicalInc, St Paul, MN, USA) at four Australian sites. Participants (n = 21) had moderate-severe OSA, were surgically naive, and unable to tolerate CPAP. Similar to the Schwartz pilot study, sleep studies were performed at 1, 3, and 6 months. Nineteen of the 21 participants in the study had baseline and 6-mo polysomnography (PSG). There was a significant improvement ($P < 0.05$) from baseline to 6 mo in: AHI (43.1 ± 17.5 to 19.5 ± 16.7) and Epworth Sleepiness Scale (ESS) (12.1 ± 4.7 to 8.1 ± 4.4). The investigators reported two adverse events: an infection requiring device removal and Stimulation lead cuff dislodgement requiring replacement. Van de Heyning et al.[216]carried out two consecutive open prospective studies with another device, reporting their results in 2012. The Inspire II Upper Airway Stimulation (UAS)

system (Inspire Medical Systems) was implanted similar to the HGNS with the exception that this device only has a single respiration sensor .AHI was reduced significantly from a baseline of 38.9 ± 9.8 to 10.0 ± 11.0 ($P < 0.01$) at the 6-mo post implant visit. Across all participants in study Part 1 and Part 2, both ESS and Functional Outcomes of Sleep Questionnaire improved significantly from baseline The Inspire UAS system is composed of a stimulation lead, a sensing lead, and an implantable pulse generator (IPG), which together sense respiration patterns and deliver stimulation to the hypoglossal nerve synchronously with inspiration. The sensing lead incorporates a differential pressure sensor that detects respiratory cycles by their pressure variations. The Implantable pulse generator contains an algorithm that synchronizes hypoglossal nerve stimulation with respiration signals. The algorithm parameters can be adjusted as per the needs of each patient. The IPG predicts the onset of inspiration, delivering stimulation pulses between the end of expiration and the beginning of the next expiratory phase of each respiratory cycle.[217]Stimulation Lead delivers mild stimulation to maintain multilevel airway patency during sleep, incorporates a cuff section that includes 3 electrodes that can be configured in a variety of unipolar or bipolar electrode configurations for stimulation.

The UAS system is implanted on the right side of the patient while the patient is under general anesthesia through three surgical incisions. The main trunk of the hypoglossal nerve (XII) is exposed by means of a horizontal incision in the upper

neck at the inferior border of the Submandibular gland. The nerve is followed anteromedially until it branched into a lateral and a medial (m-XII) division. The stimulation lead is placed on the m-XII branch to recruit the tongue protrusion function. A second incision is made horizontally at the fourth intercostal region. The dissection is aimed at the upper border of the underlying rib. A tunnel of 5 cm is created posteroanteriorly between the external and internal intercostal muscles. The ventilatory sensor is placed in the tunnel, with the sensing side facing the pleura. The third incision is made horizontally, 2 to 4 cm inferior to the right clavicle. A pocket is created inferior to the incision and superficial to the pectoralis major muscle to accommodate the IPG. With a subcutaneous tunneling device, the leads of the stimulation electrode and the pressure sensor were led into the infraclavicular pocket and connected to the implanted pulse generator. Proper function of the whole system is confirmed before closure.[218] No unanticipated safety concerns have been observed from early feasibility studies.[219]

Goding et al.[220] sought to determine objective Fluoroscopic measures in 26 participants implanted with the HGNS system. Under general anesthesia, they examined changes in the anterior- posterior dimension of the retropalatal and retrolingual airway spaces and hyoid bone position with stimulation. All participants had an increase in retrolingual airway (9 ± 3 mm), whereas 65% of participants had enlargement of the retropalatal airway in whom the average increase was 5 ± 3 mm.

There was a trend toward increased BMI in those participants having failed to show expansion of the retropalatal airway. Anterior displacement of the hyoid occurred in 92% of participants.

The basic science experiments and feasibility studies served as the basis for multicenter prospective studies. The largest prospective trial to date is the Stimulation Therapy for Apnea Reduction (STAR) trial.[220] Eligible implant participants had moderate-severe OSA (AHI 20–50), CPAP intolerance and BMI ≤ 32.participants underwent surgical implantation of the hypoglossal nerve stimulation system and were followed for at least 12 months to assess effectiveness and adverse events. Devices were titrated in the sleep laboratory during full-montage attended PSG, similar to CPAP titration, to optimize comfort and effectiveness. Outcome demonstrated clinically and statistically significant improvements at 12 months. Two thirds of the implanted participants were considered complete responders to therapy by previously published surgical success criteria and had successful management of their OSA with a decrease in median AHI from 30 to 6. Risk and morbidity data were favorable with no permanent hypoglossal nerve weakness, no serious device-related infection requiring explantation, and significantly less postoperative discomfort compared to traditional pharyngeal or skeletal sleep apnea surgeries.

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STATEMENT OF THE THESIS

- To evaluate pharyngeal changes in patients with an implanted upper airway stimulation (UAS) system; and
- To compare the pharyngeal airway changes between UAS and continuous positive airway pressure (CPAP) therapy.

It is hypothesized that there are no significant changes in the upper airway in response to electrical stimulation of the hypoglossal nerve and that there are no differences in the airway stimulation between CPAP and UAS activation.

MANUSCRIPT

Evaluation of pharyngeal airway in response to Hypoglossal nerve stimulation and Continuous positive airway pressure.

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INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive collapse of the upper airway during sleep resulting in nocturnal hypoxemia and recurrent arousals.[1] OSA should be approached as a chronic disease, requiring long-term, multidisciplinary management. According to the American Sleep Association, OSA affects more than 12 million Americans, and when left untreated, it has been linked to high blood pressure, heart attacks, strokes, car accidents, work-related accidents, and depression.[2] OSA is estimated to affect approximately 8% of men, and 2% of women, averaging 5% of the general population, with several of them going undiagnosed, thinking of themselves as healthy individuals.[3] Current OSA treatments include both nonsurgical and surgical methods (Table 1). CPAP is the standard of care for treating OSA, however, the general effectiveness of CPAP therapy is dependent on patient acceptance and adherence to treatment.[4] Despite the uniform success of CPAP therapy, patient compliance remains a problem. Compliance rates at 12 months have been reported as low as 54% making a successful long-term treatment difficult to achieve, and leaving patients with only surgical options.[5]

A relatively novel and cutting edge treatment in OSA for patients unable or unwilling to use CPAP therapy is the upper airway electrical stimulation (UAS) therapy using a fully implanted system. The Inspire UAS system (Inspire Medical Systems, Inc, Maple Grove, MN) is a recently FDA approved system offered for the treatment of moderate-to-severe obstructive sleep apnea. This procedure has been shown to decrease the severity and symptoms of OSA in select patients.[6-8] The potential of the

hypoglossal nerve stimulation as a therapeutic approach for the treatment of OSA was initially described by Eisele et al.[9] and Schwartz et al.[10] The branches of the hypoglossal nerve that innervate the genioglossus predominantly contain efferent (motor) fibers, and the stimulation of those branches activate the genioglossus muscle with minimal afferent (sensory) feedback. The device is implanted in the chest, and is composed of a stimulation lead, a sensing lead, and an implantable pulse generator, which together sense respiration patterns and deliver stimulation to the hypoglossal nerve synchronously with inspiration (figure 1). The patient can turn the therapy on before bedtime, and off in the morning using a remote control. When the device is activated, it senses the person's breathing patterns, delivering mild stimulation in order to keep the airway open, acting in a similar way than a pacemaker. The level of stimulation can be custom to each patient, with a low stimulation usually around averaging 1.4V, and a high around 4V. The sensing lead incorporates a differential pressure sensor that detects respiratory cycles by their pressure variations. The implantable pulse generator (IPG) contains an algorithm that synchronizes hypoglossal nerve stimulation with respiration signals while the patient is sleeping in order to prevent collapse of the tongue and soft palate.[11] The IPG predicts the onset of inspiration, delivering stimulation pulses between the end of expiration and the beginning of the next expiratory phase of each respiratory cycle.[12] The stimulation lead delivers mild stimulation to maintain multilevel airway patency during sleep, incorporates a cuff section that includes 3 electrodes that can be configured in a variety of unipolar or bipolar electrode configurations for stimulation.[12]

The hypoglossal nerve is accessed through a horizontal incision in the upper neck at the inferior border of the submandibular gland. The median time for implantation has been reported to average 140 minutes (between 65-360min), with most patients spending the night at the hospital.[6] The UAS system is implanted on the right side of the patient while under general anesthesia, through three surgical incisions (figure 1). The main trunk of the hypoglossal nerve (XII) is exposed by a horizontal incision in the upper neck at the inferior border of the Submandibular gland. The nerve is followed anteromedially until it branched into a lateral and a medial (m-XII) division. The stimulation lead is placed on the m-XII branch to recruit the tongue protrusion function.[6] A second incision is made horizontally at the fourth intercostal region. . A tunnel of 5cm is created posteroanteriorly between the external and internal intercostal muscles. The ventilatory sensor is placed in the tunnel, with the sensing side facing the pleura.[6] The third incision is made horizontally, 2 to 4 cm inferior to the right clavicle. A pocket is created inferior to the incision to accommodate the IPG. Proper function of the whole system is confirmed before closure.[6] No unanticipated safety concerns have been observed from early feasibility studies.[13]
UAS is not new regarding OAS treatment, but advance s in technology seem to be making such option a more viable one, for long-term management of this chronic disease.

Imaging as always was a key concept in orthodontic diagnosis and treatment planning. Cone-beam computed tomography (CBCT) provides a three-dimensional

view of the hard and soft tissue structures of the head and neck, allowing us to examine areas, volumes and complex hollow structures, including the airway, all while being able to modulate the radiation dose (Palomo and El Hakan 2010)[14] Though the relationship between the hyoid bone and the airway remains controversial, both structures are readily identifiable on CBCT images taken in orthodontics. Automatic segmentation of the airway has been shown to be a reliable way to report the oropharyngeal volume and the nasopharyngeal volume, while being much more time efficient compared to manual segmentation (Palomo and El Hakan 2010).[14]

The aim of this study was to analyze the morphologic, volumetric, cross-sectional surface area and linear changes of the upper airway in a systematic fashion in patients with OSA before and after upper airway stimulation and CPAP therapy and to compare the pharyngeal airway changes with implantable upper airway stimulation system and continuous positive airway pressure therapy.

MATERIALS AND METHODS

Seven patients with moderate or severe OSA who underwent surgical implantation for the upper airway stimulation therapy at the University Hospitals were evaluated by CBCT scans in regular breathing. CPAP and upper airway stimulation therapy All After informed consent from UHCMC, patients were trained prior to the CBCT so as to reduce anxiety, increase reproducibility among subjects, and optimize image

collection. The CBCTs scans were done on the same scanner Hitachi CB Mercuray Scanner (Hitachi Medical Systems America, Twinsburg, Ohio) in natural head position while the patients were seated. Images were collected in four 6 seconds time period. The first scan was taken in a cycle of resting breathing. Second scan was taken during stimulation at comfortable amplitude near that used during sleep. Third scan was taken with breathing on +10cmH20. Last scan changes to -2cmH20, designed to nearly collapse of the upper airway. The study was approved by University Hospitals and Case Western Reserve University review board. Exclusion criteria included patients with evidence of AHI more than 65,BMI more than 32.0, neuromuscular disease, Hypoglossal nerve palsy, severe restrictive or obstructive pulmonary disease, moderate to severe pulmonary hypertension, severe valvular heart disease and Prior upper airway surgeries not related to OSA. The radiographs were taken with a 2mA, 120kVp and 12-in field of view. Every radiograph was comprised of 512 slices, with a slice thickness of 0.3777 mm, a resolution of 1024 x 1024 pixels, and 12 bits per pixel (4096 gray scale).Measurements were then made using Dolphin 3D (version 11.9, Dolphin Imaging & Management Solutions, Chatsworth, Calif). All CBCTs were oriented according to the protocol outlined by Wu et al (Wu 2011). Orientation of the CBCT in the coronal view was achieved by aligning the axial plane with the center of the left and right optical foramina. In the axial view, the CBCT was rotated until the coronal plane was aligned with the center of the left and right foramen ovale. The sagittal plane was placed to pass through the formen cecum, serving as a midsagittal marker. In the sagittal view, the pitch of the head was altered

until the axial plane passed through McRae's line (Basion-Opisthion).After proper orientation; a lateral cephalogram was created in order to gather linear cephalometric measurements. Landmarks (Table 2, figure 2) were identified on the tomographs, and Airway volumes (Table 3, figure 3) were calculated using the sinus/airway feature in Dolphin 3D imaging. The minimal cross section area of the total airway volume (MinAX) was calculated using the "enable minimum axial area" feature.

Data Analysis

Images were grouped to 4 groups, Resting breathing, during stimulation, +10cmH2O CPAP and -2cmH20. The descriptive statistics of the four groups was performed using SPSS Version 22 (IBM Corporation, Armonk, NY, USA). All measurements were repeated on a 10 randomly selected images and intra-rater reliability was reported using the intra-class correlation coefficient. For each measurement the Wilcoxon test was used to compare differences between the 4fourgroups. For all tests, $P < 0.05$ was considered statistically significant.

RESULTS

Intra-rater reliability on the 10 randomly selected subjects ranged from 0.893-0.900 indicating good reliability among the sample measurements (Table 4). Descriptive statistics describing the linear measurements (table 5) and the volumetric measurements (table 6).

Stimulation Group

The volume of the upper airway increased significantly by 48% as a result of the upper airway stimulation figure 4. The Hypopharynx volume increased by 63% more than the Nasopharynx 15% and the Oropharynx which increased by 54%. The average area of the smallest airway before stimulation was 100.5 $mm^{2,}$ and after stimulation it was 139.2 $mm^{2.}$ Significant increase in the linear cephalometric measurements after the stimulation, the retro-palatal, retro-glossal and the hypopharynx increased by 29%, 51% and 58% respectively. The hyoid bone to mandibular plane measurement decreased with the stimulation, indicating an elevation of the hyoid. The average hyoid to mandibular plane measurement before stimulation was 19.62 mm; in the literature, more than 15 mm is considered abnormal and associated with OSA. The hyoid bone which is a predictor of airway obstruction also changes and moves superiorly and closer to the mandible to record average of 14.826 after the stimulation figure 5. All the variables in resting breathing and stimulation groups are compared in table (Table 7and 8)

CPAP +10CM H2O

The volume of the upper airway increased significantly by 36% as a result of the positive CPAP figure 6. The Hypopharynx volume increased by 50% more than the

Nasopharynx 17.7 % and the Oropharynx which increased by 23 %. The average area of the smallest airway changed from 100.5 mm2 to 130.2 mm2 with the CPAP therapy. Significant changes in the cephalometric linear measurements with the CPAP reflected by increase of the length of the rerto-palatal, retro-glossal and the hypopharynx by 21%, 51% and 30% respectively. No changes in the hyoid bone position vertically or horizontally. All the variables in resting breathing and CPAP groups are compared in table. (Table 9 and 10)

Comparisons between the stimulation and the CPAP groups showed statistically significant increases only in the movement of the hyoid bone vertically and horizontally. (Table 11 and 12)

-2 CM H2O

The volume of the upper airway was nearly collapsed with the negative pressure. The total airway was changed by -28% with decrease in all the linear and volumetric variables and no change in hyoid bone position. All the variables in resting breathing and -2CM H2O groups are compared in table. (Table 13 and 14)

DISCUSSION

CBCT imaging allows for the three dimensional investigation of hollow structures, including the airway. Thus, with 3D imaging, studies are examining volumes are areas rather than lengths and angles (El Hakan and palomo 2010). [14] Various studies examining the airway have already been conducted utilizing

CBCT imaging. Because of its reliability, automatic segmentation was chosen to sculpt the upper airway.

The present article introduces a novel option for patients dealing with OSA, who are not able to achieve stability through CPAP or more traditional options.

With an incidence of OSA in 8% in men, and 2% in women, many of our orthodontic patients are dealing with diagnosed or undiagnosed symptoms of OSA. It is important to include the airway morphology into the orthodontic treatment plan. The airway patency is more important and vital for our patients than aligning teeth. As healthcare providers, we would be serving our patients better, if we could help identifying symptoms, and possible options for our patients. A possible way to assess airway risks in our patients is by using easy to fill questionnaires, such as the STOP-Bang[15], the Berlin Questionnaire[16], Epsworth Sleepiness scale[17], or sleep disorder questionnaire.[18] Cephalometric analyses may also be useful in identifying potential markers. The sagittal and vertical position of different structures such as soft palate, tongue, airway, and hyoid position measurements could help detect an airway problem. Previous studies have shown differences in the craniofacial anatomy between healthy individuals and individuals with OSA. Pracharktam et al. compared radiographs of twenty-eight OSA patients to a control group of habitual snorers and found out that hyoid bone position is more inferior in OSA patients.[19] In a different study Hans et al used four variables age, BMI, hyoid to mandibular plane and tongue length to produce craniofacial risk index.[20] This index was applied to sixty-six snorers to test the ability of the index to determine subjects of respiratory disturbance index

(RDI) greater than 20 and less than 20, the index was found to correctly classify 72% of low RDI and 78% of subjects with high RDI.

In the current study, 3D imaging helped us to evaluate the pharyngeal airway changes. The findings suggest that unilateral stimulation of the hypoglossal nerve, using an implantable UAS system, increases airway area at multiple levels. It was expected that the unilateral hypoglossal nerve stimulation would open the retro-lingual airway space which will increase the OP and HP volumes , based on the fact that the stimulation lead was placed to recruit the genioglossus muscle which led to forward movement of the tongue, resulting in an anterior–posterior enlargement of the retro-lingual airway area during stimulation. What was not expected was the slight increase at the retro-palatal region and the nasopharynx volumes. One of the possible explanations of the retro-palatal effect seen is due to mechanical linkage between the soft palate and the tongue base.[21,22] Anatomically, the soft palate is linked to the tongue base through the anterior palatal pillar. When stimulation moves the tongue base forward, it might result in palatal advancement through anterior displacement of the anterior pillar moving the soft palate anteriorly, and causing an increase in the retro palatal area.

Continuous positive airway pressure (CPAP) therapy is still prescribed as the first line of therapy and considered the gold standard in the treatment of OSA patients. However, CPAP therapy has compliance limitations, and patients still seek alternative treatment options, including upper airway surgery. However, no airway studies looked at the airway function during CPAP therapy. In this study, CPAP

enlarged the airway with a significant increase in the NP, OP and HP areas.

The position of the hyoid bone could be of significant importance to the craniofacial practitioner, as the hyoid bone is an anatomic structure that is easily identified and evaluated on lateral cephalograms.[23]Also could be an indication of airway length as well as one of the determinants of tongue position. As the airway lengthens vertically, airway instability may increase.[24] Vertical changes in hyoid bone position with age were investigated by Nelson et al in a study of Bolton-Brush subjects who had longitudinal long-term records available.[25]They concluded that snoring subjects showed lower hyoid bone position at all ages. In this study, the hyoid bone distance to the mandibular plane decreased with stimulation, accompanied by a forward movement of the hyoid bone which explains the mechanism of the airway opening by the whole upward and forward movement of the hyoid apparatus, while in the CPAP group hyoid bone movement was minimal which explains the different mechanism of airway opening by augmenting the tone of the upper airway dilator muscles there by reducing susceptibility to collapse. The relationship between oropharyngeal obstruction and hyoid bone position has been previously reported[19,20,25].

This study accounts for airway shape and size only when the patient is awake and in an upright, seated position and is static. When the patient is in the supine position and asleep, the tissues further relax and obstruct the airflow. Thus, any measurements of the airway will actually be worse during normal sleeping in the supine position when the muscles relax. Furthermore, this study was limited by a

small sample size. More work needs to be done in this area to allow precise planning based on the expected airway changes with surgery.

Conclusions

1. UAS moves Hyoid bone significantly upward and forward.
2. UAS increases the oropharynx volume significantly compared to the CPAP.
3. CPAP shows no change on position of hyoid bone.
4. The results of this study indicate that both CPAP and the upper airway stimulation are effective ways for enlarging upper airway dimension, thus preventing it from collapse in OSA patients.
5. A novel implanted UAS system appears to be a good option for treatment of OSA patients. More studies are needed to confirm that the results shown in this article.

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Figure 1 – schematic drawing showing the UAS implantation. Permission granted by The New England Journal of Medicine ©2016, and printed with permission.

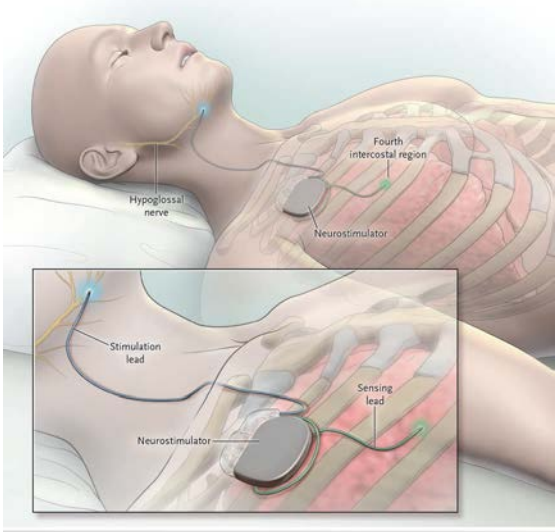


Figure 2 – The landmarks and upper airway measurements used in the present evaluation.

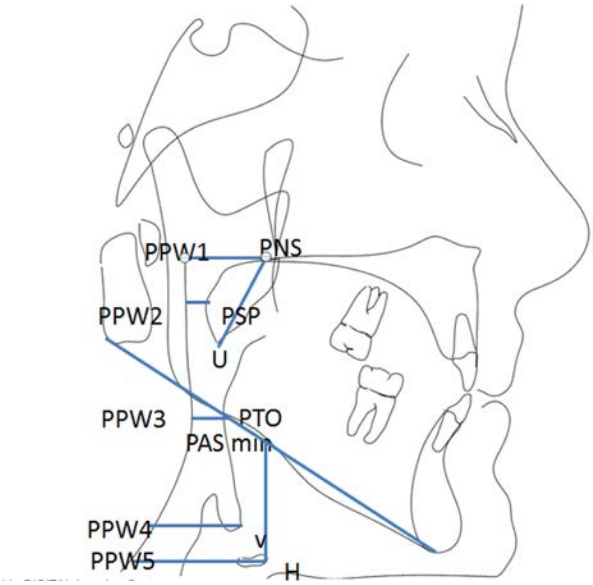


Figure 3 – Boundaries of divisions of the airway

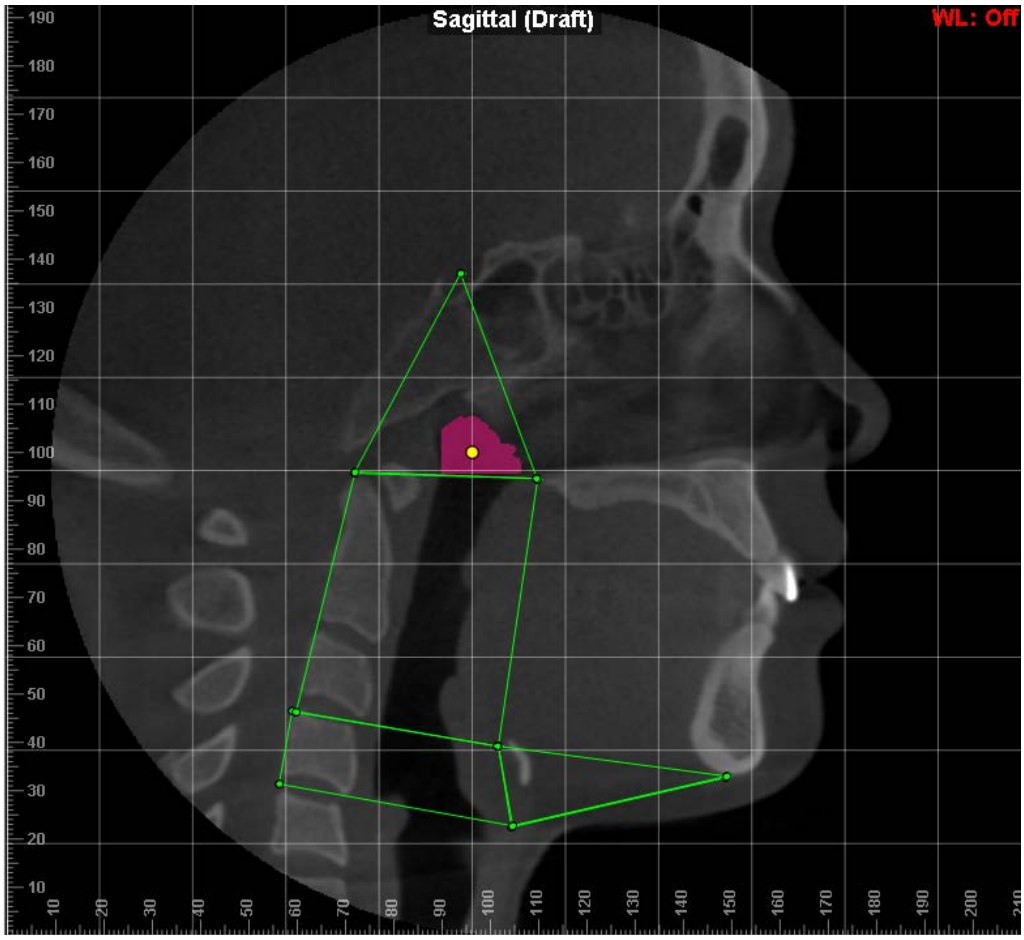


Figure 4 Airway volumes before and with stimulation

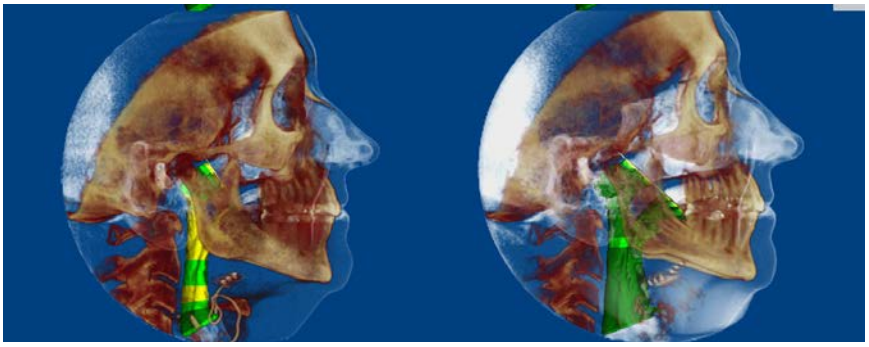


Figure 5 –Hyoid bone movement with the stimulation

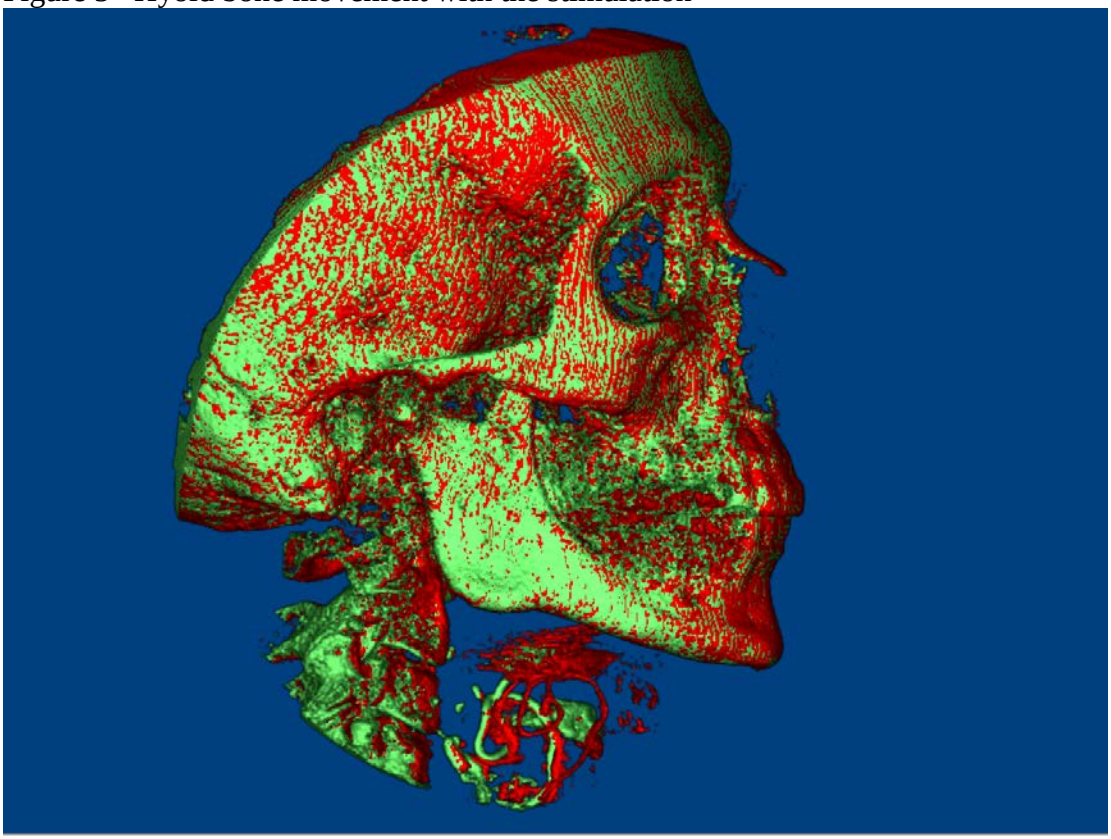
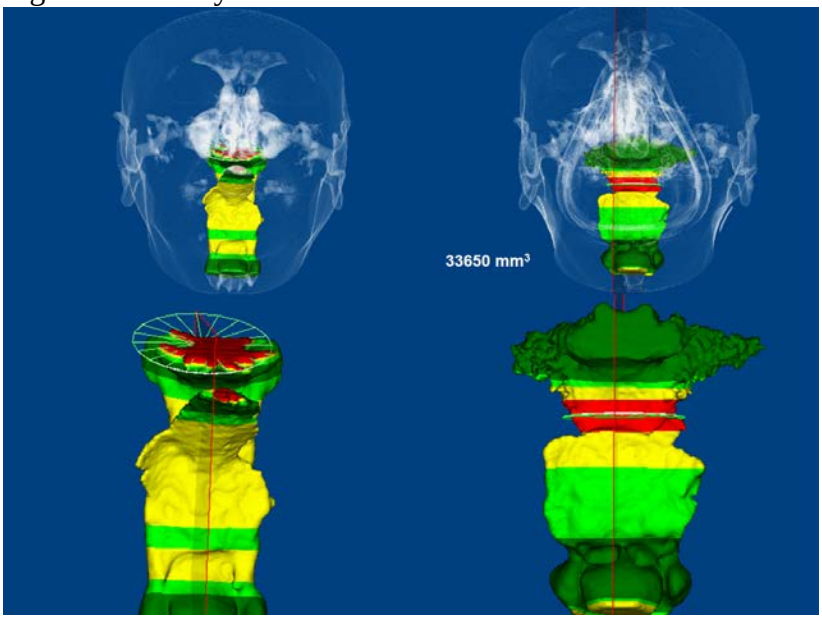


Figure 6 – airway volumes befor and with CPAP



List of Tables

Table 1. Most common surgical and non-surgical options for management of OSA

Non Surgical methods	Surgical methods
Diet and life style modification	Nasal surgery (eg, septoplasty, turbinectomy)
Pharmacologic Agents	Uvulopalatopharyngoplasty (UPPP)
Positive Airway Pressure (PAP)	Base of tongue surgery
Oral appliances	Genioglossal advancement
	Modified genioplasty
	Radiofrequency ablation
	Hyoid myotomy
	Maxillomandibular advancement
	Tracheostomy
	Bariatric surgery

Table 2 The landmarks and references lines of the upper airway

Measurement	Landmarks	Definition
Nasopharynx length	PNS-PPW1 (mm)	Measured as the distance from Posterior Nasal Spine (PNS) to posterior pharyngeal wall (PPW1).
Retro-palatal length	PSP-PPW2 (mm)	Measured as the distance between the most posterior point of the soft palate (PSP) and the posterior pharyngeal wall (PPW2).
Oropharynx length	PTO-PPW3 (mm)	Measured as the distance from the mandibular inferior border in the posterior area of the tongue (PTO) to the posterior pharyngeal wall (PPW3), which can be defined as retro-lingual region.
Hypopharynx length	V-PPW4 (mm)	Measured as the distance between the base of the epiglottic vallecular (V) and the posterior pharyngeal wall (PPW4).
Soft Palate length	PNS-U (mm)	Measured from PNS to the Uvula (U).
Hyoid bone horizontal position	H-PPW5 (mm)	Measured as the distance between the most anterosuperior point of hyoid bone (H) and PPW5.
Hyoid bone vertical position	H-MP (mm)	Measured from the most anterosuperior point of hyoid bone (H) to the mandibular plane (MP).

Table 3. Definition of anatomic boundaries.

	Anterior Boundary	Posterior Boundary	Superior Boundary	Inferior Boundary
Naso-pharynx	Line extending from sella (S) to the PNS	Line extending from S to the tip of the odontoid process		Line extending from PNS to tip of the odontoid process
Oro-pharynx	Line extending from the posterior nasal spine (PNS) to the base of the epiglottis	Line extending from the tip of the odontoid process to the posterior-superior border of CV4	Line extending from the PNS to the tip of the odontoid process	Line extending from the base of the epiglottis to the posterior-superior border of CV4
Hypo-pharynx	Line extending from the base of the epiglottis to the inferior border of the symphysis	Line extending from the posterior-superior corner of CV 4 to the inferior corner of CV 4	Line extending from the base of the epiglottis to the posterior-superior corner of CV 4	Line extending from the posterior-inferior corner of CV 4 to the inferior border of the symphysis

Table 4 reliability of measurement

Variable	Inter-correlation coefficient
Naso-pharynx volume	**.852**
Oro-pharynx volume	**.839**
Hypo-pharynx volume	**.900**
Total airway volume	**.833**
Retropalatal	**.856**
Retroglossal	**.856**
Hypopharynx	**.838**
Hyoid to Mandibular-plane	**.833**

Table 5 Descriptive analysis of linear measurements for four groups

Variable	**Resting Breathing**	**Stimulation**	**CPAP +10 CM H2O**	**-2 CM H20**
Nasopharynx	**16.91 ± 1.72**	**18.85 ± 2.6**	**17.78 ± 2.2**	**16.2 ± 2.3**
Retropalatal	**6.60 ± 2.1**	**8.54 ± 2.3**	**8.04 ± 1.09**	**5.2 ± 2.03**
Retroglossal	**7.01 ± 1.83**	**10.64 ± 2.74**	**10.62 ± 4.2**	**5.62 ± 1.68**
Hypopharynx	**12.31 ± 3.7**	**19.5 ± 3.8**	**16.07 ± 5.0**	**9.88 ± 3.2**
Hyoid to Mandibular-plane	**19.62 ± 3.8**	**14.82 ± 5.9**	**18.38 ± 5.6**	**19.88 ± 3.7**

Table 6 Descriptive analysis of volumetric variables in 4 groups

Variable	Resting Breathing	Stimulation	CPAP +10 CM H2O	-2 CM H20
Naso-pharynx volume	6123.57 ± 1587.13	7046.14 ± 2088.51	7212.71 ± 2173.37	4929.57 ± 2016.28
Oro-pharynx volume	16898.85 ± 5979.63	26047.14 ± 11712.96	20825.14 ± 10117.37	11542.71 ± 6253.07
Hypo-pharynx volume	6515.14 ± 2669.86	10624.14 ± 11712.96	9726.42 ± 3930.98	4506.14 ± 1816.80
Total airway volume	29538.00 ± 9789.26	43688.28 ±16155.27	40382.85 ± 14748.4	20972.7143±9777.96
The minimal cross section area	100.57 ± 38.74	139.2 ± 60.01	130.64 ± 64.01	52.00 ± 23.01

Table 7 between resting and stimulation volumetric variables

Variable	Resting Breathing	Stimulation	Changes in %	P value
Naso-pharynx volume	6123.57 ± 1587.13	7046.14 ± 2088.51	15%	.018
Oro-pharynx volume	16898.85 ± 5979.63	26047.14 ± 11712.96	54%	.018
Hypo-pharynx volume	6515.14 ± 2669.86	10624.14 ± 11712.96	63%	.018
Total airway volume	29538.00 ± 9789.26	43688.2857 ±16155.27	48%	.018
The minimal cross section area	100.57 ± 38.74	139.2 ± 60.01	39%	.063

Table 8 comparison between linear variables in resting and stimulation groups

Variable	Resting Breathing	Stimulation	Changes in %	P value
Nasopharynx	**16.91 ± 1.72**	**18.85 ± 2.6**	**11.5%**	**.018**
Retropalatal	**6.60 ± 2.1**	**8.54 ± 2.3**	**29%**	**.018**
Retroglossal	**7.01 ± 1.83**	**10.64 ± 2.74**	**51%**	**.018**
Hypopharynx	**12.31 ± 3.7**	**19.5 ± 3.8**	**58%**	**.018**
Hyoid to Mandibular-plane	**19.62 ± 3.8**	**14.82 ± 5.9**	**-24%**	**.028**
Hyoid Horizontal	**27.38 ± 4.1**	**35.58 ± 6.48**	**29%**	**.018**

Table 9 comparison between volumetric variables in resting and CPAP

Variable	Resting Breathing	CPAP	Changes in %	P value
Naso-pharynx volume	**6123.57 ± 1587.13**	**7212.71 ± 2173.37**	**18%**	**.018**
Oro-pharynx volume	**16898.85 ± 5979.63**	**20825.14 ± 10117.37**	**23%**	**.028**
Hypo-pharynx volume	**6515.14 ± 2669.86**	**9726.42 ± 3930.98**	**50%**	**.018**
Total airway volume	**29538.00 ± 9789.26**	**40382.85 ± 14748.4**	**36%**	**.018**
The minimal cross section area	**100.57 ± 38.74**	**130.64 ± 64.01**	**30%**	**.083**

Table 10 comparison betwwen linear variables in resting and CPAP

Variable	Resting Breathing	CPAP	Changes in %	P value
Nasopharynx	**16.91 ± 1.72**	**17.78 ± 2.2**	**8%**	**.080**
Retropalatal	**6.60 ± 2.1**	**8.04 ± 1.09**	**21%**	**.028**
Retroglossal	**7.01 ± 1.83**	**10.62 ± 4.2**	**51%**	**.018**
Hypopharynx	**12.31 ± 3.7**	**16.07 ± 5.0**	**30%**	**.028**
Hyoid to Mandibular-plane	**19.62 ± 3.8**	**18.38 ± 5.6**	**-5%**	**.463**
Hyoid Horizontal	**27.38 ± 4.1**	**27.37 ± 4.70**	**0%**	**.46**

Table 11 comparison between volumetric variables in stimulation and CPAP groups

Variable	Stimulation	CPAP	P value
Naso-pharynx volume	**7046.14 ± 2088.51**	**7212.71 ± 2173.37**	**.499**
Oro-pharynx volume	**26047.14 ± 11712.96**	**20825.14 ± 10117.37**	**.028**
Hypo-pharynx volume	**10624.14 ± 11712.96**	**9726.42 ± 3930.98**	**.091**
Total airway volume	**43688.2857 ±16155.27**	**40382.85 ± 14748.4**	**.23**
The minimal cross section area	**139.2 ± 60.01**	**130.64 ± 64.01**	**.63**

Table 12 comparison between linear variables in stimulation and CPAP groups

Variable	Stimulation	CPAP	P value
Nasopharynx	**18.85 ± 2.6**	**17.78 ± 2.2**	**.090**
Retropalatal	**8.54 ± 2.3**	**8.04 ± 1.09**	**.498**
Retroglossal	**10.64 ± 2.74**	**10.62 ± 4.2**	**.735**
Hypopharynx	**19.5 ± 3.8**	**16.07 ± 5.0**	**0.91**
Hyoid to Mandibular-plane	**14.82 ± 5.9**	**18.38 ± 5.6**	**.028**
Hyoid Horizontal	**35.58 ± 6.48**	**27.37 ± 4.70**	**.043**

Table 13 comparison betwwen volumetric variables in resting and -2 CM H20 groups

Variable	Resting Breathing	-2 CM H20	P value
Naso-pharynx volume	**6123.57 ± 1587.13**	**4929.57 ± 2016.28**	**.018**
Oro-pharynx volume	**16898.85 ± 5979.63**	**11542.71 ± 6253.07**	**.018**
Hypo-pharynx volume	**6515.14 ± 2669.86**	**4506.14 ± 1816.80**	**.028**
Total airway volume	**29538.00 ± 9789.26**	**20972.7143±9777.96**	**.019**
The minimal cross section area	**100.57 ± 38.74**	**52.00 ± 23.01**	**.053**

Table 14 comparison betwwen linear variables in resting and -2 CM H20 groups

Variable	Resting Breathing	-2 CM H20	P value
Nasopharynx	**16.91 ± 1.72**	**16.2 ± 2.3**	**.043**
Retropalatal	**6.60 ± 2.1**	**5.2 ± 2.03**	**.028**
Retroglossal	**7.01 ± 1.83**	**5.62 ± 1.68**	**.018**
Hypopharynx	**12.31 ± 3.7**	**9.88 ± 3.2**	**.043**
Hyoid to Mandibular-plane	**19.62 ± 3.8**	**19.88 ± 3.7**	**.465**
Hyoid Horizontal	**27.38 ± 4.1**	**26.1 ± 3.7**	**.043**